Case Report

Severe Hepatotoxicity After Therapeutic Doses of Acetaminophen

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ABSTRACT

Background: Acetaminophen overdose is a frequent cause of acute liver failure. Controversy exists over the rare association of severe hepatotoxicity or acute liver failure with therapeutic doses of acetaminophen.

Case summary: A 45-year-old white man weighing 85 kg with asymptomatic HIV, hepatitis B virus, and hepatitis C virus (HCV) infection presented with signs of severe hepatotoxicity: aspartate aminotransferase (AST), 8581 IU/L; alanine aminotransferase (ALT), 5433 IU/L; L-lactate dehydrogenase, 13,641 IU/L; and prothrombin international normalized ratio, 2.15. He reported taking acetaminophen 1000 mg QID for the previous 4 days and 1000 mg that morning because of a febrile illness. Immediate administration of continuous IV *N*-acetylcysteine 150 mg/kg for the first 90 minutes and then 50 mg/kg q4h for the next 3 days was followed by clinical improvement and a rapid decrease in AST and ALT. AST levels decreased from 8581 to 42 IU/L within 11 days. Several potential risk factors for acetaminophen hepatotoxicity (ie, chronic alcohol, tobacco, and opiate consumption, malnutrition, illness-induced starvation, HIV infection, and HCV infection) were present in this patient.

Conclusions: This patient with multiple risk factors and severe hepatotoxicity after therapeutic dosage of acetaminophen was successfully treated with *N*-acetylcysteine. (*Clin Ther.* 2006;28:755–760) Copyright © 2006 Excerpta Medica Inc.

Key words: acetaminophen, paracetamol, hepatotoxicity, toxicity, liver.

INTRODUCTION

Intentional or unintentional overdose of acetaminophen (*N*-acetyl-para-aminophenol [APAP]) has become the most frequent cause of acute liver failure in the United States, United Kingdom, and northern Europe.[1,2] However, reports of severe hepatotoxicity or acute liver failure after therapeutic doses of APAP have been rare,[3–11] and not all reported cases are well documented.[12] Therefore, some experts are still not convinced that this clinical entity exists.[13–15]

APAP is metabolized in the liver primarily by glucuronidation and sulfation.[6,12] With therapeutic doses (≤4 g daily), only 4% is converted by the cytochrome P450 (CYP) system into the reactive toxic intermediate *N*-acetyl-*p*-benzoquinoneimine (NAPQI).[14] This toxic metabolite is rendered nontoxic by binding to glutathione.[12] In the case of APAP overdose, CYP enzyme induction, glutathione depletion, or the inhibition of glucuronidation, this reactive metabolite cannot be sufficiently neutralized. Instead, NAPQI reacts with the cysteine group of hepatocellular proteins, which leads to the loss of cell function and cell death.[12]

NAPQI-protein adducts, released into the circulation from the injured liver in patients who overdosed APAP, can be detected, even if there are no large increases in transaminase levels, by using a recently introduced sensitive assay: high-performance liquid chromatography with electrochemical detection. The NAPQI-protein adducts serum concentration also correlates significantly and positively with serum aspartate aminotransferase (AST) activity.[16]

Recent research from the Acute Liver Failure Study Group revealed that in 4 (25%) of 12 indeterminate cases of acute liver failure (in which no cause was dis-

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cerned after extensive investigation), these NAPQI-protein adducts could be detected, suggesting that APAP toxicity might have been underestimated.[17] Furthermore, 10 (38%) of 26 of patients with established acute viral hepatitis A or B had detectable APAP drug levels, not adducts. These patients had higher alanine aminotransferase (ALT) levels, a higher prothrombin international normalized ratio (INR), and a higher death rate compared with the non-APAP group, suggesting an APAP injury.[18] It was concluded that APAP was likely a co-factor of at least 20% of the patients with viral hepatitis–induced acute liver failure.[18] In a study that analyzed the risk factors for fulminant hepatitis A (hepatitis A virus [HAV] viral load, bilirubin level, gender, HAV genotypes, APAP intake), of the 40 patients in whom acetaminophen intake before admission was precisely documented, those with encephalopathy were more likely to have taken APAP than those without it (80% [8/10] vs 37% [11/30], respectively; $P = 0.07$).[19] In a case-control study investigating factors associated with fulminant hepatitis B virus (HBV) infection (4 case patients) compared with nonfulminant HBV infection (9 control patients) among injection drug users,[20] 100% of case patients took APAP during their illness compared with 44% of the control patients ($P = 0.04$).

CASE SUMMARY

A 45-year-old white man with asymptomatic HIV, HBV, and hepatitis C virus (HCV) infection and a history of injection drug abuse presented with extreme weakness and malaise that developed during a 4-day febrile illness. Blood test results were surprising: AST, 6472 IU/L; serum L-lactate dehydrogenase (LDH), 10,829 IU/L; and bilirubin, 2.3 mg/dL. Eight hours later, the liver enzymes had further increased to the following values: AST, 8581 IU/L; serum ALT, 5433 IU/L; LDH, 13,641 IU/L; and prothrombin INR, 2.15. Three years earlier, he had been treated for pulmonary tuberculosis. After that, he had regular medical visits and blood examinations, and his AST level was within the normal range (<40 IU/L). The patient reported that he smoked 20 cigarettes and consumed up to 1 L of beer daily. He also stated that, 4 months earlier, he had recommenced using IV heroin after abstaining for 2 years. Because of this change in lifestyle, his body weight had dropped from 95 to 85 kg. He reported that his temperature had risen to 40°C and he took acetaminophen 1000 mg QID for 4 days and once during the morning of his admission to the hospital. He also reported taking a single dose of twelve 2-mg tablets of buprenorphine for withdrawal symptoms. During the previous 4 days, the patient had starved due to fever, malaise, and nausea.

APAP hepatotoxicity was considered in the differential diagnosis of this patient, because a patient had previously died at our hospital from acute liver failure after therapeutic doses of APAP. In that deceased patient, the characteristic confluent centrolobular liver cell necrosis had been revealed at autopsy. In the current patient, continuous IV administration of *N*-acetylcysteine was started immediately at 150 mg/kg for the first 90 minutes and then 50 mg/kg q4h for the next 3 days. After administration of 3 units of plasma, a central venous catheter was inserted. Supportive treatment consisted of continuous IV infusion with 2 L of 20% glucose solution with electrolytes and 500 mL of a solution containing branched-chain amino acids, vitamin K, sucralfate, and methadone. Twenty-two hours after the reported last intake of 1000 mg APAP, the patient's APAP blood level was 0.4 mg/L, corresponding to a drug half-life of ~4 hours, which is double the normal half-life of ~2 hours.[14] A urinalysis was positive for opiates but negative for cocaine and benzodiazepines.

After treatment with *N*-acetylcysteine, the AST, ALT, and LDH values rapidly decreased to 42, 209, and 310 IU/L, respectively, within 11 days (**Figure**). Weakness, malaise, and nausea disappeared and appetite returned. In the first few days, the prothrombin INR increased to 2.56 and bilirubin to 4.4 mg/dL, and albumin levels decreased to 2.9 g/dL. The patient's CD4 T-cell count was 288/mm^3, HIV-RNA was 2.560 copies/mL, and HCV-RNA was 81,800 IU/mL. Tests for hepatitis D virus (HDV) antibody and hepatitis B surface antigen tests yielded positive results. Tests for HBV-DNA, hepatitis B core antigen immunoglobulin M, hepatitis B e antigen, HDV antigen, herpes simplex virus DNA, and cytomegalovirus antigen pp65 all yielded negative results. There was no serologic evidence of acute or recent infection with hepatitis A virus, herpes simplex virus 6, cytomegalovirus, Epstein-Barr virus, human parvovirus B19, adenovirus, or enterovirus. The patient's wife reported that during his 4-day febrile illness, he took a total amount of 1.5 blister-pack sheets of tablets from an old package and 2 full blister-pack sheets that she had bought for him (1 package contained 2 blister-pack sheets with 10 tablets on each), corresponding to 34 tablets or 17,000 mg of APAP.

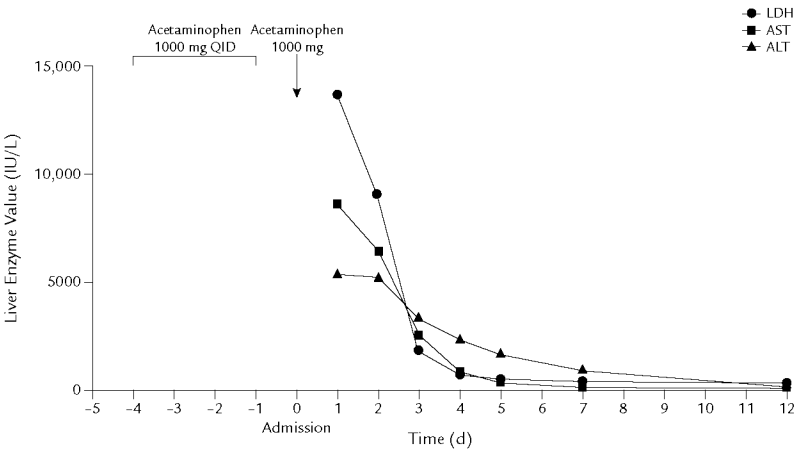

Figure. Decline of liver enzymes after administration of continuous IV *N*-acetylcysteine 150 mg/kg for the first 90 minutes and then 50 mg/kg q4h for the next 3 days to a white man weighing 85 kg who presented with signs of severe hepatotoxicity after taking therapeutic doses of acetaminophen for 4 days before and on the morning of admission. LDH = L-lactate dehydrogenase; AST = aspartate aminotransferase; ALT = alanine aminotransferase.

DISCUSSION

One problem in case reports of hepatotoxicity induced by therapeutic doses of APAP is the reliability of patients' history regarding their recent APAP intake,[14] except when APAP is administered in a hospital under direct observation.[8,10] In this case, the patient's wife independently agreed on the number of tablets taken, after having counted the blister sheets. The determination of APAP blood levels is important in assessing the amount of drug ingested and in calculating the drug half-life.[14] A limitation of this report is that the APAP blood level was not determined soon after admission to the hospital (within 10 hours of the last reported intake of APAP). This APAP blood concentration, together with the measured APAP blood level of 0.4 mg/L the next morning (22 hours after the last reported intake of 1000 mg APAP), would have permitted not only the calculation of APAP half-life in the patient but also the verification of the reported last APAP intake dose. However, these examinations would not have permitted assessment of the amount of APAP taken in the previous 4 days. After absorption of 1000 mg of APAP in an 85 kg patient, assuming a drug distribution of 1 kg/L,[14] the APAP blood level is calculated with the following formula: 1000 mg/85 kg × 1 kg/L = 11.8 mg/L. With a drug half-life of 4 hours, a drug blood level of 11.8 mg/L would decline to 0.36 mg/L within 20 hours. These concentrations are consistent with those of the described patient. Normal half-life of APAP is ~2 hours,[14] but considering the severe liver damage observed in this patient, a prolonged half-life might be expected.

Other alternative etiologies for hepatotoxicity were also explored. The liver enzyme pattern in the described patient, and the high values of LDH, AST, and ALT (**Figure**), were not indicative of an acute reactivation of the patient's HCV infection. More important, the rapid decline of enzyme levels and the rapid clinical improvement after *N*-acetylcysteine treatment suggest that this was not a viral etiology. Despite having excluded alternative possible causes in this patient, doubts may exist as to whether an unrecognized or unknown agent might

have caused the acute liver damage. The diagnosis of APAP hepatotoxicity could have been supported by detecting NAPQI-protein adducts using high-performance liquid chromatography with electrochemical determination. The presence of those adducts in the blood has been shown to correlate with AST activity.[16] Unfortunately, that diagnostic possibility was unknown to the physicians treating the patient at that time.

The role of risk factors and contributing factors to APAP hepatotoxicity in this patient were also assessed. Chronic alcohol use, malnutrition, starvation, and CYP-enzyme–inducing drugs have all been associated with APAP hepatotoxicity, and have been suggested as risk factors in many studies and case reports.[2–4,6–10,21] However, these results have not been confirmed in a prospective, double-blind, randomized, placebo-controlled trial or in other prospective trials.[13,22] This has led to long-standing controversies.[14,15,23] However, even if hundreds of participants were included, prospective randomized trials would not be appropriate for determining risk factors for a disease with a low hypothesized incidence (1 case in 1000 people to 1 case in 1,000,000 people). Theoretically, other than an APAP overdose, anything that contributes to glutathione depletion, CYP enzyme induction, or inhibition of glucuronidation should be considered a potential risk factor for APAP hepatotoxicity in certain undefined circumstances, such as those seen in this patient. In animal studies, it was suggested that chronic alcohol use induced CYP2E1 enzymes and depleted glutathione.[2,15] Malnutrition and starvation can also lead to glutathione depletion and to reduction of glucuronidation.[6,21] Even current tobacco use was found to be a possible independent risk factor in severe hepatotoxicity, acute liver failure, and death after APAP overdose.[24] Tobacco smoke contains a number of substances that are potent inducers of CYP1A2.[24] It has also been suggested that phenobarbital and phenytoin may increase APAP hepatotoxicity through inhibition of APAP glucuronidation in cultured human hepatocytes.[25] Older work suggested that central effects of opiate agonists promote hepatic glutathione depletion in mice.[12] However, this issue has not been addressed in humans.[12] Reduced glutathione levels have been observed in HIV and HCV infection.[26] Most of these potential risk factors—chronic alcohol, tobacco, and opiate consumption, malnutrition, illness-induced starvation, HIV infection, and HCV infection—were present in this patient's case.

However, because these risk factors are common,[21] but hepatotoxicity due to therapeutic doses of APAP is rare,[12] unknown conditions may exist that predispose individuals to this severe clinical entity. Such conditions may include enzyme polymorphism and interindividual genetic variation of metabolic and immunologic processes, such as the capacity to upregulate the generation of glutathione once its consumption begins, or the capacity to sulfate and glucuronate APAP. More complex mechanisms in APAP hepatotoxicity are now emerging.[12] In addition to the reaction of the toxic NAPQI metabolite with hepatocellular proteins, further mechanisms are recognized. The depletion of glutathione, caused by the NAPQI itself, has effects on the neutralization of endogenous reactive species, mitochondrial permeability, and the induction of apoptosis. Furthermore, cytokines and chemokines of the innate immune system are involved in the damage and repair mechanisms.[12]

The efficacy of *N*-acetylcysteine in the prevention and treatment of hepatotoxicity after an APAP overdose has been well established.[14,27] *N*-acetylcysteine is most efficient if administered within 8 hours, but it may offer some benefit even after 24 hours.[14] In a 53-year-old hospitalized woman who developed severe hepatotoxicity while receiving a recommended dose of APAP (4000 mg/d) under medical supervision, bilirubin levels and prothrombin time normalized after 2 days of treatment with *N*-acetylcysteine.[10] Other reported cases of acute hepatic failure associated with therapeutic doses of APAP, and which did not receive *N*-acetylcysteine, were fatal or required liver transplantation.[4,8,9] In the patient being described here, a rapid decline (AST, ALT, and LDH values decreased from 8581, 5433, and 13,641 to 42, 209, and 310, respectively, within 11 days) of the elevated liver enzymes occurred (**Figure**), and clinical improvement was observed after 3 days of *N*-acetylcysteine administration. Anaphylactoid reactions are a rare adverse event associated with *N*-acetylcysteine administration. Their incidence depends on the route of administration (PO or IV), velocity of administration, concentration of the IV formula, or a combination of these factors.[28]

Based on this case, in patients with severe hepatotoxicity related to therapeutic doses of APAP, immediate administration of *N*-acetylcysteine should be considered because its potential benefit is likely to outweigh the risk of adverse events. Blood should be frozen, stored, and sent to a reference laboratory for

detection of NAPQI-protein adducts. Additional blood should be frozen and stored for future genetic analysis of enzyme polymorphism and interindividual genetic variation. Further diagnostic support—comprising examination of blood for NAPQI-protein adducts, the patient's medical history, and clinical documentation—will enable risk factors for this rare but severe clinical entity to be better defined.

CONCLUSIONS

This patient with multiple risk factors and severe hepatotoxicity after therapeutic dosage of acetaminophen was successfully treated with *N*-acetylcysteine.

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REFERENCES

1. Lee WM. Acetaminophen and the U.S. Acute Liver Failure Study Group: Lowering the risks of hepatic failure. *Hepatology*. 2004;40:6–9.
2. Schiodt FV, Lee WM, Bondesen S, et al. Influence of acute and chronic alcohol intake on the clinical course and outcome in acetaminophen overdose. *Aliment Pharmacol Ther*. 2002;16:707–715.
3. Black M. Acetaminophen hepatotoxicity. *Annu Rev Med*. 1984;35:577–593.
4. Eriksson LS, Broome U, Kalin M, Lindholm M. Hepatotoxicity due to repeated intake of low doses of paracetamol. *J Intern Med*. 1992;231:567–570.
5. Bonkovsky HL, Kane RE, Jones DP, et al. Acute hepatic and renal toxicity from low doses of acetaminophen in the absence of alcohol abuse or malnutrition: Evidence for increased susceptibility to drug toxicity due to cardiopulmonary and renal insufficiency. *Hepatology*. 1994;19:1141–1148.
6. Zimmerman HJ, Maddrey W. Acetaminophen (paracetamol) hepatotoxicity with regular intake of alcohol: Analysis of instances of therapeutic misadventure [published correction appears in *Hepatology*. 1995;22:1898]. *Hepatology*. 1995;22:767–773.
7. Schiodt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. *N Engl J Med*. 1997;337:1112–1117.
8. Kadas I, Konczol F, Illes T. Fatal acute liver damage caused by a therapeutic dose of paracetamol [in Hungarian]. *Orv Hetil*. 1998;139:189–191.
9. Mofredj A, Cadranel JF, Darchy B, et al. Hepatotoxicity caused by therapeutic doses of paracetamol in alcoholics. Report of 2 cases of fatal hepatitis in cirrhosis [in French]. *Ann Med Interne (Paris)*. 1999;150:507–511.
10. Kurtovic J, Riordan SM. Paracetamol-induced hepatotoxicity at recommended dosage. *J Intern Med*. 2003;253:240–243.
11. Vitols S. Paracetamol hepatotoxicity at therapeutic doses. *J Intern Med*. 2003;253:95–98.
12. Kaplowitz N. Acetaminophen hepatotoxicity: What do we know, what don't we know, and what do we do next? *Hepatology*. 2004;40:23–26.
13. Kuffner EK, Dart RC, Bogdan GM, et al. Effect of maximal daily doses of acetaminophen on the liver of alcoholic patients: A randomized, double-blind, placebo-controlled trial. *Arch Intern Med*. 2001;161:2247–2252.
14. Rumack BH. Acetaminophen hepatotoxicity: The first 35 years. *J Toxicol Clin Toxicol*. 2002;40:3–20.
15. Prescott LF. Paracetamol, alcohol and the liver. *Br J Clin Pharmacol*. 2000;49:291–301.
16. Muldrew KL, James LP, Coop L, et al. Determination of acetaminophen-protein adducts in mouse liver and serum and human serum after hepatotoxic doses of acetaminophen using high-performance liquid chromatography with electrochemical detection. *Drug Metab Dispos*. 2002;30:446–451.
17. Davern TJ II, James LP, Fontana RJ, et al. Serum acetaminophen adducts reliably distinguish acetaminophen toxicity from other causes of acute liver failure. *Hepatology*. 2003;38 Suppl 1:538–39A. Abstract.
18. Polson JE, Ocama P, Larson AM, et al. Role of acetaminophen in acute liver failure due to viral hepatitis. *Hepatology*. 2003;38(Suppl 1):544A. Abstract.
19. Rezende G, Roque-Afonso AM, Samuel D, et al. Viral and clinical factors associated with the fulminant course of hepatitis A infection. *Hepatology*. 2003;38:613–618.
20. Garfein RS, Bower WA, Loney CM, et al. Factors associated with fulminant liver failure during an outbreak among injection drug users with acute hepatitis B. *Hepatology*. 2004;40:865–873.
21. Whitcomb DC, Block GD. Association of acetaminophen hepatotoxicity with fasting and ethanol use. *JAMA*. 1994;272:1845–1850.
22. Schenker S, Speeg KV Jr, Perez A, Finch J. The effects of food restriction in man on hepatic metabolism of acetaminophen. *Clin Nutr*. 2001;20:145–150.
23. Rumack BH. Acetaminophen misconceptions. *Hepatology*. 2004;40:10–15.
24. Schmidt LE, Dalhoff K. The impact of current tobacco use on the outcome of paracetamol poisoning. *Aliment Pharmacol Ther*. 2003;18:979–985.
25. Kostrubsky SE, Sinclair JF, Strom SC, et al. Phenobarbital and phenytoin increased acetaminophen hepatotoxicity due to inhibition of UDP-glucuronosyltransferases in cultured human hepatocytes. *Toxicol Sci*. 2005;87:146–155.

26. Barbaro G, Di Lorenzo G, Soldini M, et al. Hepatic glutathione deficiency in chronic hepatitis C: Quantitative evaluation in patients who are HIV positive and HIV negative and correlations with plasmatic and lymphocytic concentrations and with the activity of the liver disease. *Am J Gastroenterol*. 1996;91:2569–2573.
27. Tsai CL, Chang WT, Weng TI, et al. A patient-tailored N-acetylcysteine protocol for acute acetaminophen intoxication. *Clin Ther*. 2005;27:336–341.
28. Horowitz BZ, Hendrickson RG, Pizarro-Osilla C. Not so fast! *Ann Emerg Med*. 2006;47:122–123.

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