Case Report

Therapeutic Dose of Acetaminophen with Fatal Hepatic Necrosis and Acute Renal Failure

Bancha Satirapoj MD*,
Peerata Lohachit MD**, Thirachai Ruamvang MD***

** Department of Medicine, Phramongkutklao Hospital and College of Medicine*
*** Department of Medicine, Nopparat Rajathanee Hospital*
**** Department of Pathology, Bhumipol Adulyadej Hospital*

A 33-year-old woman without evidence of previous liver disease developed fulminant hepatic failure following the therapeutic dose of acetaminophen 3 days prior to admission. At admission, liver and renal function revealed hepatocellular injury with jaundice, and acute renal failure, total serum bilirubin 12.5 mg/dL, direct serum bilirubin 8.1 mg/dL, aspartate aminotransferase 8460 IU/L, alanine aminotransferase 4640 IU/L, blood urea nitrogen 36 mg/dL, and serum creatinine 5.2 mg/dL. Two days later, she developed multi-organ failure including hemodynamic disturbance with irreversible shock, and expired. Autopsy was performed, liver pathology showed severe centrilobular and midzonal necrosis, compatible with toxic hepatic necrosis, and renal pathology showed focal loss of tubular epithelial cells and partial occlusion of tubular lumen by cellular debris, compatible with acute tubular necrosis. Physicians should be aware of potential hepatotoxicity and nephrotoxicity of acetaminophen, even if given at therapeutic dosage in acute febrile illness.

Keywords: *Acetaminophen, Fulminant hepatic failure, Acute tubular necrosis*

J Med Assoc Thai 2007; 90 (6): 1244-7
Full text. e-Journal: *http://www.medassocthai.org/journal*

Fulminant hepatic failure (FHF) is defined as the rapid development of severe acute liver injury with impaired synthetic function and encephalopathy. FHF and acute liver injury resulting from acetaminophen overdose has been extensively reported in the UK, USA, France and Canada[1,2]. Acetaminophen is a dose related toxin; most cases of FHF occur after ingestion of large doses exceeding 10 gm/day in an attempt to commit suicide. Severe liver injury can rarely occur when doses as low as 3-4 gm/day [3] or unintentional poisoning are taken[4].

The authors report here a patient with FHF in association with the history of therapeutic dose of acetaminophen ingestion. Liver and renal biopsy revealed toxic hepatic necrosis and acute tubular necrosis, respectively.

Correspondence to : Satirapoj B, Department of Medicine, Phramongkutklao Hospital and College of Medicine, Bangkok, 10400, Thailand. E-mail: satirapoj@yahoo.com

Case Report

A 33 year-old Thai woman was admitted to the hospital in October 2005 with a history of one-day acute confusion, mild jaundice, and abdominal discomfort. Three days prior to admission, she visited the outpatient clinic with a history of fever, headache, and sore-throat. Her medications included a total dose of 4000 mg acetaminophen, ranitidine, dimenhydramine, and roxithromicin. She denied previous medical problems and usage of other medication. On admission, she appeared confused. Physical examination revealed body temperature of 37.7°C, pulse rate of 96/minute, respiratory rate of 28/minute and blood pressure of 90/60 mmHg. She was disoriented, mild icteric sclera without anemia and dehydration. Other physical examinations were unremarkable. The initial blood chemistries showed hemoglobin level of 11.8 g/dL, white blood cell count of 12,250/mm^3, platelet count of 210,000/mm^3, blood urea nitrogen of 36 mg/dL, serum creatinine of 5.2 mg/dL, and plasma glucose of 50 mg/dL. Urinalysis revealed

specific gravity of 1.010, red blood cells of 5-10 and white blood cells of 0-1 per high power field and 1+ albumin. Liver function test showed hepatocellular injury with mild cholestatic jaundice: total serum protein 5.7 g/dL, serum albumin 2.5 g/dL, total serum bilirubin 12.5 mg/dL, direct serum bilirubin 8.1 mg/dL, aspartate aminotransferase (AST, sGOT) 8460 IU/L, alanine aminotransferase (ALT, SGPT) 4640 IU/L, and alkaline phosphatase 338 IU/L. Arterial blood gas showed metabolic acidosis and respiratory alkalosis: pH 7.30, PaO_2 147 mmHg, $PaCO_2$ 16 mmHg, and HCO_3 9 mEq/L. Coagulation time was prolonged. Serological investigations were negative for hepatitis B and C. Blood for acetaminophen levels was 10.5 mg/L at 48 hours preceding admission. Blood culture for bacteria was negative.

During admission, broad spectrum antibiotics was administered, fresh frozen plasma (FFP) was commenced to normalize coagulogram, metabolic acidosis and hypercatabolic renal failure were corrected with continuous venovenous hemofiltration(CVVH). Two days preceding admission, she developed multi-organ failure involving liver, kidney, respiratory and hematologic systems along with hemodynamic disturbance with irreversible shock and expired later on.

Autopsy findings:

Gross appearance revealed a pale Thai female with moderate jaundice. All internal organs showed scattering petichial hemorrhage. Diffuse pulmonary congestion, focal pulmonary hemorrhage, and pleural effusion were observed in bilateral thoracic cavities. Intra-abdominal cavity contained about one liter of ascitic fluid. Fatty liver with cholestasis was noted. Both kidneys were mildly enlarged. The brain was slightly swollen.

Microscopic findings:

Lung parenchymal tissue showed diffuse pulmonary congestion with focal extensive pulmonary hemorrhage. Liver revealed severe hydropic and acidophilic degeneration of liver cells. There were focal centrilobular and midzonal necrosis with slight inflammatory infiltration by mononuclear cells in the portal areas. These liver findings were compatible with severe toxic hepatic injury, as shown in Fig. 1. Acute tubular necrosis was evidenced by focal loss of tubular epithelial cells and partial occlusion of tubular lumen by cellular debris as shown in Fig. 2. Brain tissue was diffusely edematous.

Discussion

Pertinent findings in the present case can be summarized as follows:

1. acute liver failure and liver pathology compatible with severe toxic hepatic injury
2. encephalopathy
3. coagulopathy
4. acute renal failure with severe metabolic acidosis
5. hemodynamic disturbance with shock
6. acute respiratory failure with pulmonary edema

The authors reported a case of FHF and later

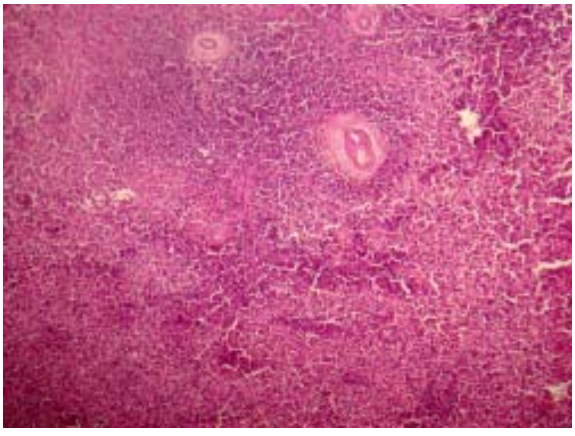

Fig. 1 Light microscopic examination of liver tissue sample shows focal centrilobular and midzonal necrosis with slight inflammatory infiltration by mononuclear cells in the portal areas

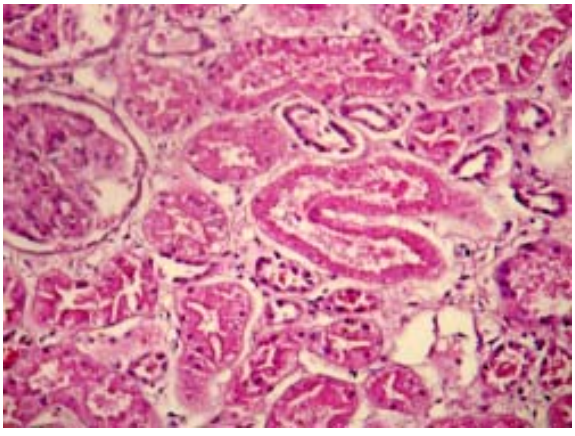

Fig. 2 Light microscopic examination of renal tissue sample shows focal loss of tubular epithelial cells and partial occlusion of tubular lumen by cellular debris

on progressed to multi-organ failure. Various causes of FHF such as viral hepatitis, sepsis including bacterial infection and tropical infection (scrub typhus, leptospirosis), hepatic ischemia, autoimmune hepatitis, drugs, and toxins were excluded. Extremely high aminotransferase values (typically exceeding 3500 IU per liter) helped the authors to distinguish the toxic effects of drugs from viral hepatitis. The presented patient had criteria suggestive of acetaminophen toxicity as the cause of FHF were a serum ALT > 1,000 IU/L, the history of acetaminophen ingestion, detection of acetaminophen in the serum, and hepatocyte injury predominantly in the centrilobular region in liver biopsy as the result of acetaminophen toxicity.

Acetaminophen toxicity produces the most common form of acute liver failure in the United States, accounting for 39% of cases in a recent report[5]. Acetaminophen rapidly causes hepatocyte injury, predominantly in the centrilobular region. Hepatotoxicity rarely occurs if consumption of less than 150 mg of acetaminophen per kg body weight[6]. Moreover, severe liver injury or fatal hepatic necrosis rarely happens when doses as low as 3-4 gm/day[3] or unintentionally taken[4]. There is concern that alcohol abusers, anorexia nervosa or starvation, and patients who take enzyme-inducing medications or multiple minor overdoses over a short period of time may be at risk from acetaminophen concentrations lower than those that would affect others. The presented patient had no evidence of the above risk factors; it is possible that an idiosyncratic mechanism or the inter-individual variation in hepatic pool size of glutathione and the inter-individual variation in CYP2E1 activity precipitated the acute liver injury.

Patients whose plasma acetaminophen concentration lies above the treatment lines are at risk of severe liver damage, but its validity beyond 15 hours is uncertain because of the paucity of data from untreated patients[7]. The presented patient showed detectable plasma acetaminophen after 48 hr, this might be a predictor of fatal hepatic necrosis.

The mechanism of toxicity is similar in the kidney and liver. A toxic intermediate, NAPQI, is formed locally from the cytochrome P450 pathway and then binds covalently to cellular macromolecules, causing cell injury or death. Renal impairment had been estimated to occur in 53% of cases with FHF[8]. Renal tissue usually reveals acute tubular necrosis as evident in the presented patient[9]. Administration of N-acetylcysteine (NAC) is recommended in any case of FHF in which acetaminophen overdose is a suspected or possible cause. Thus, in patients with FHF of unknown etiology, it is wise to assume a possible acetaminophen overdose.

Conclusion

Because acetaminophen is the leading cause of FHF and there is an available antidote, acetaminophen levels should be drawn in all patients presenting with FHF, irrespective of dosage and timing. The patient with very high ALT levels exceeding 1,000 IU/L, FHF, and acute renal failure should prompt consideration of this etiology even when the evidence is lacking.

Acknowledgments

This work was supported by Department of Medicine, Nopparat Rajathanee Hospital, Phramongkutklao Hospital, and College of Medicine.

References

1. Wallace CI, Dargan PI, Jones AL. Paracetamol overdose: an evidence based flowchart to guide management. Emerg Med J 2002; 19: 202-5.
2. Makin A, Williams R. Paracetamol hepatotoxicity and alcohol consumption in deliberate and accidental overdose. QJM 2000; 93: 341-9.
3. Kurtovic J, Riordan SM. Paracetamol-induced hepatotoxicity at recommended dosage. J Intern Med 2003; 253: 240-3.
4. Schiodt FV, Rochling FA, Casey DL, Lee WM. Acetaminophen toxicity in an urban county hospital. N Engl J Med 1997; 337: 1112-7.
5. Watson WA, Litovitz TL, Klein-Schwartz W, Rodgers GC Jr, Youniss J, Reid N, et al. 2003 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2004; 22: 335-404.
6. Lewis RK, Paloucek FP. Assessment and treatment of acetaminophen overdose. Clin Pharm 1991; 10: 765-74.
7. Kadas I, Konczol F, Illes T. Fatal acute liver damage caused by a therapeutic dose of paracetamol. Orv Hetil 1998; 139: 189-91.
8. Blakely P, McDonald BR. Acute renal failure due to acetaminophen ingestion: a case report and review of the literature. J Am Soc Nephrol 1995; 6: 48-53.
9. Bjorck S, Svalander CT, Aurell M. Acute renal failure after analgesic drugs including paracetamol (acetaminophen). Nephron 1988; 49: 45-53.

รายงานผู้ป่วยภาวะตับและไตวายเฉียบพลันจากยาพาราเซตามอลในขนาดปกติ

บัญชา สถิระพจน์, ภิรตา โลหชิต, ธีระชัย ร่วมวัง

รายงานผู้ป่วยหญิงไทยอายุ 33 ปีมาพบแพทย์ด้วยอาการสับสน ร่วมกับภาวะตับวายเฉียบพลัน ให้ประวัติรับประทานยาพาราเซตามอล ขนาดปกติประมาณ 4 กรัมต่อวันเป็นเวลา 3 วันก่อนมาโรงพยาบาล ปฏิเสธโรคประจำตัวอื่น ๆ รวมทั้งโรคตับ ผลการทำงานของตับและไตแรกรับพบ total bilirubin 12.5 mg/dL, direct bilirubin 8.1 mg/dL, aspartate aminotransferase 8460 IU/L, alanine aminotransferase 4640 IU/L, blood urea nitrogen 36 mg/dL, และ serum creatinine 5.2 mg/dL ขณะนอนโรงพยาบาล 2 วันต่อมาเกิดอวัยวะสำคัญต่าง ๆ ทำงานล้มเหลวตามมาจนเกิดภาวะช็อก และเสียชีวิต ผลการตรวจทางพยาธิสภาพตับและไตพบ degeneration of liver cells includes severe centrilobular and midzonal necrosis และ focal loss of renal tubular epithelial cells ร่วมกับ partial occlusion of renal tubular lumen by cellular debris ซึ่งลักษณะเข้าได้กับ toxic hepatic necrosis และ acute tubular necrosis ดังนั้นในผู้ป่วยที่มาพบแพทย์ด้วยปัญหาตับและไตวายเฉียบพลันควรตระหนักถึงภาวะเป็นพิษจากยาพาราเซตามอลไว้ แม้ว่าผู้ป่วยจะรับประทานยาพาราเซตามอลในขนาดปกติ