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Case report and review of the role of late N-acetylcysteine administration in fulminant hepatic failure secondary to acetaminophen toxicity in infancy

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Abstract

Objective: To describe a rare case of fulminant hepatic failure in an infant secondary to acetaminophen toxicity reversed with the late administration of N-acetylcysteine (NAC).

Design: Case report, clinical.

Setting: Tertiary care pediatric intensive care unit (PICU).

Patient: A 4 month-old female admitted to the PICU with metabolic acidosis, hepatomegaly and a decreased level of consciousness progressing to liver failure subsequently found to be caused by acetaminophen toxicity.

Main results: This patient was admitted to the PICU with severe metabolic acidosis, hepatomegaly and a decreased level of consciousness, which progressed to fulminant hepatic failure with severe encephalopathy. The cause of the liver failure was later found to be caused by acetaminophen toxicity. According to a Arescue protocols used at our institution, intravenous NAC, consisting of a loading dose of 150 mg/kg followed by a doses of 50 mg/kg and 100 mg/kg infused over 4 and 16 hours, respectively, was administered *at least* 72 hours after the last possible oral dose of acetaminophen. Within 24 hours of initiating NAC therapy, the patient experienced a dramatic improvement in her liver function and encephalopathy, and was extubated and ultimately discharged from the PICU.

Conclusion: NAC therapy remains the standard of care in known acetaminophen toxicity, particularly when the patient presents within 24 hours of the toxic ingestion. However, the late administration of NAC can both reverse liver failure and be life-saving, and should be considered for children with liver failure regardless of the time of presentation or diagnosis.

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Introduction

Acetaminophen is the most widely used analgesic-antipyretic in the world. Its broad acceptance has been based on its high toxic-to-therapeutic ratio,[1] as well as the association of Reyes syndrome with the use of salicylates.[2] Acetaminophen toxicity in the pediatric population is not uncommon, with over 32 000 children under the age of 6 years experiencing toxic exposure in 1999.[3] However, acetaminophen toxicity is rarely reported in the very young. Indeed, only one other case report of pediatric acetaminophen toxicity has involved younger patients (6 and 7 weeks of age)[4] than the case presented here.

N-acetylcysteine (NAC) has been shown to be an effective antidote for acute acetaminophen toxicity, particularly if therapy has been initiated within 24 hours of the acute ingestion.[5] Furthermore, there is evidence to suggest that NAC may be useful for patients who present later than 24 hours after ingestion. We present the case of an infant who recovered from fulminant acute hepatic failure with severe encephalopathy, secondary to acetaminophen toxicity, after receiving intravenous NAC 72 hours after admission to hospital. This case highlights the potential role of late NAC administration in acetaminophen overdose.

Case report

A previously healthy 4-month-old female was admitted to a regional hospital after suffering a brief, generalized seizure at home. Further history related by the mother described an irritable infant who had diarrhea, vomiting, and feeding intolerance for 2 days prior to

admission. The child was afebrile and tachycardic. Physical examination of the child at the time was unremarkable and failed to reveal any cause for the seizure episode. Routine blood work including a complete blood count and differential, electrolytes, and renal function were normal. Cranial computed tomography (CT) scans and electroencephalograms (EEG) performed at this time were also reported as normal. However, the child continued to vomit and remained in hospital for the next 3 days with a diagnosis of viral gastroenteritis and received oral and intravenous hydration. The patient received no prescribed medications while in hospital, other than 2 doses of acetaminophen (10 mg/kg) for irritability. The patient was discharged only to be re-admitted to the emergency department 5 days later. The presentation at this time included persistent vomiting and tap-watery diarrhea. A general practitioner had diagnosed an otitis media the day before, and his prescription of clarithromycin did not improve the infant's symptoms. The salient features on examination in the emergency department included marked irritability, abdominal distension, and hepatomegaly. The child appeared only mildly dehydrated, however, venous blood gas analysis demonstrated a significant metabolic acidosis with a pH of 7.27, pCO_2 of 12 torr [1.6 kPa], and a HCO_3 of 6 mEq/l. A complete blood count revealed a white cell count of 21.4 x 10^9/l, and hemoglobin (Hbg) of 9.7 g/dl. Electrolytes and urinalysis were within the normal range. Serial venous blood gas analyses demonstrated only partial correction of the metabolic acidosis despite aggressive isotonic fluid rehydration (30 ml/kg) and two sodium bicarbonate boluses (1 mEq/kg). The patient was then expeditiously transferred to our tertiary pediatric intensive care unit (PICU) for further assessment.

On arrival, the patient was noted to be adequately hydrated and in no apparent distress. The infant was tachycardic, mildly tachypneic, and afebrile. During the neurological examination, the infant spontaneously moved all extremities but had occasional dysconjugate gaze and only intermittent withdrawal to painful stimuli. The only other pertinent finding on examination at this time was a distended abdomen with a firm liver edge palpable 4 cm below the right costal margin. Repeat blood work revealed a partially compensated metabolic acidosis (pH of 7.36, pCO_2 of 23 torr [3 kPa], HCO_3 of 14 mEq/l, and a base deficit of -10.5). Electrolytes were within normal limits however the serum lactate and ammonia were elevated at 5.5 mEq/l and 126 mg/dl, respectively. Serum glucose was recorded at 54 mg/dl. Other abnormal laboratory investigations included: AST of 225 U/l, ALT of 118 U/l, alkaline phosphatase (AP) of 242 U/l, INR of 2.3 and a PTT of 50 seconds. A qualitative urine toxicology screen performed at the time was negative except for the presence of acetaminophen, a medication the infant received at the referring hospital. Radiological imaging revealed a normal chest radiograph with the abdominal series demonstrating mildly distended loops of bowel without evidence of obstruction and a large liver. No additional pertinent history was obtained from the mother other than the absence of consanguinity and a negative family history for similar illnesses. The family also adamantly denied the administration of any medications other than those prescribed by their general practitioner, including acetaminophen or other homeopathic remedies.

The patient was admitted to the PICU for observation. Bacterial and viral cultures of blood, urine, and stool were obtained to rule out infection. A lumbar puncture was not performed due to the patient's persistent coagulopathy, for which she received fresh frozen plasma. A metabolic disorder work-up was initiated based on the history of seizure activity, the patient's decreased level of consciousness, as well as the mild liver dysfunction, and elevated lactate and ammonia. The patient appeared to stabilize over the next several hours although the metabolic acidosis failed to completely correct. Unfortunately, the patient's liver function began to deteriorate further, approximately 48 hours after the time of admission to the PICU. The coagulation indices revealed an INR of 4.7, PTT of 51 seconds and a D-dimer > 4000 mg/l. The patient also became anemic, dropping her Hbg to 7.1 g/dl, despite no overt evidence of external bleeding. The patient was transfused with both packed red blood cells and fresh frozen plasma. At the conclusion of the transfusions, repeat blood work demonstrated a mild correction of the INR to 3.9 and an elevation of the Hbg to 10.3 g/dl. However, the patient's liver enzymes continued to dramatically rise over a period of 24 hours (AST of 6051 U/l, ALT of 3342 U/l, AP of 339 U/l). The lactate also remained elevated at 5.6 mEq/l despite adequate fluid resuscitation. The clinical condition of the patient also began to deteriorate over this same time period. The patient experienced increased respiratory distress, increasing encephalopathy, and evidence of external hemorrhage with small amounts of melena. The fulminant course of the liver failure led to the involvement of the transplantation service. The patient was intubated and ventilated for increasing respiratory distress. An abdominal ultrasound with doppler studies revealed good portal and hepatic venous blood flow. The liver had increased in size but there was no indication of cirrhosis. An abdominal CT scan highlighted the massive hepatomegaly and also ruled out further intra-abdominal pathology. The patient was listed for transplant shortly thereafter.

The cause for the acute deterioration in liver function, now complicated by multi-organ dysfunction, was still unclear. Although a metabolic disorder or

infectious process could lead to rapid hepatic failure, preliminary metabolic studies and cultures were negative. Toxic ingestion was still a consideration, thus a quantitative serum toxicology screen was ordered. This revealed an acetaminophen level of 2493 mmol/l (toxicity > 990 mmol/l). Acetaminophen levels on blood drawn earlier in the morning and at the time of admission (approximately 36 hours earlier) revealed levels of 3800 mmol/l and 6649 mmol/l, respectively (*Fig. 1*). The patient had not received any acetaminophen from the time of admission to our center. Indeed, a review of the transfer record and conversations with the referring physicians revealed that the patient had only received acetaminophen at the time of admission to the referring center 5 days earlier. The family maintained that no medication other than the clarithromycin was administered to the infant. This medication bottle was analyzed and found to contain no acetaminophen. With this information, continuous intravenous NAC therapy was promptly instituted according to a 48-hour rescue protocol used at this institution.[7] Over the ensuing 24 hours, the infant dramatically improved, prompting her removal from the national transplant list. Liver enzymes dropped to a third of peak values and the INR decreased to 2.0. The child's encephalopathy also improved and the patient was extubated within 48 hours of NAC administration. The infant continued to improve and was eventually discharged from the PICU 48 hours after discontinuing the NAC therapy.

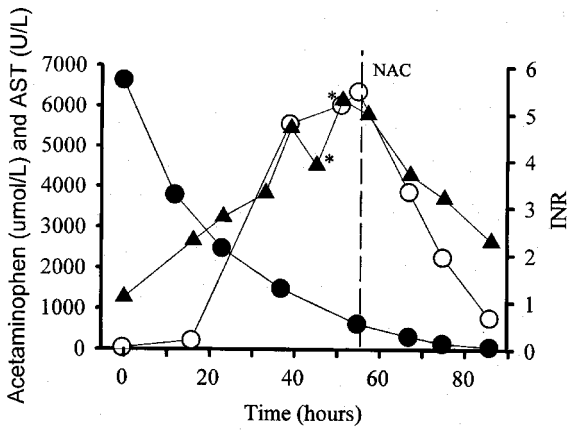

Fig. 1. Temporal changes in acetaminophen (solid circle), AST (open circle) and INR (solid triangle) after admission to the PICU (Time 0). Asterisk (*) indicates INR after transfusion with fresh frozen plasma. The dotted vertical line labeled NAC indicates the time of treatment with N-acetylcysteine. Both AST and INR levels peaked approximately 50 hours after admission to the PICU and decreased rapidly after the initiation of NAC therapy. The time of ingestion of acetaminophen was unknown.

Discussion

Acetaminophen toxicity progressing to hepatic failure in infancy is rare. Indeed, only one other case report involving younger patients than presented here has been reported in the literature.[4] NAC is an accepted therapy for acute acetaminophen toxicity ($\geq$ 140 mg/kg in children and $\geq$ 7.5 g in adults), particularly if the ingestion has occurred within 24 hours, and its use is based on a toxicity nomogram. This report highlights a role for the late administration of NAC in liver failure and severe encephalopathy.

The Rumack-Matthew Toxicity Nomogram[2] allows the clinician to determine the relative probability of hepatotoxicity for a given patient based on the time and amount of acetaminophen ingested. This nomogram is widely used in adult practice yet it has some limitations. First, it should be used only for an acute, single ingestion of acetaminophen. Second, the nomogram is not able to accurately predict either fulminant hepatic failure or death. Third, its application to patients who present greater than 24 hours after ingestion or after repeated ingestion is still unclear. Finally, its applicability to young children is also unclear as the metabolism of acetaminophen is age-dependent.[8]

Over 90% of acetaminophen is primarily metabolized in the liver by either glucuronidation or sulfation, with these pathways representing the major route for metabolism in young children.[8] Approximately 5% of acetaminophen is excreted unchanged in the urine while the remainder is metabolized by the cytochrome system.[9] Specifically, acetaminophen is metabolized by isozymes of cytochrome P450 to N-aminobenzoquinoneamine (NAPQI), a highly reactive and toxic metabolite which covalently binds cellular proteins leading to cell injury and death. In the presence of adequate stores of glutathione, NAPQI is reduced to a non-toxic mercapturate conjugate, which is excreted in the urine. Glutathione stores are only slowly replenished, and thus in severe overdoses glutathione can become depleted, leading to an accumulation of NAPQI and hepatotoxicity.[9] Interestingly, a lower frequency of severe toxicity has been observed in infants and young children when compared to older children ingesting similar mg/kg doses of acetaminophen.[2] The mechanisms for this may be due to the relative immaturity of the cytochrome system in the infant liver, which produces lesser quantities of toxic metabolites.[8] Despite the relative protective effect of immature hepatic metabolism, the patient in the present case still demonstrated extraordinarily high levels of acetaminophen resulting in severe hepatotoxicity.

NAC is an approved antidote for acetaminophen toxicity and has been shown to prevent hepatotoxicity

if given within 24 hours of ingestion.[1] Its mechanism of action is primarily through the repletion of glutathione stores via its conversion to cysteine and ultimately to glutathione. Additionally NAC can directly reduce NAPQI to another non-toxic metabolite.[1] Although the role of NAC for ingestions occurring greater than 24 hours is still unclear, there is evidence to support its use when acetaminophen toxicity leads to fulminant hepatic failure and encephalopathy.[5]

Initial evidence to support this role came in Harrison and Keays[5] retrospective review of 100 cases of fulminant hepatic failure secondary to paracetamol overdose. The comparison of the non-treatment group to the group receiving NAC greater than 10 hours after ingestion (median time 16 hours), demonstrated significant reductions in mortality and encephalopathy in the treatment group. This study was followed by a prospective randomized control trial[6] evaluating intravenous NAC in fulminant hepatic failure secondary to paracetamol involving 50 patients. As in the previous study, the NAC group experienced significantly higher survival, less cerebral edema, and decreased use of inotropic agents compared to the non-treatment group. Interestingly, NAC therapy was initiated at a mean of 53 hours (range 36-80 hours) after the ingestion of paracetamol, suggesting that even the late administration of NAC improved patient outcome in fulminant hepatic failure.

In the present case, NAC therapy was instituted approximately 72 hours after the last possible time that acetaminophen *could* have been ingested. Indeed, based on peak acetaminophen levels obtained at the time of admission to the PICU, our patient would have had to ingest almost 5 g of acetaminophen as a single dose. This amount of acetaminophen could only have been administered by an adult caregiver, but it is still unclear whether the acetaminophen was given as a single or in repeated doses. An ongoing investigation has established that the mother had given the infant an unknown quantity of acetaminophen prior to coming to our institution, suggesting that this may be a case of Munchausen Syndrome by proxy (MSBP).[11] Although the differential diagnosis for a patient presenting with metabolic acidosis, encephalopathy, and liver dysfunction with a disproportionately elevated INR can include metabolic and infectious disorders, this spectrum of signs can also be observed in severe acetaminophen toxicity. Acetaminophen overdose was not initially considered in the present case largely due to the age of the patient, and an apparently reliable history obtained from the family. Interestingly, clarithromycin has been implicated as a cause of hepatic failure in one case report,[10] and a previously unrecognized interaction between clarithromycin and acetaminophen may exist when taken in excessive doses.

The time of ingestion and the amount of acetaminophen taken are still unclear but we believe that NAC therapy was a crucial element in this patients recovery. A 48 hour continuous intravenous protocol was used rather than a 20 hour protocol to reduce the incidence of adverse events.[6] This protocol consisted of a loading dose of NAC at 150 mg/kg followed by an infusion of 50 mg/kg for 4 hours. A dose of 100 mg/kg was then infused over 16 hours until the hepatic encephalopathy resolved. The reported rate of adverse events with this protocol has been estimated to be 12%, with skin rash being the most common, particularly with the loading dose. Our patient tolerated the protocol well with no evidence of adverse reaction.

In conclusion, recent clinical data suggests that NAC therapy should be considered for fulminant hepatic failure and encephalopathy, even if the ingestion of acetaminophen has occurred greater than 24 hours after presentation. Our case report supports this role for NAC. Despite ongoing debate on the route and duration of therapy, the 48 hour intravenous protocol used at our institution was effective and safe, and may have played a critical part in the recovery of our patient.

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