INFORMATION TO USERS

This manuscript has been reproduced from the microfilm master. UMI films the text directly from the original or copy submitted. Thus, some thesis and dissertation copies are in typewriter face, while others may be from any type of computer printer.

The quality of this reproduction is dependent upon the quality of the copy submitted. Broken or indistinct print, colored or poor quality illustrations and photographs, print bleedthrough, substandard margins, and improper alignment can adversely affect reproduction.

In the unlikely event that the author did not send UMI a complete manuscript and there are missing pages, these will be noted. Also, if unauthorized copyright material had to be removed, a note will indicate the deletion.

Oversize materials (e.g., maps, drawings, charts) are reproduced by sectioning the original, beginning at the upper left-hand corner and continuing from left to right in equal sections with small overlaps. Each original is also photographed in one exposure and is included in reduced form at the back of the book.

Photographs included in the original manuscript have been reproduced xerographically in this copy. Higher quality 6" x 9" black and white photographic prints are available for any photographs or illustrations appearing in this copy for an additional charge. Contact UMI directly to order.

UMI

A Bell & Howell Information Company
300 North Zeeb Road, Ann Arbor MI 48106-1346 USA
313/761-4700 800/521-0600

Glucocorticoids and the risks of ocular hypertension or open-angle glaucoma

Edeltraut Garbe

Mc Gill University

A thesis submitted to the Faculty of Graduate Studies and Research in partial fulfillment of the requirements for the degree of Master of Science in Epidemiology and Biostatistics

ABSTRACT

This thesis presents results of a case-control study investigating the excess risk of ocular hypertension or open-angle glaucoma associated with the use of oral, inhaled and nasal glucocorticoids. Data on 9,793 cases and 38,325 control subjects were obtained from the computerized administrative health databases of the province of Québec, Canada.

For oral glucocorticoids, a 40 % increase in the risk of ocular hypertension or open-angle glaucoma was observed. The risk increased with higher daily doses and increasing duration of treatment.

Exposure to inhaled glucocorticoids was not associated with an elevated risk, except when they were administered in high doses over extended periods of time. No elevated risk was observed for exposure to nasal glucocorticoids.

The study results are discussed in view of pharmacological data for different forms of glucocorticoids and compared to findings for ophthalmic glucocorticoids. The database is used to illustrate empirical explorations of concerns about bias.

RÉSUMÉ

Cette thèse présente les résultats d'une étude cas-témoins dont le but était de déterminer le risque d'hypertonie oculaire ou de glaucome à angle ouvert associé à l'utilisation de glucocorticoïdes oraux, inhalés et nasaux. Les données sur 9 793 cas et 38 325 témoins ont été obtenues à partir des fichiers administratifs sanitaires informatisés de la province de Québec, Canada.

Une augmentation du risque d'hypertonie oculaire ou de glaucome à angle ouvert de 40 % a été observée après l'utilisation de glucocorticoïdes oraux. Le risque s'élevait avec l'augmentation des doses quotidiennes et de la durée du traitement.

L'exposition aux glucocorticoïdes inhalés n'était pas associée à une augmentation du risque sauf lorsqu'ils étaient administrés à hautes doses pour des périodes de temps prolongées. Aucune augmentation du risque ne fut observée suita à l'exposition aux glucocorticoïdes nasaux.

Les résultats de cette recherche sont discutés dans le contexte des données pharmacologiques concernant les différents types de glucocorticoïdes et sont comparés aux résultats sur les glucocorticoïdes ophtalmiques. La base de données est utilisée pour illustrer l'exploration empirique de questions concernant des biais.

TO JOACHIM

TABLE OF CONTENTS

LIST OF TABLES

ACKNOWLEDGEMENTS

First of all, I would like to express my appreciation and sincere gratitude to my thesis supervisor, Dr. Samy Suissa. His expertise, continuous support and guidance have been instrumental in carrying out this research project.

Further, I wish to thank my thesis co-supervisor, Dr. Jacques Le Lorier, for his support, sustained interest and encouragement in helping to complete this project and for the opportunity he provided me to use his data file of the RAMQ database in order to carry out this project.

Throughout the period of this research project, I received invaluable advice on a number of important methodologic issues and in the preparation of the manuscripts from Dr. Jean-Francois Boivin who was a member of my Thesis Supervisory Committee. I am particularly grateful to him for providing me with his support also during the time of his sabbatical year.

I also thank Francois Derderian and Veronique Pagé who advised me in the data management of this large data file.

I am also grateful to my first teacher in epidemiology, Dr. Walter O. Spitzer who introduced me to the principles and methods of epidemiology at the McGill-Potsdam Institute of Pharmacoepidemiology and Technology Assessment in Germany and encouraged me to further persue a Masters degree at McGill University in Canada.

Finally, I wish to thank the Deutscher Akademischer Austauschdienst (DAAD) in Germany for supporting my studies at McGill University with a fellowship.

PREFACE

This thesis consists of five chapters, including the introduction, three manuscripts intended for journal publication and an overall summary and conclusion. The introduction provides an overview of the literature relevant to all aspects of this work and summarizes the study objectives. The first two manuscripts report the main study findings, characterizing the excess risk of ocular hypertension or open-angle glaucoma for different glucocorticoid exposures. The third manuscript discusses in further detail three specific methodologic issues which arose in the context of this study. The final chapter provides an overall summary of the findings reported in the three preceding manuscripts. Tables and references are provided at the end of each manuscript or chapter.

Since the three manuscripts will be submitted for publication to different medical journals there is some repetition of material in the literature review and in the methods and discussion sections.

Despite these limitations, I decided to use the option of writing the thesis as a series of papers, since this approach ensures that the results will reach a wide audience within a relatively short period of time. It also gave me valuable experience in reporting the results of a study in a way suitable for publication in a scientific journal.

The format of this thesis is approved by the Faculty of Graduate Studies and Research, McGill University. The following statement from the 'Guidelines Concerning Thesis Preparation' must be included in the Preface:

'Candidates have the option, subject to the approval of their Department, of including, as part of the thesis, copies of the text of a paper(s), submitted for publication, or the clearly duplicated text of a published paper(s), provided that these copies are bound as integral part of the thesis.
- If this option is chosen, connecting texts, providing logical bridges between the different papers, are mandatory.

- The thesis must still conform to all other requirements of the 'Guidelines Concerning Thesis Preparation' and should be in a literary form that is more than a mere collection of manuscripts published or to be published. The thesis must include, as separate chapters or section: (1) a table of contents, (2) a general abstract in English and French, (3) an introduction which clearly states the rationale and objectives of the study, (4) a comprehensive general review of the background literature to the subject of the thesis, when this review is appropriate, and (5) a final overall conclusion and/or summary.
- Additional material (procedural and design data as well as descriptions of equipment) must be provided in sufficient detail (e.g. in appendices) to allow clear and precise judgement to be made of the importance and originality of the research reported in the thesis.
- In the case of manuscripts co-authored by the candidate and others, the candidate is required to make an explicit statement in the thesis of who contributed to such work and to what extent. Supervisors must attest to the accuracy of such statements at the doctoral oral defense. Since the task of the examiners is made more difficult in these cases, it is in the candidate's interest to make perfectly clear the responsibilities of all the authors of the co-authored papers. Under no circumstances can a co-author of any component of such a thesis serve as an examiner for that thesis.'

AUTHORSHIP

This thesis presents the findings of research that I initiated and developed. I formulated the principal research questions independently and was responsible for the data management, statistical analysis and manuscript preparation. The co-authors of the three manuscripts were all members of my Thesis Supervisory Committee who offered constructive criticism throughout the entire research project and manuscript preparation.

STATEMENT OF ORIGINALITY

To my knowledge, this is the first systematic study to evaluate the risk of ocular hypertension or open-angle glaucoma after the exposure to inhaled and nasal glucocorticoid use. It is also the first to assess this risk for oral glucocorticoids in a population-based approach and to study the effect of dose and duration of treatment for these clinical endpoints. In addition, it is the first study which provides summary risk estimates for the exposure to oral and ophthalmic glucocorticoids within the same study.

CHAPTER 1

INTRODUCTION

Glucocorticoids, also called corticosteroids or just simply steroids, are medications that exhibit strong anti-inflammatory, immunosuppressive and antiallergic effects when given in higher than naturally occurring doses. These pharmacological properties have made them powerful agents in the treatment of a wide variety of inflammatory and other diseases. Their use is, however, limited by their numerous side effects which can affect all organ systems (1). The study presented here investigates the risk of ocular hypertension or open-angle glaucoma as a potential side effect of glucocorticoid administration, examining the risk of these adverse events for different forms of glucocorticoids. Ocular hypertension is considered the most important risk factor for primary open-angle glaucoma (POAG). Glaucoma is an important cause of severe loss of vision and blindness in industrialized countries. According to data from the Model Reporting Area for Blindness Statistics in the United States it was the second single cause of blindness incidence and prevalence in the United States (2). In 1970, blindness from glaucoma affected 16.2 persons per 100,000 and was responsible for 11.1 % of all cases of blindness in the registry (3). Similar figures have been published for the blindness registry of England and Wales, where glaucoma accounted for 13 % of all reported cases of blindness (2). In the case of corticosteroid-induced glaucoma, progression of the disease can usually be interrupted by discontinuation of the steroid if the disease is detected sufficiently early. It is therefore of great importance to identify which patients receiving glucocorticoids are at risk for this adverse and potentially serious health outcome and should be subjected to active case-finding procedures.

1.1 Ocular Hypertension and Open-Angle Glaucoma

1.11 Definition, Classification and Clinical Aspects

Open-angle glaucoma has traditionally been defined as an eye disease with elevated intraocular pressure associated with optic nerve damage and a slowly progressive loss of visual sensitivity (4). The optic disk, which is the site of passage of millions of axons that connect retinal ganglion cells to the brain, may appear deeply excavated due to glaucomatous atrophy of optic nerve fibres, an appearance referred to as 'cupping' of the optic disk and considered characteristic of glaucoma. The association between raised intraocular pressure, typical glaucomatous changes of the optic disk and subsequent loss of vision led to the pathogenic theory that ocular hypertension causes the damage to the optic nerve (5). Today, raised intraocular pressure is no longer part of the definition, since it is realized that the intraocular pressure may be normal in some patients (often referred to as 'low-tension glaucoma' or, more recently, 'normal-tension glaucoma') and that not all patients with elevated intraocular pressure will develop the disease (4). High intraocular pressure still remains an important risk factor for the disease which is reflected in the definition of glaucoma by the American Academy of Ophthalmology (AAO). The AAO defines glaucoma as a group of diseases with certain common features, including intraocular pressure that is too high for the continuing health of the eye, cupping and atrophy of the optic nerve head and visual field loss (6).

Ocular hypertension is a diagnosis used for those individuals who have a consistent elevation of ocular pressure above the generally accepted norm of 21 mm Hg without evidence of optic nerve damage or visual field change. Although intraocular pressure values in the population do not follow a normal distribution, the cutoff point of 21 mm Hg corresponds to two standard deviations above the population mean (2).

Open-angle glaucoma is classified into a primary and secondary forms based on the etiology of the disease. If no apparent cause is found, the glaucoma is considered primary.

In secondary open-angle glaucoma, an ocular or systemic abnormality is identified that appears to be responsible for the alteration in aqueous humor dynamics. Causes of secondary glaucomas include previous or concomitant ocular conditions such as ocular inflammation, ocular trauma, intraocular hemorrhage or intraocular tumors and systemic conditions such as glucocorticoid administration (7).

Open-angle glaucoma is distinguished from angle-closure glaucoma, based on the appearance of the anterior chamber angle through which the aqueous humor drains. If this angle is wide open, the glaucoma is classified as open-angle glaucoma. The other type of glaucoma with a shallow anterior chamber and narrow chamber angle is classified as angle-closure glaucoma. A third group of glaucomas is occasionally distinguished from these two forms and classified as developmental glaucomas. This group is characterized by a developmental abnormality of the anterior chamber angle and is usually detected during childhood. Among the different types of glaucoma, POAG is the most frequent type in adults (2).

The onset of ocular hypertension and open-angle glaucoma is usually insidious and asymptomatic. Visual dysfunction from open-angle glaucoma is first manifested in the mid-peripheral field of vision, whereas central vision functions such as visual acuity are preserved until late in the course of the disease. Due to its relatively asymptomatic course, open-angle glaucoma is often not diagnosed in its early stage (8). Population screening surveys have demonstrated that roughly half of the patients who suffer from open-angle glaucoma were unaware of the presence of the disease (9-12).

Ocular hypertension is diagnosed by tonometry, a relatively simple, painless and inexpensive method of determining intraocular pressure (2,13). The diagnosis of open-angle glaucoma involves different diagnostic procedures, including ophthalmoscopy for the examination of the optic disk and nerve-fiber layer, tonometry for the measurement of intraocular pressure, perimetry for visual field testing and gonioscopy for inspection of the anterior chamber angle (4). For screening or active case-finding of open-angle glaucoma, tonometry has been recommended by some authors, due to its simplicity and low cost (14-

16). The use of this technique for screening alone will, however, miss a substantial portion of patients, due to the existence of normal-tension glaucoma (13).

All treatment options for open-angle glaucoma are directed towards a reduction of the intraocular pressure. There are three main approaches to lower the intraocular pressure: drug treatment, laser therapy (trabeculoplasty) and surgery (trabeculectomy). Medical treatment is usually given first and laser therapy and surgical procedures are applied when drug treatment fails. Recently, trabeculectomy has been advocated as first treatment of choice in more advanced cases (17,18).

Medical management of POAG is generally based on four different drug classes: α-adrenergic agonists, β-blockers, direct and indirect parasympathomimetic agents and carbonic anhydrase inhibitors (9,19). Initial treatment is usually with either a β-blocker or an α-agonist. The latter is the first choice in patients with pulmonary disease (20). All drugs for glaucoma treatment with the exception of carbonic anhydrase inhibitors are topical ophthalmic preparations directly administered to the eye. Carbonic anhydrase inhibitors are administered orally or intravenously.

Patients with ocular hypertension should only be treated when they are at risk of developing glaucoma. However, a precise indicator of future glaucomatous damage is still lacking in these patients. Ocular hypertension with intraocular pressures over 30 mm Hg is usually considered a high-risk condition requiring treatment (14,21). Some authors have advised treatment at less elevated intraocular pressure levels, particularly in the presence of other risk factors (14,22). Patients whose intraocular pressure is only moderately elevated are usually followed without treatment, but subjected to periodic visual field and optic disk examinations.

Treatment of normal-tension glaucoma has traditionally been the same as that of high-tension glaucoma, employing standard medical treatment, laser or surgery. The benefit of treatment is, however, uncertain and it has been recommended to administer treatment only in cases of well-documented progression of the disease (18,23).

1.12 Epidemiology of Ocular Hypertension and Open-Angle Glaucoma

Several large population surveys have been conducted to determine the prevalence of ocular hypertension and/or POAG (11,12,24-28). These studies usually included only subjects 40 years of age or older (12,26,29) or in some studies even only older subjects (11,24,27,28). The reported prevalence of ocular hypertension ranged from 2.2 % to 6.8 % and that of POAG from 0.5 % to 2.1 %. In surveys conducted in populations with a high proportion of black subjects, higher prevalences of POAG were reported (30). It has been hypothesized that the variations in prevalence in different studies may partly be explained by different diagnostic criteria and screening techniques (2). Screening for glaucoma usually included tonometry, ophthalmoscopy and perimetry. The latter was not routinely performed in all studies (12,25) which may have led to an underestimate of glaucoma prevalence in these studies (31). In two more recent studies which routinely employed perimetry and were conducted in predominantly Caucasian populations, in Beaver Dam, Wisconsin, and Rotterdam, Netherlands, prevalences of POAG of 2.1 % and 1.1 % were reported, respectively (11,27). In comparison with open-angle glaucoma, angle-closure glaucoma is rare, being seven times less prevalent in the United States than open-angle glaucoma (4).

The need for prolonged follow-up of a large cohort has made it difficult to adequately determine the incidence of glaucoma. Data in these studies are often incomplete due to substantial loss to follow-up (2,31). Some follow-up studies were only conducted in selected groups of subjects as for example in patients with high intraocular pressures (2). The available data suggest that the incidence of POAG in populations with normal intraocular pressure is very low, approximately 0.1 - 0.25 % per year (2,5,32,33).

The main risk factors affecting prevalence and incidence of open-angle glaucoma are high intraocular pressure, old age, a family history of glaucoma and black race. The influence of other factors, such as gender, systemic hypertension, diabetes mellitus and severe myopia, is less well understood.

High intraocular pressure represents the most consistent risk factor (4). Several population surveys have shown higher prevalences of POAG with increasing intraocular pressure (34-36). The probability of optic nerve injury appears to increase exponentially with ocular pressure values (4). In one study, the prevalence of optic nerve damage was found to be 7% in patients with intraocular pressures of 25-29 mm Hg, 14 % in those with pressures of 30-34 mm Hg, 52 % in patients with pressures of 35-39 mm Hg and still increasing in patients with higher pressure values (36). Incidence data suggest that the higher the baseline intraocular pressure, the greater the subsequent risk of developing glaucomatous optic nerve damage (37). There is, however, still a substantial portion of patients with POAG who have ocular pressures within the normal range. This proportion ranges beween 25 % and 62 % in population-based surveys (11,24,27,37).

Age has been characterized as an important risk factor for ocular hypertension and POAG in a large number of studies (2,10-12,24-26,29,38-40). POAG is rare below the age of 40, with most cases being diagnosed after the age of 60. In the Bedford Glaucoma Survey, the prevalence of POAG was 0.22 % among subjects 40-49 years old, 0.10 % for 50-59, 0.57 % for 60-69, 2.81 % for 70-79 and 14.29 % for patients over the age of 80 (41). Age was identified as the major independent predictor of glaucoma incidence in the Collaborative Glaucoma Study (34). In this study, subjects over age 60 had almost a sevenfold higher incidence of glaucoma than those under age 40.

A family history of POAG is generally considered to be a significant risk factor. Close relatives of glaucoma patients are found to have an increased prevalence of POAG, which ranges from 4-16 % in various reports (2,42,43). Although the exact hereditary mode is unknown, indirect evidence suggests that it is most likely multifactorial and complex (31).

POAG is more prevalent, develops at an earlier age, and is more severe in blacks as compared with whites (3,26,44-46). The Baltimore Eye Survey was a population-based survey of the prevalence of POAG in over 5000 subjects of whom almost half were black. Age-adjusted prevalence rates were four to five times higher in blacks than in whites. Rates among blacks ranged from 1.23 % in those aged 40 through 49 years to 11.26 % in

those 80 years and older, whereas rates in whites ranged from 0.92 % to 2.16 %, respectively (26).

Numerous studies have reported an association between an increase in blood pressure and a rise in intraocular pressure (38,47-52). In one of these studies, a positive correlation was observed between a change in systolic blood pressure and a change in intraocular pressure (52). For POAG, the association is less well understood. Some studies reported an association between systemic hypertension and POAG (51,53), whereas in other studies low perfusion pressure appeared to be more important for the development of the disease (54). In the Rotterdam Eye Study, systemic hypertension was associated with high-tension glaucoma, but not with normal-tension glaucoma (47). The increased risk of POAG associated with these vascular risk factors is believed to be related to a deterioration of the perfusion of the optic nerve head (54).

Diabetes mellitus appears to be associated with an increased risk of ocular hypertension. Many studies reported higher intraocular pressure values in diabetic than in non-diabetic patients (38,55-57), whereas other studies observed an increased frequency of elevated intraocular pressure in diabetic patients (51,55,58) or an increased prevalence of diabetes in patients with ocular hypertension (29,51). The relationship between diabetes mellitus and POAG is less conclusive. Some studies have shown a higher prevalence of POAG in diabetics (55). In the Beaver Dam Eye Study, open-angle glaucoma was more prevalent in subjects with older-onset diabetes than in subjects without diabetes (40). Diabetes was not associated with POAG in the Baltimore Eye Survey (56) and in the Framinham Eye Study (59).

Most studies have found an association between myopia and ocular hypertension (29,49,60-63). Some studies have shown an increased prevalence of POAG among myopes (64) or an increased frequency of myopia among patients suffering from POAG (60). Particularly severe myopia is considered to be a risk factor for POAG (65). Leske has, however, pointed out that the diagnosis of glaucoma in patients with severe myopia presents difficulties, since the appearance of the optic nerve in myopic eyes may be

misleading and myopic fundus changes can give rise to field defects that resemble those in glaucoma (2).

There is conflicting evidence regarding the gender-related risk of ocular hypertension and glaucoma. Some studies have found significantly higher intraocular tensions in females (2,12,48), but other studies have reported similar mean intraocular pressures for both sexes (38,58,66). No significant association between POAG and gender was seen in the Baltimore Eye Survey (26), the Beaver Dam Eye Study (27) and other studies (2,12,48). In the Framingham Eye Study, men were more than twice as likely as women to have open-angle glaucoma (66) and this risk was found to be increased more than threefold in the Rotterdam Eye Study (11). The opposite was reported from Sweden, where a higher incidence of POAG was found among females (32).

The presence of an enlarged disk or a large cup-to-disk ratio are occasionally listed as predictors for glaucoma development (67). Since optic nerve damage is usually accompanied by an enlarged cup-to-disk ratio, the finding of a large ratio can also be regarded as an early sign of the disease rather than a risk factor (2).

1.2 Glucocorticoids

Glucocorticoids are hormones secreted by the adrenal cortex or synthetic analogues of these hormones. Naturally produced glucocorticoids by the adrenal cortex are hydrocortisone (cortisol) and corticosterone (68). The output of glucocorticoids from the adrenal cortex is regulated through the so-called hypothalamic-pituitary-adrenal (HPA) axis, a complex feedback loop involving several intermediate releasing factors and hormones (69). High levels of circulating hydrocortisone in the blood exert a negative-feedback control in this loop leading to a lower production of endogenous glucocorticoids. Exogenous steroids in pharmacologic doses also suppress the HPA axis leading to cessation of secretion of endogenous corticosteroids by the adrenal glands. The degree and duration of hypothalamic-pituitary-adrenal (HPA) axis suppression produced

by therapeutically administered glucocorticoids is highly variable among patients (69) and depends on dose, frequency and time of administration, and duration of glucocorticoid therapy. Substantial suppression of the HPA axis can occur within a week (68). Measurement of the degree of suppression of the HPA axis has frequently been used as a pharmacologic marker to determine whether topically administered glucocorticoids may exhibit systemic side effects (70).

The pharmacology of glucocorticoids, which affect almost all body systems, is complex. In physiologic doses, systemic glucocorticoids are administered to replace deficient endogenous hormones. In pharmacologic doses, they are used in a wide variety of diseases for their antiinflammatory and immunosuppressant properties. Treatment indications include rheumatic disorders and collagen diseases, severe allergic conditions, asthma, ulcerative colitis and Crohn's disease, sarcoidosis, chronic active hepatitis, cerebral edema, acute spinal cord injury, nephrotic syndrome, myasthenia gravis, thyroiditis, acute gout, hypercalcemia, hematologic diseases due to circulating antibodies, cancer, certain ocular diseases, nonbacterial and nonviral ocular inflammations, organ transplant rejections and a wide variety of skin diseases (1,71). In spite of their widespread clinical use, no published epidemiologic data were found about the utilization of systemic glucocorticoids.

Dosage ranges for systemic glucocorticoids are extremely wide, and patient responses are quite variable. It is generally recommended that the amount of drug each patient receives be individualized according to the diagnosis, severity, prognosis and probable duration of the disease, and patient response and tolerance. The physiologic or replacement dosage is approximately 20 mg of hydrocortisone per day which is the daily amount of glucocorticoid secreted by the adrenal cortex. A pharmacologic dosage is any dosage greater than a physiologic dosage, which includes maintenance or low dosage (a dosage slightly in excess of physiologic amounts, e.g., 5-15 mg of prednisone daily), moderate dosage (approximately 0.5 mg of prednisone/kg daily), high dosage (approximately 1-3 mg of prednisone/kg daily) and massive dosage (approximately 15-30 mg of prednisone/kg daily) (119). For maintenance treatment, the minimum amount to produce

the desired effect must be used, to minimise long-term toxicity. To facilitate dosing of different oral glucocorticoid preparations, relative potencies of their antiinflammatory effect and approximate equivalent dosages have been established by various laboratory assays (Table 1) (71). These equivalent dosages apply only to oral and intravenous routes of glucocorticoid administration (71).

Complications of systemic glucocorticoid therapy are numerous and may develop either relatively acutely or after long-term administration. Examples of acute side effects are central nervous system changes, fluid and electrolyte disorders, gastrointestinal disturbances and impaired glucose tolerance (1). Other side effects which often develop only after long-term administration include osteoporosis and fractures, avascular necrosis of the bone, iatrogenic Cushing's syndrome, systemic hypertension, myopathy, certain dermatologic side effects, cataracts, and growth impairment in children (1). Side effects may also result from abrupt withdrawal of the steroid which may lead to acute adrenal insufficiency (71). The incidence of unwanted effects of one kind or another depends on the drug used, dosage and duration of therapy but can be as high as 50 % (68).

In most diseases, glucocorticoids are administered systemically. However, certain diseases can be treated by topical administration of the drugs. Topical glucocorticoid preparations have been developed in an attempt to obtain high local concentrations of the glucocorticoid while minimizing systemic side effects. Topical applications are available for the skin, eyes, ears, nose, lungs and large bowel. Corticosteroids may also be injected intralesionally in chronic dermatoses or into joints in rheumatoid arthritis. Knowledge about the systemic bioavailability of topically administered steroids is generally scarce. The systemic bioavailability generally depends on the drug used, the underlying disease and the mode of topical administration. The following paragraphs will focus on ophthalmic, nasal and inhaled glucocorticoids, because these routes of glucocorticoid administration were investigated in regard to their potential to cause ocular hypertension or open-angle glaucoma.

Ophthalmic corticosteroids are used for the symptomatic relief of inflammatory conditions of the conjunctiva, cornea, iris and sclera. They are also used in injuries of the outer and anterior segment of the eye and after ocular surgery to prevent scarring. In these conditions, they appear to be as effective as systemic steroids. Systemic steroids are generally required only when deeper ocular structures are involved (71,72).

Inhaled glucocorticoids are now believed to constitute the most effective therapy for asthma (73). Since it was recognized that airway inflammation is present even in patients with mild asthma, therapy with inhaled glucocorticoids is now recommended at a much earlier stage (74-76). Some studies have shown that use of inhaled glucocorticoids has markedly increased over recent years suggesting that physicians have responded to current guidelines in asthma treatment (77-79). In New Zealand, inhaled steroid sales (in 100 μg equivalents) increased from less than 50 millions doses in 1985 to almost 200 millions doses in 1991 (78). In Saskatchewan, Canada, the percentage of patients treated with inhaled glucocorticoids more than tripled from 1989 to 1993, rising from 6.1 % per 1,000 persons in 1989 to 19.9 % in 1993 (77).

If low doses of inhaled glucocorticoids (below 1 mg/day) do not control asthma, a dose increase is recommended before starting treatment with oral glucocorticoids (70,74,75). Systemic bioavailability of inhaled glucocorticoids may result from glucocorticoids deposited in the mouth and then swallowed or from glucocorticoids absorbed from the lungs. The amount of systemic bioavailability of the steroid depends on a number of factors, including the type of delivery device used, the technique of administration of the drug and the first-pass effect of the respective steroid in the case of oropharyngeal deposition (80). Since many of the new glucocorticoids undergo extensive first-pass metabolism in the liver, the systemic bioavailability consists mainly of the inhaled fraction (80). Studies which investigated systemic effects of inhaled steroids gave inconsistent results (73). Some studies showed a suppression of the HPA axis by steroids whereas others did not. A recent review concluded that for doses of up to 1500 μg of inhaled glucocorticoids, there is little evidence of systemic side effects (73). At higher doses, there is some evidence of suppression of the HPA axis. Higher doses may therefore present a

potential for systemic side effects, although clinically they are generally well tolerated (73).

Nasal corticosteroids are used for the symptomatic treatment of seasonal allergic or perennial rhinitis and in the treatment of nasal polyposis. They are also used to treat small nasal polyps and to prevent their recurrence following surgical removal (81). It is estimated that worldwide more than eight million prescriptions were written for nasal glucocorticoids in 1993 (82). The same glucocorticoid substances as for inhaled use are available for intranasal use; however, recommended doses for the latter are markedly lower than those for the former route of administration. Usually, the dose for intranasal use is less than half that recommended for inhaled use (83-85). However, up to 50 % or more of the nasally administered steroid may be absorbed from the nasal mucosa (81). A portion of nasally administered corticosteroid is also swallowed and absorbed from the gastrointestinal tract. Although a systemic bioavailability of 49 % has been reported after nasal administration of flunisolide, no HPA axis suppression was seen (85). Concerns have been expressed about HPA axis suppression after long-term intranasal glucocorticoid use in patients with perennial rhinitis or in patients who use excessive doses (86).

1.3 Glucocorticoids and the Risk of Ocular Hypertension and Open-Angle Glaucoma

Corticosteroids have been shown to increase intraocular pressure in animals (87), in perfusion-cultured human eyes (88) and in humans. One of the first reports of intraocular pressure elevations in humans was published in 1954, when Francois described a series of eight patients who developed ocular hypertension during treatment with corticosteroid eyedrops (89). All of these patients had had normal intraocular pressure documented before the start of eyedrop therapy. In patients in whom the eyedrops were discontinued, intraocular pressure values returned to normal. Since then, many more case reports and some clinical studies have been published reporting the association. The case reports and studies of glucocorticoid-induced ocular hypertension and open-angle glaucoma will be

presented by route of glucocorticoid administration. This is for purely organizational reasons and does not imply differences in the pathogenesis of the condition or its clinical presentation.

The risk of ocular hypertension associated with ophthalmic glucocorticoids was investigated in a number of prospective clinical studies. These studies were usually conducted over a period of four to eight weeks. Glucocorticoid eyedrops were usually administered to only one eye, whereas the untreated eye served as a control (90-101). Different patient populations were investigated: normal volunteers, glaucoma suspects, patients with open-angle glaucoma and relatives of glaucoma patients. Almost all patients with open-angle glaucoma exhibited a marked increase in intraocular pressure that often necessitated cessation of drug application (91,92,95). About 90 % of glaucoma suspects and first degree relatives of glaucoma patients showed an increase in intraocular pressure, but this pressure rise was often less pronounced than that of the glaucoma patients (95). In normal volunteers, a great heterogeneity of the pressure response was seen (93). Based on the pressure response, both Armaly and Becker classified normal individuals as low, intermediate and high responders (95,102). Despite the fact that they used different criteria for their classification systems, they found a similar percentage of the three levels of response, with around 65 % of volunteers belonging to the low, 30 % to the intermediate and 5 % to the high response level (91,92,95,102,103). A high response level characterized patients with pressure rises of more than 15 mm Hg after four weeks of glucocorticoid eyedrops. The low response group was defined by a pressure rise of less than 5 mm Hg. In the low responder group, the pressure seemed to have reached its maximum after four weeks, whereas it was still increasing in the intermediate and high responder group (102).

The intraocular pressure elevation was usually limited to the treated eye although some investigators also reported pressure rises in the untreated eye in the intermediate and high responder groups (103). A pressure rise was already seen after the first week of treatment in some individuals. Hypertensive ocular pressure values were often not reached before two or more weeks of drug administration (91,93). The magnitude of the pressure

elevation appeared to be related to the potency and dose of the drug (98,100,104), but it did not depend on pretreatment values of intraocular pressure (94). In normal volunteers, the magnitude of the effect was significantly greater in the older age group (93). Intraocular pressure values usually returned to pretreatment values upon discontinuation of drug administration. In patients with other forms of glaucoma, such as angle-closure glaucoma, secondary glaucoma or congenital glaucoma, no increased frequency of high or intermediate responders was seen (103).

Based on the variations in the degree of response to topical steroids in normal volunteers, glaucoma patients and their first degree relatives, Becker and Armaly proposed that the intraocular pressure response to corticosteroids was inherited and that the genes controlling this response were related to the inheritance of primary open-angle glaucoma (105,106). Their theories about the mode of inheritance could not be confirmed in family and twin studies conducted later (96,97,107). These studies revealed a lower concordance of glucocorticoid testing results than would be expected from the Armaly and Becker theories. Furthermore, the intraocular pressure response to topical dexamethasone was not very reproducible except in the high responder group (108). Regardless of the theories about heritability of the glucocorticoid response or its relationship to primary open-angle glaucoma, it appears that a substantial minority of the general population will develop ocular hypertension when treated with topical ophthalmic steroids. Certain individuals, particularly those with primary open-angle glaucoma and their first-degree relatives appear to be at a greater risk of an ocular hypertensive response. A higher risk has also been observed in patients with diabetes mellitus (55) and in patients with severe myopia (65). If the ocular hypertension remains undetected and ophthalmic glucocorticoid treatment is prolonged, a secondary open-angle glaucoma may develop (89,104,109-112). Two cases of blindness secondary to corticosteroid ointment administered to the eyes or eyelids have been reported (113,114).

Ocular hypertension and open-angle glaucoma were also described following oral glucocorticoid treatment (115-120); however, for this route of glucocorticoid administration the risk appears to be less well defined. Contrary to the numerous

prospective clinical studies which were conducted to study the risk for ophthalmic glucocorticoids, no such studies are available for oral glucocorticoids. A few small retrospective studies were designed to perform eye examinations in patients who had been receiving oral glucocorticoids for various indications over prolonged periods of time (121-128). Most of these studies measured the intraocular pressure as main outcome parameter, since ocular hypertension and open-angle glaucoma occurred too infrequently to analyse them as main outcome events. Some studies did not have a control group (121,127,128). In others, the intraocular pressure was found to be higher in the steroid-treated group than in a control group (122,124,126). Little is known about the influence of the dose and duration of glucocorticoid treatment. Higher doses appeared to contribute to an increase in intraocular pressure values in one study (124), whereas they were not found to be of importance in two other studies (122,126). It is generally believed that oral glucocorticoids are associated with a lower risk of ocular hypertension and open-angle glaucoma than ophthalmic glucocorticoids (129-131). Some authors believe that oral glucocorticoids have to be administered over months or years before ocular hypertension develops, whereas it is generally acknowledged that weeks of treatment with topical ophthalmic steroids may be enough to cause this adverse effect (129,132). The hypothesis of a longer exposure requirement for oral glucocorticoids appears to be based on case reports which described ocular hypertension or open-angle glaucoma only after months or years of oral glucocorticoid treatment (115,116,120,123,125). However, some cases were also reported after shorter exposure periods, for example in one case after four days of treatment with oral glucocorticoids (118) and in another after 13 days (117). These latter reports indicate that the necessary exposure period may not be longer for oral glucocorticoids than for topical ophthalmic steroids. Reported long exposure periods may at least partly be due to delayed detection of intraocular pressure rises.

Recently, ocular hypertension and open-angle glaucoma have been described following treatment with glucocorticoid nasal sprays and inhaled glucocorticoids (82,133). Upon discontinuation of the steroids, a return to normal intraocular pressure values was observed. In one of the cases, hypertensive open-angle glaucoma was reported after six months of treatment with inhaled beclomethasone diproprionate for asthma (133). In

another patient who received beclomethasone nasal spray for perennial rhinitis, normal intraocular pressure was observed after one month of treatment, but it was found elevated after five months (82). In a third patient, ocular hypertension developed only after the glucocorticoid dose was increased (82). Prospective studies which investigate this effect are not available.

Some reports described ocular hypertension and open-angle glaucoma after treatment with periorbital and facial glucocorticoids administered as creams and ointments (114,134-138). Many of these cases were only detected in an already advanced stage of glaucoma after many months or years of glucocorticoid administration (114,134,136,138). In some cases, a normalization of intraocular pressure values was documented after discontinuation of the glucocorticoid (136,139). The ocular hypertension following this route of administration is mostly believed to be due to a direct conjunctival contamination by the steroid (134,135,137,139). The corticosteroid may inadvertently be administered to the eye during administration of the ointment or seep over the lid margin after administration. The possibility of ocular pressure elevations due to systemic absorption of periorbital or facial glucocorticoids is considered remote (135).

The route of glucocorticoid administration does not affect the basic clinical picture of corticosteroid-induced open-angle glaucoma (140). In adults, this glaucoma closely resembles primary hypertensive open-angle glaucoma and is characterized by elevated intraocular pressure, gonioscopically open angles, and typical optic nerve damage and visual field loss (131). Clinically, it is symptom free until considerable damage to visual function has occurred (103). The elevated intraocular pressure values usually return to normal within days or weeks of steroid discontinuation (91,103,115,117,118,141). This reversibility of raised intraocular pressure also serves as a diagnostic feature which helps to establish the diagnosis of corticosteroid-induced glaucoma and differentiates it from primary open-angle glaucoma. Whereas the ocular hypertension induced by steroid treatment is usually reversible upon discontinuation of the drug, this is not the case for the glaucomatous damage which has already resulted (124). A few cases have been reported where the ocular hypertension persisted after discontinuation of glucocorticoid treatment

and medical or surgical treatment had to be instituted (110-112,114,136,142). This persisting ocular hypertension may be a consequence of permanent alterations in the aqueous humor outflow channels in patients with longstanding ocular hypertension or an unmasking of an underlying glaucoma by glucocorticoid administration (140).

Discontinuing the glucocorticoid is the most effective management of corticosteroid-induced ocular hypertension or glaucoma. Standard antiglaucoma treatment may be required initially until normalization of intraocular pressure values occurs (140). If the intraocular pressure does not return to normal despite corticosteroid withdrawal or if glucocorticoid therapy must continue, routine medical or surgical antiglaucoma treatment may be instituted (140).

The mechanism by which corticosteroids induce intraocular pressure elevations has not been fully determined. The raised pressure appears to be secondary to an increased resistance to aqueous humor outflow (91,93,122) and is associated with morphologic changes in the trabecular meshwork, a sieve-like structure through which aqueous humor leaves the eye (143,144). A number of theories have been proposed to explain the diminished outflow facility (103,131,145). Some authors attribute the decreased outflow to an accumulation of polymerized glycosaminglycans (GAGs) in the trabecular meshwork. Steroids are believed to inhibit the catabolism of GAGs thus leading to an accumulation of these mucopolysaccharides in the trabecular meshwork with a resulting reduction of its porosity (104). Others have suggested an increase in the expression of collagen, elastin or fibronectin in the extracellular matrix. It has also been hypothesized that glucocorticoids may decrease the expression of extracellular proteinases or lead to an accumulation of trabecular debris (131). The different sensitivity of patients to exogenous glucocorticoids may be due to an abnormality in ocular cortisol metabolism in some patients. 5-ß-dihydrocortisol, a glucocorticoid metabolite, has been found to accumulate in cultured trabecular cells from patients with chronic open-angle glaucoma (146). This metabolite has been shown to potentiate the effect of topically applied dexamethasone on the intraocular pressure in rabbits (147) and may account for the different sensitivity of patients to endogenous and exogenous glucocorticoids (146-149).

1.4 Administrative Health Databases

Over the past 20 years, large administrative health databases have emerged as an important tool in pharmacoepidemiologic research. Such databases offer several important features for epidemiologic studies: they are usually large, with patient numbers ranging from several hundred thousand to well over a million, and therefore allow the study of rare adverse events of pharmaceuticals in large populations. The largest of the computerized databases is a Medicaid database in the United States (COMPASS) with 8.3 million patients available for study (150). Administrative databases also allow epidemiologic studies to be undertaken in reasonable time and at relatively low cost, because the study variables are already available in computerized form and need not be obtained in time-consuming and expensive processes of data collection. Some databases also provide well defined denominator information, thereby allowing to study incidence and prevalence of diseases in defined populations. Computerized databases have provided useful information about utilization of drugs after their introduction to the market. Their use in postmarketing surveillance complements safety information from premarketing clinical trials and allows for the study of drug-related risks in the general population without the often strict inclusion criteria of clinical trials. Use of computerized databases in pharmacoepidemiologic research is, however, not undisputed (151). Since these databases are usually designed for administrative purposes, such as billing and record keeping, important information about risk factors for a disease may not be contained in the database, thus creating a potential for bias. Exposure is usually defined by records of dispensed prescriptions, and misclassification of exposure may result if patients did not take the dispensed medication. It has, however, been pointed out that this measure of exposure may represent one of the most accurate methods of assessing drug utilization in the elderly, since over half of those patients may have difficulty in recalling their medication when directly questionned (152). Diagnostic coding in computerized databases is commonly done according to the International Classification of Diseases, Ninth Revision (ICD-9) coding scheme (153). In this scheme, many different ICD-9 codes may be compatible with the same disease process and a combination of several codes into a single diagnostic code may be necessary. Since there is no incentive for a provider to code

specifically, e.g., to code 'duodenal ulcer with bleeding' instead of 'upper gastrointestinal bleeding otherwise not specified', coding may only be done in broad categories, rendering it impossible to investigate very specific disease categories with claims data without validating the computerized data against medical records. Carson and Strom have pointed out that researchers using diagnostic codes in computerized databases must be 'lumpers' rather than 'splitters' (150).

In Québec, the provincial health insurance plan covers the cost of prescription drugs and medical services for all individuals of 65 years of age and older. Claims for reimbursement of medical services and drug dispensations are directed by physicians and pharmacists to the Régie de L'Assurance Maladie du Québec (RAMQ), the government body responsible for the payment of prescription claims and physician services. Of the estimated 770,925 elderly in Quebec, 753,446 were registered with the RAMQ in 1990 (152). Data in the records include a unique identification number for each patient, demographic data such as the patient's gender and age, drug dispensations, diagnoses, medical procedures and the specialty of the physician who submits the claim to the RAMQ. Among the information available for each drug dispensation are the drug name, the dispensation date, the dose per unit of administration, the mode of administration (e.g. tablet, suppository, etc.) and the prescribed quantity and treatment duration. Drugs dispensed to patients during stay in hospitals or nursing homes are not contained in the database. The information on medical procedures includes those done for diagnostic or therapeutic purposes whether performed in a hospital or in a private office. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision (ICD-9) (153). The accuracy of the prescription claims data in the RAMQ database has recently been validated, demonstrating a fairly high level of accuracy (152).

1.5 Study Objectives and Presentation of Articles

The objective of the study presented in this thesis is to investigate the risk of ocular hypertension or open-angle glaucoma associated with different routes of glucocorticoid administration. A case-control study design was employed using as a data source the provincial health databases of Québec. Oral, inhaled and nasal glucocorticoid use were studied as the main exposures, and the influence of dose and duration of treatment for each of these routes of glucocorticoid administration was investigated. Use of ophthalmic glucocorticoids served as an adjustment factor, and to illustrate some methodologic issues in designing case-control studies.

The first article presents the results for exposure to oral glucocorticoids and the second article those for inhaled and nasal glucocorticoids. The third article discusses sources of bias in pharmacoepidemiologic research within the study context and presents empirical analyses to illustrate these biases.

Table 1. Relative Potencies of Glucocorticoids and Equivalent Dosages

Compound	Antiinflammatory Potency	Equivalent Dosage
Cortisone	0.80	25.00
Hydrocortisone	1.00	20.00
Prednisolone	4.00	5.00
Prednisone	4.00	5.00
Methylprednisolone	5.00	4.00
Triamcinolone	5.00	4.00
Dexamethasone	25.00	0.75
Bethamethasone	25.00	0.75

1.6 Bibliography

1. Holland, E.G. and A.T. Taylor. 1991. Glucocorticoids in clinical practice. *J. Fam. Pract.* 32:512-519.

2. Leske, M.C. 1983. The epidemiology of open-angle glaucoma: a review. *Am. J. Epidemiol.* 118:166-191.

3. Hiller, R. and H.A. Kahn. 1975. Blindness from glaucoma. *Am. J. Ophthalmol.* 80:62-69.

4. Quigley, H.A. 1993. Open-angle glaucoma. *N. Engl. J. Med.* 328:1097-1106.

5. Hart, W.M.J. 1987. The epidemiology of primary open-angle glaucoma and ocular hypertension. In The glaucomas. R. Rich, M.B. Shields, and T. Krupin, editors. C. V. Mosby Comp. 789-795.

6. Tucker, J.B. 1993. Screening for open-angle glaucoma. *Am. Fam. Physician* 48:75-80.

7. Shields, M.B. 1992. Classification of the glaucomas. In Textbook of glaucoma. M.B. Shields, editor. Williams & Wilkins, Baltimore. 167-171.

8. Sheldrick, J.H. and A.J.H. Sharp. 1994. Glaucoma screening clinic in general practice: prevalence of occult disease, and resource implications. *Brit. J. Gen. Pract.* 44:561-565.

9. Danyluk, A.W. and D. Paton. 1991. Diagnosis and management of glaucoma. *Clin. Symp.* 43:2-32.

10. Sommer, A., J.M. Tielsch, J. Katz, H.A. Quigley, J.D. Gottsch, J. Javitt, and K. Singh. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch. Ophthalmol.* 109:1090-1095.

11. Dielemans, I., J.R. Vingerling, R.C. Wolfs, A. Hofman, D.E. Grobbee, and P.T. de Jong. 1994. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 101:1851-1855.

12. Hollows, F.C. and P.A. Graham. 1966. Intraocular pressure, glaucoma and glaucoma suspects in a defined population. *Br. J. Ophthalmol.* 50:570-586.

13. Eddy, D.M., L.E. Sanders, and J.F. Eddy. 1983. The value of screening for glaucoma with tonometry. *Surv. Ophthalmol.* 28:194-205.

14. Jay, J.L. 1992. Primary open-angle glaucoma. *Practitioner* 236:199-202.

15. Gillespie, J.E. 1980. Glaucoma: A review and guide to detection. *Virginia Med.* 107:606-611.

16. Robertson, D. 1977. Tonometry screening on the medical service. *Arch. Intern. Med.* 137:443-445.

17. Jay, J.L. 1992. Rational choice of therapy in primary open angle glaucoma. *Eye* 6:243-247.

18. Sherwood, M.B., C.S. Migdal, R.A. Hitchings, M. Sharir, T.J. Zimmerman, and J.S. Schultz. 1993. Initial treatment of glaucoma: surgery or medications. *Surv. Ophthalmol.* 37:293-305.

19. Hurvitz, L.M., P.L. Kaufman, A.L. Robin, R.N. Weinreb, K. Crawford, and B. Shaw. 1991. New developments in the drug treatment of glaucoma. *Drugs* 41:514-532.

20. Kanski, J.J. 1994. The glaucomas. In Clinical ophthalmology. A systematic approach. J.J. Kanski, editor. Butterworth Heinemann, London. 234

21. Chandler, P.A. and W.M. Grant. 1965. Lectures on glaucoma. P.A. Chandler and W.M. Grant, editors. Lea & Febiger, Philadelphia. 115-117.

22. Goldman, H. 1975. An analysis of some concepts concerning chronic simple glaucoma. *Am. J. Ophthalmol.* 80:409-413.

23. Werner, E.B. 1989. Low-tension glaucoma. In The glaucomas. R. Rich, M.B. Shields, and T. Krupin, editors. C. V. Mosby Comp. 797-812.

24. Bengtsson, B. 1981. The prevalence of glaucoma. *Br. J. Ophthalmol.* 65:46-49.

25. Kahn, H.A. and R.C. Milton. 1980. Revised Framingham eye study prevalence of glaucoma and diabetic retinopathy. *Am. J. Epidemiol.* 111:769-776.

26. Tielsch, J.M., A. Sommer, J. Katz, R.M. Royall, H.A. Quigley, and J. Javitt. 1991. Racial variations in the prevalence of primary open-angle glaucoma. The Baltimore Eye Survey. *JAMA* 266:369-374.

27. Klein, B.E., R. Klein, W.E. Sponsel, T. Franke, L.B. Cantor, J. Martone, and M.J. Menage. 1992. Prevalence of glaucoma. The Beaver Dam Eye Study. *Ophthalmology* 99:1499-1504.

28. Coffey, M., A. Reidy, R. Wormald, W.X. Xian, L. Wright, and P. Courtney. 1993. Prevalence of glaucoma in the west of Ireland. *Br. J. Ophthalmol.* 77:17-21.

29. David, R., L. Zangwill, D. Stone, and Y. Yassur. 1987. Epidemiology of intraocular pressure in a population screened for glaucoma. *Br. J. Ophthalmol.* 71:766-771.

30. Tielsch, J.M., J. Katz, K. Singh, H.A. Quigley, J.D. Gottsch, J. Javitt, and A. Sommer. 1991. A population-based evaluation of glaucoma screening: the Baltimore Eye Survey. *Am. J. Epidemiol.* 134:1102-1110.

31. Wilson, M.R. 1990. Epidemiological features of glaucoma. *Int. Ophthalmol. Clin.* 30:153-160.

32. Bengtsson, B. 1989. Incidence of manifest glaucoma. *Br. J. Ophthalmol.* 73:483-487.

33. Lundberg, L., K. Wettrell, and E. Linner. 1987. Ocular hypertension. A prospective twenty-year follow-up study. *Acta Ophthalmol.* 65:705-708.

34. Armaly, M.F., D.E. Krueger, L. Maunder, B. Becker, J. Hetherington,Jr., A.E. Kolker, R.Z. Levene, A.E. Maumenee, I.P. Pollack, and R.N. Shaffer. 1980. Biostatistical analysis of the collaborative glaucoma study. I. Summary report of the risk factors for glaucomatous visual-field defects. *Arch. Ophthalmol.* 98:2163-2171.

35. Perkins, E.S. 1973. The Bedford glaucoma survey. I. Long-term follow-up of borderline cases. *Br. J. Ophthalmol.* 57:179-185.

36. Pohjampelto, P.E. and J. Palva. 1974. Ocular hypertension and glaucomatous nerve damage. *Acta Ophthalmol.* 52:194-200.

37. Sommer, A. 1989. Intraocular pressure and glaucoma. *Am. J. Ophthalmol.* 107:186-188.

38. Klein, B.E., R. Klein, and K.L. Linton. 1992. Intraocular pressure in an American community. The Beaver Dam Eye Study. *Invest. Ophthalmol. Vis. Sci.* 33:2224-2228.

39. Shields, M.B. 1992. Primary open-angle glaucoma. In Textbook of glaucoma. M.B. Shields, editor. Williams & Wilkins, Baltimore. 172-197.

40. Klein, B.E., R. Klein, and S.C. Jensen. 1994. Open-angle glaucoma and older-onset diabetes. The Beaver Dam Eye Study. *Ophthalmology* 101:1173-1177.

41. Bankes, J.L., E.S. Perkins, S. Tsolakis, and J.E. Wright. 1968. Bedford glaucoma survey. *BMJ* 1:791-796.

42. Perkins, E.S. 1974. Family studies in glaucoma. *Br. J. Ophthalmol.* 58:529-535.

43. Kolker, A.E. 1972. Family studies in glaucoma. Ten-year follow-up (preliminary report). *Israel. J. Med. Sci.* 8:1357-1361.

44. Wilensky, J.T., N. Gandhi, and T. Pan. 1978. Racial influences in open-angle glaucoma. *Ann. Ophthalmol.* 10:1398-1402.

45. David, R., D. Livingston, and M.H. Luntz. 1978. Ocular hypertension: a comparative follow-up of black and white patients. *Br. J. Ophthalmol.* 62:676-678.

46. Martin, M.J., A. Sommer, K. Witt, J. Katz, and R.M. Royall. 1985. Race and primary open-angle glaucoma. *Am. J. Ophthalmol.* 99:383-387.

47. Dielemans, I., J.R. Vingerling, D. Algra, A. Hofman, D.E. Grobbee, and P.T. de Jong. 1995. Primary open-angle glaucoma, intraocular pressure, and systemic blood pressure in the general elderly population. The Rotterdam Study. *Ophthalmology* 102:54-60.

48. Bengtsson, B. 1972. Some factors affecting the distribution of intraocular pressure in a population. *Acta Ophthalmol.* 50:33-46.

49. Seddon, J.M., B. Schwartz, and G. Flowerdow. 1983. Case-control study of ocular hypertension. *Arch. Ophthalmol.* 101:891-894.

50. Klein, B.E. and R. Klein. 1981. Intraocular pressure and cardiovascular risk variables. *Arch. Ophthalmol.* 99:837-839.

51. Leske, M.C. and M.J. Podgor. 1983. Intraocular pressure, cardiovascular risk variables, and visual field defects. *Am. J. Epidemiol.* 118:280-287.

52. McLeod, S.D., S.K. West, H.A. Quigley, and J.L. Fozard. 1990. A longitudinal study of the relationship between intraocular and blood pressures. *Invest. Ophthalmol. Vis. Sci.* 31:2361-2366.

53. Wilson, M.R., E. Hertzmark, A.M. Walker, K. Childs-Shaw, and D.L. Epstein. 1987. A case-control study of risk factors in open angle glaucoma. *Arch. Ophthalmol.* 105:1066-1071.

54. Tielsch, J.M., J. Katz, A. Sommer, H.A. Quigley, and J.C. Javitt. 1995. Hypertension, perfusion pressure, and primary open-angle glaucoma. A population-based assessment. *Arch. Ophthalmol.* 113:216-221.

55. Becker, B. 1971. Diabetes mellitus and primary open-angle glaucoma. The XXVII Edward Jackson Memorial Lecture. *Am. J. Ophthalmol.* 71:1-16.

56. Tielsch, J.M., J. Katz, H.A. Quigley, J.C. Javitt, and A. Sommer. 1995. Diabetes, intraocular pressure, and primary open-angle glaucoma in the Baltimore Eye Survey. *Ophthalmology* 102:48-53.

57. Klein, B.E., R. Klein, and S.E. Moss. 1984. Intraocular pressure in diabetic persons. *Ophthalmology* 91:1356-1360.

58. Carel, R.S., A.D. Korczyn, M. Rock, and I. Goya. 1984. Association between ocular pressures and certain health parameters. *Ophthalmology* 91:311-314.

59. Kahn, H.A., H.M. Leibowitz, J.P. Ganley, M.M. Kini, T. Colton, R.S. Nickerson, and T.R. Dawber. 1977. The Framingham Eye Study. II. Association of ophthalmic pathology with single variables previously measured in the Framingham Heart Study. *Am. J. Epidemiol.* 106:33-41.

60. Perkins, E.S. and C.D. Phelps. 1982. Open-angle glaucoma, ocular hypertension, low tension glaucoma, and refraction. *Arch. Ophthalmol.* 100:1464-1467.

61. David, R., L.M. Zangwill, Z. Tessler, and Y. Yassur. 1985. The correlation between intraocular pressure and refractive status. *Arch. Ophthalmol.* 103:1812-1815.

62. Abdalla, M.I. and M. Hamdi. 1970. Applanation ocular tension in myopia and emmetropia. *Br. J. Ophthalmol.* 54:122-125.

63. Tomlinson, A.L. and C.L. Phillips. 1970. Applanation tension and axial length of the eyeball. *Br. J. Ophthalmol.* 54:548-553.

64. Daubs, J.G. and R.P. Crick. 1981. Effect of refractive error on the risk of ocular hypertension and open angle glaucoma. *Trans. Ophthalmol. Soc. U. K.* 101:121-126.

65. Podos, S.M., B. Becker, and W.R. Morton. 1966. High myopia and primary open-angle glaucoma. *Am. J. Ophthalmol.* 62:1038-1043.

66. Leibowitz, H.M., D.E. Krueger, L.R. Maunder, R.C. Milton, M.M. Kini, H.A. Kahn, R.J. Nickerson, J. Pool, T.L. Colton, J.P. Ganley, J.I. Loewenstein, and T.R. Dawber. 1980. The Framingham Eye Study monograph: An ophthalmological and epidemiological study of cataract, glaucoma, diabetic retinopathy, macular degeneration, and visual acuity in a general population of 2631 adults, 1973-1975. *Surv. Ophthalmol.* 24:335-610.

67. Wilson, M.R. 1990. Epidemiological features of glaucoma. *Int. Ophthalmol. Clin.* 30:153-160.

68. Laurence, D.R. and P.N. Bennett. 1992. Endocrinology I: adrenal corticosteroids, antagonists, corticotrophin. In Clinical pharmacology. D.R. Laurence and P.N. Bennett, editors. Churchill Livingstone, Edinburgh. 549-563.

69. Gallant, C. and P. Kenny. 1986. Oral glucocorticoids and their complications. A review. *J. Am. Acad. Dermatol.* 14:161-177.

70. Barnes, N.C. 1993. Safety of high-dose inhaled corticosteroids. *Resp. Med.* 87 (Suppl.A):27-31.

71. Haynes, R.C.J. 1990. Adrenocorticotropic hormone;adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In Goodman and Gilman's The Pharmacological Basis of Therapeutics. A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor, editors. Pergamon Press, New York. 1431-1462.

72. McEvoy, G.K. 1993. AHFS Drug Information. American Society of Hospital Pharmacists, Bethesda,MD.

73. Barnes, P.J. 1995. Inhaled glucocorticoids for asthma. *N. Engl. J. Med.* 332:868-875.

74. British Thoracic Society. 1990. Guidelines for management of asthma in adults: I-chronic persistent asthma. *BMJ* 301:651-653.

75. British Thorac Society and others. 1993. Guidelines for the management of asthma: a summary. *BMJ* 306:776-782.

76. National Institutes of Health, U.D.o. 1992. International Consensus Report on Diagnosis and Treatment of Asthma. *National Heart, Lung and Blood Institute* pub no 92-3091:

77. Habbick, B., M.J. Baker, M. McNutt, and D.W. Cockcroft. 1995. Recent trends in the use of inhaled beta2-adrenergic agonists and inhaled corticosteroids in Saskatchewan. *Can. Med. Assoc. J.* 153:1437-1443.

78. Pearce, N., R. Beasley, J. Crane, C. Burgess, and R. Jackson. 1995. End of the New Zealand asthma mortality epidemic. *Lancet* 345:41-44.

79. McManus, P. and D. Birkett. 1993. Recent trends in the use of antiasthmatic drugs. *Med. J. Aust.* 159:831-832.

80. Sorva, R.A. and M.T. Turpeinen. 1994. Asthma, glucocorticoids and growth. *Ann. Med.* 26:309-314.

81. Mabry, R.L. 1992. Corticosteroids in the management of upper respiratory allergy: the emerging role of steroid nasal sprays. *Otolarngol. Head. Neck. Surg.* 107:855-860.

82. Opatowsky, I., R.M. Feldman, R. Gross, and S.T. Feldman. 1995. Intraocular pressure elevation associated with inhalation and nasal corticosteroids. *Ophthalmology* 102:177-179.

83. Brogden, R.N. and D. McTavish. 1992. Budesonide. An updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. *Drugs* 44:375-407.

84. Brogden, R.N., R.C. Heel, T.M. Speight, and G.S. Avery. 1992. Beclomethasone Diproprionate. A reappraisal of its pharmacodynamic properties and therapeutic efficacy after a decade of use in asthma and rhinitis. *Drugs* 28:99-126.

85. Pakes, G.E., R.N. Brogden, R.C. Heel, T.M. Speight, and G.S. Avery. 1980. Flunisolide: a review of its pharmacological properties and therapeutic efficay in rhinitis. *Drugs* 19:397-411.

86. Estelle, F., R. Simons, and K.J. Simons. 1989. Optimum pharmacological management of chronic rhinitis. *Drugs* 38:313-331.

87. Zhan, G.L., O.C. Miranda, and L.Z. Bito. 1992. Steroid glaucoma: corticosteroid-induced ocular hypertension in cats. *Exp. Eye. Res.* 54:211-218.

88. Clark, A.F., K. Wilson, A.W. de Kater, R.R. Allingham, and M.D. McCartney. 1995. Dexamethasone-induced ocular hypertension in perfusion-cultured human eyes. *Invest. Ophthalmol. Vis. Sci.* 36:478-489.

89. Francois, J. 1954. Cortisone et tension oculaire. *Ann. Oculist.* 187:805-816.

90. Das, S.N. and R.A. Hitchings. 1971. Steroid glaucoma. *Trans. Ophthalmol. Soc. UK.* 91:749-756.

91. Becker, B. and D.W. Mills. 1963. Corticosteroids and intraocular pressure. *Arch. Ophthalmol.* 70:500-507.

92. Armaly, M.F. 1963. Effect of corticosteroids on intraocular pressure and fluid dynamics. II. The effect of dexamethasone in the glaucomatous eye. *Arch. Ophthalmol.* 70:492-499.

93. Armaly, M.F. 1963. Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. *Arch. Ophthalmol.* 70:482-491.

94. Levene, R., A. Wigdor, A. Edelstein, and J. Baum. 1967. Topical corticosteroid in normal patients and glaucoma suspects. *Arch. Ophthalmol.* 77:593-597.

95. Becker, B. 1965. Intraocular pressure response to topical corticosteroids. *Invest. Ophthalmol. Vis. Sci.* 4:198-205.

96. Schwartz, J.T., F.H. Reuling, M. Feinleib, R.J. Garrison, and D.J. Collie. 1973. Twin study on ocular pressure after topical dexamethasone. 1. Frequency distribution of pressure response. *Am. J. Ophthalmol.* 76:126-136.

97. Schwartz, J.T., F.H. Reuling, M. Feinleib, R.J. Garrison, and D.J. Collie. 1973. Twin study on ocular pressure following topically applied dexamethasone. II. Inheritance of variation in pressure response. *Arch. Ophthalmol.* 90:281-286.

98. Kitazawa, Y. 1976. Increased intraocular pressure induced by corticosteroids. *Am. J. Ophthalmol.* 82:492-495.

99. Weinreb, R.N., J.R. Polansky, S.G. Kramer, and J.D. Baxter. 1985. Acute effects of dexamethasone on intraocular pressure in glaucoma. *Invest. Ophthalmol. Vis. Sci.* 26:170-175.

100. Ramsell, T.G., W. Trillwood, and G. Draper. 1967. Effects of prednisolone eye drops. A trial of the effects of prednisolone phosphate eye drops on the intra-ocular pressure of normal volunteers. *Br. J. Ophthalmol.* 51:398-402.

101. Miller, D., J.D. Peczon, and C.G. Whitworth. 1965. Corticosteroids and functions in the anterior segment of the eye. *Am. J. Ophthalmol.* 59:31-34.

102. Armaly, M.F. 1965. Statistical attributes of the steroid hypertension response in the clinically normal eye. I. The demonstration of three levels of response. *Invest. Ophthalmol. Vis. Sci.* 4:187-197.

103. Armaly, M.F. 1986. Corticosteroid glaucoma. In Glaucoma. J.E. Cairns, editor. Grune&Stratton, London. 697-710.

104. Kass, M.A. and T. Johnson. 1989. Corticosteroid-induced glaucoma. In The glaucomas. R. Rich, M.B. Shields, and T. Krupin, editors. C.V. Mosby Company, St.Louis. 1161-1168.

105. Becker, B. and K.A. Hahn. 1964. Topical corticosteroids and heredity in primary open-angle glaucoma. *Am. J. Ophthalmol.* 57:543-551.

106. Armaly, M.F. 1966. The heritable nature of dexamethasone-induced ocular hypertension. *Arch. Ophthalmol.* 75:32-35.

107. Francois, J., C.H. Heintz-de Bree, and R.C. Tripathi. 1966. The cortisone test and the heredity of primary open-angle glaucoma. *Am. J. Ophthalmol.* 62:844-852.

108. Palmberg, P.F., A. Mandell, J.T. Wilensky, S.M. Podos, and B. Becker. 1975. The reproducibility of the intraocular pressure response to dexamethasone. *Am. J. Ophthalmol.* 80:844-856.

109. Butcher, J.M., M. Austin, J. McGalliard, and R.D. Bourke. 1994. Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. *BMJ* 309:43

110. Goldmann, H. 1962. Cortisone glaucoma. *Arch. Ophthalmol.* 68:621-626.

111. Burde, R.M. and B. Becker. 1970. Corticosteroid-induced glaucoma and cataracts in contact lens wearers. *JAMA* 213:2075-2077.

112. Brubaker, R.F. and J.A. Halpin. 1975. Open-angle glaucoma associated with topical administraion of flurandrenolide to the eye. *Mayo Clin. Proc.* 50:322-326.

113. Frenkel, M. 1969. Blindness due to steroid induced glaucoma. *IMJ - Illinois Medical Journal* 135:160-163.

114. Vie, R. 1980. Glaucoma and amaurosis associated with long-term application of topical corticosteroids to the eyelids. *Acta Derm. Venereol.* 60:541-542.

115. Alfano, J.E. 1963. Changes in the intraocular pressure associated with systemic steroid therapy. *Am. J. Ophthalmol.* 56:245-247.

116. Covell, L.L. 1958. Glaucoma induced by systemic steroid therapy. *Am. J. Ophthalmol.* 45:108-109.

117. Long, W.F. 1977. A case of elevated intraocular pressure associated with systemic steroid therapy. *Am. J. Optom. & Physiol. Optics* 54:248-252.

118. Stern, J.J. 1953. Acute glaucoma during cortisone therapy. *Am. J. Ophthalmol.* 36:389-390.

119. Laval, J. and R. Collier. 1955. Elevation of intraocular pressure due to hormonal steroid therapy in uveitis. *Am. J. Ophthalmol.* 39:175-182.

120. Harris, J.L. 1960. Glaucoma associated with steroid therapy and atopic dermatitis. *Am. J. Ophthalmol.* 49:351-353.

121. Adhikary, H.P., R.A. Sells, and P.K. Basu. 1982. Ocular complications of systemic steroid after renal transplantation and their association with HLA. *Br. J. Ophthalmol.* 66:290-291.

122. Bernstein, H.N. and B. Schwartz. 1962. Effects of long term systemic steroids on ocular pressure and tonographic values. *Arch. Ophthalmol.* 68:742-754.

123. Williamson, J., R.W. Paterson, D.D. McGavin, M.K. Jasani, J.A. Boyle, and W.M. Doig. 1969. Posterior subcapsular cataracts and glaucoma associated with long-term oral corticosteroid therapy. In patients with rheumatoid arthritis and related conditions. *Br. J. Ophthalmol.* 53:361-372.

124. Tripathi, R.C., B.S. Kirschner, M. Kipp, B.J. Tripathi, D. Slotwiner, N.S. Borisuth, T. Karrison, and J.T. Ernest. 1992. Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. *Gastroenterology* 102:1957-1961.

125. Smith, C.L. 1966. "Corticosteroid glaucoma" a summary and review of the literaure. *Am. J. Med. Sci.* 252:239-244.

126. Godel, V., V. Feiler-Ofry, and R. Stein. 1972. Systemic steroids and ocular fluid dynamics. I. Analysis of the sample as a whole. Influence of dosage and duration of therapy. *Acta Ophthalmol.* 50:655-663.

127. Lee, P.F. 1958. The influence of systemic steroid therapy on the intraocular pressure. *Am. J. Ophthalmol.* 46:328-331.

128. Pateron, G.D. and R. Owen. 1966. Further studies on systemic steroids. In Drug mechanisms in glaucoma. G. Paterson, S.J.H. Miller, and G.D. Paterson, editors. J.&A. Churchill LTD, London. 249-253.

129. David, D.S. and J.S. Berkowitz. 1969. Ocular effects of topical and systemic corticosteroids. *Lancet* 2:149-151.

130. Grant, W.M. 1969. Ocular complications of drugs. Glaucoma. *JAMA* 207:2089-2091.

131. Skuta, G.L. and R.K. Morgan. 1996. Corticosteroid-induced glaucoma. In The glaucomas. R. Ritch, M.B. Shields, and T. Krupin, editors. Mosby, St. Louis. 1177-1188.

132. Abel, R. and I.H. Leopold. 1987. Ocular diseases. In Avery's drug treatment. Principles and practice of clinical pharmacology and therapeutics. T.M. Speight, editor. Adis, Auckland. 387-417.

133. Dreyer, E.B. 1993. Inhaled steroid use and glaucoma. *N. Engl. J. Med.* 329:1822

134. Nielson, N. and P.N. Sorensen. 1978. Glaucoma induced by application of corticosteroids to the periorbital region. *Arch. Dermatol.* 114:953-954.

135. Cubey, R.B. 1976. Glaucoma following the application of corticosteroid to the skin of the eyelids. *Brit. J. Dermatol.* 95:207-208.

136. Aggarwal, R.K., T. Potamitis, N.H. Chong, M. Guarro, P. Shah, and S. Kheterpal. 1993. Extensive visual loss with topical facial steroids. *Eye* 7:664-666.

137. Howell, J.B. 1976. Eye diseases induced by topically applied steroids. The thin edge of the wedge. *Arch. Dermatol.* 112:1529-1530.

138. McLean, C.J., R.F. Lobo, and D.J. Brazier. 1995. Cataracts, glaucoma, and femoral avascular necrosis caused by topical corticosteroid ointment. *Lancet* 345:330

139. Zugerman, C., D. Saunders, and F. Levit. 1976. Glaucoma from topically applied steroids. *Arch. Dermatol.* 112:1326

140. Hodapp, E.A. and M.A. Kass. 1982. Corticosteroid-induced glaucoma. In The secondary glaucomas. R. Rich and M.B. Shields, editors. C. V. Mosby Comp. St.Louis. 258-265.

141. Becker, B. and D.W. Mills. 1963. Elevated intraocular pressure following corticosteroid eye drops. *JAMA* 185:884-886.

142. Spiers, F. 1965. A case of irreversible steroid-induced rise in intraocular pressure. *Acta Ophthalmol.* 43:419-422.

143. Rohen, J.W., E. Linner, and R. Witmer. 1973. Electron microscopic studies on the trabecular meshwork in two cases of corticosteroid-glaucoma. *Exp. Eye. Res.* 17:19-31.

144. Roll, P. and O. Benedikt. 1979. Elektronenoptische Untersuchung des Trabekelwerkes bei einem Kortikosteroidglaukom. *Klin. Monatsbl. Augenheilkd.* 174:421-428.

145. Spaeth, G.L., M.M. Rodrigues, and S. Weinreb. 1977. Steroid induced glaucoma: A. Persistent elevation of intraocular pressure. B. Histopathological aspects. *Trans. Amer. Ophthalmol. Soc.* 75:353-381.

146. Southren, A.L., G.G. Gordon, P.R. Munnangi, J. Vittek, J. Schwartz, C. Monder, M.W. Dunn, and B.I. Weinstein. 1983. Altered cortisol metabolism in cells cultured from trabecular meshwork specimens obtained from patients with primary open-angle glaucoma. *Invest. Ophthalmol. Vis. Sci.* 24:1413-1417.

147. Southren, A.L., G.G. Gordon, D. l'Hommedieu, S. Ravikumar, M.W. Dunn, and B.I. Weinstein. 1985. 5 beta-Dihydrocortisol: possible mediator of the ocular hypertension in glaucoma. *Invest. Ophthalmol. Vis. Sci.* 26:393-395.

148. Weinstein, B.I., P. Munnangi, G.G. Gordon, and A.L. Southren. 1985. Defects in cortisol-metabolizing enzymes in primary open-angle glaucoma. *Invest. Ophthalmol. Vis. Sci.* 26:890-893.

149. Weinstein, B.I., G.G. Gordon, and A.L. Southren. 1983. Potentiation of glucocorticoid activity by 5 beta-dihydrocortisol: its role in glaucoma. *Science* 222:172-173.

150. Carson, J.L. and B.L. Strom. 1994. Medicaid databases. In Pharmacoepidemiology. B.L. Strom, editor. J. Wiley & Sons, Chichester. 199-216.

151. Shapiro, S. 1989. The role of automated record linkage in the postmarketing surveillance of drug safety: A critique. *Clin. Pharm. Ther.* 46:371-386.

152. Tamblyn, R., G. Lavoie, L. Petrella, and J. Monette. 1995. The use of prescription claims databases in pharmacoepidemiological research: The accuracy and comprehensiveness of the prescription claims database in Quebec. *J. Clin. Epidemiol.* 48:999-1009.

153. WHO, 1977. Manual of the international statistical classification of diseases, injuries, and causes of death based on the recommendations of the ninth revision conference, 1975. World Health Organization, Geneva.

CHAPTER 2

ORAL GLUCOCORTICOIDS

AND THE RISKS OF

OCULAR HYPERTENSION OR OPEN-ANGLE GLAUCOMA

2.1 Preface to the Manuscript

This manuscript presents the results of the first part of the study which investigated the risk of ocular hypertension or open-angle glaucoma after exposure to oral glucocorticoids. In the previous chapter, case reports and retrospective studies which point to an increased risk for this route of glucocorticoid administration have been reviewed and some of their limitations discussed. Limitations resulted from the often small sample sizes of retrospective studies which did not allow to study the effect of the dose or duration of oral glucocorticoid treatment on the risk of ocular hypertension or open-angle glaucoma. Furthermore, the reversibility of these events after withdrawal of oral glucocorticoids has not been investigated in a systematic study design.

The introduction of the article summarizes the knowledge from case reports and clinical studies concerning ocular hypertension and open-angle glaucoma for ophthalmic and oral glucocorticoids. The methods section describes the case-control design of the study in detail, including the sources of data, the definition of cases and controls, the different categories defining oral glucocorticoid exposure, covariates and data analysis.

The results for the different categories of oral glucocorticoid exposure are discussed under various perspectives: 1) in comparison with findings obtained for ophthalmic glucocorticoids in prospective clinical trials; 2) in view of pharmacokinetic data for oral glucocorticoids and pathophysiologic hypotheses about glucocorticoid-induced ocular hypertension and open-angle glaucoma; 3) considering limitations of the study data.

This article which will be submitted for publication should be quoted as follows:

Garbe E, Suissa S, Boivin JF, LeLorier J. Oral glucocorticoids and the risk of ocular hypertension or open-angle glaucoma. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, McGill University, 1996.

2.2 Abstract

Objective: To quantify the excess risk of ocular hypertension or open-angle glaucoma in patients taking oral glucocorticosteroids.

Design: Case-control study.

Setting: Quebec universal health insurance program for the elderly (RAMQ database).

Patients: The study included Quebec Medicare enrollees 66 years of age or older. The 9,793 case patients were ophthalmology patients with a new diagnosis of borderline glaucoma or open-angle glaucoma or were newly started on treatment for ocular hypertension or glaucoma between 1988 and 1994. The 38,325 control patients were randomly selected among RAMQ enrollees who had consulted an ophthalmologist in the same month and year as the case.

Main Outcome Measures: The odds ratio of ocular hypertension or open-angle glaucoma was determined in patients using oral glucocorticoids relative to nonusers, using conditional logistic regression analysis. The analysis adjusted for age, gender, diabetes mellitus, systemic hypertension, ophthalmic glucocorticoids, glucocorticoid injections, number of prescriptions filled, number of physician claims, and number of days hospitalized.

Measurements and Main Results: The adjusted odds ratio of ocular hypertension or open-angle glaucoma for current users of oral glucocorticoids as compared with nonusers was 1.41 (95 % CI, 1.22 to 1.63). The odds ratio increased with increasing daily glucocorticoid dose, in hydrocortisone-equivalent milligrams: the adjusted odds ratio was 1.26 (95 % CI, 1.01 to 1.56) for 1 to 39 mg/d, 1.37 (95 % CI, 1.06 to 1.76) for 40 to 79 mg/d and 1.88 (95 % CI, 1.40 to 2.53) for 80 mg/d or more. The risk for systemic glucocorticosteroids increased with increasing duration of treatment over 11 months of exposure: the adjusted odds ratio was 1.31 (95 % CI, 0.94 to 1.82) for 1 to 2 months of continuous use, 1.64 (95 % CI, 1.16 to 2.30) for 3 to 5 months of continuous use and 1.87 (95 % CI, 1.35 to 2.60) for 6 to 11 months of continuous use. No further increase in the odds ratio was seen beyond 11 months of continuous use, although the risk remained elevated at 1.53 (95 % CI, 1.13 to 2.05).

Conclusions: Use of systemic glucocorticoids increases the risk of ocular hypertension or open-angle glaucoma. The magnitude of the risk is directly related to the dose and duration of exposure to oral glucocorticoids. The findings of this study suggest that periodic intraocular pressure measurement in patients taking oral glucocorticoids, especially in those requiring high doses and extended duration of therapy, may be warranted.

2.3 Introduction

Ocular hypertension is a well-documented side effect of topical ophthalmic glucocorticoids. The ocular hypertensive response has been characterized in a large number of prospective clinical studies with routine tonometric follow-up (1). Topical steroids caused ocular pressure elevations in about 35 % of subjects with clinically normal eyes, with about 5 % of subjects exhibiting a rise in ocular pressure of 15 mm Hg or more after four to eight weeks of administration (2-4). The intraocular pressure values usually returned to normal within few weeks of discontinuation of the steroid (1). Topical steroid-induced ocular hypertension may progress to chronic open-angle glaucoma, if it remains undetected and untreated. The literature contains numerous case reports of severe visual impairment and blindness following prolonged corticosteroid administration to the eye (5-10). The symptomless nature of the ocular pressure elevation has prompted ophthalmologists to recommend routine monitoring of intraocular pressure in patients receiving prolonged treatment with ophthalmic steroids (11).

Several case reports have suggested that oral administration of glucocorticoids can also result in ocular hypertension and open-angle glaucoma (12-17). In contrast to the many studies which were initiated following case reports of ocular hypertension and open-angle glaucoma induced by topical ophthalmic glucocorticoids, investigations of the effects of oral corticosteroids on ocular pressure have, however, remained relatively scarce. Prospective clinical studies with routine tonometric follow-up examinations are not available. A few retrospective studies were conducted in patients who had been taking

oral glucocorticoids for variable periods of time and for various indications (18-24). These studies were generally small, yielding only few cases of ocular hypertension or open-angle glaucoma, and therefore did not allow the analysis of these events as main outcomes. In most studies, the mean intraocular pressure was found to be higher in the steroid-treated group than in a non-steroid treated control group (18-20). Most ophthalmologists believe that oral glucocorticoids also increase the risk of ocular hypertension and open-angle glaucoma, but that they are associated with a lower risk than ophthalmic steroids (25-27). Little is known about the influence of the dose or duration of oral glucocorticoid treatment on ocular hypertension and open-angle glaucoma. Some authors have hypothesized that systemic corticosteroids need to be administered for months or years to cause ocular hypertension and glaucoma whereas it is generally acknowledged that weeks of treatment with topical ophthalmic steroids may be enough to cause these adverse effects (25,28).

In this study, we investigate the risk of ocular hypertension or open-angle glaucoma associated with use of oral glucocorticoids, using a large-scale epidemiologic design. In particular, we investigate whether the risk varies according to the dose and duration of exposure to oral glucocorticoids, and whether a residual risk remains after stopping their use.

2.4 Methods

Sources of Data

To address these issues we conducted a case-control study among the elderly population of Quebec for the years 1987 to 1994, using data from the provincial health insurance plan database, which covers the cost of prescription drugs and medical services for all individuals 65 years of age or older. The prescription claims are filed to the Régie de l'assurance maladie du Québec (RAMQ), the government body responsible for the payment of prescription claims and physician services. Of the estimated 770,925 elderly in

Quebec, over 750,000 were registered with the RAMQ in 1990 because they had received at least one health care service (29). Prescription claims data in the database have recently been validated and shown to be reasonably accurate and comprehensive (29). Data in the records include information on the patient's gender and age, filled prescriptions, medical procedures, diagnoses, and the specialty of the physician who directs the claim to the RAMQ. The prescription data contain information on all prescriptions filled by recipients, including the drug name, dispensation date, the dosage form, dose, treatment duration and quantity of drug dispensed. Drugs dispensed to patients during stay in hospitals or nursing homes are not included in the database. Information on diagnostic and therapeutic procedures whether performed in a hospital or in an office is also listed in the database. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision (ICD-9) (30). Each patient in the database has a unique identification number which is encrypted to protect confidentiality when the files are used for research. Two subsets of the RAMQ database were used for the study: a 10 % random sample from 1987 to 1994 and a 20 % random sample from 1990 to 1992. Duplicates were eliminated from the latter sample.

Case Selection

Cases were subjects aged 66 years or older who consulted an ophthalmologist and either filled a first prescription for treatment of ocular hypertension or open-angle glaucoma or had a diagnosis of glaucoma or underwent surgery for glaucoma. Whichever of these three case defining events came first, was set as the index date for that case. If a case was defined by a prescription of treatment for ocular hypertension or glaucoma and the prescription was not filled on the same day as the visit to the prescribing ophthalmologist, the day of the visit to the ophthalmologist was set as the index date. Medication for ocular hypertension and glaucoma included topical betablockers, topical parasympathomimetics, topical alpha agonists and carboanhydrase inhibitors. Apart from carboanhydrase inhibitors which may be given orally or intravenously, all the other drugs are topically administered to the eye. The following four-digit ICD-9 diagnoses were employed in the

case definition: Borderline glaucoma (including the diagnosis of ocular hypertension), open-angle glaucoma and unspecified glaucoma (ICD-9 codes 365.0, 365.1 and 365.9). To qualify as a new or incident case of glaucoma, subjects were required to have been enrolled in the database for at least one year without having had a diagnosis of glaucoma or received treatment for glaucoma.

Control Selection

Controls were randomly selected among patients in the database who were visiting an ophthalmologist but did not have a diagnosis of ocular hypertension or glaucoma or receive treatment for these conditions. Like cases, controls were required to have been enrolled in the database for at least one year to become eligible. The day of the visit to the ophthalmologist was set as the index date. Up to four controls were matched to each case on the index month and year of the case to account for seasonal and secular trends in medication use.

Patients with a diagnosis of angle-closure glaucoma or secondary glaucomas were excluded from the case and control groups.

Oral Glucocorticoid Exposure

To investigate the exposure to oral glucocorticoids according to dose, recency of use and the duration of continuous use, we identified all dispensations for oral glucocortoids filled in the year before the index date by cases and controls. Oral glucocorticoids on the Quebec provincial drug formulary include cortisone, hydrocortisone, prednisone, prednisolone, triamcinolone, methylprednisolone, dexamethasone, and betamethasone. Each glucocorticoid prescription was converted to hydrocortisone-equivalent milligrams on the basis of the specific glucocorticoid preparation, dose in milligrams, and the prescription size. The determination of equivalencies was based on relative glucocorticoid potencies published in standard reference texts (31,32) (Table 1). We calculated the

average daily dose by dividing the number of hydrocortisone-equivalent milligrams dispensed during a specified time period by the number of days in that period. We considered patients exposed if their supply of oral glucocorticoids continued into the 14-day period before the index date ('current users'). In this group of patients, we examined the influence of the glucocorticoid dose, with the dose defined as the average daily dose based on the most recent dispensation before the index date. To examine the influence of duration of exposure to oral glucocorticoids, we defined four categories of duration of continuous use until the index date. Continuous users were categorized into continuous users for 1-2 months, 3-5 months, 6-11 months and 12 (or more) months. To characterize the residual effect of oral glucocorticoid use, we created three time windows of exposure recency before the index date: The 1-14 day period defined 'current use', while 15-45 days and 46-365 days defined the period when exposure stopped.

Covariates

Covariates included age, gender, systemic hypertension, diabetes mellitus, ophthalmic glucocorticoids, glucocorticoid injections, and characteristics of health care system use in the 365 days before the index date. Old age, systemic hypertension and diabetes mellitus have all been described as risk factors for the development of ocular hypertension and open-angle glaucoma (33,34). We defined systemic hypertension by filling a prescription for any of the following antihypertensive medications before the index date: thiazide diuretics, centrally acting antiadrenergic agents, peripherally acting antiadrenergic agents, ß-adrenergic blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, and vasodilators. Although some of these drugs are also used for other disease pathologies, in the elderly the resulting degree of misclassification by that definition is at most moderate (35). Diabetes mellitus was defined by any dispensation of oral hypoglycemic therapy or insulin before the index date. We classified dispensations of ophthalmic glucocorticoids and glucocorticoid injections as current and former use, and included both use categories into our analyses. Current use was defined as a drug supply which continued into the 14-day period before the index date, while former use was any

drug supply which ended between 365 days and 15 days before the index date. The following health care system use characteristics, included as markers for general health, were investigated: number of prescriptions filled for all drugs, number of physician claims for services, and number of days hospitalized.

Statistical Analysis

The relative risk of ocular hypertension or open-angle glaucoma for each exposure group was estimated from odds ratios calculated by conditional logistic regression using the SAS PHREG program (36). We constructed individual models characterizing patients according to hydrocortisone dose equivalent in mg, duration of continuous glucocorticoid use and recency of exposure to glucocorticoid tablets. For these analyses, the reference category was the absence of exposure to glucocorticoid tablets in the year before the index date. We further divided the case group into two subgroups according to whether cases had been defined by only a diagnosis of glaucoma or whether they had received treatment for ocular hypertension or glaucoma and estimated the odds ratios of exposure to oral glucocorticoids separately for both subgroups. All models simultaneuously controlled for the effects of demographic variables, diabetes mellitus, systemic hypertension, ophthalmic glucocorticoids, glucocorticoid injections and the health care system use characteristics listed above. We further calculated the unadjusted odds ratio of glucocorticoid tablets in patients who were classified as current users of systemic steroids and had received the dispensation in conjunction with a diagnosis indicating pulmonary problems, including asthma, chronic bronchitis, chronic obstructive bronchitis, emphysema, dyspnea and pulmonary fibrosis. Two-tailed p values less than .05 were considered significant and 95 % confidence intervals were calculated for all relative risks.

2.5 Results

Of the 22,707 patients who had received a diagnosis of or treatment for ocular hypertension or glaucoma, 1,165 did not fulfill the inclusion criterion of consulting an ophthalmologist and 11,260 did not meet the eligibility criterion of being in the database for at least one year before the index event. A diagnosis of angle-closure and secondary open-angle glaucoma led to the exclusion of another 485 patients. Four patients were excluded because information on age was not available. The final case group therefore included 9,793 patients of who 5,003 had received a diagnosis of ocular hypertension or glaucoma, but no glaucoma treatment at the index date. Of the remaining cases, 4,720 had been started on drug treatment for glaucoma or high intraocular pressure and 70 had received a laser trabeculoplasty. We identified 69,556 noncases with ophthalmologist visits one year or more after their first listing in the database. After the exclusion of controls with incomplete information, the final control group included 38,325 patients.

Characteristics of cases and controls are summarized in Table 2. Cases were more likely to be females and tended to be slightly older than controls. More controls had been treated for diabetes mellitus which reflects the choice of ophthalmology patients as a control group. The distribution of systemic hypertension was similar among cases and controls. More cases than controls had dispensations for corticosteroid eyedrops. Dispensations for corticosteroid injections were similar in cases and controls, as were the total number of drug dispensations in the year before the index date. A higher number of physician claims for services had been submitted for cases in the 365 days before the index date. Cases had been hospitalized more often than controls in the year before the index date, but the duration of hospitalization tended to be shorter in cases than in controls.

Table 3 shows that 2.7 % of cases were current users of glucocorticoid tablets compared with 1.9 % of control patients, to yield an odds ratio of 1.41 (95 % CI, 1.22 to 1.63). The risk of ocular hypertension or open-angle glaucoma was significantly increased only in current users of glucocorticoid tablets. Patients whose drug supply of glucocorticoid tablets ended 15 to 45 days before the index date had an odds ratio of 1.18 (95 % CI, 0.87

to 1.62). The odds ratio for patients whose supply of glucocorticoid tablets ended 46 to 365 days before the index date was 0.92 (95 % CI, 0.78 to 1.08).

In Table 4, we observe a dose-response relationship in current users of glucocorticoid tablets, with the estimated relative risk of ocular hypertension or open-angle glaucoma increasing with the average daily dose of glucocorticoid tablets. Patients with an average daily dose of 1-39 mg hydrocortisone mg equivalents had an estimated relative risk of 1.25 (95 % CI, 1.00 to 1.55) which increased to 1.40 (95 % CI, 1.10 to 1.78) for patients with an average daily dose of 40-79 mg hydrocortisone equivalents and to 1.89 (95 % CI, 1.43 to 2.49) for patients who were taking 80 or more mg hydrocortisone equivalent. These estimates remained similar after adjustment.

In Table 5, the relative risk of ocular hypertension or open-angle glaucoma is seen to increase with the duration of continuous use of glucocorticoid tablets before the index date. Patients who had continuously been treated with glucocorticoid tablets for 1-2 months had an odds ratio of 1.31 (95 % CI, 0.94 to 1.82). The respective odds ratio for patients with 3-5 months of continuous use was 1.64 (95 % CI, 1.16 to 2.30) and that for patients with 6-11 months of continuous use was 1.87 (95 % CI, 1.35 to 2.60). No further increase in risk was seen in patients who had been continuously treated for 12 or more months, although the risk remained elevated at 1.53 (95 % CI, 1.13 to 2.05).

2.6 Discussion

This large population based study of 9,793 cases and 38,325 controls overcomes sample size limitations of previous research. We were able to investigate the influence of the corticosteroid dose and duration of exposure, while simultaneously controlling for several important risk factors, including age, diabetes mellitus, systemic hypertension and topical corticosteroid application to the eye. Our results suggest that systemic glucocorticoids increase the risk of ocular hypertension or open-angle glaucoma. We demonstrated that the magnitude of the risk is directly related to the steroid dose. Previous investigations of the risk associated with the dose of systemic corticosteroid were inconclusive. One study documented an increase in mean intraocular pressure with increasing dose which could not be confirmed in another study (18,20). For topical corticosteroid application to the eye, a marked dose-response relationship has been demonstrated by Kitazawa (37). Administration of betamethasone eyedrops 0.01 %, 0.02 %, 0.05 % or 0.1 % for four weeks to subjects known as steroid responders resulted in mean intraocular pressure elevations from baseline measurements of 2.4, 8.1, 17.0, or 23.7 mm Hg, respectively. In concordance with clinical belief, we found a lower odds ratio for oral glucocorticoids than for topical steroid administration to the eye, with an odds ratio of 1.72 (95 % CI, 1.55 to 1.92) being associated with the latter exposure. However, in patients who received the equivalent of 80 mg oral hydrocortisone per day, the risk appeared to be of similar magnitude as that observed in patients using ophthalmic steroids.

An increased risk was already apparent in the first months of continuous treatment with glucocorticoid tablets. This observation is in contrast to the previous belief expressed by some authors that ocular hypertension as a result of steroid treatment will not develop before months and often years of oral steroid administration (28,38). This view appears to have been derived from a number of case reports in which steroid tablets were administered over long periods of time before patients were diagnosed with ocular hypertension or open-angle glaucoma (13,14,17,21). The diagnosis in these cases may, however, have simply been missed in the early stages, due to the asymptomatic nature of ocular hypertension and open-angle glaucoma until late in the disease. Delayed detection

of these conditions may therefore offer an alternative explanation for the previously reported long exposure periods. We are aware of at least two case reports which described development of ocular hypertension within days of administration of steroid tablets, with normalization of pressure values following steroid withdrawal (12,15). These clinical observations also support the notion that the required exposure period may not be different for oral and ocular corticosteroids.

The risk was only significantly increased in patients who had received oral steroids in the last 14 days before the index date. Patients whose drug supply ended 15 to 45 days before the index date did no longer exhibit a significant increase in risk. This finding suggests that the ocular pressure elevation induced by oral steroids is usually reversible within two weeks of cessation of steroid treatment and confirms isolated clinical observations on a large population based scale (12,14,15). Normalization of elevated intraocular pressure appears to occur within the same time period that has been established for ophthalmic glucocorticoids in a number of clinical studies in subjects with clinically normal eyes (1). Some investigators have reported cases with persistent elevations of intraocular pressure following cessation of ophthalmic glucocorticoids (2,39,40). These cases may, however, represent open-angle glaucoma that was 'unmasked' by the use of corticosteroids (27).

Several mechanisms have been proposed by which corticosteroids may lead to intraocular pressure elevation. The most important factor appears to be an increase in the resistance to aqueous humor outflow (2,41). Several observations suggest the presence of a high concentration of steroid-specific receptors in trabecular meshwork cells that likely play a role in the development of steroid-induced ocular hypertension (42,43). Corticosteroid-induced ocular pressure elevations are associated with morphologic changes in the trabecular meshwork (44,45). An accumulation of polymerized glycosaminoglycans in the trabecular meshwork has been proposed by some authors, whereas others believe that corticosteroid-induced intraocular pressure elevation is related to an increase in the expression of collagen, elastin or fibronectin in the extracellular matrix (27). Accumulation of trabecular debris due to the suppression of phagocytosis by the trabecular endothelium has been put forward as another hypothesis (27).

It has not been established whether the mechanism by which corticosteroids raise intraocular pressure is the same for oral and ophthalmic corticosteroids (14,20). Pharmakokinetic and experimental data are compatible with a common pathogenic mechanism for both routes of administration. Oral glucocorticoids have a high systemic bioavailability ranging from 70 % for betamethasone over 80 % for dexamethasone and methylprednisolone to 98 % for prednisone (46). A considerable concentration of systemic steroids may thus reach the eye. Studies conducted in patients undergoing surgery for cataract and open-angle glaucoma have demonstrated biologically relevant concentrations of glucocorticoids in aqueous humor (47,48). The observations of our study which demonstrated a dose-response relationship for oral glucocorticoids and a similar time pattern of onset of ocular hypertension for both routes of administration would support the hypothesis of a common pathogenic mechanism.

Some issues of the study design need to be addressed. Steroid-induced ocular side effects may present as ocular hypertension or open-angle glaucoma, depending on the duration of treatment and the susceptibility of the individual to the ocular hypertensive effect (49). Ocular hypertension used to be part of the definition of open-angle glaucoma and is now considered to be the most important risk factor for the disease (50). The data did not allow us to analyse ocular hypertension and open-angle glaucoma as separate outcome events. We therefore do not know what proportion of patients treated with oral glucocorticoids had already developed permanent damage to the optic nerve. Our case definition permitted us to differentiate two subgroups of cases according to whether glaucoma treatment had been instituted at the index date or not. We hypothesized that, in accordance with customary treatment practice, treated cases were more likely to include patients with glaucomatous damage to the optic nerve than untreated patients, although some overlap between both subgroups cannot be excluded. We analysed the odds ratios for both subgroups separately, regarding the subgroups as proxies for the severity of the disease. The risk estimate for oral glucocorticoids was of similar magnitude in both subgroups. Patients who had received glaucoma treatment at the index date had an odds ratio of 1.38 (95 % CI, 1.14 to 1.67), whereas the respective odds ratio in the untreated case group was 1.43 (95 % CI, 1.18 to 1.73). These results indicate that patients who

receive oral glucocorticoid treatment may need therapeutic intervention for the regulation of intraocular pressure values, be it to prevent the occurrence of open-angle glaucoma or the progression of the disease.

Study patients were defined by ophthalmologist visits, chosing the index date of controls on the basis of the date of the ophthalmologist consultation. This choice of study subjects was motivated by several considerations. One concern was the asymptomatic nature of the outcome condition which makes it likely that a large portion of cases would be misclassified as controls when chosing general population controls without restriction to those consulting ophthalmologists. Large scale population screening surveys for glaucoma have demonstrated that about half of all glaucoma patients are not aware of having the disease (51,52). In Québec, patients over 40 years of age who consult an ophthalmologist will usually be subjected to routine tonometry. In chosing patients with ophthalmologist visits as a control group, we greatly reduced the possibility that our controls were in fact non-diagnosed cases. Some cases may still have been included among the controls, because they were not properly classified as such in the database. If this had happened it would have reduced our chance to demonstrate an increased risk, and the true odds ratio would be higher in this case (53).

In our choice of study subjects we also had to consider that doctors may refer steroid treated patients more frequently to ophthalmologists for control investigations than other patients, since systemic corticosteroids also increase the risk of cataracts, a side effect which is more widely acknowledged than the pressure elevating effect of systemic steroids and which may constitute a reason of its own to refer patients for eye investigations (31,54). If systemic steroid users were more likely to consult an ophthalmologist than nonusers, they would have a higher chance of being diagnosed as a case. Such a selection process resulting from differential referral rates would lead to an exaggerated risk estimate for systemic steroid use. In defining all study patients as ophthalmology patients, the concern about differential referral becomes a lesser issue.

In our analyses, we controlled for several conditions which have been discussed as risk factors for ocular hypertension and chronic open-angle glaucoma, including age, gender, systemic hypertension, diabetes mellitus, corticosteroid injections and ophthalmic steroid use (33). Controlling for these conditions, and for variables related to previous health care use as markers of general ill health did not materially alter the results. Our reliance on claims-based prescription data did not permit us to control for other potentially important factors, most importantly a family history of glaucoma. We have no reason to believe that prescription of oral steroids is associated with this risk factor.

Some of the diseases treated with oral glucocorticoids may be associated with an increased risk of ocular hypertension and glaucoma. Rheumatoid arthritis, a frequent cause for treatment with oral steroids, is associated with a slightly higher incidence of scleritis and episcleritis than that seen in the normal population and these two conditions may occasionally lead to the development of secondary open-angle glaucoma as a complication of the disease. This may lead to an overestimate of the risk estimate for oral steroids. Diagnostic coding in the database did not permit us to reliably separate rheumatoid arthritis from degenerative joint diseases and to arrive at separate risk estimates for both conditions to address the above concern. Instead, we estimated the risk of ocular hypertension or open-angle glaucoma in patients who had received systemic steroid treatment for asthma, chronic obstructive bronchitis and related pulmonary problems, since these conditions are usually not associated with an increased risk of eye diseases. The odds ratio in these patients was 1.39 (95 % CI, 1.02 to 1.89) and thus of similar magnitude as that observed in all patients on oral glucocorticoids.

What implications should the results of our study have for clinical practice? In patients requiring prolonged oral glucocorticoid therapy periodic monitoring of intraocular pressure appears warranted, as such treatment may contribute to the development of ocular hypertension. Based on our results, a first tonometry would appear appropriate a few weeks after institution of steroid treatment, especially in patients requiring high doses of oral steroids. Similar control recommendations have been given by ophthalmologists for the extended use of topical steroids to the eye (11,27,55). In the case of these topical

steroid preparations the prescription is frequently given by ophthalmologists who are aware of the associated ocular risks of these agents. In contrast, systemic steroids are predominantly prescribed by other specialists and general practitioners who may be more concerned with other systemic side effects of these drugs. The results of this study should alert physicians to the potential ocular side effects of oral steroid treatment. While the intraocular pressure elevation caused by corticosteroids is usually reversible, the damage it can produce is not (56).

Table 1. Oral Glucocorticoids: Relative Potency and Current Use by Cases and Controls*

Agent	Relative Potency	Cases (n=9,793)	Controls (n=38,325)
Cortisone	0.8	12	25
Hydrocortisone	1.0	2	6
Prednisone	4.0	243	665
Prednisolone	4.0	2	4
Triamcinolone	5.0	0	3
Methylprednisolone	5.0	1	10
Dexamethasone	25.0	1	11
Betamethasone	25.0	3	7
At least one glucocorticoid		264	729

*Subjects may have been exposed to more than one glucocorticoid preparation

Table 2. Characteristics of Cases and Controls*

Characteristic	CASES % (n=9,793)	CONTROLS % (n=38.325)
Age		
65-69	23.5	25.7
70-74	29.7	29.5
75-84	38.9	36.4
≥85	8.0	8.4
Gender		
Male	34.5	37.9
Female 65.5	62.1	
Diabetes treated with		
Oral antidiabetics	10.5	11.1
Insulin	2.4	2.9
Systemic hypertension	56.8	55.7
Health care utilization in the 365 days preceding the index date		
No. of prescriptions		
≤15	33.9	34.6
16 - 30	22.5	21.6
> 30	43.6	43.8
No. of physician claims		
≤10	38.5	41.4
11-20	33.7	30.6
> 20	27.8	27.9
No. of days hospitalized		
0	64.7	67.9
1-15	28.5	23.3
> 15	6.8	8.8
Dispensation of ophthalmic glucocorticoids		
current	5.3	3.1
former	7.3	5.3
no	87.4	91.6
Dispensation of glucocorticoid injections		
current	0.2	0.2
former	1.9	1.9
no	97.9	97.9

* Percentages may not equal 100 due to rounding.

Table 3. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma According to Recency of Oral Glucocorticoid Use

Use Category	Cases (%) (n=9,793)	Controls (%) (n=38,325)	Crude Odds Ratio	Adjusted* Odds Ratio	95 % CI
Nonusers	94.9	95.7	1.00	1.00	
1-14 days	2.7	1.9	1.43	1.41	1.22-1.63
15-45 days	0.5	0.4	1.21	1.18	0.87-1.62
46-365 days	1.9	2.0	0.95	0.92	0.78-1.08

* Adjusted for age, gender, diabetes mellitus, systemic hypertension, ophthalmic glucocorticoids, glucocorticoid injections, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

Table 4. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma According to Average Daily Dose of Oral Glucocorticoids (in Hydrocortisone mg Equivalents)*

Dose, mg/day	Cases (%)+ (n=9,793)	Controls (%)+ (n=38,325)	Crude Odds Ratio	Adjusted** Odds Ratio	95 % CI
0	94.9	95.7	1.00	1.00	
1-39	1.2	0.9	1.25	1.26	1.01-1.56
40-79	0.9	0.6	1.40	1.37	1.06-1.76
80 +	0.7	0.4	1.89	1.88	1.40-2.53

* Exposed cases and controls are only current users of glucocorticoid tablets

+ Percentages do not add up to 100, because former users (2.4 % of cases and 2.4 % of controls) are excluded from this analysis

** Adjusted for age, gender, diabetes mellitus, systemic hypertension, ophthalmic glucocorticoids, glucocorticoid injections, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

Table 5. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma According to Duration of Continuous Use of Oral Glucocorticoids

Duration of Continuous Use (Months)*	Cases (%) (n=9,793)	Controls (%) (n=38,325)	Crude Odds Ratio	Adjusted† Odds Ratio	95 % CI
Nonusers	94.9	95.7	1.00	1.00	
No continuous use	3.0	3.0	1.00	0.98	0.86-1.12
Duration of use:					
1-2	0.5	0.4	1.31	1.29	0.93-1.80
3-5	0.5	0.3	1.64	1.63	1.16-2.30
6-11	0.5	0.3	1.87	1.87	1.34-2.60
12 (+)	0.6	0.4	1.53	1.52	1.13-2.05

* In current users of oral glucocorticoids

† Adjusted for age, gender, diabetes mellitus, systemic hypertension, ophthalmic glucocorticoids, glucocorticoid injections, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

2.7 Bibliography

1. Armaly, M.F. 1986. Corticosteroid glaucoma. In Glaucoma. J.E. Cairns, editor. Grune & Stratton, London. 697-710.

2. Becker, B. and D.W. Mills. 1963. Corticosteroids and intraocular pressure. *Arch. Ophthalmol.* 70:500-507.

3. Armaly, M.F. 1965. Statistical attributes of the steroid hypertension response in the clinically normal eye. I. The demonstration of three levels of response. *Invest. Ophthalmol. Vis. Sci.* 4:187-197.

4. Becker, B. 1965. Intraocular pressure response to topical corticosteroids. *Invest. Ophthalmol. Vis. Sci.* 4:198-205.

5. Francois, J. 1954. Cortisone et tension oculaire. *Ann. Oculist.* 187:805-816.

6. Butcher, J.M., M. Austin, J. McGalliard, and R.D. Bourke. 1994. Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. *BMJ* 309:43

7. Goldmann, H. 1962. Cortisone glaucoma. *Arch. Ophthalmol.* 68:621-626.

8. Burde, R.M. and B. Becker. 1970. Corticosteroid-induced glaucoma and cataracts in contact lens wearers. *JAMA* 213:2075-2077.

9. Brubaker, R.F. and J.A. Halpin. 1975. Open-angle glaucoma associated with topical administraion of flurandrenolide to the eye. *Mayo Clin. Proc.* 50:322-326.

10. Frenkel, M. 1969. Blindness due to steroid induced glaucoma. *IMJ - Illinois Medical Journal* 135:160-163.

11. Hodapp, E.A. and M.A. Kass. 1982. Corticosteroid-induced glaucoma. In The secondary glaucomas. R. Rich and M.B. Shields, editors. C. V. Mosby Comp. St. Louis. 258-265.

12. Long, W.F. 1977. A case of elevated intraocular pressure associated with systemic steroid therapy. *Am. J. Optom. & Physiol. Optics* 54:248-252.

13. Covell, L.L. 1958. Glaucoma induced by systemic steroid therapy. *Am. J. Ophthalmol.* 45:108-109.

14. Alfano, J.E. 1963. Changes in the intraocular pressure associated with systemic steroid therapy. *Am. J. Ophthalmol.* 56:245-247.

15. Stern, J.J. 1953. Acute glaucoma during cortisone therapy. *Am. J. Ophthalmol.* 36:389-390.

16. Laval, J. and R. Collier. 1955. Elevation of intraocular pressure due to hormonal steroid therapy in uveitis. *Am. J. Ophthalmol.* 39:175-182.

17. Harris, J.L. 1960. Glaucoma associated with steroid therapy and atopic dermatitis. *Am. J. Ophthalmol.* 49:351-353.

18. Godel, V., V. Feiler-Ofry, and R. Stein. 1972. Systemic steroids and ocular fluid dynamics. I. Analysis of the sample as a whole. Influence of dosage and duration of therapy. *Acta Ophthalmol.* 50:655-663.

19. Krakau, C.E., B. Bengtsson, and C. Holmin. 1983. The glaucoma theory updated. *Acta Ophthalmol.* 61:737-741.

20. Bernstein, H.N. and B. Schwartz. 1962. Effects of long term systemic steroids on ocular pressure and tonographic values. *Arch. Ophthalmol.* 68:742-754.

21. Williamson, J., R.W. Paterson, D.D. McGavin, M.K. Jasani, J.A. Boyle, and W.M. Doig. 1969. Posterior subcapsular cataracts and glaucoma associated with long-term oral corticosteroid therapy. In patients with rheumatoid arthritis and related conditions. *Br. J. Ophthalmol.* 53:361-372.

22. Adhikary, H.P., R.A. Sells, and P.K. Basu. 1982. Ocular complications of systemic steroid after renal transplantation and their association with HLA. *Br. J. Ophthalmol.* 66:290-291.

23. Lee, P.F. 1958. The influence of systemic steroid therapy on the intraocular pressure. *Am. J. Ophthalmol.* 46:328-331.

24. Pateron, G.D. and R. Owen. 1966. Further studies on systemic steroids. In Drug mechanisms in glaucoma. G. Paterson, S.J.H. Miller, and G.D. Paterson, editors. J. & A. Churchill LTD, London. 249-253.

25. David, D.S. and J.S. Berkowitz. 1969. Ocular effects of topical and systemic corticosteroids. *Lancet* 2:149-151.

26. Grant, W.M. 1969. Ocular complications of drugs. Glaucoma. *JAMA* 207:2089-2091.

27. Skuta, G.L. and R.K. Morgan. 1996. Corticosteroid-induced glaucoma. In The glaucomas. R. Ritch, M.B. Shields, and T. Krupin, editors. Mosby, St. Louis. 1177-1188.

28. Abel, R. and I.H. Leopold. 1987. Ocular diseases. In Avery's drug treatment. Principles and practice of clinical pharmacology and therapeutics. T.M. Speight, editor. Adis, Auckland. 387-417.

29. Tamblyn, R., G. Lavoie, L. Petrella, and J. Monette. 1995. The use of prescription claims databases in pharmacoepidemiological research: The accuracy and comprehensiveness of the prescription claims database in Quebec. *J. Clin. Epidemiol.* 48:999-1009.

30. Anonymous1977. Manual of the international statistical classification of diseases, injuries, and causes of death based on the recommendations of the ninth revision conference, 1975. WHO, editor. World Health Organization, Geneva.

31. Haynes, R.C.J. 1990. Adrenocorticotropic hormone;adrenocortical steroids and their synthetic analogs; inhibitors of the synthesis and actions of adrenocortical hormones. In Goodman and Gilman's The Pharmacological Basis of Therapeutics. A.G. Gilman, T.W. Rall, A.S. Nies, and P. Taylor, editors. Pergamon Press, New York. 1431-1462.

32. McEvoy, G.K. 1993. AHFS Drug Information. American Society of Hospital Pharmacists, editor. Bethesda, Md. 1895

33. Leske, M.C. 1983. The epidemiology of open-angle glaucoma: a review. *Am. J. Epidemiol.* 118:166-191.

34. Wilson, M.R. 1990. Epidemiological features of glaucoma. *Int. Ophthalmol. Clin.* 30:153-160.

35. Gurwitz, J.H., J. Avorn, R.L. Bohn, R.J. Glynn, M. Monane, and H. Mogun. 1994. Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 272:781-786.

36. Sas Institute Inc. 1992. The PHREG procedure. In SAS technical report P-229. SAS/STAT software: changes and enhancements. Release 6.07. Sas Institute Inc. Cary. 435-479.

37. Kitazawa, Y. 1976. Increased intraocular pressure induced by corticosteroids. *Am. J. Ophthalmol.* 82:492-495.

38. Armaly, M.F. 1968. Genetic factors related to glaucoma. *Ann. N. Y. Acad. Sci.* 151:861-875.

39. Spiers, F. 1965. A case of irreversible steroid-induced rise in intraocular pressure. *Acta Ophthalmol.* 43:419-422.

40. Spaeth, G.L., M.M. Rodrigues, and S. Weinreb. 1977. Steroid induced glaucoma: A. Persistent elevation of intraocular pressure. B. Histopathological aspects. *Trans. Amer. Ophthalmol. Soc.* 75:353-381.

41. Armaly, M.F. 1963. Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. *Arch. Ophthalmol.* 70:482-491.

42. Hernandez, M.R., E.J. Wenk, B.I. Weinstein, P. Abumohor, S.M. Podos, M.W. Dunn, and A.L. Southren. 1983. Glucocorticoid target cells in human outflow pathway: autopsy and surgical specimens. *Invest. Ophthalmol. Vis. Sci.* 24:1612-1616.

43. Weinreb, R.N., E. Bloom, J.D. Baxter, J. Alvarado, N. Lan, J. O'Donnell, and J.R. Polansky. 1981. Detection of glucocorticoid receptors in cultured human trabecular cells. *Invest. Ophthalmol. Vis. Sci.* 21:403-407.

44. Rohen, J.W., E. Linner, and R. Witmer. 1973. Electron microscopic studies on the trabecular meshwork in two cases of corticosteroid-glaucoma. *Exp. Eye. Res.* 17:19-31.

45. Roll, P. and O. Benedikt. 1979. Elektronenoptische Untersuchung des Trabekelwerkes bei einem Kortikosteroidglaukom. *Klin. Monatsbl. Augenheilkd.* 174:421-428.

46. Clark, W.G., D.C. Brater, and A.R. Johnson. 1992. Pharmacokinetic characteristics of drugs. In Goth's medical pharmacology. W.G. Clark, D.C. Brater, and A.R. Johnson, editors. C.V.Mosby, St.Louis. 773-792.

47. Weinstein, B.I., N. Kandalaft, R. Ritch, C.B. Camras, D.J. Morris, S.A. Latif, P. Vecsei, J. Vittek, G.G. Gordon, and A.L. Southren. 1991. 5alpha-dihydrocortisol in human aqueous humor and metabolism of cortisol by human lenses in vitro. *Invest. Ophthalmol. Vis. Sci.* 32:2130-2135.

48. Knisely, T.L., J. Hosoi, R. Nazareno, and R.D. Granstein. 1994. The presence of biologically significant concentrations of glucocorticoids but little or no cortisol binding globulin within aqueous humor: relevance to immune privilege in the anterior chamber of the eye. *Invest. Ophthalmol. Vis. Sci.* 35:3711-3723.

49. Armaly, M.F. 1966. Characteristics of the steroid effect on intraocular pressure and aqueous dynamics. In Drug mechanisms in glaucoma. G. Paterson, S.J.H. Miller, and G.D. Paterson, editors. J. & A.Churchill LTD, London. 191-228.

50. Quigley, H.A. 1993. Open-angle glaucoma. *N. Engl. J. Med.* 328:1097-1106.

51. Sommer, A., J.M. Tielsch, J. Katz, H.A. Quigley, J.D. Gottsch, J. Javitt, and K. Singh. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch. Ophthalmol.* 109:1090-1095.

52. Dielemans, I., J.R. Vingerling, R.C. Wolfs, A. Hofman, D.E. Grobbee, and P.T. de Jong. 1994. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 101:1851-1855.

53. Rothman, K.J. 1986. Modern epidemiology. Little, Brown and Co. Boston. 87

54. Laurence, D.R. and P.N. Bennett. 1992. Endocrinology I: adrenal corticosteroids, antagonists, corticotrophin. In Clinical pharmacology. D.R. Laurence and P.N. Bennett, editors. Churchill Livingstone, Edinburgh. 549-563.

55. Kass, M.A. and T. Johnson. 1989. Corticosteroid-induced glaucoma. In The glaucomas. R. Rich, M.B. Shields, and T. Krupin, editors. C. V. Mosby Company, St. Louis. 1161-1168.

56. Tripathi, R.C., B.S. Kirschner, M. Kipp, B.J. Tripathi, D. Slotwiner, N.S. Borisuth, T. Karrison, and J.T. Ernest. 1992. Corticosteroid treatment for inflammatory bowel disease in pediatric patients increases intraocular pressure. *Gastroenterology* 102:1957-1961.

CHAPTER 3

INHALED AND NASAL GLUCOCORTICOIDS

AND THE RISKS OF

OCULAR HYPERTENSION OR OPEN-ANGLE GLAUCOMA

3.1 Preface to the Manuscript

This manuscript presents the results of the second part of the study which examines the risk of ocular hypertension or open-angle glaucoma after exposure to inhaled and nasal glucocorticoids. Published case reports which suggest an increased risk for these two exposures were described in the introduction section of the thesis. This section also outlines the importance and increasing use of inhaled glucocorticoids in the treatment of asthma and describes the treatment indications for nasal glucocorticoids.

The introduction of the manuscript presents the case reports following administration of inhaled and nasal glucocorticoids in the context of the increasing use of these drugs and their propensity to cause systemic effects. The methodology used to study the risk for either route of administration does not differ in an important way from that described in the previous manuscript. The definition of cases and controls remains the same and exposure to either route is also investigated with respect to the dose and duration of treatment. However, unlike the case of oral glucocorticoids, the effect of the dose of inhaled or nasal glucocorticoids cannot be studied by converting each prescription into hydrocortisone-equivalent milligrams, since equivalent potencies have not been established for these routes of administration. Instead, we categorized the dose based on dose recommendations published by manufacturers and in the medical literature. Exposure to oral glucocorticoids for which an increased risk has been shown in the previous manuscript now serves as an adjustment variable in the analysis.

The results for the exposure to these two forms of glucocorticoids are discussed in view of findings from pharmacologic studies. Certain aspects of the study design and limitations of the data are discussed.

This article will be submitted for publication and should be quoted as follows:

Garbe E, LeLorier J, Boivin JF, Suissa S. Inhaled and nasal glucocorticoids and the risks of ocular hypertension or open-angle glaucoma. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, McGill University, 1996.

3.2 Abstract

Objective: To determine whether the use of inhaled and nasal glucocorticoids is associated with an increased risk of ocular hypertension or open-angle glaucoma.

Design: Case-control study.

Setting: Quebec universal health insurance program for all elderly (RAMQ database).

Patients: RAMQ enrollees aged 66 years and older. The 9,793 cases were ophthalmology patients with a new diagnosis of borderline glaucoma or open-angle glaucoma or were newly started on treatment for ocular hypertension or glaucoma between 1988 and 1994. The 38,325 controls were randomly selected among noncases who consulted an ophthalmologist in the same month and year as the case.

Main Outcome Measures: The odds ratio of ocular hypertension or open-angle glaucoma was determined in patients using inhaled or nasal glucocorticoids relative to nonusers, using conditional logistic regression analysis. The odds ratio was adjusted for age, gender, diabetes mellitus, systemic hypertension, current use of ophthalmic and oral glucocorticoids and characteristics of health care system use in the year before the index event.

Measurement and Main Results: Current dispensations of inhaled and nasal glucocorticoids regardless of dose or duration of use were not associated with an increased risk of ocular hypertension or open-angle glaucoma. The adjusted odds ratio was 1.02 (95 % CI, 0.89 to 1.18) for inhaled steroids and 1.08 (95 % CI, 0.88 to 1.33) for nasal steroids. Patients who had received high doses of inhaled steroids for the last three or more months before the index event presented an increased risk, with an odds ratio of 1.44 (95 % CI, 1.01 to 2.06).

Conclusion: Prolonged administration of high doses of inhaled glucocorticoids may increase the risk of ocular hypertension or open-angle glaucoma. This finding is consistent with pharmacologic data which indicate the possibility of systemic effects for high doses of inhaled glucocorticoids and suggests that in these patients intraocular pressure control may be warranted.

3.3 Introduction

The development of highly potent, topically active corticosteroids has enabled patients to benefit from the therapeutic effects of corticosteroids while minimizing undesirable systemic effects. Use of inhaled glucocorticoids has markedly increased in the management of asthma (1,2), following guidelines which advocate earlier use of antiinflammatory agents in the course of the disease (3). Nasal steroids have emerged as another important topical route of steroid administration. They have broad applications in the treatment of many types of rhinitis, most importantly in those of atopic origin (4,5). It has been estimated that in excess of eight million prescriptions were written worldwide for nasal steroids in 1993 (6).

In comparison with oral corticosteroids, topical corticosteroids have fewer and milder side effects overall (7). Side effects may occur at the site of action or result from systemic absorption of the drugs. Inhaled and nasal steroids may be absorbed from the nasal mucosa and oropharynx, from the gut after swallowing, as well as from the lungs. Corticosteroids absorbed from the oropharynx, nasal mucosa and the lungs bypass first-pass metabolism in the liver, resulting in reduced hepatic metabolic degradation of the active compound. For the amount absorbed, the propensity to cause systemic effects is comparable to that of an intravenous injection.

In recent years, increasing concern has been expressed over possible systemic side effects of inhaled and nasal steroids, following a trend to prescribe higher doses of these drugs (4,8,9). Two recent case reports have suggested that systemic absorption of inhaled and nasal glucocortiocoids may lead to ocular hypertension and open-angle glaucoma (6,10). Ocular hypertension and open-angle glaucoma are well-characterized side effects of topical ophthalmic glucocorticids, with the majority of cases resulting from this route of steroid administration (11,12). Other routes of corticosteroid administration have also been associated with ocular hypertension and open-angle glaucoma, including oral glucocorticoids, periocular steroid injections and corticosteroid creams, lotions or ointments placed on the eyelids, face, or even remote sites (11).

In this study, we investigate whether use of inhaled and nasal steroids is associated with an increased risk of ocular hypertension or open-angle glaucoma, using a large-scale epidemiologic design. The following questions will be addressed by our study: Are patients using inhaled or nasal corticosteroids at an increased risk of developing ocular hypertension or open-angle glaucoma and if so, how large is the risk compared with subjects not using these drugs? Does the risk vary according to dose or duration of use of inhaled or nasal glucocorticoid?

3.4 Methods

Sources of Data

We conducted a case-control study among the elderly population in Québec for the years 1987 to 1994, using data from the provincial health insurance plan database which covers the cost of prescription drugs and medical services for all individuals 65 years of age or older. In Québec, prescription claims are filed to the Régie de l'assurance maladie du Québec (RAMQ), the government body responsible for medicare registration and the payment of prescription claims and physician services. Of the estimated 770,925 elderly in Québec, over 750,000 were registered with the RAMQ in 1990 (13). Prescription claims data in the database have recently been validated and shown to be fairly accurate and comprehensive (13). Data in the records include information on the patient's gender and age, medication use, medical procedures, diagnoses, and the specialty of the physician who directs the claim to the RAMQ. The prescription data contain information on all prescriptions filled by Medicare recipients, including the drug name, dispensation date, the dosage form and prescribed dose, treatment duration and quantity of drug dispensed. Drugs dispensed to patients during stay in hospitals or nursing homes are not included in the database. Information on diagnostic and therapeutic procedures whether performed in a hospital or in an office is also listed in the database. Diagnoses are coded according to the International Classification of Diseases, Ninth Revision (ICD-9) (14). Each patient in the database has a unique identification number which is encrypted to protect

confidentiality when the files are used for research. Two subsets of the RAMQ database were used for case and control selection: a 10 % random sample from 1987 to 1994 and a 20 % random sample from 1990 to 1992. Duplicates were eliminated from the latter sample.

Case Selection

Cases were RAMQ enrollees aged 66 years or older who consulted an ophthalmologist and either had a diagnosis of ocular hypertension or open-angle glaucoma or received medical or surgical treatment for these conditions. The index date for the case was defined as the first of these case defining events. If a case was defined by a prescription of glaucoma treatment and the prescription was not filled on the same day as the visit to the prescribing ophthalmologist, the day of the visit to the ophthalmologist was set as the index date. Medication for ocular hypertension and glaucoma included topical betablockers, topical parasympathomimetics, topical alpha agonists and carboanhydrase inhibitors. The following four-digit ICD-9 diagnoses were employed in the case definition: Borderline glaucoma (including the diagnosis of ocular hypertension), open-angle glaucoma and unspecified glaucoma (ICD-9 codes 365.0, 365.1 and 365.9). To qualify as new or incident case of glaucoma, subjects were required to have been enrolled in the database for at least one year without having had a diagnosis of ocular hypertension or glaucoma or having received treatment for these conditions.

Control Selection

Controls were randomly selected among all noncases in the database who were visiting an ophthalmologist. Like cases, controls were required to have been enrolled in the database for at least one year to become eligible as a control. The day of the visit to the ophthalmologist was set as the index date. Four controls were matched to each case on the index month and year of the case to account for seasonal and secular trends in medications.

Patients with a diagnosis of angle-closure glaucoma or secondary glaucomas were excluded from the case and control groups.

Glucocorticoid Exposure

We identified all prescriptions for inhaled and nasal glucocorticoids that had been filled by cases and controls in the year before the index date and studied the risk of current exposure for both routes of administration. We defined current exposure as a drug supply which continued into the 14-day period before the index date. To investigate the exposure to inhaled and nasal steroids according to dose, we calculated the average daily dose of inhaled and nasal steroids by dividing the total quantity (in μg) by the days of supply for that prescription. The average daily dose of the most recent prescription before the index date served to categorize use of inhaled and nasal steroids into either low-to-medium or high dose exposure, based on dose recommendations in published articles which often exceed those given by pharmaceutical manufacturers (3,7,15,16). The following average daily doses were used to define high dose exposure for different inhaled corticosteroid preparations listed on the provincial drug formulary: equal to or more than 1,600 μg of beclomethasone, budesonide or triamcinolone or 1,500 μg of flunisolide. For nasal corticosteroids, the following average daily doses defined high dose exposure: more than 200 μg of fluticasone or flunisolide and more than 400 μg of beclomethasone, budesonide or triamcinolone (16). Doses of inhaled and nasal steroids below these limits were classified as low-to-medium dose exposure. To study the risk of prolonged exposure, we further examined the risk in patients who had used inhaled or nasal steroids continuously for the last three or more months before the index date. For inhaled steroids, we investigated the risk of high-dose continuous exposure by analysing patients who had received high doses of inhaled steroids for at least three months before the index date.

Covariates

Covariates included age, gender, systemic hypertension, diabetes mellitus, current exposure to ophthalmic and oral glucocorticoids, and characteristics of health care system use in the year before the index date. Old age, systemic hypertension and diabetes mellitus have all been described as risk factors for the development of ocular hypertension and open-angle glaucoma (17,18). Systemic hypertension was defined by filling a prescription for the following antihypertensive medications before the index date: thiazide diuretics, centrally acting antiadrenergic agents, peripherally acting antiadrenergic agents, ß-adrenergic blockers, angiotensin converting enzyme inhibitors, calcium channel blockers, and vasodilators. Although some of these drugs are also used in the treatment of other diseases, the resulting degree of misclassification by that definition is assumed to be at most moderate (19). We defined diabetes mellitus by any use of oral hypoglycemic therapy or insulin before the index date. We investigated the following health care system use characteristics in the year before the index date as markers for general ill health: number of prescriptions filled for all drugs, number of patient-specific physician claims for services, and number of days hospitalized.

Statistical Analysis

The relative risk for ocular hypertension or open-angle glaucoma for each exposure group was estimated from odds ratios calculated by conditional logistic regression using the SAS PHREG program (20). We constructed individual models characterizing patients according to dose and continuous use of inhaled and nasal steroids. All models simultaneously controlled for the demographic and other health care utilization characteristics as well as for the other covariates just listed. For these analyses, the reference category was the absence of exposure to inhaled and nasal glucocorticoids. Two-tailed p values less than .05 were considered significant and 95 % confidence intervals were calculated for all relative risks.

3.5 Results

We identified 22,707 patients who had received a diagnosis or treatment for ocular hypertension or glaucoma. Of those, 1,165 did not fulfill the inclusion criterion of consulting an ophthalmologist and 11,260 did not meet the eligibility criterion of being in the database for at least one year before the index event. A diagnosis of angle-closure and secondary open-angle glaucoma led to the exclusion of another 485 patients. Another four patients were excluded because information on age was not available, leaving a final case group of 9,793 patients. Of those, 4,720 patients received medical treatment and 70 patients a laser trabeculoplasty at the index date, whereas the remaining 5,003 cases were identified by a diagnosis, but did not receive treatment. For selection of controls, we identified 69,556 noncases who had visited an ophthalmologist one year after their entry into the database. After the exclusion of controls with incomplete information and matching on the index month and year of the case, the final control group included 38,325 patients.

Characteristics of cases and controls are summarized in Table 1. Cases were more likely to be females and tended to be slightly older than controls. More controls had been treated for diabetes mellitus reflecting the choice of ophthalmology patients as a control group. Systemic hypertension was similarly distributed among cases and controls. More cases than controls had dispensations for glucocorticoid eyedrops and glucocorticoid tablets. The total number of drug dispensations in the year before the index date was similar for cases and controls. A higher number of physician claims for services had been written for cases in the year before the index date. Cases had been hospitalized more often than controls during that time period, but the duration of hospitalization tended to be shorter in cases than in controls.

Table 2 lists the different inhaled and nasal glucocorticoids on the provincial drug formulary and shows the frequency of current use for cases and controls. We did not find an increased risk of ocular hypertension or open-angle glaucoma in patients with current exposure to inhaled or nasal steroids. 2.9 % of cases and 2.7 % of controls had been

prescribed inhaled steroids at the index date, yielding an adjusted odds ratio of 1.02 (95 % CI, 0.89 to 1.18). Exposure to nasal steroids was markedly lower for cases and controls, with current exposure in only 1.2 % of cases and 1.1 % of controls, resulting in an adjusted odds ratio of 1.08 (95 % CI, 0.88 to 1.33).

About 50 % of all patients with current prescriptions for inhaled glucocorticoids had been subjected to high doses at the index date (Table 3). In the unadjusted analysis, high dose use of inhaled steroids was almost significant in increasing the risk with an odds ratio of 1.21 and a lower confidence bound of 1.00. Simultaneous adjustment for all covariates slightly decreased the odds ratio for high dose exposure with an odds ratio of 1.15 (95 % CI, 0.94 to 1.39). Low -to-medium dose use of inhaled steroids was not associated with an increase in risk with an adjusted odds ratio of 0.93 (95 % CI, 0.77; 1.12). The risk was also not elevated in patients who had used high doses of nasal steroids at the index date (Table 4).

The risk of ocular hypertension or glaucoma was significantly increased in patients who had used high doses of inhaled glucocorticoids continuously for the last three months or longer. The adjusted odds ratio for this group of patients was 1.44 (95 % CI, 1.01 to 2.06) (Table 5). In contrast, no increase in risk was observed in patients who had continuously used low-to-medium doses of inhaled steroids. The odds ratio in this group of patients was 0.97 (95 % CI, 0.84 to 1.13).

Continuous use of nasal steroids was relatively rare in our study sample, with only about 0.2 % of patients exposed to nasal steroids continuously for the last three or more months before the index date. Twenty-one study patients had had high-dose continuous exposure to nasal steroids, a number too small to arrive at stable statistical estimates for high-dose continuous use. We therefore only analysed continuous use of nasal steroids regardless of dose. For this use category, there was no indication of an increase in risk, with an adjusted odds ratio of 1.02 (95 % CI, 0.59 to 1.77) (Table 6).

3.6 Discussion

It has long been recognized that high doses of inhaled glucocorticoids may cause systemic effects (8,9). The results of our study suggest that prolonged continuous use of high doses of inhaled glucocorticoids may increase the risk of ocular hypertension or open-angle glaucoma. Both factors, high dose administration and prolonged continuous duration of use had to be present in order to elevate the risk. No significant increase in risk was observed in continuous users of low-to-moderate doses of inhaled steroids or in current users of high doses regardless of the duration of high-dose administration. For ophthalmic steroids, dose and duration of use have equally been characterized as important factors in the risk of ocular hypertension. It has been demonstrated in prospective clinical trials that ophthalmic steroids must often be administered over weeks before ocular hypertension develops and that with increasing ophthalmic steroid dose, the intraocular pressure elevation becomes more pronounced (11,12,21).

We defined high-dose use of inhaled steroids as an average daily dose of at least 1,500 μg of flunisolide or 1,600 μg of the other inhaled steroids on the provincial drug formulary. A number of studies have tried to establish which doses of different inhaled steroid compounds may be associated with a risk of systemic effects. These studies have often measured adrenocortical suppression as a marker of systemic effects (22-25). A recent review of these studies concluded that doses of 1,500 μg per day or less in adults appear to have little if any effect on pituitary-adrenal function (8). The results of our study support this finding, measuring ocular hypertension and open-angle glaucoma as clinical endpoints.

We did not observe an elevated risk of ocular hypertension or open-angle glaucoma after high dose use of nasal steroids. Nasal steroids are usually administered in much smaller doses than inhaled steroids, and a lower risk of systemic side effects may be anticipated by their smaller doses. Recommended doses for intranasal administration usually do not exceed 400 μg per day, whereas inhaled steroids are recommended in doses up to 1,500

to 2,000 μg per day (15,16,26,27). Even though different amounts of steroids may be absorbed from the lungs and from the nasal mucosa, the difference in absorption from these tissues appears to be less pronounced than the difference in the doses administered. For flunisolide, the systemic bioavailability has been determined to be 39 % after inhalation and 49 % after intranasal administration, respectively (26).

Continuous use of nasal steroids for three or more months before the index date was not associated with any increase in risk of ocular hypertension or open-angle glaucoma. This finding is in accordance with pharmacodynamic studies investigating the impact of prolonged exposure to nasal steroids on pituitary-adrenal function which have shown that intranasal administration of flunisolide, for periods of up to six months, and fluticasone or budesonide, for periods of up to twelve months, are not associated with suppresion of adrenal function (26-28). In our study sample, only a small number of patients were continuously exposed to nasal steroids. This was not unexpected, since seasonal allergic rhinitis, one of the main indications for nasal glucocorticoids, usually requires steroid administration only over limited periods of time. As a result of the low number of continuous users, we could not investigate the risk for high dose continuous use of nasal steroids and consequently, can not rule out an increased risk for this use category.

It is generally believed that glucocorticoids raise the intraocular pressure by increasing the resistance to aqueous humor outflow (29-31). Trabecular meshwork cells contain a high concentration of steroid-specific receptors that likely play a role in the development of steroid-induced ocular hypertension (32,33). Histopathologic studies have demonstrated morphologic changes in the trabecular meshwork of eyes with corticosteroid-induced ocular hypertension (34,35). Several theories have been proposed to explain the morphologic changes in the trabecular meshwork. Some authors have suggested that corticosteroids inhibit the metabolism of glycosaminglycans, leading to an accumulation of polymerized glycosaminoglycans in the trabecular meshwork (31). Others believe that the corticosteroid-induced intraocular pressure elevation is related to an increase in the expression of collagen, elastin or fibronectin in the extracellular matrix (11).

Some issues of the study design need to be addressed. Our reliance on claims-based diagnostic and prescription data did not permit us to distinguish patients with ocular hypertension from those with open-angle glaucoma or allow us to analyse both conditions as separate outcome events. It is known from numerous case reports that prolonged steroid-induced intraocular pressure elevations may result in serious glaucomatous damage to the optic nerve (36-41). Duration of steroid exposure and susceptibility of the individual to the ocular hypertensive response appear to be important factors which contribute to the clinical presentation as either ocular hypertension or open-angle glaucoma (42). The distinction between both outcome conditions appears to be of minor importance for recommendations concerning the ophthalmologic monitoring of steroid-treated patients. Patients with either condition will usually need ophthalmologic follow-up, either to decide whether glaucoma treatment should be initiated or to monitor treatment effectiveness.

Only patients who consulted an ophthalmologist were included in the study. One important consideration in this choice of study subjects was the prolonged asymptomatic course of the outcome conditions. It is known from large scale population screening surveys for glaucoma that about half of all patients with open-angle glaucoma are not aware of the presence of the disease (43,44). Case patients will usually be ophthalmology patients. If controls were selected as general population controls regardless of ophthalmologist consultations, they might in fact include a considerable number of nondiagnosed cases. In defining control patients by ophthalmologist visits, such misclassification will be of lesser concern, since elderly patients who consult an ophthalmologist will usually routinely have their intraocular pressure measured. Some cases may still have been included among the controls, because they were not properly classified as such in the database. If this happened, it reduced our chance of demonstrating an increased risk, and the true odds ratio is then higher than the estimates we obtained.

In our choice of study subjects we had also to account for the fact that seasonal allergic rhinitis is often accompanied by eye symptoms, such as itching, erythema and tearing of the eyes. It can therefore be expected that a considerable number of patients with seasonal

allergic rhinitis also consult an ophthalmologist because of their ocular symptoms. Since seasonal allergic rhinitis is often treated with nasal corticosteroids, patients receiving these drugs may have a higher chance of referral to an ophthalmologist than general population controls, especially since nasal steroids provide little or no benefit against eye symptoms (15,26). A higher referral rate to ophthalmologists for nasal steroid users may exaggerate the risk estimate for nasal steroid use, since patients with ophthalmologist consultations have a higher chance of being detected as a case. In defining our study sample by ophthalmologist visits, we avoid this bias which could result from differential referral rates to ophthalmologists.

Controls were matched to cases on the index month and year of the case to allow for seasonal and secular trends in disease and medication use. Taking calendar time into account is of obvious importance in the risk estimate for nasal steroids, since these drugs are frequently used to treat seasonal allergic rhinitis. Asthma patients may equally suffer from seasonal exacerbations of their disease, since asthma is often aggravated by lower airway infection, air pollution and cold air. By matching on calendar time, we also acounted for the marked change which has occurred in asthma treatment during the eight-year study period. Inhaled steroids are now being recommended at a much earlier stage in the course of the disease, and consequently, are used more frequently (1,2,45).

We controlled in our analysis for several factors which have been discussed as risk factors for ocular hypertension and open-angle glaucoma, including age, gender, systemic hypertension, diabetes mellitus, ophthalmic steroids and steroid tablets. We could not adjust for other possible risk factors as e.g. a family history of open-angle glaucoma or severe myopia, since information about these conditions could not be obtained from the database. However, we have no reason to believe that prescriptions of inhaled or nasal corticosteroids are associated with these factors and therefore do not expect confounding of the results by these variables.

The results of our study should alert physicians to the possibility that inhaled steroids may cause ocular hypertension and open-angle glaucoma, especially when they have been

administered in high doses over extended periods of time. The use of these drugs should be routinely questioned in newly diagnosed cases of ocular hypertension and open-angle glaucoma. If patients receive high doses of inhaled steroids over several months, ocular pressure should be monitored. Further research is needed to investigate the clinical course of ocular hypertension and open-angle glaucoma associated with inhaled glucocorticoids.

Table 1. Characteristics of Cases and Controls*

Characteristic	CASES, % (n=9,793)	CONTROLS % (n=38,325)
Age		
65-69	23.5	25.7
70-74	29.7	29.5
75-84	38.9	36.4
≥85	8.0	8.4
Gender		
Male	34.5	37.9
Female	65.5	62.1
Diabetes treated with		
Oral antidiabetics	10.5	11.1
Insulin	2.4	2.9
Systemic hypertension	56.8	55.7
Health care utilization in the 365 days preceding the index date		
No. of prescriptions		
≤15	33.9	34.6
16 - 30	22.5	21.6
> 30	43.6	43.8
No. of physician claims		
≤10	38.5	41.4
11-20	33.7	30.6
> 20	27.8	27.9
No. of days hospitalized		
0	64.7	67.9
1-15	28.5	23.3
> 15	6.8	8.8
Current dispensations of		
Glucocorticoid eyedrops	5.3	3.1
Glucocorticoid tablets	2.7	1.9

* Percentages may not equal 100 due to rounding

Table 2. Current Use of Inhaled and Nasal Glucocorticoids by Cases and Controls*

Agent	Cases (n=9,793)	Controls (n=38,325)
Inhaled		
Beclomethasone	219	848
Flunisolide	2	5
Budesonide	61	181
Triamcinolone	2	1
At least one inhaled glucocorticoid	281	1029
Nasal		
Beclomethasone	80	298
Flunisolide	22	79
Budesonide	11	25
Triamcinolone	2	13
Fluticasone	1	9
At least one nasal glucocorticoid	114	422

* Subjects may have been exposed to more than one glucocorticoid preparation

Table 3. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma According to Dose of Inhaled Glucocorticoids*

Dose	Cases (%) (n=9,793)	Controls (%) (n=38,325)	Crude Odds Ratio	Adjusted~ Odds Ratio	95 % CI
0	97.1	97.3	1.00	1.00	
Low-medium dose	1.4	1.5	0.95	0.93	0.77-1.12
High dose	1.4	1.2	1.21	1.15	0.94-1.39

* Exposed cases and controls are only current users of inhaled glucocorticoids

~ Adjusted for age, gender, diabetes mellitus, systemic hypertension, use of ophthalmic, oral and nasal glucocorticoids, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

Table 4. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma According to Dose of Nasal Glucocorticoids*

Dose	Cases (%) (n=9,793)	Controls (%) (n=38,325)	Crude Odds Ratio	Adjusted~ Odds Ratio	95 % CI
0	98.8	98.9	1.00	1.00	
Low-medium dose	0.7	0.6	1.11	1.14	0.86-1.51
High dose	0.5	0.5	1.00	1.02	0.74-1.39

* Exposed cases and controls are only current users of nasal glucocorticoids

~ Adjusted for age, gender, diabetes mellitus, systemic hypertension, use of ophthalmic, oral and inhaled glucocorticoids, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

Table 5. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma for Continuous* Use of Inhaled Glucocorticoids According to High-Dose, Low-to-Medium Dose or No Continuous Use

Characteristics Of Use	Cases (%) (n=9,793)	Controls (%) (n=38,325)	Crude Odds Ratio	Adjusted† Odds Ratio	95 % CI
Nonusers	97.1	97.3	1.00	1.00	
Continuous use:					
none	1.4	1.3	1.05	1.00	0.82-1.21
low-to-medium dose	1.1	1.1	0.97	0.95	0.77-1.19
high dose	0.4	0.3	1.52	1.44	1.01-2.06

*Continuous use for at least three months before the index date

† Adjusted for age, gender, diabetes mellitus, sytemic hypertension, use of ophthalmic, oral and nasal glucocorticoids, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

Table 6. Odds Ratios for Ocular Hypertension or Open-Angle Glaucoma According to Continuous* Use or any Other Use of Nasal Steroids

Characteristics Of Use	Cases (%) (n=9,793)	Controls (%) (n=38,325)	Crude Odds Ratio	Adjusted+ Odds Ratio	95 % CI
Nonusers	98.8	98.9	1.00	1.00	
Any use	1.0	0.9	1.06	1.09	0.87-1.37
Continuous use	0.2	0.2	1.01	1.02	0.59-1.77

* Continuous use for at least three months before the index date

+ Adjusted for age, gender, diabetes mellitus, systemic hypertension, use of ophthalmic, oral and inhaled glucocorticoids, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

3.7 Bibliography

1. Habbick, B., M.J. Baker, M. McNutt, and D.W. Cockcroft. 1995. Recent trends in the use of inhaled beta2-adrenergic agonists and inhaled corticosteroids in Saskatchewan. *Can. Med. Assoc. J.* 153:1437-1443.

2. McManus, P. and D. Birkett. 1993. Recent trends in the use of antiasthmatic drugs. *Med. J. Aust.* 159:831-832.

3. Reed, C.E. 1990. Aerosol glucocorticoid treatment of asthma. *Am. Rev. Respir. Dis.* 141 (Suppl.):S82-S88.

4. Mabry, R.L. 1992. Corticosteroids in the management of upper respiratory allergy: the emerging role of steroid nasal sprays. *Otolarngol. Head. Neck. Surg.* 107:855-860.

5. Estelle, F., R. Simons, and K.J. Simons. 1989. Optimum pharmacological management of chronic rhinitis. *Drugs* 38:313-331.

6. Opatowsky, I., R.M. Feldman, R. Gross, and S.T. Feldman. 1995. Intraocular pressure elevation associated with inhalation and nasal corticosteroids. *Ophthalmology* 102:177-179.

7. Jackson, R.V. and R.V. Bowman. 1995. Corticosteroids. *Med. J. Aust.* 162:663-665.

8. Barnes, P.J. 1995. Inhaled glucocorticoids for asthma. *N. Engl. J. Med.* 332:868-875.

9. Barnes, N.C. 1993. Safety of high-dose inhaled corticosteroids. *Resp. Med.* 87 (Suppl.A):27-31.

10. Dreyer, E.B. 1993. Inhaled steroid use and glaucoma. *N. Engl. J. Med.* 329:1822

11. Skuta, G.L. and R.K. Morgan. 1996. Corticosteroid-induced glaucoma. In The glaucomas. R. Ritch, M.B. Shields, and T. Krupin, editors. Mosby, St. Louis. 1177-1188.

12. Armaly, M.F. 1986. Corticosteroid glaucoma. In Glaucoma. J.E. Cairns, editor. Grune & Stratton, London. 697-710.

13. Tamblyn, R., G. Lavoie, L. Petrella, and J. Monette. 1995. The use of prescription claims databases in pharmacoepidemiological research: The accuracy and comprehensiveness of the prescription claims database in Quebec. *J. Clin. Epidemiol.* 48:999-1009.

14. WHO 1977. Manual of the international statistical classification of diseases, injuries, and causes of death based on the recommendations of the ninth revision conference, 1975. World Health Organization, Geneva.

15. Brogden, R.N. and D. McTavish. 1992. Budesonide. An updated review of its pharmacological properties, and therapeutic efficacy in asthma and rhinitis. *Drugs* 44:375-407.

16. Brogden, R.N., R.C. Heel, T.M. Speight, and G.S. Avery. 1992. Beclomethasone Diproprionate. A reappraisal of its pharmacodynamic properties and therapeutic efficacy after a decade of use in asthma and rhinitis. *Drugs* 28:99-126.

17. Leske, M.C. 1983. The epidemiology of open-angle glaucoma: a review. *Am. J. Epidemiol.* 118:166-191.

18. Wilson, M.R. 1990. Epidemiological features of glaucoma. *Int. Ophthalmol. Clin.* 30:153-160.

19. Gurwitz, J.H., J. Avorn, R.L. Bohn, R.J. Glynn, M. Monane, and H. Mogun. 1994. Initiation of antihypertensive treatment during nonsteroidal anti-inflammatory drug therapy. *JAMA* 272:781-786.

20. Sas Institute Inc. 1992. The PHREG procedure. In SAS technical report P-229. SAS/STAT software: changes and enhancements. Release 6.07. Sas Institute Inc. Cary. 435-479.

21. Kitazawa, Y. and T. Horie. 1981. The prognosis of corticosteroid-responsive individuals. *Arch. Ophthalmol.* 99:819-823.

22. Mygind, N. and I. Hansen. 1973. Beclomethasone dipropionate aerosol effect on the adrenals in normal persons. *Acta Allergol.* 28:211-218.

23. Wyatt, R., J. Waschek, M. Weinberger, and B. Sherman. 1978. Effects of inhaled beclomethasone dipropionate and alternate-day prednisone on pituitary-adrenal function in children with chronic asthma. *N. Engl. J. Med.* 299:1387-1392.

24. Smith, M.J. and M.E. Hodson. 1983. Effects of long-term inhaled high dose beclomethasone dipropionate on adrenal function. *Thorax* 38:676-681.

25. Ninan, T.K., I.W. Reid, P.E. Carter, P.J. Smail, and G. Russel. 1993. Effects of high doses of inhaled corticosteroids on adrenal function in children with severe persistent asthma. *Thorax* 48:599-602.

26. Pakes, G.E., R.N. Brogden, R.C. Heel, T.M. Speight, and G.S. Avery. 1980. Flunisolide: a review of its pharmacological properties and therapeutic efficay in rhinitis. *Drugs* 19:397-411.

27. Bryson, H.M. and D. Faulds. 1992. Intranasal fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in allergic rhinitis. *Drugs* 43:760-775.

28. Clissold, S.P. and R.C. Heel. 1984. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs* 28:485-518.

29. Armaly, M.F. 1963. Effect of corticosteroids on intraocular pressure and fluid dynamics. I. The effect of dexamethasone in the normal eye. *Arch. Ophthalmol.* 70:482-491.

30. Becker, B. and D.W. Mills. 1963. Corticosteroids and intraocular pressure. *Arch. Ophthalmol.* 70:500-507.

31. Kass, M.A. and T. Johnson. 1989. Corticosteroid-induced glaucoma. In The glaucomas. R. Rich, M.B. Shields, and T. Krupin, editors. C.V. Mosby Company, St.Louis. 1161-1168.

32. Hernandez, M.R., E.J. Wenk, B.I. Weinstein, P. Abumohor, S.M. Podos, M.W. Dunn, and A.L. Southren. 1983. Glucocorticoid target cells in human outflow pathway: autopsy and surgical specimens. *Invest. Ophthalmol. Vis. Sci.* 24:1612-1616.

33. Weinreb, R.N., E. Bloom, J.D. Baxter, J. Alvarado, N. Lan, J. O'Donnell, and J.R. Polansky. 1981. Detection of glucocorticoid receptors in cultured human trabecular cells. *Invest. Ophthalmol. Vis. Sci.* 21:403-407.

34. Rohen, J.W., E. Linner, and R. Witmer. 1973. Electron microscopic studies on the trabecular meshwork in two cases of corticosteroid-glaucoma. *Exp. Eye. Res.* 17:19-31.

35. Roll, P. and O. Benedikt. 1979. Elektronenoptische Untersuchung des Trabekelwerkes bei einem Kortikosteroidglaukom. *Klin. Monatsbl. Augenheilkd.* 174:421-428.

36. Francois, J. 1954. Cortisone et tension oculaire. *Ann. Oculist.* 187:805-816.

37. Butcher, J.M., M. Austin, J. McGalliard, and R.D. Bourke. 1994. Bilateral cataracts and glaucoma induced by long term use of steroid eye drops. *BMJ* 309:43

38. Goldmann, H. 1962. Cortisone glaucoma. *Arch. Ophthalmol.* 68:621-626.

39. Burde, R.M. and B. Becker. 1970. Corticosteroid-induced glaucoma and cataracts in contact lens wearers. *JAMA* 213:2075-2077.

40. Brubaker, R.F. and J.A. Halpin. 1975. Open-angle glaucoma associated with topical administraion of flurandrenolide to the eye. *Mayo Clin. Proc.* 50:322-326.

41. Frenkel, M. 1969. Blindness due to steroid induced glaucoma. *IMJ - Illinois Medical Journal* 135:160-163.

42. Armaly, M.F. 1966. Characteristics of the steroid effect on intraocular pressure and aqueous dynamics. In Drug mechanisms in glaucoma. G. Paterson, S.J.H. Miller, and G.D. Paterson, editors. J. & A.Churchill LTD, London. 191-228.

43. Sommer, A., J.M. Tielsch, J. Katz, H.A. Quigley, J.D. Gottsch, J. Javitt, and K. Singh. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch. Ophthalmol.* 109:1090-1095.

44. Dielemans, I., J.R. Vingerling, R.C. Wolfs, A. Hofman, D.E. Grobbee, and P.T. de Jong. 1994. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 101:1851-1855.

45. Pearce, N., R. Beasley, J. Crane, C. Burgess, and R. Jackson. 1995. End of the New Zealand asthma mortality epidemic. *Lancet* 345:41-44.

CHAPTER 4

CORTICOSTEROIDS AND THE RISKS OF OCULAR HYPERTENSION OR OPEN-ANGLE GLAUCOMA.

METHODOLOGIC CONSIDERATIONS IN THE CONTEXT OF A DATABASE CASE-CONTROL STUDY

4.1 Preface to the Manuscript

This manuscript presents in further detail methodologic considerations in the design of the study, some of which have already been discussed to some extent in the previous manuscripts.

One important methodologic issue was the selection of appropriate controls, i.e., the identification of the pertinent study base. As we discussed before, we deliberately chose controls among ophthalmology patients and not among all patients in the database in order to avoid misclassification and selection bias. In this third part of the study, a second group of controls was chosen randomly among all patients in the database to empirically investigate the previously discussed concerns about bias. Risk estimates for the exposure to oral, inhaled, nasal and ophthalmic glucocorticoids are presented comparing exposure in cases with that in the two control groups. Differences in these estimates are discussed in view of the conditions leading to bias. A database can provide an interesting tool to empirically investigate concerns about bias resulting from the choice of controls, since a second control group can be selected within a database at hardly any extra cost (apart from that resulting from extra programming time).

Other biases which will be discussed include confounding by indication and reverse causality bias. Use of the database will be illustrated to also further explore some of these concerns for bias.

This article will be submitted for publication and should be quoted as follows:

Garbe E, Boivin JF, LeLorier J, Suissa S. Glucocorticoids and the risk of ocular hypertension or open-angle glaucoma. Methodologic considerations in the context of a database case-control study. Unpublished manuscript. Montreal: Department of Epidemiology and Biostatistics, 1996

4.2 Abstract

In database case-control research, controls are often chosen in a way that they represent a random sample of all noncases. This choice of controls is intended to guard against selection bias. Data from a case-control study are presented to demonstrate that such a definition of controls may lead to selection bias under two conditions: (1) if the target disease has a prolonged asymptomatic clinical course and its detection depends on a specific physical examination and (2) if exposed patients have a higher likelihood of having the disease detected than unexposed patients. This paper also illustrates that a computerized database can be useful to explore empirically opportunities for bias. In the context of the study, bias resulting from the selection of controls was investigated, and other forms of bias, such as confounding by indication and reverse causality bias, are addressed.

4.3 Introduction

Large administrative health databases constitute an important tool in pharmacoepidemiologic research. They allow for study of the utilization and effects of drugs in large populations at limited cost and in reasonable time. Such databases have provided useful information about the magnitude of drug-related risks in the postmarketing surveillance of drugs. Their use complements safety information from premarketing clinical trials, since drug-related risks can be studied in the general population without the often strict inclusion criteria and limited sample sizes of clinical trials. Some databases also provide well-defined denominator information, allowing study of the incidence and burden of disease in defined populations. Use of databases in analytic epidemiologic studies is, however, not undisputed and may be limited in situations when information about important risk factors for the disease cannot be obtained (1).

A great number of analytic epidemiologic studies conducted within the setting of an computerized database employ a case-control design. In these studies, controls are often chosen randomly among all patients in the database who did not fulfill the stated inclusion and exclusion criteria of cases (2-4). The choice of randomly sampled controls is the preferred approach, since, in theory, it guards against selection bias.

In this paper, we show that randomly selected population controls do not always represent the optimal choice of control subjects in database research, especially in the investigation of the risk of diseases which have a prolonged asymptomatic clinical course. We recently conducted a database case-control study which investigated the effect of glucocorticoids on the risk of ocular hypertension or open-angle glaucoma, both of which are asymptomatic conditions until late in the disease. In the context of this study, we determined that the choice of randomly sampled controls might lead to biased risk estimates for some routes of glucocorticoid administration which led us to opt for a different control group. In the following, we will present a summary of important features of the study design and discuss some of our methodologic considerations for this study. We will also comment on the possibility for biases from reverse-causality and confounding by indication. Finally, we illustrate how a database can be useful in assessing empirically the effects of these biases.

4.4 Study Design

Background and Study Objective

The objective of the study was to investigate the risk of ocular hypertension or open-angle glaucoma associated with oral, inhaled, nasal and ophthalmic glucocorticoid use. It is well established that ophthalmic glucocorticoids may increase the risk of ocular hypertension and open-angle glaucoma (5,6). Although ocular hypertension and open-angle glaucoma have also occasionally been described following other routes of steroid administration, the risk has been less well characterized for these other forms of glucocorticoids (5).

Study Setting

The study utilized data from the provincial health insurance database in Québec, Canada, also known as RAMQ (Régie de l'assurance maladie du Québec) database. The database has been described in detail elsewhere (7). In brief, data in the records include demographic patient data with a unique patient identification code, detailed information on filled prescriptions, diagnostic and therapeutic procedures, and diagnoses according to the International Classification of Diseases, Ninth Revision (ICD-9) (8). A high level of reliability and validity of the prescription data has been demonstrated (7). The study was conducted using a 10 % random sample of the database from the years 1987 to 1994 and a 20 % random sample from the years 1990 to 1992, after excluding duplicates from both samples.

Case Definition

We defined cases as RAMQ enrollees over 66 years of age who had consulted an ophthalmologist and received either a diagnosis of ocular hypertension or glaucoma or medical or surgical treatment for these conditions. The date of the event, called the index date, was taken as the earliest of these case-defining events. Only incident cases were considered, i.e. cases were required to have been enrolled in the database for at least one year without being a case. Medications for ocular hypertension and glaucoma included the following drug categories: topical betablockers, topical parasympathomimetics, topical alpha agonists and carboanhydrase inhibitors. ICD-9 codes for the case definition included the codes for borderline glaucoma (including ocular hypertension), open-angle glaucoma and unspecified glaucoma. Patients with a diagnosis of angle-closure or secondary glaucoma were excluded from the case and control samples.

Control Definition

We selected controls in two different ways: from the entire population and from those subjects who consulted an ophthalmologist. For the latter sample, control patients were randomly selected among subjects who had visited an ophthalmologist in the same month and year as the case without fulfilling the case definition ('ophthalmology controls'). The date of the visit to the ophthalmologist was set as the index date.

The other control group, chosen to empirically investigate concerns about biases, was selected among all subjects without restriction to ophthalmologist consultations ('general population controls'). General population controls were subjects who had obtained a prescription in the same index month and year as a case without fulfilling the case criteria. The date of the prescription was set as the index date.

Controls were matched to cases on the index month and year to account for seasonal and secular trends in medication. Up to 4 controls were matched to each case in both control groups.

For reasons of simplicity, we will refer to the study sample with ophthalmology controls as 'ophthalmology sample' and to that with general population controls as 'general population sample'.

Glucocorticoid Exposure

We focussed in our study on current use of glucocorticoids, since ocular hypertension in most instances is reversible after glucocorticoid withdrawal. Current users of glucocorticoids were defined as patients who were exposed at the index date or whose drug supply with the respective glucocorticoid continued into the 14-day period before the index date. In this definition, the date of dispensation of the glucocorticoid had to precede the index date.

To address a concern about reverse causality bias for ophthalmic corticosteroids, we also investigated glucocorticoid use by modifying the definition of current exposure. In the modified definition, current users were patients as defined above, with the exception that the date of dispensation did not have to precede the index date, but could fall on the same day as the index date.

Covariates

Covariates included age, gender, systemic hypertension, diabetes mellitus, and selected characteristics of health care system use in the 365 days before the index date. Systemic hypertension and diabetes mellitus have both been described as risk factors for the development of ocular hypertension and open-angle glaucoma. The following health care system use characteristics were investigated: number of prescriptions filled for all drugs, number of patient-specific physician claims for services, and number of days hospitalized. These health care utilization variables were included as markers for general ill health.

Statistical Analysis

We estimated the relative risk for ocular hypertension or open-angle glaucoma for each form of glucocortiocoid exposure from odds ratios calculated by conditional logistic regression (9). For these analyses, the reference category was the absence of exposure to the respective glucocorticoid. All models simultaneously controlled for the different routes of corticosteroid administration and the covariates listed above. All two-tailed p values less than .05 were considered significant and 95 % confidence intervals were calculated for all relative risks.

4.5 Results

The final case group included 9,793 patients. As controls, 38,325 patients were identified for the ophthalmology control sample and 38,887 patients for the general population control sample. The two control samples showed different characteristics with respect to demographic variables and the covariates measured (Table 1). Cases tended to be more similar in their characteristics to ophthalmology controls than to general population controls. General population controls were younger than ophthalmology controls and included a higher percentage of males. Fewer of them had received treatment for diabetes mellitus and they had made less use of the health care system in the year before the index date, as indicated by the variables measured.

Crude and adjusted odds ratios for the different routes of glucocorticoid administration are presented in Table 2 (ophthalmology sample) and Table 3 (general population sample). For ophthalmic glucocorticoids, we observed a striking difference in the magnitude of the risk estimate in both study samples. The adjusted odds ratio was 1.67 (95 % CI, 1.50 to 1.86) in the ophthalmology sample and 8.00 (95 % CI, 6.82 to 9.32) in the general population sample. Use of nasal glucocorticoids was also associated with different risk estimates in both study samples. The adjusted odds ratio for nasal glucocorticoids was 1.08 (95 % CI, 0.88 to 1.33) in the ophthalmology sample and 1.35 (95 % CI, 1.08 to 1.68) in the general population sample. No difference in risk was observed for oral glucocorticoids, with an adjusted odds ratio of 1.40 in both samples. For inhaled glucocorticoids, we observed a risk of similar magnitude in both samples. The adjusted odds ratio for this route of administration was 1.02 (95 % CI, 0.89 to 1.18) in the ophthalmology sample and 0.96 (95 % CI, 0.83 to 1.10) in the general population control sample.

In Table 4, we demonstrate crude and adjusted odds ratios for current exposure to all forms of glucocorticoids for the original and modified definition of current use. For oral, inhaled and nasal glucocorticoids, the risk estimates were very similar for both exposure definitions. We observed a marked difference in the risk estimate for ophthalmic

glucocorticoids according to the exposure definition used. The adjusted odds ratio was 1.67 (95 % CI, 1.50 to 1.86) if the last glucocorticoid dispensation preceded the index date and 3.08 (95 % CI, 2.86 to 3.33) if the last dispensation fell on the same date as the index date.

4.6 Methodologic Considerations

The two control groups differed with respect to age and gender distribution, the prevalence of diabetes mellitus and health care utilization in the year before the index date, indicating that ophthalmology controls are not representative of the population as a whole. The higher percentage of diabetic patients in ophthalmology controls reflects the association of diabetes mellitus with a variety of ocular diseases. The observed differences in demographic factors and other covariates between the two control groups are not of concern with respect to bias, since we adjusted for these variables in our analysis. In the general population sample, we observed a higher risk of ocular hypertension or open-angle glaucoma with increasing age, in female patients and in patients with diabetes mellitus. These observations are in agreement with results obtained in other population-based studies (10).

4.6.1 Choice of Controls

The risk estimate for ophthalmic glucocorticoids and to a lesser degree for nasal glucocorticoids varied according to the choice of controls. In sampling a second control group from the general population, we were testing a hypothesis about bias that depended on two considerations: 1) that a majority of cases of ocular hypertension or open-angle glaucoma are asymptomatic and detected during ophthalmologist visits only and 2) that the rate of ophthalmologic surveillance is higher in patients exposed to ophthalmic glucocorticoids than in a non-exposed control group. A higher rate of referral of exposed

patients to ophthalmologists will lead to increased detection of the outcome and inflate the risk estimate when not accounted for by proper choice of a control group.

It is well recognized that open-angle glaucoma has an insidious onset and is usually asymptomatic until late in the disease (11-13). Large population-based screening surveys have shown that about 50 % of all patients with open-angle glaucoma are not aware of having the disease (14,15). Most cases of ocular hypertension and open-angle glaucoma will be diagnosed during ophthalmologist visits, since special equipment and expertize are needed to diagnose these conditions. Intraocular pressure measurements will usually be routinely performed in elderly patients who consult an ophthalmologist. It is recommended that intraocular pressure values be monitored in patients receiving ophthalmic glucocorticoids, in order to detect ocular hypertension as a side effect of these drugs (5,12,13).

In case-control studies, controls should be selected in such a way that cases and controls are 'representative of the same base experience' (16). We believe that the study base of our study are not all patients in the database, but only patients with ophthalmologist consultations, due to the asymptomatic nature of the outcome condition. In his review on control selection in case-control studies, Wacholder addresses this problem: 'When the probability of case identification among members of a primary base depends on a variable, the study base principle is violated and there can be selection bias, unless control selection depends proportionally on values of that variable' (17). In our study, this variable is the ophthalmologist visit, since diagnosis of the case status in our study usually requires a visit to an ophthalmologist. Thus, controls should equally be selected as patients with ophthalmologist consultations to satisfy the study base principle. Identification of the appropriate study base in our study is a prerequisite to help avoid selection bias, which will otherwise result from selective ophthalmologic surveillance of exposed patients.

A similar opportunitiy for selection bias has been described by Horwitz and Feinstein in studies investigating the association of estrogens and endometrial cancer (18). Although they did not refer to it in terms of the 'study base principle', Horwitz and Feinstein arrived

at a similar conclusion for the selection of controls in their study. They referred to the resulting bias as 'detection bias' and stated that this form of bias 'will arise whenever a target disease that can occur in asymptomatic or other subclinical forms is likely to be preferentially diagnosed in persons exposed to the alleged etiologic agent'. To compensate for the bias in the case group they suggested that controls should have an opportunity 'to have received the same type of selection' as cases.

The elevated risk estimate for nasal glucocorticoids in the general population sample appears to be due to the same mechanism that we proposed for ophthalmic glucocorticoids. Nasal glucocorticoids are often prescribed for seasonal allergic rhinitis, a condition which is frequently accompanied by ocular symptoms, such as itching, erythema and tearing of the eyes. As a consequence, these patients may be referred to ophthalmologists more often than control patients, resulting in preferential ophthalmologic surveillance in exposed patients and leading to an inflated association between nasal glucocorticoid use and the outcome. The difference in risk estimates between both samples was much smaller for nasal glucocorticoids than for ophthalmic glucocorticoids. This may be due to the fact that only some of the patients on nasal steroids will be referred for ophthalmologic control investigation, whereas we believe that the control rate is much higher in patients treated with ophthalmic glucocorticoids. Nasal glucocorticoids are not prescribed for allergic rhinitis alone, but may also be prescribed for other conditions which are not necessarily associated with ocular symptoms. Among patients treated with nasal glucocorticoids for allergic rhinitis, only a certain percentage will suffer from ocular symptoms and of those, only some will be referred to ophthalmologists.

For oral and inhaled glucocorticoids, we observed a very similar risk in both study samples. As explained above, selection bias in our study resulted from a combination of two conditions: an asymptomatic target disease and preferential surveillance of exposed study subjects. We believe that the latter condition was not met for patients receiving inhaled and oral glucocorticoids. There was no reason to believe that patients receiving inhaled glucocorticoids for asthma should be referred to ophthalmologists more often than other patients. Although an association between oral glucocorticoids and ocular

hypertension had occasionally been reported, nonophthalmologists are usually not sufficiently aware of this possible side effect so that it may not have had impact on referral pattern (12). The exposure to oral and inhaled glucocorticoids may therefore serve to illustrate the need for both conditions to produce bias. In the absence of preferential surveillance of exposed subjects, the similar results in the general population and ophthalmology study sample also serve to illustrate the validity of the latter.

4.6.2 Confounding by Indication

Confounding by indication can occur when the effect of a drug cannot be separated from the effect of a disease for which the drug is described. It is believed that confounding by indication is usually less of a problem in studies focussing on side effects of drugs, but more so in studies investigating intended effects (19). Although less common, confounding by indication may also present a problem in the study of unintended drug effects. In the context of our study example, confounding by indication cannot be excluded in the risk estimate for ophthalmic steroids. Ophthalmic steroids are commonly prescribed for inflammatory diseases of the anterior chamber of the eye. As a complication of these diseases, ocular hypertension and glaucoma may develop, resulting from inflammation of the trabecular meshwork of the eye or from scarring and formation of synechiae leading to outflow obstruction of the aqueous humor (20). In the context of a database study, it is not feasible to separate corticosteroid-induced ocular hypertension from ocular hypertension caused by inflammation of the eye and thus to eliminate completely concerns about confounding by indication. Confounding by indication would lead to an exaggerated risk estimate for ophthalmic steroid use. Based on the evidence from clinical studies and case reports it is usually believed that ophthalmic steroids carry a higher risk for ocular hypertension and open-angle glaucoma than oral steroids (5,21,22). This belief also appears biologically plausible, since the bioavailability of the steroid in the eye is expected to be greater after ophthalmic than after oral dosing. The data of our study show a higher risk estimate for ophthalmic than for oral steroids, although the difference in the risk for both routes of administration was trivial. The similarity of the risk estimates

for both routes of administration indicates that concerns about bias as a consequence of confounding by indication might be a lesser problem for ophthalmic steroids than theoretically anticipated.

Oral steroids are used in a great variety of diseases, some of which may also involve the eyes. It is well recognized that rheumatic disorders which are frequently treated with oral glucocorticoids may be accompanied by inflammatory disorders of the eyes. Although ocular hypertension and open-angle glaucoma are not a primary manifestation of these diseases, they may develop as a complication of the eye inflammation, as has been discussed for ophthalmic steroids. To exclude confounding by indication for oral steroid use, we calculated the odds ratio for oral steroids in all patients who had received the dispensation of an oral steroid in conjunction with a diagnosis indicating pulmonary problems as e.g. asthma, emphysema and chronic obstructive bronchitis, since we considered these diseases as unrelated to ocular disease. The odds ratio for oral glucocorticoids in these patients was 1.39 (95 % CI, 1.02 to 1.89) which was almost the same as that obtained for all oral glucocorticoid users. Therefore confounding by indication for oral glucocorticoids did not appear to represent a problem in our study sample.

4.6.3 Reverse Causality Bias

We observed a marked difference in the risk estimate for ophthalmic glucocorticoids, depending on whether the date of the last dispensation had to precede the index date or whether it could fall on the same date as the index date. Allowing the date of the last dispensation to include the index date almost doubled the risk estimate for ophthalmic steroids. We believe that this difference in risk estimates is due to reverse causality bias (23), a bias which has also been referred to as 'protopathic bias' by Feinstein (24). This form of bias occurs when cause and effect are being confused. It is mostly thought of as a problem of prevalence studies where it may occasionally be difficult to decide whether the exposure under study preceded the outcome or was instituted as a consequence of the

outcome (23,25). In the case of our study example, treatment with ophthalmic corticosteroids may be initiated in certain cases to treat ocular hypertension. Treatment with ophthalmic corticosteroids, or with ophthalmic corticosteroids in conjunction with intraocular pressure-lowering drugs, is indicated when ocular hypertension has developed as a complication of an inflammatory process in the eye (20). Antiinflammatory medication in these cases constitutes a causal treatment against ocular hypertension, whereas the accompanying glaucoma treatment is aimed to induce a rapid normalization of ocular pressure values. To minimize concerns about reverse causality bias, it is crucial to define exposure in such a way that it clearly precedes the outcome under study. Although we sampled incident cases in our study, reverse causality bias may occur if the temporal relationship of exposure and outcome is neglected. As we have demonstrated, inclusion or exclusion of one day in the exposure definition may change the risk estimate in an important way. In our study, reverse-causality bias was only of concern for ophthalmic corticosteroids. No important differences were seen in the risk estimates for the other routes of steroid administration applying both exposure definitions.

4.7 Conclusion

Choosing a control group for a case-control study from all individuals in the source population that produced the cases has been described as the simplest way to satisfy the study base principle (26). In database case-control research, the entire database usually serves as a source from which controls are randomly selected, since cases are equally identified from this population. This approach of control selection is valid in most instances, but caution is needed when investigating the risk of diseases with a prolonged asymptomatic clinical course. Although cases are still identified among all subjects in the database, they no longer represent as base experience all subjects, but only subjects who had an opportunity of having the disease diagnosed. Accordingly, controls will have to be drawn from this source population and can no longer be selected randomly among all subjects in the database. Serious selection bias may result if exposed patients are preferentially diagnosed and controls are not selected from the appropriate study base. In

our study example, we identified as source population for cases and controls subjects with visits to ophthalmologists, since ophthalmologist visits are usually a prerequisite to have ocular hypertension and glaucoma diagnosed. For glucocorticoid exposures that were not associated with increased ophthalmologic monitoring, the risk estimates were similar in both study samples, characterizing preferential surveillance of exposed subjects as a second necessary condition for the occurrence of selection bias in the study setting. Our example illustrates that a database may also serve to empirically explore concerns about biases.

Table 1. Characteristics of Cases and Controls*

Characteristic	CASES % (n=9,793)	OPHTHALMOLOGY CONTROLS % (n=38,325)	GEN. POPULATION CONTROLS % (n=38,887)
Age			
65-69	23.5	25.7	28.0
70-74	29.7	29.5	30.3
75-84	38.9	36.4	33.3
≥85	8.0	8.4	8.4
Gender			
Male	34.5	37.9	41.5
Female	65.5	62.1	58.5
Diabetes treated with			
Oral antidiabetics	10.5	11.1	9.3
Insulin	2.4	2.9	1.9
Systemic hypertension	56.8	55.7	56.2
Health care utilization in the year preceding the index date			
No. of prescriptions			
≤15	33.9	34.6	34.8
16 - 30	22.5	21.6	23.1
> 30	43.6	43.8	42.1
No. of physician claims			
≤10	38.5	41.4	52.4
11-20	33.7	30.6	24.8
> 20	27.8	27.9	22.8
No. of days hospitalized			
0	64.7	67.9	72.1
1-15	28.5	23.3	19.3
> 15	6.8	8.8	8.6

* Percentages may not equal 100 due to rounding

Table 2. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma According to Route of Corticosteroid Administration (Ophthalmology Sample)*

Route of Steroid	Cases (%)† (n=9,793)	Controls (%)† (n=38,325)	Crude Odds Ratio	Adjusted** Odds Ratio	95 % CI
Nonusers	89.0	92.0	1.00	1.00	
Ophthalmic	5.3	3.1	1.73	1.67	1.50-1.86
Oral	2.7	1.9	1.43	1.40	1.21-1.62
Nasal	2.9	2.7	1.06	1.08	0.88-1.33
Inhaled	1.2	1.1	1.07	1.02	0.89-1.18

* Exposure: current use of the respective glucocorticoid

† Percentages may exceed 100 due to concomitant intake of more than one form of steroid

** Adjusted for age, gender, diabetes mellitus, systemic hypertension, current use of the other glucocorticoids listed, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

Table 3. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma According to Route of Glucocorticoid Administration (General Population Sample)*

Route of Steroid	Cases (%)[+] (n=9,793)	Controls (%)[+] (n=38,887)	Crude Odds Ratio	Adjusted** Odds Ratio	95 % CI
Nonusers	89.0	94.6	1	1	
Ophthalmic	5.3	0.6	8.91	8.00	6.82-9.32
Oral	2.7	1.8	1.54	1.40	1.20-1.62
Nasal	1.2	0.9	1.38	1.35	1.08-1.68
Inhaled	2.9	2.7	1.06	0.96	0.83-1.10

*Exposure: current use of the respective glucocorticoid

[+] Percentages may exceed 100 due to concomitant intake of more than one form of steroid

**Adjusted for age, gender, diabetes mellitus, systemic hypertension, current use of the other glucocorticoids listed, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

Table 4. Odds Ratios of Ocular Hypertension or Open-Angle Glaucoma Excluding or Including the Index Date as Date of last Dispensation (Ophthalmology Sample)*

Route of Steroid	Excluding Index Date		Including Index Date	
	Crude Odds Ratio	Adjusted~ Odds Ratio (95% CI)	Crude Odds Ratio	Adjusted~ Odds Ratio (95% CI)
Ophthalmic	1.73	1.67 (1.50; 1.86)	3.14	3.08 (2.86; 3.33)
Oral	1.43	1.40 (1.21; 1.62)	1.44	1.41 (1.22; 1.63)
Nasal	1.06	1.08 (0.88; 1.33)	1.05	1.10 (0.89; 1.35)
Inhaled	1.07	1.02 (0.89; 1.18)	1.08	1.02 (0.88; 1.17)

* Exposure: current use of the respective glucocorticoid

~ Adjusted for age, gender, diabetes mellitus, systemic hypertension, current use of the other glucocorticoids listed, number of prescriptions, number of physician claims, and hospitalization during the last year before the index date

4.8 Bibliography

1. Shapiro, S. 1989. The role of automated record linkage in the postmarketing surveillance of drug safety: A critique. *Clin. Pharm. Ther.* 46:371-386.

2. Gurwitz, J.H., R.L. Bohn, R.J. Glynn, M. Monane, H. Mogun, and J. Avorn. 1994. Glucocorticoids and the risk for initiation of hypoglycemic therapy. *Arch. Intern. Med.* 154:97-101.

3. Gurwitz, J.H., R.L. Bohn, R.J. Glynn, M. Monane, H. Mogun, and J. Avorn. 1993. Antihypertensive drug therapy and the initiation of treatment for diabetes mellitus. *Ann. Intern. Med.* 118:273-278.

4. Avorn, J., R.L. Bohn, H. Mogun, J.H. Gurwitz, M. Monane, D. Everitt, and A. Walker. 1995. Neuroleptic drug exposure and treatment of parkinsonism in the elderly: A case-control study. *Am. J. Med.* 99:48-54.

5. Skuta, G.L. and R.K. Morgan. 1996. Corticosteroid-induced glaucoma. In The glaucomas. R. Ritch, M.B. Shields, and T. Krupin, editors. Mosby, St. Louis. 1177-1188.

6. Palmberg, P.F., A. Mandell, J.T. Wilensky, S.M. Podos, and B. Becker. 1975. The reproducibility of the intraocular pressure response to dexamethasone. *Am. J. Ophthalmol.* 80:844-856.

7. Tamblyn, R., G. Lavoie, L. Petrella, and J. Monette. 1995. The use of prescription claims databases in pharmacoepidemiological research: The accuracy and comprehensiveness of the prescription claims database in Quebec. *J. Clin. Epidemiol.* 48:999-1009.

8. WHO 1977. Manual of the international statistical classification of diseases, injuries, and causes of death based on the recommendations of the ninth revision conference, 1975. World Health Organization, Geneva.

9. Sas Institute Inc. 1992. The PHREG procedure. In SAS technical report P-229. SAS/STAT software: changes and enhancements. Release 6.07. Sas Institute Inc. Cary. 435-479.

10. Leske, M.C. 1983. The epidemiology of open-angle glaucoma: a review. *Am. J. Epidemiol.* 118:166-191.

11. Quigley, H.A. 1993. Open-angle glaucoma. *N. Engl. J. Med.* 328:1097-1106.

12. Kass, M.A. and T. Johnson. 1989. Corticosteroid-induced glaucoma. In The glaucomas. R. Rich, M.B. Shields, and T. Krupin, editors. C.V. Mosby Company, St. Louis. 1161-1168.

13. Hodapp, E.A. and M.A. Kass. 1982. Corticosteroid-induced glaucoma. In The secondary glaucomas. R. Rich and M.B. Shields, editors. C. V. Mosby Comp. St. Louis. 258-265.

14. Sommer, A., J.M. Tielsch, J. Katz, H.A. Quigley, J.D. Gottsch, J. Javitt, and K. Singh. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch. Ophthalmol.* 109:1090-1095.

15. Dielemans, I., J.R. Vingerling, R.C. Wolfs, A. Hofman, D.E. Grobbee, and P.T. de Jong. 1994. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 101:1851-1855.

16. Miettinen, O.S. 1985. The 'case-control' study: valid selection of subjects. *J. Chron. Dis.* 38:543-548.

17. Wacholder, S., D.T. Silverman, J.K. McLaughlin, and J.S. Mandel. 1992. Selection of controls in case-control studies. II. Types of controls. *Am. J. Epidemiol.* 135:1029-1041.

18. Horwitz, R.I. and A.R. Feinstein. 1978. Alternative analytic methods for case-control studies of estrogens and endometrial cancer. *N. Engl. J. Med.* 299:1089-1094.

19. Strom, B.L. and K.L. Melmon. 1994. The use of pharmacoepidemiology to study beneficial drug effects. In Pharmacoepidemiology. B.L. Strom, editor. John Wiley & Sons, Chichester. 449-467.

20. Shields, M.B. 1992. Glaucomas associated with ocular inflammation. In Textbook of glaucoma. M.B. Shields, editor. Williams & Wilkins, Baltimore. 356-373.

21. David, D.S. and J.S. Berkowitz. 1969. Ocular effects of topical and systemic corticosteroids. *Lancet* 2:149-151.

22. Grant, W.M. 1969. Ocular complications of drugs. Glaucoma. *JAMA* 207:2089-2091.

23. Kramer, M.S. 1988. Clinical Epidemiology and Biostatistics. Springer-Verlag, Heidelberg.

24. Feinstein, A.R. 1985. Clinical Epidemiology: The architecture of clinical research. W. B. Saunders, Philadelphia.

25. Collet, J.P., J.F. Boivin, and W.O. Spitzer. 1994. Bias and confounding in pharmacoepidemiology. In Pharmacoepidemiology. B.L. Strom, editor. J. Wiley & Sons, Chichester. 609-627.

26. Wacholder, S., J.K. McLaughlin, D.T. Silverman, and J.S. Mandel. 1992. Selection of controls in case-control studies: I. Principles. *Am. J. Epidemiol.* 135:1019-1028.

CHAPTER 5

SUMMARY AND CONCLUSION

This is the first population-based study that quantified the risk of ocular hypertension or open-angle glaucoma associated with exposure to oral, inhaled and nasal glucocorticoids. Its large sample size of 9,793 cases and 38,325 controls made it possible to analyse the influence of the dose and duration of treatment for each of these routes of glucocorticoid administration, while simultaneously adjusting for several important risk factors.

Exposure to oral glucocorticoids increased the risk of ocular hypertension or open-angle glaucoma. The magnitude of the risk was directly related to the steroid dose, with an increase in risk following higher oral glucocorticoid doses. A similar dose-response relationship had been demonstrated for ophthalmic glucocorticoids in a prospective clinical trial (1). High doses of oral glucocorticoids, defined by an equivalent of 80 mg of hydrocortisone per day or more, presented a risk of similar magnitude as that observed for ophthalmic glucocorticoids. The systemic bioavailability is usually high for oral glucocorticoids, ranging from around 70 % for betamethasone, to 80 % for dexamethasone and methylprednisolone, to 98 % for prednisone (2). A considerable portion of the glucocorticoid will therefore reach the eye after oral ingestion.

An increased risk of the outcome was already apparent in the first months of treatment with oral glucocorticoids, suggesting that the required exposure period may be similar for oral and ophthalmic glucocorticoids. Some authors believe that oral glucocorticoids need to be administered longer than ophthalmic glucocorticoids in order to induce ocular hypertension (3,4). This assumption appears to be based on a number of clinical case reports in which ocular hypertension was described only after months or years of exposure to oral glucocorticoids (5-8). The patients in these reports did, however, not have routine tonometric investigations which was the case in studies examining the required exposure

period for ophthalmic glucocorticoids. The detection of ocular hypertension may therefore have been delayed due to its insidious course, giving rise to the impression of longer exposure periods for oral glucocorticoids.

The risk of ocular hypertension or open-angle glaucoma increased over the first 11 months of continuous exposure to oral glucocorticoids, but no further increase in risk was observed for 12 (or more) months, although the risk remained elevated. The previous clinical studies which investigated the risk of ocular hypertension for ophthalmic glucocorticoids only examined shorter exposure periods, usually in the range of four to eight weeks. In these studies, the pressure rise did not seem to have reached its maximum at the end of the study in some of the patients (9). This observation points to the possibility that the risk may still be increasing in the first months of treatment.

The risk was only significantly increased in patients who had received oral glucocorticoids in the last 14 days before the index date. This finding corresponds to results obtained for ophthalmic glucocorticoids which suggest that the intraocular pressure elevation induced by ophthalmic glucocorticoids is usually reversible within two weeks of discontinuation of the steroid treatment (9,10) and confirms isolated clinical observations for oral glucocorticoids on a large population-based scale.

Exposure to inhaled and nasal glucocorticoids, without taking into account dose or duration of treatment was not associated with an elevated risk of ocular hypertension or open-angle glaucoma. However, patients who had been exposed to high doses of inhaled glucocorticoids for at least three months presented a significantly increased risk. This latter result is consistent with pharmacologic studies which have measured adrenocortical suppression as a marker for the possibility of systemic effects. A recent review of these studies concluded that only high doses of inhaled steroids suppress adrenocortical function (11).

No increase in risk was observed for high doses of nasal glucocorticoids. Nasal glucocorticoids are usually given in much lower doses than inhaled glucocorticoids and

the sparse pharmacologic data available suggest that these lower doses do not lead to suppression of adrenocortical function (12-14). Only few patients had been continuously exposed to nasal steroids for three or more months, and no elevated risk was seen for this exposure category. Contrary to inhaled steroids, which are often used in asthma over extended periods of time, nasal steroids were rarely used for longer treatment periods, reflecting the limited treatment duration in seasonal allergic rhinitis, one of its major treatment indications. The effect of prolonged high dose exposure to nasal steroids could not be evaluated in this study, since too few patients belonged to this exposure category.

An important methodologic consideration in this study was the choice of study subjects who were defined as patients with ophthalmologist visits. This choice was largely motivated by the prolonged asymptomatic clinical course of ocular hypertension and open-angle glaucoma. As a consequence of this asymptomatic course, the disease often remains undiagnosed, as has been shown in several population surveys (15-18). Most cases of ocular hypertension and open-angle glaucoma will be diagnosed on the occasion of ophthalmologist visits, since only ophthalmologists usually have the diagnostic tools and expertise to diagnose these conditions. In case-control studies, cases and controls should be representative of the same base experience. Since in this study case identification usually depended on a visit to an ophthalmologist, control selection should equally depend on this variable, not to violate the study base principle. Ophthalmology patients were therefore identified as the source population for cases and controls. In order to examine empirically the bias resulting from a violation of the study base principle, a second group of controls was randomly sampled from the database which was not required to have consulted an ophthalmologist. It was demonstrated that serious selection bias results if the study base principle is violated and exposed patients are more likely to be examined by an ophthalmologist.

Preferential ophthalmologic surveillance was of concern for the exposure to ophthalmic and nasal glucocorticoids. For ophthalmic glucocorticoids, monitoring of intraocular pressure is recommended during extended administration (19-21). For nasal steroids, no recommendations exist as to routine intraocular pressure monitoring; however, patients

treated with these drugs for seasonal allergic rhinitis may suffer from accompanying ocular symptoms which in turn may lead to a referral to an ophthalmologist. The results differed for both routes of glucocorticoid administration according to the choice of the control group, with a positive bias resulting from the selection of nonophthalmology controls. This difference in the risk estimates was large for the exposure to ophthalmic glucocorticoids and smaller for that to nasal glucocorticoids, corresponding to the fact that the difference in the intensity of ophthalmologic surveillance between exposed and unexposed patients is probably much higher for the former than for the latter exposure. For oral and inhaled glucocorticoids, a similar risk estimate was observed in both study samples. Preferential intraocular pressure monitoring in the exposed was of lesser concern for these two forms of glucocorticoids. The similarity of the estimates of the relative risk for these two forms of glucocorticoids indicates that in our study setting two conditions had to be met in order to produce bias: violation of the study base principle in defining the source population for an asymptomatic target disease and preferential surveillance of exposed patients.

Other potential biases included confounding by indication and reverse causality bias. Ophthalmic glucocorticoids are often prescribed for the treatment of inflammatory conditions of the eye, whereas oral glucocorticoids may be used in the treatment of diseases which are accompanied by ocular inflammation. Inflammation of the eye may lead to ocular hypertension and secondary open-angle glaucoma as a complication of the disease, thus giving rise to the concern about confounding by indication for these two routes of steroid administration. For oral glucocorticoids, this concern was addressed by estimating the risk only in patients with pulmonary diseases which were considered unrelated to ocular inflammation. The observed similarity of the risk estimate between this subgroup and that in all patients indicated that for oral glucocorticoids confounding by indication was not a major problem. The slightly higher risk for exposure to ophthalmic glucocorticoids than for oral glucocorticoids appeared biologically plausible based on the assumed greater bioavailability of ophthalmic steroids in the eye. Since this risk estimate was still fairly similar to that observed for oral glucocorticoids, concerns about an inflated

risk estimate for ophthalmic steroids as a consequence of confounding by indication appeared to be a lesser problem than theoretically anticipated.

It was demonstrated that for ophthalmic glucocorticoids reverse causality bias may result if the date of the last dispensation did not clearly precede the index date. Ophthalmic glucocorticoids may be initiated as a treatment for ocular hypertension when this occurs as a complication of an inflammatory process in the eye. Allowing the date of the last dispensation to include the index date almost doubled the risk estimate for ophthalmic glucocorticoids; however, no relevant change was observed in the risk of the other forms of glucocorticoids.

Based on the results of this study, intraocular pressure monitoring appears warranted in patients using oral or high doses of inhaled glucocorticoids on a regular basis. Use of these drugs should be routinely verified in newly detected cases of ocular hypertension or open-angle glaucoma. This study also demonstrates the importance of identifying the adequate study base in case-control research of diseases with a prolonged asymptomatic clinical course.

5.1 Bibliography

1. Kitazawa, Y. 1976. Increased intraocular pressure induced by corticosteroids. *Am. J. Ophthalmol.* 82:492-495.

2. Clark, W.G., D.C. Brater, and A.R. Johnson. 1992. Pharmacokinetic characteristics of drugs. In Goth's medical pharmacology. W.G. Clark, D.C. Brater, and A.R. Johnson, editors. C. V. Mosby, St. Louis. 773-792.

3. Abel, R. and I.H. Leopold. 1987. Ocular diseases. In Avery's drug treatment. Principles and practice of clinical pharmacology and therapeutics. T.M. Speight, editor. Adis, Auckland. 387-417.

4. David, D.S. and J.S. Berkowitz. 1969. Ocular effects of topical and systemic corticosteroids. *Lancet* 2:149-151.

5. Alfano, J.E. 1963. Changes in the intraocular pressure associated with systemic steroid therapy. *Am. J. Ophthalmol.* 56:245-247.

6. Covell, L.L. 1958. Glaucoma induced by systemic steroid therapy. *Am. J. Ophthalmol.* 45:108-109.

7. Williamson, J., R.W. Paterson, D.D. McGavin, M.K. Jasani, J.A. Boyle, and W.M. Doig. 1969. Posterior subcapsular cataracts and glaucoma associated with long-term oral corticosteroid therapy. In patients with rheumatoid arthritis and related conditions. *Br. J. Ophthalmol.* 53:361-372.

8. Harris, J.L. 1960. Glaucoma associated with steroid therapy and atopic dermatitis. *Am. J. Ophthalmol.* 49:351-353.

9. Armaly, M.F. 1986. Corticosteroid glaucoma. In Glaucoma. J.E. Cairns, editor. Grune & Stratton, London. 697-710.

10. Becker, B. and D.W. Mills. 1963. Corticosteroids and intraocular pressure. *Arch. Ophthalmol.* 70:500-507.

11. Barnes, P.J. 1995. Inhaled glucocorticoids for asthma. *N. Engl. J. Med.* 332:868-875.

12. Pakes, G.E., R.N. Brogden, R.C. Heel, T.M. Speight, and G.S. Avery. 1980. Flunisolide: a review of its pharmacological properties and therapeutic efficay in rhinitis. *Drugs* 19:397-411.

13. Bryson, H.M. and D. Faulds. 1992. Intranasal fluticasone propionate. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic potential in allergic rhinitis. *Drugs* 43:760-775.

14. Clissold, S.P. and R.C. Heel. 1984. Budesonide. A preliminary review of its pharmacodynamic properties and therapeutic efficacy in asthma and rhinitis. *Drugs* 28:485-518.

15. Danyluk, A.W. and D. Paton. 1991. Diagnosis and management of glaucoma. *Clin. Symp.* 43:2-32.

16. Sommer, A., J.M. Tielsch, J. Katz, H.A. Quigley, J.D. Gottsch, J. Javitt, and K. Singh. 1991. Relationship between intraocular pressure and primary open angle glaucoma among white and black Americans. The Baltimore Eye Survey. *Arch. Ophthalmol.* 109:1090-1095.

17. Dielemans, I., J.R. Vingerling, R.C. Wolfs, A. Hofman, D.E. Grobbee, and P.T. de Jong. 1994. The prevalence of primary open-angle glaucoma in a population-based study in The Netherlands. The Rotterdam Study. *Ophthalmology* 101:1851-1855.

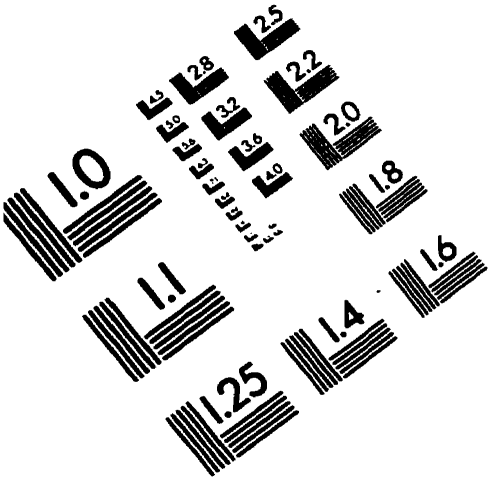
18. Hollows, F.C. and P.A. Graham. 1966. Intraocular pressure, glaucoma and glaucoma suspects in a defined population. *Br. J. Ophthalmol.* 50:570-586.

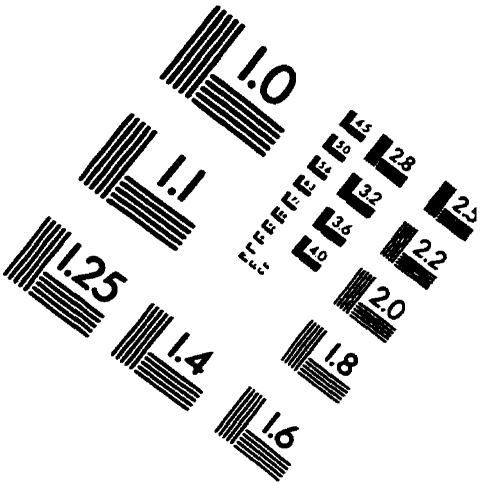
19. Skuta, G.L. and R.K. Morgan. 1996. Corticosteroid-induced glaucoma. In The glaucomas. R. Ritch, M.B. Shields, and T. Krupin, editors. Mosby, St. Louis. 1177-1188.

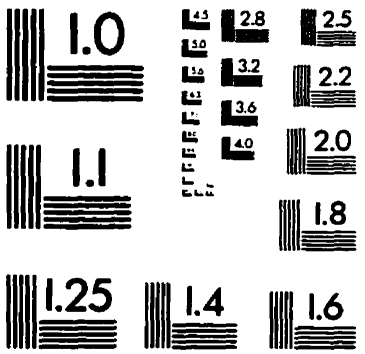
20. Kass, M.A. and T. Johnson. 1989. Corticosteroid-induced glaucoma. In The glaucomas. R. Rich, M.B. Shields, and T. Krupin, editors. C. V. Mosby Company, St. Louis. 1161-1168.

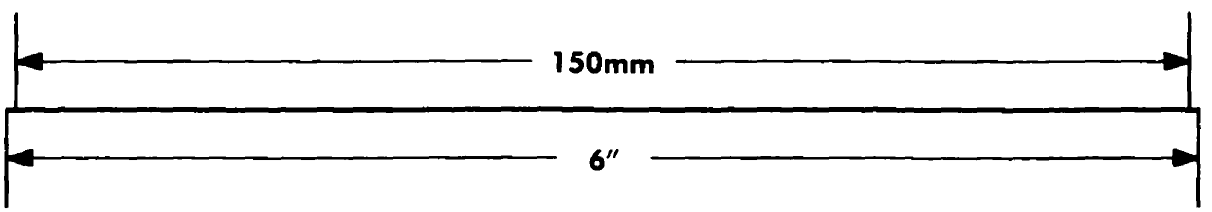
21. Hodapp, E.A. and M.A. Kass. 1982. Corticosteroid-induced glaucoma. In The secondary glaucomas. R. Rich and M.B. Shields, editors. C. V. Mosby Comp. St. Louis. 258-265.

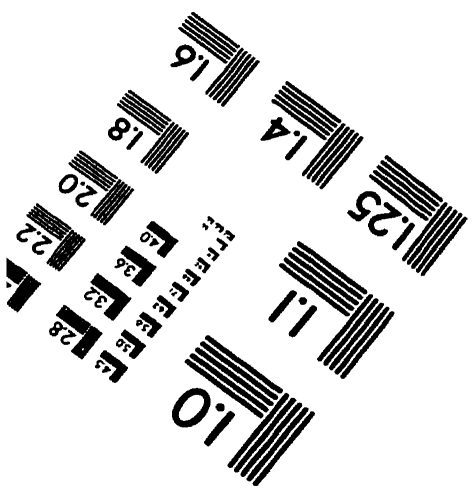
IMAGE EVALUATION TEST TARGET (QA-3)

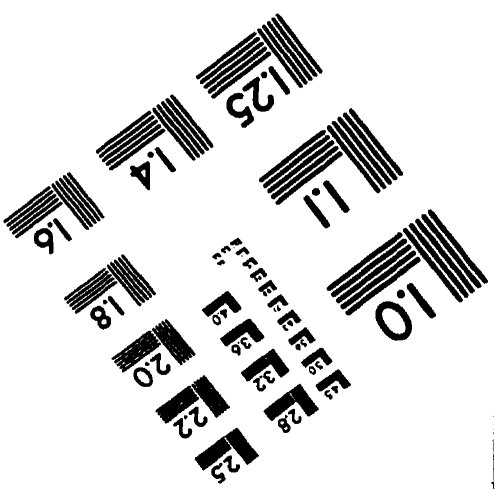












APPLIED IMAGE, Inc
1653 East Main Street
Rochester, NY 14609 USA
Phone: 716/482-0300
Fax: 716/288-5989