

## Recovery of Acetaminophen-Induced Fulminant Hepatic Failure and Encephalopathy after Ten Days of Intravenous N-Acetylcysteine Administration in Twin Boys

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Received date: December 08, 2016; Accepted date: January 18, 2017; Published date: January 20, 2017

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### Abstract

We describe a case of liver failure in twin infants after frequent therapeutic doses of acetaminophen over 4 days at home to manage pyrexia due to a viral illness. The children were treated successfully with intravenous N-acetylcysteine (NAC) following the hospital's protocol. This case highlights the importance of parental awareness of acetaminophen hepatotoxicity and physicians' advice to parents in preventing hepatotoxicity induced by acetaminophen overdose during viral illness. Although Twin 1 met the King's College Hospital criteria for liver transplantation, he was successfully treated with intravenous N-acetylcysteine for 10 days.

**Keywords:** N-acetylcysteine; Hepatotoxicity; Acetaminophen

**Abbreviations:** NAC: N-acetylcysteine; FHF: Fulminant Hepatic Failure.

### Background

Acetaminophen is considered a safe medication and is a favored analgesic and antipyretic [1-7]. It can be purchased over the counter without a prescription. Despite this, frequent use of unintended inappropriate dosing or failure to recognize the risks associated with standard dosing can contribute to acetaminophen toxicity.

Medication errors at home are frequently caused by inadvertent administration of multiple doses [7]. Leading causes of overdose include: 1) "ingesting acetaminophen along with other hepatotoxic drugs, 2) using adult preparations rather than paediatric preparations, 3) combined administration of an over-the-counter medication with acetaminophen, 4) failure to read and understand the label's instructions, 5) administration of medication under the supervision of another child, and 6) using the incorrect measuring device" [1-3,7].

The parents' or caretaker's lack of knowledge of acetaminophen toxicity can contribute to child poisoning. This is regarded as intentional poisoning [7,8] and often has major consequences for the child, parents, and healthcare institutions. Furthermore, failure to recognize early symptoms can delay diagnosis and treatment. The onset of symptoms after possible toxic ingestion is often overlooked due to their non-specificity [8], which increases the likelihood of delayed reporting of acetaminophen intoxication.

We carried out this study to highlight the importance of parental awareness of acetaminophen hepatotoxicity and physicians' advice to

parents in preventing hepatotoxicity induced by acetaminophen overdose during viral illness.

### Case Description

Twins aged 10 months were admitted to a primary hospital due to a viral infection lasting for five days and were treated with acetaminophen and antibiotics. While the infants were in the hospital, their condition worsened, and they were transferred to tertiary hospitals for further management.

Twin 2 was brought to King Fahad Medical City's emergency paediatric hospital, and twin 1 was admitted to another tertiary hospital in the same city due to bed availability. As per the referral medical report, twin 1 received 160 mg acetaminophen orally every HR (120 mg/kg/day), and twin 2 was given it less frequently (96 mg/kg/day) for five consecutive days, after which the patients' conditions did not improve. Despite acetaminophen therapy, the fevers continued, and they developed diarrhoea and vomiting.

### Clinical Findings

On admission, their parents reported that the twins had no history of chronic disease. Twin 2 was admitted to the paediatric intensive care unit (ICU) at King Fahad Medical City hospital for two days due to metabolic acidosis and profound liver failure.

### Diagnosis and Assessment

#### Twin 2

The positive findings on physical examination for twin 2 included an enlarged liver 4 cm below the costal margin. An initial laboratory investigation within 2 h of his arrival at our hospital revealed the

following: alanine aminotransferase (ALT) 744 IU/L; albumin 5.3 mmol/L; ammonia 30  $\mu$ mol/L; acetaminophen 58  $\mu$ mol/L; activated partial thromboplastin time (APTT) 42.9 s; prothrombin time 13.4 s; and an international normalized ratio (INR) of 1:0. In addition, his salicylate was <0.36 mmol/L, hepatitis was positive, polymerase chain reaction (PCR) tests for influenza A&B were positive, Epstein-Barr virus IgG and IgM were negative, lactate was 2.4 mmol/L, and amylase and lipase levels were normal.

## Treatment

Following clinical laboratory confirmation of hepatotoxicity and acetaminophen levels of 80  $\mu$ mol/L, an intravenous loading dose of N-acetylcysteine was initiated at 150 mg/kg over 1 h, followed by a second dose of N-acetylcysteine of 50 mg/kg over 4 h, and finally 100 mg/kg N-acetylcysteine over 16 h per day for three days.

The clinical laboratory analysis was repeated on the second day, and the patient's ALT levels were 577 IU/L. The INR measured on the third day was 0.8. These parameters improved progressively, and ALT levels were 306 IU/L on the third day when the patient was transferred to the normal ward. After five days, his ALT was 160 IU/L; the patient was discharged, and his parents were advised to bring him to the outpatient clinic for a check-up.

## Diagnosis and Assessment

### Twin 1

Twin 1 was admitted to the hospital pale and restless, as revealed in his medical report of the physical examination upon admission. Although his abdomen was soft and lax with positive bowel sounds, he had gastrointestinal bleeding, and an arterial blood gas test showed metabolic acidosis and hyperlactataemia. The infant was admitted to the paediatric ICU and electively intubated.

An initial laboratory investigation within a few h of arrival revealed the following: ALT 8933 IU/L; the aspartate aminotransferase (AST) result was very high and could not be detected by the machine; albumin 56  $\mu$ mol/L; acetaminophen 1944  $\mu$ mol/L; APTT 54 s; prothrombin time 66.8 s; and INR 7. In addition, the infant's salicylate was <0.36 mmol/L, potassium 3.6 mmol/L, chloride 118 mmol/L, lactate 11 mmol, gamma-glutamyltransferase 33 U/L, and magnesium 1.25 mmol/L.

## Treatment

Following clinical laboratory confirmation of hepatotoxicity and an acetaminophen level of 1944.8  $\mu$ mol/L, a loading dose of NAC was initiated at 150 mg/kg over 1 h, followed by a second iv dose of 50 mg/kg NAC over 4 h. Then, 300 ml of fresh frozen plasma and 5 mg of vitamin K was given by the i.v, followed immediately by 100 mg/kg NAC over 16 h and continued at 10 mg/kg/hour thereafter. The rate was reduced to 6.25 mg/kg/hour after three consecutive ALT level results of <1000 IU/L and normalization of INR. There was no further bleeding after 48 h of NAC administration.

The clinical laboratory analysis was repeated on the second day and revealed the following: ALT 4607 IU/L; AST 4948 IU/L; albumin 21 g/dL; total bilirubin 56  $\mu$ mol/L; direct bilirubin 38  $\mu$ mol/L; INR 2.0; PTT 38 s; lactate 11.6 mmol/L; and ammonia 53  $\mu$ mol/L. The aminotransferase concentration and coagulation parameters improved progressively. On the fourth day, Twin 1 became lethargic and

developed a generalized seizure, for which he received Keppra. A magnetic resonance imaging brain scan revealed abnormal patchy signals in the infra- and supratentorial regions of the brain with ischemic changes. The patient's condition improved and he was transferred from the ICU to a normal paediatric ward. He continued with a maintenance dose of 6.25 mg/kg/hr NAC over 10 days until liver enzymes improved and his ALT was 450 IU/L, AST was 150 IU/L, and INR was 1.4. The patient was discharged, and his parents were advised to bring him to the outpatient clinic for a check-up.

## Follow-up and outcome

After one month, the parents brought the twin boys to be checked; a blood test was done for both infants.

**Twin 2:** ALT was less than 5, AST was not tested, and INR was 1.

**Twin 1:** ALT was 68, AST was 87, and INR was 1. No further symptoms were mentioned by the parents.

Serology tests showed that there is no evidence of infection by hepatitis A, B, or C virus.

## Discussion

Acetaminophen toxicity onset symptoms after possible toxic ingestion are often overlooked due to their non-specificity [8], which increases the likelihood of delayed reporting of acetaminophen intoxication.

Acetaminophen toxicity has been observed even at low concentrations. Many studies have reported that severe hepatotoxicity in children is caused by cumulative toxicity from repeated therapeutic doses rather than a single overdose [3,9,10]. High concentrations in the toxic range due to long-term treatment with acetaminophen are life-threatening and associated with a high risk of mortality [1,3,8]. Regardless of the level of toxicity, healthcare providers should consider acetaminophen toxicity in any child who has received acetaminophen and presents signs of acute hepatic dysfunction. General symptoms of liver disease can mimic those of other illnesses and include abdominal pain, abnormal stools, and flu-like symptoms, such as fatigue, nausea, vomiting, muscle or joint pain, and fever [8]. Acetaminophen hepatotoxicity has the same symptoms; however, these symptoms are also treated with analgesics. Since acetaminophen is a favored pain-control medication and antipyretic for children, failure to isolate early symptoms of acetaminophen hepatotoxicity can support the further administration of acetaminophen and exacerbate liver injury and toxicity [8].

There is major clinical evidence that supports N-acetylcysteine as the optimal antidote to successfully prevent hepatotoxicity [5]. The commonly recommended loading dose is 140 mg/kg followed after 4 h with a maintenance dose of 70 mg/kg administered orally every 4 h, usually for 72 h. However, intravenous administration is recommended when the patient cannot tolerate oral administration or has fulminant hepatic failure [1,7]. The most commonly used intravenous protocol is to administer 150 mg/kg over 1 hour, followed by 50 mg/kg over 4 h, and then 100 mg/kg over 16 h. A modified intravenous dosing formulation is recommended for paediatric patients who weigh <40 kg to prevent excessive fluid accumulation. Conversely, the rapid administration of N-acetylcysteine, over a 1 hour period, can cause allergic and anaphylactic reactions, such as angioedema, hypotension, and bronchospasm [1]. Reporting acetaminophen toxicity early and initiating N-acetylcysteine therapy, within 8 h, led to a quick recovery,

with the desired outcome. Moreover, the incidence of hepatotoxicity is 10% and usually does not progress to liver failure or mortality [4]. In this report, Twin 2 supported this outcome as his liver toxicity was not as severe as Twin 1. By contrast, delaying the start of N-acetylcysteine therapy increases the patient's risk of developing fulminant hepatic failure or death [1,4]. Furthermore, the efficacy of N-acetylcysteine decreases with the increasing time between ingestion and treatment. Twin 1 had severe liver toxicity and was eligible for liver transplantation, according to the King College Hospital's criteria for liver transplantation; however, according to the guidelines for the administration of N-acetylcysteine, the child could not undergo liver transplantation. The N-acetylcysteine treatment was prolonged to 10 days because of the initial improvement in liver toxicity markers.

Positive outcomes have been observed, following the oral administration of N-acetylcysteine started at 0-4 h or 4-8 h after acetaminophen ingestion, with no difference in outcome [5-7]. Meanwhile, in patients who received N-acetylcysteine 10 or 16-24 HR after ingestion of acetaminophen, 6.1 and 41% developed hepatotoxicity [5-7]. Therefore, evaluating the initiation time of the therapy and duration of ingestion is crucial in determining the efficacy of N-acetylcysteine therapy.

N-acetylcysteine should be administered until serum acetaminophen is undetectable (<10 µg/mL) and the patient's clinical symptoms have improved with liver function tests being normal. In cases of hepatotoxicity, N-acetylcysteine should be continued until: a) serum liver transaminases are <1000 IU/L, b) bilirubin and coagulation results are normal, and c) the patient becomes clinically healthy, receives a liver transplant, or dies [4].

## Conclusion

In our study, N-acetylcysteine is an appropriate treatment for FHF after repeated. Supratherapeutic doses for children, even a candidate for liver transplant, and should be extended beyond the usual course of therapy until the liver function and clinical signs improvement. Supporting this, Twin 2 had the desired treatment outcome after three

days of N-acetylcysteine administration, while Twin 1 fully recovered after a course of 10 days of intravenous, despite being a candidate for liver transplant.

Finally, based on our study, there are eventually differences in hepatic metabolism that can affect hepatotoxicity in infants and young children. Therefore, the clinical consequences of these differences should provoke further investigation in cases of children suspected of acetaminophen toxicity.

## Conflict of Interest

The authors declare they have nothing to disclose.

## References

1. American Academy of Pediatrics (2001) Acetaminophen Toxicity in Children. *Pediatrics* 108: 4.
2. Zhao L, Pickering G (2011) Paracetamol Metabolism and Related Genetic Differences. *Drug Metab Rev* 43: 41-52.
3. Williams RT (1967) Comparative Patterns of Drug Metabolism. *Fed Proc* 26: 1029-1039.
4. Algren DA (2008) Review of N-acetylcysteine for the Treatment of Acetaminophen (Paracetamol) Toxicity in Pediatrics. *The World Health Organization* 1-18.
5. Heard KJ (2008) Acetylcysteine for Acetaminophen Poisoning. *N Engl J Med* 359: 285-292.
6. Smilkstein MJ, Knapp GL, Kulig KW, Rumack BH (1988) Efficacy of Oral N-Acetylcysteine in the Treatment of Acetaminophen Overdose. *N Engl J Med* 319: 1557-1562.
7. Ogilvie JD, Rieder MJ, Lim R (2012) Acetaminophen Overdose in Children. *184*: 1492-1496.
8. Ward RM, Bates BA, Benitz WE, Burchfield DJ, Ring JC, et al. (2001) Acetaminophen Toxicity in Children. *Pediatrics* 10: 1020-1024.
9. Fontana RJ (2006) "Unintentional" Acetaminophen Overdose on the Rise: Who is responsible?. *Can J Gastroenterol* 20: 319-324.
10. Hodgman MJ, Garrard AR (2012) A Review of Acetaminophen Poisoning. *Crit Care Clin* 28: 499-516.