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Thank you for asking us to respond to the correspondence by Youri Yordanov and colleagues regarding the REVERT trial [1]. We are grateful to the authors for taking the time to read our paper and for making such positive comments.

In response, perhaps we can offer some further insights that might be of interest, particularly in terms of the method of treatment allocation chosen.

We agree that envelope randomization has the potential to be corrupted and risks selection bias. Computer-based or telephone-based methods of allocation are considered methodologically stronger and such methods were encouraged by external reviewers during the trial's development. We considered these methods but also had to weigh up the practical issues of carrying out research in the Emergency Department (ED) environment in this population of patients and other aspects of our trial design.

As the authors point out, ED research can be challenging and we were keen to recruit our patients whenever they presented to the department.

Indeed, not to do so would introduce selection bias in itself and result in a less representative population sample. To this end, we wanted to ensure that all trial procedures were as straightforward as possible and achievable in the busy ED while being methodologically robust. The use of envelopes as described was specifically chosen as it enabled recruiting clinicians, simultaneous access to the treatment allocation, standardized instructions, and an outcome record all on one card. For clarity, our trial protocol, outlining these methodological issues, was published in advance of trial completion [2].

We successfully argued that this method of treatment allocation together with the additional security measures that we used would simplify the process, support recruitment of all eligible patients, and enable appropriate completion of the trial while maintaining acceptable allocation concealment. Analysis of unpublished trial data for the time and day of participant recruitment seems to lend support for this approach, with ~30% of patients being recruited outside of normal office hours with recruitment targets consistently met or exceeded.

We agree that carrying out pragmatic and widely applicable studies in patients with acute conditions in the ED requires a flexible and innovative approach, but with careful planning and consideration, this does not need to be at the expense of accepted research standards. We thank Youri Yordanov and colleagues for highlighting this aspect of our research.

Acknowledgements

Conflicts of interest

There are no conflicts of interest.

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Massive paracetamol overdose associated with mitochondrial dysfunction and pancytopenia, without hepatotoxicity

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Severe mitochondrial dysfunction following paracetamol overdose is rare but life threatening. This can occur without the development of liver failure. In addition, paracetamol overdose can be present with a high anion gap metabolic acidosis and needs to be kept as a differential in patients who present with an altered conscious state. We describe a case of massive paracetamol ingestion associated with mitochondrial dysfunction and subsequent pancytopenia.

A 21-year-old woman (weight 60 kg) with a past history of anorexia nervosa and depression was presented to the Emergency Department with an altered conscious state 13 h after paracetamol overdose. An empty packet count demonstrated a potential consumption of 239 g (3900 mg/kg) of immediate-release paracetamol, obtained over the counter at a pharmacy.

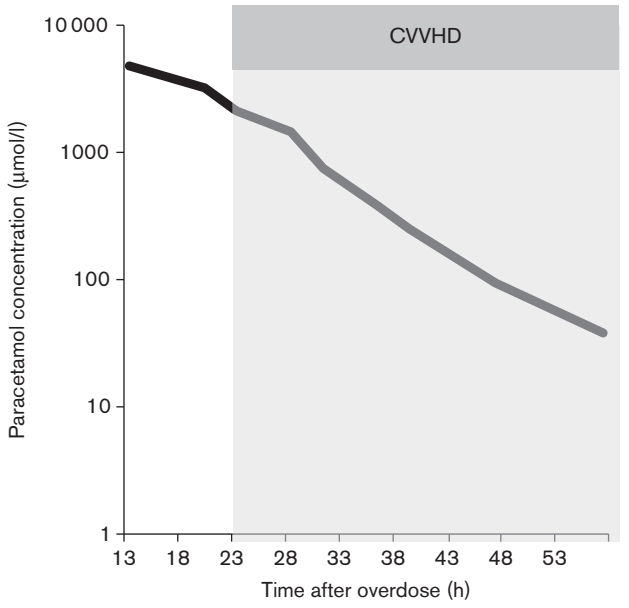
On arrival to the Emergency Department, examination revealed a blood pressure of 85/67 mmHg, pulse of 118 bpm, hypothermia (34.4°C) and hyperglycaemia (18.6 mmol/l). Her blood pressure improved to 103/67 without any treatment. Bedside venous blood gas showed a high anion gap metabolic acidosis (pH 7.18, pCO_2 37 mmHg, HCO_3 11 mmol/l, lactate 11.3 mmol/l, and anion gap 33 IU/l). She was agitated, confused alternating with a drowsy state, which necessitated intubation to facilitate medical management. Fifty grams of charcoal

was administered and intravenous acetylcysteine started. Computerized tomography scan of the brain was normal. The initial plasma paracetamol concentration was 4783 μmol/l, alanine transaminase was 43 IU/l and International Normalized Ratio (INR) was 1.5. Her initial full blood count was normal, with a haemoglobin of 152 g/l, white cell count of 5.7×10^9/l and platelet count of 179×10^9/l. The results for urinary ketones and drug screen were negative.

In light of the altered conscious state, persistent lactic acidosis despite correction of hypotension and large plasma paracetamol concentration continuous veno-venous haemo-diafiltration (CVVHDF) was initiated 23 h after ingestion and continued for 37 h. During dialysis, the third and subsequent acetylcysteine infusion doses were doubled. Acid–base status improved over the following 12 h.

Plasma paracetamol concentrations obtained before and during dialysis are shown in Fig. 1. Platelet count was downtrending (140×10^9/l) before dialysis initiation. By day 3, full blood examination showed a haemoglobin of 83 g/l, white cell count of 3.8×10^9/l (normal $4–11 \times 10^9$/l) and platelet count of 37×10^9/l. Her pancytopenia resolved by day 7. Alanine transaminase peaked at 296 IU/l on day 5 and INR at 1.9 on day 2 after ingestion. The patient was extubated on day 6 with normal neurological status and discharged to an inpatient psychiatric facility on day 10. She confirmed ingestion of 239 g of paracetamol and denied taking any sedatives.

Fig. 1



Logarithmic plot of paracetamol concentration values after overdose. CVVHD, concentration continuous veno-venous haemo-diafiltration.

Massive paracetamol overdose resulting in mitochondrial dysfunction manifesting as hypothermia, hyperglycaemia, altered conscious state and lactic acidosis has been reported, but is rare [1,2]. There is evidence of down-regulation of mitochondrial genes following paracetamol exposure [3]. In-vitro studies demonstrate inhibition of mitochondrial complex III and loss of mitochondrial respiration occurring in association with paracetamol concentrations below human hepatotoxic thresholds, suggesting that paracetamol at high concentrations rather than the hepatotoxic metabolite NAPQI (*N*-acetyl-p-benzoquinone-imine) may cause mitochondrial dysfunction [4]. Pancytopenia has been reported following paracetamol overdose, but is also rare [5].

The features of our case were consistent with mitochondrial dysfunction and a resulting metabolic acidosis [2]. This is distinct to metabolic acidosis caused by liver failure secondary to paracetamol overdose. Similarly, the production of 5-oxoproline (pyroglutamic acid) can result in a high anion gap metabolic acidosis from ingestion of paracetamol. 5-Oxoproline production, which is due to inhibition of the gamma-glutamyl cycle, can occur not only from large overdoses but also from therapeutic ingestion [6]. Although we did not measure 5-oxoproline and acknowledge that it may coexist, it is unlikely it would have resulted in the clinical presentation of our patient. In addition, there is no clear correlation between paracetamol and 5-oxoproline concentrations [7].

CVVHDF was performed, which assisted in improving acid–base status. Plasma paracetamol half-life calculations in this case are unlikely to reliably describe the contribution of CVVHDF to paracetamol elimination, given that absorption and elimination were occurring simultaneously following massive ingestion. However, overall elimination half-life did not change significantly in association with the use of CVVHDF, as reported previously [1]. There is limited evidence that intermittent haemodialysis is more efficient than CVVHDF in terms of increasing paracetamol elimination, but in this case CVVHDF was utilized because of availability [8]. Acetylcysteine dosing was doubled due to the theoretical benefit following massive ingestion and to replace the amount potentially removed by dialysis [2,8].

This case represents a clinically relevant rare manifestation of a commonly utilized medication taken in overdose. Although it is unknown whether CVVHDF assisted in the prevention of hepatotoxicity in this case, an extracorporeal elimination technique should be considered as a treatment option in patients following massive paracetamol overdose who exhibit signs of mitochondrial dysfunction. Because of the limited evidence as regards management of massive paracetamol ingestions, advice from a clinical toxicologist should be sought in these cases. Current evidence suggests that

intermittent haemodialysis is the technique of choice for increasing paracetamol elimination.

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Conflicts of interest

There are no conflicts of interest.

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