CASE REPORT

Haemodialysis in acute paracetamol poisoning

L Serjeant,[1] J Evans,[1] F Sampaziotis,[2,3] W G Petchey[1,4]

[1]Department of Nephrology, Cambridge University Hospitals NHS Trust, Cambridge, UK
[2]Department of Hepatology, Cambridge University Hospitals NHS Trust, Cambridge, UK
[3]Anne McLaren Laboratory, Cambridge Stem Cell Institute, University of Cambridge, Cambridge, UK
[4]Nuffield Department of Surgical Sciences, Transplantation Research Immunology Group, University of Oxford, Oxford, UK

Correspondence to
Dr WG Petchey, William.petchey@nds.ox.ac.uk

Accepted 3 January 2017

SUMMARY

A woman aged 23 years presented late with clinical and biochemical features of a life-threatening paracetamol (acetaminophen) overdose. Despite instigating *N*-acetylcysteine treatment, due to evidence of mitochondrial dysfunction together with an exceedingly high paracetamol level, the decision was made to dialyse the patient acutely to remove the parent drug. This was highly effective, and with on-going supportive care, the patient made a full recovery without the need for transplantation. This case highlights the role of extracorporeal therapy as a *treatment* option in selected cases of paracetamol overdose, consistent with the international guidelines.

BACKGROUND

Paracetamol overdose is a common presentation to the emergency department (ED) and can be life threatening.

Haemodialysis is not a well-recognised *treatment* option for paracetamol overdose. This case demonstrates the role of haemodialysis in selected cases, in accordance with the international guidelines.

We hope to raise awareness of the effective role of haemodialysis in acute paracetamol overdose and propose that such intervention may avoid worse outcomes.

CASE PRESENTATION

A woman aged 23 years was bought to the ED having taken a large mixed overdose of predominantly paracetamol. The exact quantity and timing of the overdose were unknown, but possibly as much as 47.5 g paracetamol (864 mg/kg bodyweight) as well as codeine, ibuprofen and alcohol had been consumed in the preceding 24 hours. A family member had found her drowsy and confused the following morning and called the emergency services. She was unable to give further history, but stated that the overdose was taken with suicidal intent. Additional information was gathered from family members and paramedics.

She had a known psychiatric history of depression, bulimia, alcohol abuse, self-harm and suicide attempts. She had no other medical history of note, took no regular medications and had no known allergies. She usually lives with her parents (who were not at home at the time) and had recently returned from South Africa, following discharge from an eating disorder facility there.

On arrival, our patient had fluctuating consciousness with confusion and was unable to provide a full history. Vital signs and examination were otherwise unremarkable and, specifically, there were no clinical signs of opiate toxicity.

INVESTIGATIONS

Her initial blood tests demonstrated lactic acidosis (pH 7.22, pCO_2 3.9 kPa, base excess (BE) −11 mmol/L and lactate 7.9 mmol/L). Renal function was normal (creatinine 52 μmol/L), liver function was deranged (alanine aminotransferase (ALT) 562 U/L, alkaline phosphatase 122 U/L and bilirubin 12 μmol/L), but synthetic function was not yet affected (International Normalised Ratio (INR) 0.99). Plasma ammonia level was 72 μmol/L. Her paracetamol level was 536 mg/L.

Two hours later, despite aggressive fluid resuscitation and instigating *N*-acetylcysteine (NAC), the acidosis persisted (pH 7.21, pCO_2 4.1 kPa, BE (BE) −10.5 mmol/L and bicarbonate 17.1 mmol/L), the lactate remained elevated at 5.6 mmol/L and the patient remained confused. In light of the above, the patient underwent haemodialysis and following this, all markers of acid–base homeostasis improved, as did cognition.

ALT rose to 4487 U/L at peak (24 hours after admission), but subsequently fell. The activated partial thromboplastin time (APTT) was highest 12 hours after admission (43.8 s) and prothrombin time (PT) highest at 24 hours after admission (25.5 s; INR 2.13).

TREATMENT

On presentation, NAC infusion and fluid resuscitation was started in the ED.

After discussion with the National Poisons Information Service (NPIS, UK), she was referred for haemodialysis. She had a central venous catheter inserted and a 3 hour haemodialysis session was started (High-flux polysulfone 1.8 m^2 membrane, Qb 300 mL/min, Qd 800 mL/min, K3 dialysate), 7 hours after her initial presentation to the ED. NAC concentration was doubled during the dialysis session. Paracetamol levels following dialysis were 63 mg/L.

Fluid resuscitation with potassium replacement was continued. She also received empirical antibiotics (piperacillin with tazobactam), fluconazole, omeprazole and high-dose vitamin B and C supplementation.

OUTCOME AND FOLLOW-UP

The patient responded well to treatment, spending one night in the High Dependency Unit after haemodialysis for monitoring and to complete the NAC infusion.

She stayed on in the hepatology ward for a further three nights for observation and liaison psychiatry input. Her liver function tests were continuing to improve at discharge, though not yet normalised. She was discharged to a specialist psychiatric rehabilitation centre. Two weeks after initial presentation, her liver, renal and synthetic functions were completely normal.

To cite: Serjeant L, Evans J, Sampaziotis F, *et al*. *BMJ Case Rep* Published online: [*please include* Day Month Year] doi:10.1136/bcr-2016-218667

DISCUSSION

Paracetamol is a commonly overdosed drug and toxicity, caused by accumulation of the harmful intermediate metabolite *N*-acetyl-*p*-benzoquinone imine (NAPQI), is the most common cause of acute liver failure and indication for liver transplantation in the developed world.[1–3] The mainstay of medical treatment is NAC, which supplements endogenous glutathione stores and promotes conjugation of NAPQI to a non-toxic metabolite.[4 5] Despite the availability and efficacy of this antidote, paracetamol toxicity can require liver transplantation and remains fatal in some cases.[6] This is often in the case of a large ingestion (paracetamol dose >500 mg/kg total body weight) where a less recognised pattern of paracetamol poisoning can occur.[7] These patients develop mitochondrial dysfunction, presenting with altered consciousness and lactic acidosis, often prior to the onset of acute liver injury (ALI).[6 8] The role of NAC in these cases is less well understood, but it is thought that the antidote cannot protect against the burden of toxicity or reverse the mitochondrial effects.[8]

Predicting outcomes and prognosis in paracetamol overdose is challenging. Recent work by Cairney *et al*[9] suggests that the risk of developing an ALI or hepatotoxicity is directly related and proportionate to the paracetamol levels at presentation. In this prospective series, patients presenting with a paracetamol level of >500 mg/L (as in our patient's case) were twice as likely to develop ALI compared with those with levels below this (27% vs ≤13%) and three times as likely to develop hepatoxocity (18% vs ≤6%).[9] Worryingly, even in patients treated promptly with NAC (within 8 hours of ingestion), those with initial paracetamol levels of >500 mg/L were still more likely to develop ALI compared with those with levels of ≤500 mg/L (33% vs ≤12.5%; p<0001), suggesting that the dose of NAC in extremely large overdoses is either inadequate or ineffective.[9]

Paracetamol has a molecular weight similar to NAC. The standard delivered dose of NAC in the UK is 300 mg/kg in the first 24 hours. Therefore, assuming that 100% of ingested paracetamol is converted to NAPQI, our patient (who ingested 864 mg/kg) will generate far more NAPQI than could be neutralised by the antidote (which reacts in a 1:1 fashion with NAC). Unfortunately, NAC, especially in large doses, is often poorly tolerated by patients.[10] While in some patients medical therapy may be sufficient despite severe multiorgan failure, others may not survive without emergency liver transplantation.[6] The modified Kings College Criteria for transplantation is a well-recognised validated scoring system used to identify patients in need of urgent liver transplantation.[11 12] The criteria are listed in table 1.[13]

Table 1 The modified Kings College Criteria for transplantation[13]

Category 1	Aetiology: paracetamol poisoning: pH <7.25 >24 hours after overdose and after fluid resuscitation
Category 2	Aetiology: paracetamol poisoning: coexisting PT >100 s or INR >6.5 s, and serum creatinine >300 μmol/L or anuria, and grade 3–4 encephalopathy
Category 3	Aetiology: paracetamol poisoning: serum lactate >24 hours after overdose >3.5 mmol/L on admission or >3 mmol/L after fluid resuscitation
Category 4	Aetiology: paracetamol poisoning: two of the three criteria from category 2 with clinical evidence of deterioration (eg, increased ICP, FiO_2 >50%, increasing inotrope requirements) in the absence of clinical sepsis

ICP, intra-cranial pressure; INR, International Normalised Ratio; PT, prothrombin time.

Paracetamol is at least moderately dialysable,[7 14] being a small, water-soluble molecule with a relatively low volume of distribution. However, given the efficacy of NAC in most cases, the use of haemodialysis in overdose has been confined to a supportive role as renal replacement therapy in the setting of multiorgan failure.[7]

The Extracorporeal Treatments in Poisoning (EXTRIP) group is an international consensus group, who reviews the available evidence and produces guidelines for extracorporeal treatments in relation to a number of commonly encountered toxins.[7] In 2014, EXTRIP published guidance on acetaminophen poisoning; these guidelines affirm NAC as the primary treatment, but recommend adjunct haemodialysis where there is evidence of mitochondrial dysfunction (fluctuating consciousness and persistent lactic acidosis despite fluid resuscitation) and exceedingly high drug levels (proven by paracetamol level >900 mg/L).[7] In these instances, the concentration of NAC is doubled during dialysis to account for increased clearance of the antidote.[14 15] Our patient had drug levels below the EXTRIP cut-off, but after discussion with the NPIS, due to the clinical context and our patient's very low body mass index and malnourished state, we elected to use extracorporeal therapy. Haemodialysis is effective in correcting the acidosis and removing the paracetamol,[14 16] thus allowing recovery where NAC alone may have been insufficient, with the possible sequelae of transplantation or death.

In our patient, her acid–base balance and lactate identify her as a possible candidate for transplantation (based on current criteria). However, haemodialysis effectively corrected the lactic acidosis and removed the toxin to allow a prompt recovery. This may have also reduced the severity of the liver injury developed.

Learning points

- Paracetamol overdose is a common presentation to the emergency department and can be life threatening.
- NAC infusion is the mainstay of management. Haemodialysis is not a well-recognised *treatment* option for paracetamol overdose.
- It is important to seek expert opinion in poison cases, even if common, in the presence of unusual clinical features.
- Prognosis in paracetamol overdose is difficult to assess. According to the Kings criteria for liver transplantation, our patient may have been a candidate for transplantation had adjunctive haemodialysis not successfully reversed the lactic acidosis and removed the toxin to reduce the severity of the subsequent liver injury.
- This case demonstrates the role of haemodialysis in selected cases, in accordance with the international guidelines, and we propose that such intervention may help avoid adverse outcomes that could include hepatotoxicity, liver failure or the need for transplantation.

Contributors WGP conceived the idea of submission as a case report. LS and JE wrote the manuscript, with hepatology input from FS and supervision/nephrology input by WGP.

Competing interests None declared.

Patient consent Obtained.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Leise MD, Poterucha JJ, Talwalkar JA. Drug-induced liver injury. *Mayo Clin Proc* 2014;89:95–106.
2 Serper M, Wolf MS, Parikh NA, *et al*. Risk factors, clinical presentation, and outcomes in overdose with acetaminophen alone or with combination products: results from the acute liver failure study group. *J Clin Gastroenterol* 2016;50:85–91.
3 Bunchorntavakul C, Reddy KR. Acetaminophen-related hepatotoxicity. *Clin Liver Dis* 2013;17:587–607, viii.
4 Buckley NA, Dawson AH, Isbister GK. Treatments for paracetamol poisoning. *BMJ* 2016;353:i2579.
5 Prescott LF, Illingworth RN, Critchley JA, *et al*. Intravenous *N*-acetylcystine: the treatment of choice for paracetamol poisoning. *Br Med J* 1979;2:1097–100.
6 Bourdeaux C, Bewley J. Death from paracetamol overdose despite appropriate treatment with *N*-acetylcysteine. *Emerg Med J* 2007;24:e31.
7 Gosselin S, Juurlink DN, Kielstein JT, *et al*. Extracorporeal treatment for acetaminophen poisoning: recommendations from the EXTRIP workgroup. *Clin Toxicol (Phila)* 2014;52:856–67.
8 Shah AD, Wood DM, Dargan PI. Understanding lactic acidosis in paracetamol (acetaminophen) poisoning. *Br J Clin Pharmacol* 2011;71:20–8.
9 Cairney DG, Beckwith HK, Al-Hourani K, *et al*. Plasma paracetamol concentration at hospital presentation has a dose-dependent relationship with liver injury despite prompt treatment with intravenous acetylcysteine. *Clin Toxicol (Phila)* 2016;54:405–10.
10 Bateman DN, Dear JW, Thanacoody HK, *et al*. Reduction of adverse effects from intravenous acetylcysteine for paracetamol poisoning: a randomised controlled trial. *Lancet* 2014;383:697–704.
11 Craig DG, Ford AC, Hayes PC, *et al*. Systematic review: prognostic tests of paracetamol-induced acute liver failure. *Aliment Pharmacol Ther* 2010;31:1064–76.
12 Bernal W, Donaldson N, Wyncoll D, *et al*. Blood lactate as an early predictor of outcome in paracetamol-induced acute liver failure: a cohort study. *Lancet* 2002;359:558–63.
13 Zalewska K. *POLICY POL195/4. Liver transplantation: selection criteria and recipient registration*. NHS Blood and Transplant, 2015. http://odt.nhs.uk/transplantation/guidance-policies/
14 Ghannoum M, Kazim S, Grunbaum AM, *et al*. Massive acetaminophen overdose: effect of hemodialysis on acetaminophen and acetylcysteine kinetics. *Clin Toxicol (Phila)* 2016;54:519–22.
15 Sivilotti ML, Juurlink DN, Garland JS, *et al*. Antidote removal during haemodialysis for massive acetaminophen overdose. *Clin Toxicol (Phila)* 2013;51:855–63.
16 Wu ML, Tsai WJ, Deng JF, *et al*. Hemodialysis as adjunctive therapy for severe acetaminophen poisoning: a case report. *Zhonghua Yi Xue Za Zhi (Taipei)* 1999;62:907–13.