Delayed and prolonged elevated serum paracetamol level after an overdose — possible causes and implications

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ABSTRACT
We report the case of a 29-year-old man who ingested about 50 g of standard-preparation paracetamol plus other medications. The serum paracetamol level remained low in the first 24 hours. It peaked 54 hours after ingestion and remained high for 5 days. An N-acetylcysteine (NAC) infusion was started at admission, but was ceased 36 hours later as the clinical and laboratory signs were reassuring. On Day 3, the patient’s liver function deteriorated and a rising serum paracetamol level was noted; hence, an NAC infusion was reintiated. Despite this, the patient developed fulminant hepatic failure. This case underlines the importance of monitoring paracetamol levels and liver function for at least 72 hours after a suspected large overdose of paracetamol before discontinuing NAC infusion.

Clinical records
A 29-year-old man (weight, 60 kg) presented to hospital 2 hours after a rapid ingestion of about 50 g (100 × 500 mg) of standard-preparation paracetamol, 200 mg of olanzapine, 750 mg of amitriptyline, 2 g of sodium valproate and an unknown quantity of alcohol. This history was based on the empty medication packets found by paramedic officers at his house. No further information was available to confirm or refute the history provided.

The patient’s Glasgow Coma Scale score was 3 at presentation. Endotracheal intubation was performed for airway protection. He was haemodynamically stable, had an unremarkable physical examination and had a normal electrocardiogram. Results of all initial blood tests (biochemical analysis, full blood count, coagulation studies) were within normal ranges. On presentation, his blood alcohol level was 0.28 g/dL. His initial serum paracetamol level (2 hours after ingestion) was 503 μmol/L. A urine dipstick test was negative for opioids, cannabis and amphetamines. His serum valproate levels were within the non-toxic range.

His past history included depression, alcohol misuse, multiple suicide attempts and chronic back pain after a motor vehicle accident 6 months previously. His regular medicines included amitriptyline, valproate, olanzapine and paracetamol.

Based on the history of ingestion of a large amount paracetamol, intravenous N-acetylcysteine (NAC) infusion was commenced. The dose given was 150 mg/kg over 60 minutes, then 50 mg/kg over 4 hours, then 100 mg/kg over 16 hours, based on the Australasian consensus statement on paracetamol overdose.1 Activated charcoal was not administered because he presented 2 hours after ingestion.

Serum paracetamol was measured regularly. His paracetamol level (Figure 1) remained below the paracetamol nomogram,1 except for the 14-hour and 18-hour levels, which were mildly elevated.

Twenty-four hours after paracetamol ingestion, serum paracetamol levels were low (38 μmol/L), and they remained low at 30 hours. Results of liver function tests remained normal throughout the first 2 days (Figure 2). The patient was extubated uneventfully 30 hours after ingestion. As his paracetamol levels and liver function tests were normal, and there was doubt regarding the amount of paracetamol he had ingested, it was decided to stop the NAC infusion 36 hours after ingestion.

Fifty-four hours after ingestion, paracetamol levels were found to be high again (Figure 1) and liver enzyme levels started to rise (Figure 2). This was accompanied by increasing confusion (grade 2 encephalopathy), rising serum lactate levels and a worsening coagulation profile. There was no obvious explanation for the rise in serum paracetamol levels after the initial fall.

The patient’s NAC infusion was restarted with a repeat bolus. His clinical state and biochemical profile rapidly deteriorated. He was reintubated and required multiorgan support. He developed hyperacute fulminant liver failure and multiorgan failure. He developed clinically obvious but non-life-threatening bleeding secondary to severe coagulopathy. He was referred to a hepatologist and was under close observation for an urgent liver transplant. An intracerebral pressure monitor was placed to monitor intracranial pressures following correction of his coagulopathy. NAC was continued for 10 days, until serum liver enzyme levels normalised. After treatment in the intensive care unit, his condition began to improve slowly, and he was extubated 3 weeks after admission and discharged from the ICU 4 weeks after presentation.
Discussion

To our knowledge, this is the first case report describing a patient presenting at an early stage with a large paracetamol overdose that resulted in delayed and prolonged elevations of serum paracetamol levels and subsequent fulminant hepatic failure requiring extended treatment with NAC.

Paracetamol is rapidly absorbed from the small intestine. Peak serum concentrations occur within 1–2 hours. The standard preparation is usually distributed within 4 hours of ingestion.1 The cause of the delayed peak seen in the case we present was unclear, despite exploration of all possible causes for this unusual presentation.

There have been a few case reports of dual paracetamol peaks with sustained-release preparations.2-5 This possibility was thoroughly investigated. However, it was clear from the empty tablet blister packets found at the incident scene that the patient had taken only standard-preparation paracetamol. The possibility of a second overdose being administered in the ICU was ruled out after a thorough investigation.

Paracetamol levels were assayed using the Roche Modular PPE using the acetaminophen assay kit K8001, K8002,6 which has been shown to have good intra- and interassay precision. It is known that high lipid levels can interfere with this assay. In this case, the patient's lipid profile was within normal limits.

It is possible that the coingestion of amitriptyline and olanzapine played a role in slowing gastric emptying. The patient did not exhibit signs of major antidepressant or antipsychotic poisoning, but this does remain a distant possibility as a contributing cause. Valproate can also cause hepatotoxicity. However, serum valproate levels were tested for 2 days after presentation, and were in the non-toxic range.

Coingestion of opioids and first-generation antihistamines has resulted in delayed paracetamol peak concentrations after immediate-release paracetamol overdose,7 but there was no evidence of opioids in the polypharmacy this patient had taken.

The dissolution profile of the paracetamol may be delayed due to clumping of tablets and possible pharma-cobezoar production, as has been suggested previously.3 This may, in part, explain the prolonged period of absorption seen after this overdose, but this is difficult to predict and diagnose.

This patient developed evidence of fulminant liver failure 72 hours after admission. This was 12 hours after the NAC infusion was stopped because the paracetamol levels and the liver function tests had normalised. Complications developed despite NAC antidote therapy being commenced within 2 hours of ingestion of the overdose and NAC infusion being continued for 36 hours after presentation.

It has been postulated that the amount of NAC provided by the standard intravenous protocol may not be adequate to provide enough sulfhydryl group replacement to completely conjugate the toxic intermediary paracetamol metabolite (N-acetyl-para-benzoquinoneimine) to nontoxic cysteine and mercapturate paracetamol metabolites in cases of massive paracetamol overdose.3
Similar elevations in hepatic aminotransferases have been noted in a patient with gastric paresis following massive ingestion of immediate-release paracetamol and despite early commencement of NAC after ingestion.\textsuperscript{8} Gastric paresis was not diagnosed in our patient.

It has been reported previously that patients with massive ingestions may have altered absorption kinetics due to the solubility of acetaminophen being exceeded, or due to physiological or chemical alteration of gastrointestinal emptying or motility.\textsuperscript{9,10} Administration of activated charcoal at a time point beyond the recommended 2 hours post-ingestion of immediate-release paracetamol may reduce the absorbed dose and reduce peak serum paracetamol concentrations. This has been reported previously.\textsuperscript{11} Patients such as ours may benefit from gastrointestinal decontamination beyond the recommended 1-hour interval.\textsuperscript{1}

This case underlines the importance of monitoring paracetamol levels and liver function for at least 72 hours in suspected cases of massive overdose before discontinuing NAC.

**Competing interests**

None declared.

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