

CASE REPORT

Early lactic acidosis after acetaminophen overdose

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Abstract

We describe a patient who presented with an early lactic acidosis and reduced consciousness after an acetaminophen overdose. Although infrequently recognised, early lactic acidosis after acetaminophen poisoning is actually not uncommon and is related to mitochondrial toxicity induced by a toxic metabolite and the acetaminophen itself. Therefore, acetaminophen intoxication should be suspected in patients with altered mental status and lactic acidosis.

Introduction

Lactic acidosis is frequently observed during hypoxia, hypoperfusion or cellular damage. After acetaminophen poisoning, late lactic acidosis is often seen in the setting of liver toxicity. However, early lactic acidosis, which is usually associated with coma, can occur after acetaminophen toxicity as well. We here report on a case we recently encountered and discuss the molecular mechanisms involved.

Case report

A 76-year-old woman suddenly fell to the ground in her home and was found unresponsive by her husband, who heard her fall in the next room. No signs of seizure were observed. Her previous medical history was relevant for hypothyroidism and cognitive impairment for which a putative diagnosis of vascular dementia had been made. A cerebral CT scan was performed and showed areas of cerebral ischaemia of an older date but no other abnormalities. She was haemodynamically stable and her respiration was adequate. The Glasgow coma score was E1M5V1 and therefore she was intubated and admitted to our ICU. At admission, laboratory tests revealed an uncompensated high anion gap metabolic acidosis associated with an elevated lactate level, leucocytosis and a mildly elevated C-reactive protein (CRP). Specifically, the relevant laboratory results were pH 7.2, pO₂ 15 kPa, pCO₂ 5.5 kPa, bicarbonate 16 mmol/l, base

excess -12 mmol/l, chloride 102 mmol/l, sodium 138 mmol/l, lactate 8.3 mmol/l, CRP 42 mg/l and leucocytes 21x10⁹/l. A chest X-ray showed a small pleural effusion on the left side and possibly a small infiltrate in the lower lobe. Initially, the clinical picture was incompletely understood; a working diagnosis of pneumonia-induced sepsis was made based on the presence of two systemic inflammatory response syndrome criteria combined with lactic acidosis and an indistinct consolidation in the lung. Broad-spectrum antibiotics and goal-directed fluid therapy were initiated. Unexpectedly, the patient regained consciousness within four hours, was extubated and showed a very swift clinical recovery. Lactate concentration normalised within the first day of admission and the patient did not develop any respiratory problems; no fever or sputum production was observed. Therefore, 24 hours after admission, the working diagnosis of pneumonia-induced sepsis was challenged and a more extensive history was taken. The patient reported she had lost consciousness several hours after taking an intentional overdose of 50 grams of acetaminophen (paracetamol) in an apparent suicide attempt. Her partner confirmed that empty strips were indeed found in their house, which corresponded to the number of pills reported by the patient; there was no report of other medication missing. N-acetylcysteine was administered immediately and the acetaminophen level (32 hours after ingestion) was measured and was shown to be 20 mg/l. Unfortunately, the patient had received a single dose of acetaminophen in the ICU 12 hours before this concentration was measured and therefore the measured concentration lacks reliability as a marker of severity of intoxication. Administration of N-acetylcysteine was continued for 24 hours after which the acetaminophen level was undetectable. The patient was observed for several days but did not develop any liver enzyme elevation and was discharged for further psychiatric evaluation and care.

Discussion

Acetaminophen is a widely used analgesic that is quite safe at therapeutic dosages. However, acetaminophen intoxication is one of the most common causes of drug poisoning worldwide and strongly associated with hepatic failure.^[1] Hepatic failure may arise several days after an acetaminophen overdose and this is generally accompanied with lactic acidosis mainly due to decreased clearance of lactate. In normal therapeutic doses acetaminophen is metabolised to non-toxic compounds that are secreted. The two most important pathways of metabolism in the liver, glucuronidation and sulfation, are responsible for the main part of acetaminophen metabolism. However, in cases of severe overdose, these two pathways become saturated giving rise to a third metabolic route, the oxidation by cytochrome P450, leading to the formation of the extremely toxic metabolite N-acetyl-p-benzoquinone-imine (NAPQI) (*figure 1*). Under normal circumstances, glutathione binds fully to NAPQI, neutralising the toxic effects.^[2] However, large quantities of NAPQI will deplete glutathione reserves and therefore instigate and propagate hepatic cell necrosis.^[3,4]

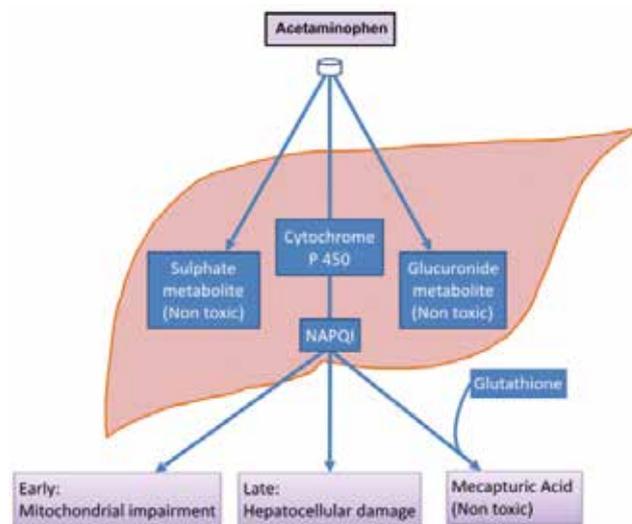


Figure 1. Molecular pathways associated with acetaminophen-induced lactic acidosis

Acetaminophen is normally degraded to non-toxic products but high doses lead to the formation of NAPQI through metabolism by the cytochrome P450 pathway. Some patients develop early mitochondrial damage whereas others will develop late hepatocellular injury, both forms of toxicity may be prevented by the administration of glutathione.

Lactic acidosis is not uncommon several days after acetaminophen overdose in the clinical picture of associated liver failure; however early lactic acidosis is more unusual and occurs independently of liver toxicity.^[5] Preclinical studies have shown that high concentrations of acetaminophen may cause early mitochondrial dysfunction as early as four hours after acetaminophen exposure to cultured liver cells.^[6,7] In cases of severe acetaminophen poisoning where high

doses of acetaminophen have been used, NAPQI may induce mitochondrial dysfunction and a reduction in mitochondrial respiration. In these cases mitochondrial dysfunction will lead to early lactic acidosis which precedes the potential subsequent hepatocellular injury caused by the excessive NAPQI formation by several days.^[8] NAPQI binds to mitochondrial proteins such as aldehyde dehydrogenase and causes downregulation of mitochondrial genes leading to a reduced cellular respiration. Following this inhibition, lactate clearance is lowered and gluconeogenesis is inhibited. Whether all the effects of acetaminophen on mitochondrial function are fully explained by NAPQI remains to be elucidated since acetaminophen itself has been shown to act as a mitochondrial toxin by coupling to mitochondrial aldehyde dehydrogenase.^[9]

Several cases of early lactic acidosis have previously been described,^[5,8,10,11] and a review of these cases revealed that these patients typically present several hours after acetaminophen exposure with the combination of a very high concentration of acetaminophen in the blood, reduced consciousness and early lactic acidosis which are all consistent with the clinical presentation we present here.^[8] Treatment of early lactic acidosis consists of the prompt administration of N-acetylcysteine, which restores glutathione availability and effectively treats and prevents lactate accumulation as well as hepatic failure.^[2,12] A previous report described that high anion gap acidosis in acute acetaminophen overdose is a common feature since it was observed in 41% of cases.^[5] Since lactate was not measured in all of these patients it is unclear what percentage was caused by lactic acidosis, but if the lactic acid was elevated this usually persisted for less than one day. Furthermore, this study showed that the occurrence of an increased early lactate was strongly associated with confusion and lethargy but did not predict hepatocellular injury. In several other reported case series of early lactic acidosis in acetaminophen poisoning, reduced consciousness is a common finding.^[8,11,13,14] Interestingly, this reduction in consciousness generally resolves within 24–48 hours, which is in line with the case reported here. Although previous studies have documented the association between early lactic acidosis and coma in acetaminophen toxicity, studies evaluating the mechanisms behind either the cause of the reduced consciousness or its rapid resolution are lacking.

Hepatotoxicity after acetaminophen overdose is generally dose dependent. Whether the exact dose (50 grams) has indeed been ingested is, as always, uncertain. The fact that empty strips were found that match the self-reported dose of ingestion suggests that this dose was indeed taken but is not definitive proof of the ingested dose. Although toxicity is generally dose dependent and early lactic acidosis is associated with intoxications with high doses of acetaminophen, there is however ample literature of patients with severe

acetaminophen intoxication who developed early lactic acidosis but did not develop increases in transaminases or hepatic failure.^[11,13-16] Individual genetic susceptibilities to acetaminophen might play a role in this phenomenon.^[17]

In conclusion, acetaminophen poisoning can result in early coma and lactic acidosis before the manifestation of hepatic injury. Therefore, acetaminophen intoxication should be suspected in patients presenting with altered mental status and lactic acidosis.

Disclosures

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