HET

Human and Experimental Toxicology
30(1) 51–54

DOI: 10.1177/0960327110366182
het.sagepub.com
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Late extensive intravenous administration of *N*-acetylcysteine can reverse hepatic failure in acetaminophen overdose

Omid Mehrpour[1], Shahin Shadnia[2] and Hossein Sanaei-Zadeh[3]

Abstract

Acetaminophen is a commonly used analgesic and has been shown to be a main cause of drug-induced liver failure. *N*-acetylcysteine (NAC) should be employed as the antidote in case of acetaminophen poisoning within the first 8-10 hours. Oral administration of NAC is universally recommended and due to the adverse effects, the intravenous administration of the agent is reserved for patients with oral intolerance and severe complications. We here report an 18-year-old man with severe liver failure due to a huge ingestion of acetaminophen, who was taken into the Loghman Hakim Hospital Poison Center 72 hours after attempted suicide. Regarding the poor prognostic clues as his level of consciousness and impaired liver functions, an extensive intravenous regimen of NAC was started. The patient survived the condition with an additional intravenous administration of NAC past the first 72 hours of treatment. We discuss that even in late phases of intoxication; high-dose intravenous NAC can serve a substantial improvement.

Keywords

N-acetylcysteine, acetaminophen overdose, acute poisoning, hepatic failure

Introduction

Acetaminophen (*N*-acetyl-*p*-aminophenol, Paracetamol), a widely used over-the-counter analgesic, is a leading cause of drug-induced acute liver failure in western countries.[1] An intake of more than 10-15 g at one time or less in adults can be harmful. The clinical course of acetaminophen intoxication can be divided into four stages. In the first stage, the symptoms are mild and laboratory findings are usually normal. Within 2−3 days, the serum aspartate aminotransferase (AST) and alanine aminotransferase (ALT) rise, as do bilirubin and prothrombin time (PT). Right upper quadrant pain and jaundice may develop. In the third stage (72 to 96 hours after ingestion), potentially lethal hepatocellular necrosis occurs.[2] Patients, who survive this period, will start to recover over the fourth stage.

Case report

An 18-year-old man was admitted due to acetaminophen overdose, according to the history That was taken from the patient's relative, we concluded that the patient ingested 75 tablets containing 325 mg acetaminophen each, followed by a second intake of 30 tablets over 24 hours (totally 34,125 mg within 24 hours). He was admitted 48 hours after the second dose with refractive vomiting, abdominal pain and jaundice. The patient was lethargic. Physical examination revealed a

[1] Department of Clinical Toxicology and Forensic medicine, Faculty of Medicine, Birjand University of Medical Sciences, Birjand, Iran
[2] Loghman-Hakim Hospital Poison Center, Faculty of Medicine and Toxicological Research Center, Shaheed Beheshti University of Medical Sciences, Tehran, Iran
[3] Department of Forensic Medicine, Faculty of Medicine, Iran University of Medical Sciences, Tehran, Iran

Corresponding author:
Omid Mehrpour, Department of Clinical toxicology and Forensic Medicine, Faculty of Medicine, Birjand University of Medical Sciences, Ghaffari Avenue, Birjand, Iran. E-mail: omehrpour@razi.tums.ac.ir; omid.mehrpour@yahoo.com.au

Table 1. Serial laboratory investigation of liver function in our patient with acetaminophen intoxication

	Day 1	Day 2	Day 3	Day 4	Day 5	Day 8	Day 11	Discharge from ICU	Discharge from hospital	Day 10 after discharge
Blood sugar (mg/mL; 70–110 mg/dL)	115	121	132	159	203	83	119	114	106	101
AST (U/L; 5–35 U/L)	700	1120	3650	1620	26	12.8	102	149	82	32
ALT (U/L; 7-56 U/L)	870	930	1150	2700	900	551	214	147	111	46
Total bilirubin (mg/dL) normal: (0.2–1.3 mg/dL)	10.3	10.9	11.7	11.2	6.2	5.9	4.7	2.6	1.8	1.5
Alk-P (U/L; 38–126 U/L)	466	296	276	281	228	193	157	100	76	58
PT (12–14 sec)	52	41	30	23.9	24.3	23.8	15.8	13.3	13.1	14.2
INR (normal: 1)	6	5.8	4.7	3.6	3.7	2.3	1.83	1.42	1.13	0.96

AST, aspartate aminotransferase; ALT, alanine aminotransferase; Alk-P, alkaline phosphatase; PT, prothrombin time; INR, international normalized ratio.

general icterus and tenderness on the right upper quadrant of abdomen. The liver function tests are summarized in Table 1. Concentrations of liver enzymes in serum were the most in the third day of admission. Acetaminophen was not detectable in blood.

The level of consciousness deteriorated 2 hours after admission and he was placed under assisted ventilation. Along with the supportive measures, he received intravenous (IV) *N*-acetylcysteine (NAC) in a loading dose of 140 mg/kg and then continued in a dose of 420 mg/kg/day (70 mg/kg q4 hours daily) for a week, and then followed by (50 mg/kg q4 hours daily) for 5 days. During the treatment period, we observed the patient, for adverse reaction like nausea, vomiting, skin reaction, bronco spasm and so on. We did not find any adverse reaction in our patient. The fourth day, the patient showed high fever and tachypnea. Bilateral pulmonary infiltrations on X-ray imaging were noted. He was successfully treated with suitable antibiotics. A high carbohydrate and low-fat diet was begun as his mental status progressively improved. The liver function tests and prothrombin time (PT) returned into normal range and he left the intensive care unit 2 weeks after admission.

The ultrasound study of liver showed a normal parenchyma and vasculature with the span of liver decreased compared to the first day. However, pleural effusion and slight ascitis were detectable by ultrasound assay until the 17th day. The patient was discharged after a whole month of hospitalization.

Discussion

Up to 0.35% of fatalities in an Iranian tertiary poison treatment center were due to acetaminophen overdosage.[3] We here report a case of acetaminophen intoxication, who received his first medical care almost 72 hours after a first ingestion of 24,375 mg of the agent. As the patient's general condition was worsening at admission with signs of severe liver failure, we started a high dose IV NAC with a total amount of almost 30,240 mg/day for a week. Although the serum concentration of acetaminophen was negative in this patient, it is notable that plasma levels should be measured between 4 and 24 hours following ingestion. A negative value does not preclude a significant overdose.

Acetaminophen is mainly metabolized in liver through conjugation with sulphate and glucoronic acid. Around 10% of the drug is oxidized by the P450 system to produce a highly reactive intermetabolite, named *N*-acetyl-*p*-benzoquinoneimine (NAPQI). This latter toxic metabolite is quickly detoxified by hepatic glutathione (GSH) conjugations and is eliminated in urine.[4,5] When GSH hepatic storage is depleted, as in case of acetaminophen overdose or alcohol abuse, NAPQI binds to hepatic cell macromolecules and initiates tissue necrosis.[6,7] A variety of factors including age, genetics, nutritional status and concordant drug and substances can affect the intoxication course.[2]

NAC acts as a cysteine prodrug and a GSH precursor. NAC is principally used to replenish the cysteine and GSH. Also, NAC is a powerful antioxidant that detoxifies free radicals.[8,9] In addition, NAC protect Hep33 cell from acetaminophen-induced oxidative injury.[10] NAC can be administered orally and intravenously. High plasma levels of NAC may cause adverse effects and oral administration for most cases is effective. In patients with acute liver failure, the IV route is recommended.[11] Severe and sometimes

life-threatening anaphylactoid reactions have been reported after IV administration of NAC. These adverse reactions subside rapidly when IV administration is discontinued or decreased.[12,13]

NAC is indicated when the acetaminophen ingestion is greater than 150 mg/kg (7.5 g in adults). Use of the NAC can provide the maximum protection when used within the first 8 to 10 hours of an acetaminophen overdose.[2] In this situation, the hepatotoxicity is rare and the rate of mortality would be reduced to less than 1%.[2]

In standard IV regime, the loading dose is 150 mg/kg over 15 min, followed by 50 mg/kg over the next 4 hours and 100 mg/kg over the 16 hours thereafter (totally 300 mg/kg over 20 hours); however, higher doses have been recommended as well.[2,14] It has been speculated that when treatment is delayed beyond 10 hours, the oral regime may be effective due to its larger total dose and directly delivered to the liver.[2]

However, even long-term high-dose NAC ingestion is safe,[9] IV administration of NAC has been associated with some adverse effects,[12,15] such as urticaria, flushing, diaphoresis, pruritus and rarely bronchospasm.[16] Adverse reactions to NAC maybe observed in 23.3% of patients.[16] Despite the high frequency of adverse effects, they were transient and easily treated.[12,15,16] But it is indicated in certain patients. Having the patient under close observation minimizes the risk of unwanted events. "Moreover, even 72 hours after acetaminophen ingestion,' our patient safely received a higher IV dose of NAC. His level of awareness improved rapidly from a deep stupor status and the liver function were restored completely. Late administration of NAC after 24 hours of ingestion is still helpful and unlike the treatment of early acetaminophen toxicity, NAC therapy should be continued past the 72 hours standard regime, until the patient recovers.[17-20] This vigorous strategy is notably useful for patients with progressive encephalopathy and loss of consciousness. We believe that in certain conditions, the NAC regimen must be flexibly changed according to the condition of poisoned individual. The adverse reactions of an IV administration can be well monitored in an intensive care unit.

Acknowledgment

The authors wish to convey their full appreciation to Professor G. Randall Bond, for his sophisticated editing of this paper.

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