CON: Fomepizole should be used more liberally in paracetamol overdose

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Abstract

Fomepizole is a promising new treatment for preventing liver injury following paracetamol (acetaminophen) overdose. However, we need robust clinical trials to be performed to demonstrate its effect on clinical outcomes that are important to our patients and important to healthcare providers. Until such trials are performed, the toxicology community should learn the lessons from the COVID pandemic – potential novel therapeutic options may be theoretically appealing, but their effectiveness needs to be assessed in robust clinical trials before they are used in clinical practice.

Title: The lessons of COVID should guide our use of fomepizole in paracetamol overdose

Running Title: Fomepizole Debate Con

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Abstract

Fomepizole is a promising new treatment for preventing liver injury following paracetamol (acetaminophen) overdose. However, we need robust clinical trials to be performed to demonstrate its effect on clinical outcomes that are important to our patients and important to healthcare providers. Until such trials are performed, the toxicology community should learn the lessons from the COVID pandemic – potential novel therapeutic options may be theoretically appealing, but their effectiveness needs to be assessed in robust clinical trials before they are used in clinical practice.

The COVID-19 pandemic has dominated healthcare for the last couple of years. The enormous challenge presented by the emergence of this new infectious disease in late 2019 resulted in drug and vaccine development being rapidly performed at '*warp speed*' . When COVID was first identified, clinicians searched for licenced

medicines with mechanisms of action consistent with a potentially effective treatment. Hydroxychloroquine was identified as a potential treatment because it has *in vitro* activity against SARS-CoV-2[1] and early small observational studies suggested a possible benefit.[2] There were high profile leaders who promoted using hydroxychloroquine to prevent and treat COVID,[3] and doctors prescribed it based on this limited evidence base. Fortunately, from the start of the pandemic, the*Recovery* platform trial tested multiple treatments in a large randomised clinical trial that measured mortality as the primary endpoint. *Recovery* conclusively demonstrated hydroxychloroquine had no benefit when 1561 hospitalised patients with COVID were treated with this drug compared to 3155 patients who received standard care.[4] In fact, subsequent a meta-analysis suggests hydroxychloroquine may harm patients.[5] Despite the initial hope that resulted in doctors prescribing hydroxychloroquine, it proved ineffective when tested in a robust large study. Fomepizole may be the toxicology community's hydroxychloroquine unless we learn the lessons of COVID and come together to perform robust randomised trials before prescribing an untested treatment.

Paracetamol (acetaminophen) overdose is common. There is a clear unmet need for new treatments. Currently, the only effective treatment for preventing liver injury after paracetamol overdose is acetylcysteine (n-acetylcysteine, NAC). If treatment is commenced within 8 hours of the overdose, then NAC is near 100% effective at preventing liver failure. However, its effectiveness drops substantially when treatment is delayed. NAC is near ineffective when treatment is delayed greater than around 20 hours after overdose.[6] For patients who present to hospital late following a significant paracetamol overdose we need effective new treatment strategies to prevent liver injury in this high risk group. Within this space, fomepizole has emerged as a potential new candidate.

Fomepizole is well known to toxicologists as an effective treatment for toxic alcohol poisoning due to its ability to inhibit the enzyme alcohol dehydrogenase.[7] The potential as a treatment for paracetamol overdose is unrelated to this mechanism of action. Fomepizole is a potent inhibitor of the cytochrome P450 enzymes that produce the paracetamol toxic metabolite (NAPQI) that is responsible for liver injury. Furthermore, in mice, fomepizole prevents liver injury after the metabolism phase of paracetamol mainly through the inhibition of c-Jun N-terminal kinase activation. The pre-clinical evidence base for fomepizole is impressive, largely due to the work of Hartmut Jaeschke's group.[8, 9] In humans, well performed clinical studies confirm that fomepizole inhibits the oxidative metabolism of paracetamol.[10] However, there is no trial evidence that fomepizole prevents liver injury in man. These trials need to be performed. Sometimes it is suggested that '*trials cannot be performed in clinical toxicology'*. As paracetamol overdose is common this is untrue. In the UK, every 5 minutes someone presents to hospital following a paracetamol overdose – the same frequency as myocardial infarction. It is hard to imagine cardiologists prescribing a medicine because it works in mouse models and defending that position by saying clinical trials cannot be performed in ischaemic heart disease.

There are a number of reasons to insist on robust, randomised trial evidence for the clinical effectiveness of fomepizole before it is used to treat paracetamol overdose in routine clinical practice. Advocates of its use suggest it has a role in large overdoses when there is a high concentration of paracetamol in the circulation. Given fomepizole's ability to inhibit the P450 enzymes this makes theoretical sense. However, P450 enzyme inhibitors have been tested in this indication in the past and failed to demonstrate clinical effectiveness.[11] If P450 enzyme inhibition is the correct target for a new therapy, there may be cheaper alternatives to the expensive option presented by using fomepizole. Finally, and perhaps most importantly, we do not know whether using a higher dose of NAC for larger overdoses will be sufficient alone to prevent liver injury in this group of patients. This approach is likely to be substantially cheaper than using fomepizole. Currently, patients receive a dose of NAC that is based only on their body weight. It is clear from the basic pharmacology, mathematical modelling[12, 13] and observational studies[14, 15] [16] that patients taking a large overdose may not be receiving enough NAC to prevent liver injury. There are new regimens for administering NAC that produce substantially lower rates of adverse drug reactions compared to the standard 21-hour regimen.[17] These new regimes allow phase 2 clinical trials of high dose NAC treatment in selected patients with a reasonable expectation of not producing dose-limiting toxicity. Before advocating a new expensive treatment, the toxicology community should focus on defining the optimal dose of NAC.

Fomepizole use in paracetamol overdose is occasionally defended as it is claimed to have an excellent safety profile. This seems to be correct in its licenced indication – treatment of toxic alcohol poisoning. We do not know if it is safe in patients who have overdosed on paracetamol and there are reasons for a degree of caution. A phase 1 trial of fomepizole demonstrated a small increase in alanine transaminase (ALT) activity in 6 of 15 healthy subjects.[18] Although unlikely, when combined with a potentially hepatotoxic dose of paracetamol this small ALT rise could translate into increased cases of significant liver injury. A fomepizole-induced increase in ALT, even if benign, may result in patients having unnecessary prolonged treatment with NAC, as ALT is the key biomarker which informs decisions to stop treatment. We do not have robust data to know the answers to these questions about safety.

Fomepizole has promise as a treatment for paracetamol overdose. But we do not have data from randomised trials about clinically important outcomes such as liver injury, hospital length of stay and liver failure and we do not have an adequate safety dataset. Now is the time for the toxicology community to follow the example of the *Recovery Trial*and come together to perform large platform trials to evaluate new treatments that have evidence of clinical efficacy from phase 2 trials. Candidate treatments include high dose NAC and fomepizole. This is the hard thing to do, the easier option is to start prescribing treatments without a robust evidence base. The danger is fomepizole becomes like hydroxychloroquine in COVID, advocated as a treatment without robust evidence of benefit for our patients.

Conflict of interest: JWD was the Chief Investigator on the POP Trial of calmangafodipir in paracetamol overdose.

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