

Nephrotoxicity associated with acute paracetamol overdose: a case report and review of the literature

與急性「對乙酰氨基酚」中毒有關的腎中毒：個案報告及文獻審查

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A 29-year-old, 65 kg, Chinese man presented to hospital 10 hours after ingesting 30 g of paracetamol (462 mg/kg body weight). The blood paracetamol level was 145 µg/ml at 10 hours post-ingestion. He had no known risk factors for hepatotoxicity and was treated with intravenous N-acetylcysteine (NAC). Serum creatinine level rose to a maximum of 455 µmol/L on day 8; it gradually declined without the need for dialysis. Little is known of the risk factors for nephrotoxicity, which may occur with or without concurrent liver damage, suggesting possible primary toxic effects on the kidney. The use of NAC in this case may have prevented the progression to liver failure and reduced the severity of the nephrotoxic effects. (*Hong Kong j. emerg.med.* 2006;13:105-110)

一名 29 歲體重 65 kg 的華裔男子在服用 30 g 對乙酰氨基酚 (462 mg/kg 體重) 的 10 小時後到醫院求診。血液裏的對乙酰氨基酚水平為 145 µg/ml (服藥 10 小時後)。他沒有肝中毒的風險因素，以靜脈滴注乙酰半胱氨酸治療。在第 8 天，血清的肌酸酐水平升至最高的 455 µmol/L，其後逐漸降低而不需要透析治療 (洗腎)。我們對於腎中毒的風險因素所知甚少，在它發生時肝中毒可以同時存在或不存在，暗示這可能是腎的原發性中毒效應。在這個案中，乙酰半胱氨酸的使用可能制止了肝衰竭的加劇，及減輕了腎中毒的嚴重程度。

Keywords: Acetaminophen, acetylcysteine, acute kidney failure, analgesics, overdose

關鍵詞: 對乙酰氨基酚、乙酰半胱氨酸、急性腎衰竭、止痛藥、服藥過量

Introduction

N-acetyl-para-aminophenol (paracetamol) was discovered in 1889.¹ It was introduced into the United Kingdom market as an analgesic and antipyretic in 1956.¹ Paracetamol is an active metabolite of phenacetin, a compound that was used for its good analgesic and antipyretic properties until it was

implicated in analgesic-abuse nephropathy.² As paracetamol is well tolerated, it is commonly used as an over-the-counter analgesic and antipyretic for headache and minor musculoskeletal pain.

Hepatotoxicity is the most remarkable feature of paracetamol overdose.³ Renal effects of paracetamol overdose are less commonly seen than hepatic effects. However, renal impairment may be more common than previously recognised. The overall incidence of acute renal failure in patients with paracetamol poisoning is less than 2%,⁴ and acute renal failure occurs in 10 to 40% of patients with severe hepatic necrosis.⁵ In 45 adolescents aged 12 to 18 years, mild and severe nephrotoxicity was observed in 8.9% and 2.2% of patients respectively.⁶ While many reports associate the renal effects of large doses of paracetamol

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with severe hepatotoxicity or hepatic failure,⁷ there are also reports of paracetamol-induced renal failure in patients with mild, or no evidence of hepatotoxicity.⁶⁻¹⁸

The objectives of this case report are to describe the clinical presentation of nephrotoxicity with acute paracetamol overdose in a low-risk patient, and to discuss the literature on paracetamol-induced nephrotoxicity.

Case report

A 29-year-old, 65 kg, Chinese man presented to hospital 10 hours after ingesting 30 grams of paracetamol (462 mg/kg body weight). Prior to admission, he had vomited five times. His medical history was unremarkable, except for a history of asthma, which was controlled on salbutamol inhaler when necessary. He was a non-smoker and drank alcohol occasionally. He denied any use of other prescription or over-the-counter medications, or alcohol.

Upon admission, the patient complained of dyspnoea, chest pain, and abdominal pain. The physical examination revealed a temperature of 36.5°C, a pulse rate of 104 beats per minute, a respiratory rate of 16 breaths per minute, and a blood pressure of 131/81 mmHg. His lungs were clear, his abdomen was soft and non-tender, and he was oriented and alert. The remainder of the physical examination was unremarkable. The blood investigation results on admission were as follows: sodium 139 mmol/L (normal range 135-145 mmol/L), potassium 3.8 mmol/L (3.3-4.9 mmol/L), chloride 99 mmol/L (96-108 mmol/L), bicarbonate 16.1 mmol/L (19-31 mmol/L), urea 3.3 mmol/L (2.8-7.7 mmol/L), creatinine 111 µmol/L (44-141 µmol/L), white blood cell count 8.33×10^9 cells/L ($4.0-10.0 \times 10^9$ cells/L), prothrombin time 14.4 sec (11-14 sec), and partial thromboplastin time 29.3 sec (21-32 sec). Hepatitis A, B and C markers were negative. The bicarbonate level normalised on the second day to 28.7 mmol/L. Serum toxicology screen was done on day 2 and was negative

except for paracetamol. Repeat serum and urine toxicology screens done on day 4 were found to be negative for commonly prescribed drugs, alcohols and its metabolites.

The patient was started on intravenous N-acetylcysteine (NAC) empirically (150 mg/kg over 1 hour). The blood paracetamol level was 145 µg/ml at 10 hours post-ingestion, which was above the treatment line on the Rumack nomogram. Hence, the NAC regime was continued till completion (50 mg/kg over 4 hours, followed by 100 mg/kg over 16 hours). He was also started on intravenous fluid therapy. The paracetamol level fell to 23.5 µg/ml on day 2 (32 hours post-ingestion), and to 2.3 µg/ml on day 3 (54 hours post-ingestion). As his liver function tests continued to deteriorate, he was given a second cycle of intravenous N-acetylcysteine (100 mg/kg over 16 hours) on hospital day 3, 52 hours post-ingestion.

On day 3, the patient developed jaundice. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) levels rose to a maximum of 6,278 U/L and >12,000 U/L, respectively, 4 days post-ingestion (Figure 1). He was monitored closely for potential acute liver failure, and a possible liver transplant was anticipated.

Five days after admission, the patient's liver function test results started to improve, but his renal function deteriorated. Serum creatinine level was normal on day 3, but rose to a maximum of 455 µmol/L on day 8; it gradually declined to 378 µmol/L by day 14 without the need for dialysis (Figure 1). During his stay, his daily urine output ranged between 1,550 and 5,010 ml. The patient was discharged from hospital on day 14. He remained alert, conscious and oriented throughout his stay.

The patient was asymptomatic at a follow-up examination 26 days post-ingestion. His creatinine, AST and ALT levels were 183 µmol/L, 16 U/L, and 30 U/L, respectively. He was lost to follow up subsequently.

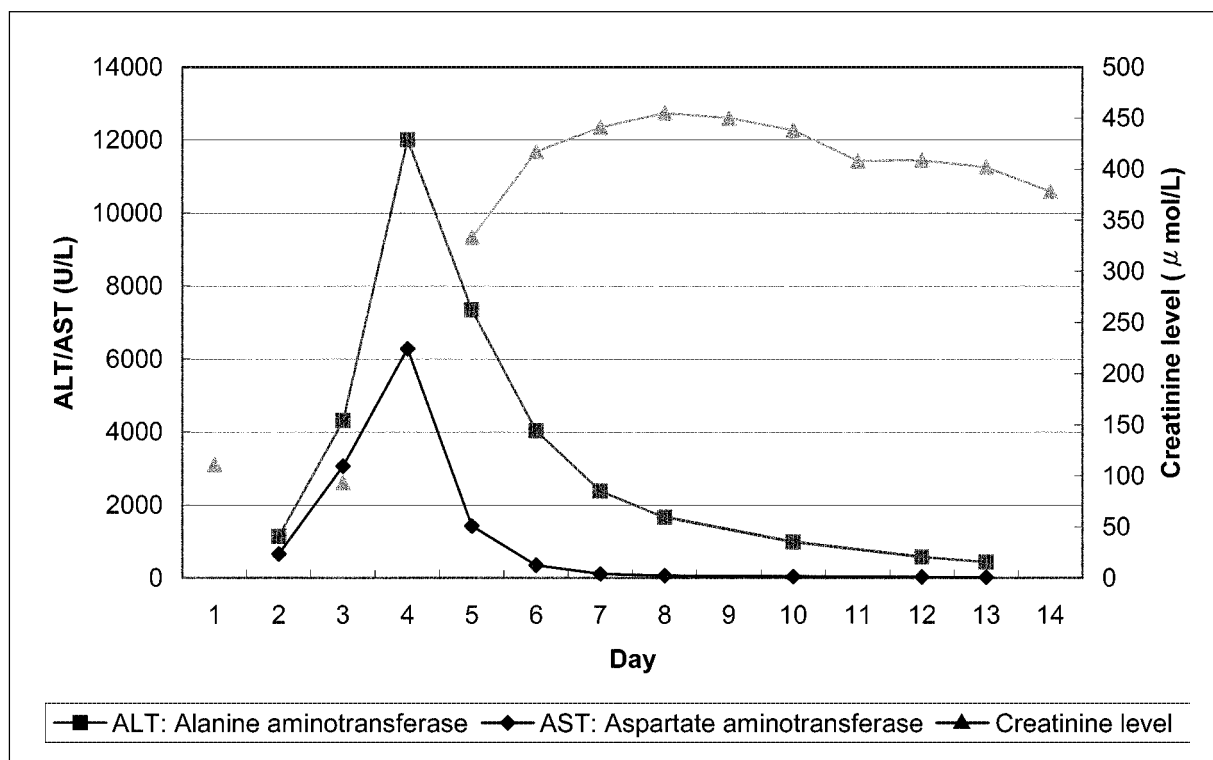


Figure 1. Trends of liver and renal function tests.

Discussion

The therapeutic dose of paracetamol in adults is 1 g three to four times a day, up to a maximum of 4 g/day.¹⁹ In children less than 12 years of age, the dose is 10-15 mg/kg/dose every four to six hours, up to a maximum of 75 mg/kg/day.¹⁹ The currently accepted toxic dose are ingestions greater than 7.5 g or 150 mg/kg in adults²⁰ and 200 mg/kg in children.^{21,22}

Our patient had grossly abnormal liver function test results that rapidly returned to normal with no evidence of hepatic encephalopathy. Acute renal impairment developed as liver function test results were returning to normal and the patient's clinical condition was improving. The renal insufficiency was of moderate severity and the renal function improved on follow up.

Renal insufficiency after paracetamol overdose is usually transient and rarely requires dialysis.¹⁷ If it

occurs, the serum creatinine typically begins to rise soon after the aminotransferase level has peaked.²³ The renal function can be expected to return to baseline within 4 weeks unless multiple organ failure develops.^{7-9,17} There is no report in the literature of patient mortality occurring without hepatic failure.

Predisposing factors to renal injury

Factors known to predispose to hepatotoxicity include alcoholism, malnourishment, and use of liver enzyme-inducing medications.^{4,7,17,24-26} Although these factors are also seen more frequently in patients with paracetamol-induced renal toxicity,^{4,7,26} little is known of the risk factors for nephrotoxicity, which may occur with or without concurrent liver damage suggesting possible primary toxic effects on the kidney. None of these factors were present in our patient.

Mechanism of renal injury

Previously, it was believed that paracetamol-induced

kidney failure occurred as a result of severe hepatic failure.^{7,14} In the presence of severe hepatotoxicity that precludes further hepatic metabolism of the parent paracetamol, there may be 'spill over' of paracetamol to the kidney where it will be metabolised.⁶ Nephrotoxicity then results when there is insufficient glutathione in the renal parenchyma. This was initially interpreted as a hepatorenal syndrome,¹⁷ where extreme intrarenal arterial and arteriolar vasoconstriction would be observed.²⁷ Wilkinson et al analysed 160 patients and found that the development of renal failure in patients with hepatic failure from any cause was closely related to the occurrence of endotoxin that would be cleared by a normal liver but not by a diseased liver.²⁸ They concluded that there is little evidence for a paracetamol-induced nephrotoxic effect.

However, there have been reports of acute renal toxicity occurring as a direct primary event rather than as a secondary event.^{13,14} When paracetamol is metabolised in both the liver and kidney, nephrotoxicity may occur independently of hepatotoxicity depending on the balance of metabolism and the glutathione stores within the kidney.⁶ Studies in the CD-1 mouse suggest that biotransformation in the kidney of paracetamol to a reactive electrophile contributes to covalent binding and subsequent nephrotoxicity.²⁹ Mitchell et al demonstrated that certain strains of rats that have high concentrations of microsomal cytochrome P450 in their kidneys developed acute tubular necrosis after a single, nonlethal dose of paracetamol.³⁰ Paracetamol given in increasing doses to male Fischer rats depleted glutathione stores in the liver and kidneys; large amounts of oxidative radiolabelled metabolite bound to hepatic and kidney protein then led to a dose-dependent acute hepatic and renal necrosis.³¹ The incidence and severity of paracetamol-induced liver and renal necrosis decreased when the rats were pre-treated with cobalt chloride, an inhibitor of cytochrome P450. When they were pre-treated with 3-methylcholanthrene, which induces drug-metabolising enzymes in the liver only, paracetamol-induced hepatic necrosis occurred; the kidneys were not affected. Covalent binding of paracetamol metabolites was also greater in liver than

kidney proteins when CD-1 mice and Sprague-Damley rats were pre-treated with 3-methylcholanthrene before being injected with paracetamol intraperitoneally.³² These studies suggest that a toxic metabolite of paracetamol was formed in situ in the kidney.

As cytochrome P450 is the terminal oxygenase controlling most drug oxidations in the kidney, liver, and other tissues, and because this enzyme system is concentrated primarily in the renal cortex, it is likely that metabolic deactivation of paracetamol to an arylating metabolite might be responsible for the renal lesion just as it is for the hepatic injury.³⁰ Compared to the liver, the cytochrome P450 enzymes in the kidney are less able to detoxify paracetamol.⁷ Thus, the renal glutathione stores are depleted more rapidly, and kidney cell injury occurs as acute tubular necrosis.

Renal biopsy

Histopathological examination by light and electron microscopy on four patients who had overdosed on paracetamol showed necrosis of the proximal and distal parts of the renal tubules, and the remaining lumen filled with shed cells.^{8,15} The patterns seen were similar to those seen in other forms of toxic nephropathy. The necrosis could be due to a direct toxic action by the drug on the vascular wall or to impaired oxygen delivery caused by injury of the capillary wall.¹⁵ The granular material in the cell lumens was postulated to be an accumulation of cellular material denatured through the toxic action of paracetamol or its metabolites, or intracellular calcium accumulations.⁸

Use of N-acetylcysteine to prevent renal injury

NAC is known to decrease hepatotoxicity.^{6,7,26,33,34} The usefulness of NAC to reduce nephrotoxicity has not been investigated. Davenport and Finn described two patients who developed acute renal failure after paracetamol overdose and treatment with NAC.¹⁴ Also, no correlation was found between nephrotoxicity and the early administration of NAC.⁶ However, the use of NAC in this case may have prevented the progression to liver failure and reduced the severity of the nephrotoxic effects.

Conclusion

In addition to hepatotoxicity, the clinical significance of nephrotoxicity in paracetamol overdose, and the importance of monitoring the renal function while caring for such patients, must be recognised. Its severity and course may not be closely related to those of hepatotoxicity, and it may occur in a low-risk patient. This case report describes one such patient. More prospective clinical studies are warranted to determine the risk factors for nephrotoxicity, which may occur with or without concurrent liver damage.

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