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Comment on Fomepizole as an adjunct in acetylcysteine treated acetaminophen overdose patients

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Dear Editor

We believe the article by Link et al.[1] carries several erroneous messages.

We accept that there is experimental evidence from rodents indicating that fomepizole is a potential treatment for preventing liver injury following paracetamol (acetaminophen) overdose. However, we cannot agree based on the evidence presented that "*fomepizole should be considered as an adjunct due to the known failure rate of NAC*".

They report an observational case series of paracetamol (acetaminophen) overdose in which fomepizole was used with standard care and acetylcysteine; six of the 14 patients have been published previously. The patients were "*consecutive with high risk factors*". The authors justify their publication as collecting safety data in paracetamol poisoning, yet admit there was no formalized protocol for administration of fomepizole and fomepizole doses varied from single administration (9/14 cases) to multiple doses. Furthermore, fomepizole was administered at 6 h in six patients and \geq 24 h in four. They state in the limitations that "*this was not an organized clinical trial designed to investigate the effectiveness of fomepizole in preventing hepatotoxicity*", but nevertheless make claims about efficacy and safety: "*This case series has demonstrated the safety with no observable side effects and possible efficacy and a potential pivotal role in APAP overdose.*"

There are published data on untreated patients with severe paracetamol poisoning. These show that the concentrations of paracetamol seen in these patients are by no means always fatal [2,3], much less when treated promptly with acetylcysteine [4]. Using the authors method of assessment (paracetamol–aminotransferase multiplication product) only five of fourteen were high risk (product $>10,000$ mg/Lx IU/L) [5]. One treated with haemodialysis showed no liver injury (case 7); liver injury may have peaked in two when fomepizole was started (cases 9, 13); two showed increased liver injury after fomepizole (cases 8, 14). Unfortunately, the lack of a protocol meant that ALT/AST activities were not measured at the time of fomepizole administration, making interpretation difficult. Ten were treated with acetylcysteine within 8 h, nine of whom were only at low-to-moderate risk (product 1500–10,000 mg/Lx IU/L) of developing hepatotoxicity [5]. These important data were omitted from the paper's Abstract and Discussion.

As the authors state, studies of this type can never establish efficacy and their claim that fomepizole resulted in "*better than expected outcomes*" does them a disservice. Fomepizole may have promise in paracetamol overdose but we do not yet 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.

Although there are substantial differences in the situations between COVID-19 and acetaminophen poisoning, we would advocate for a similarly well-funded approach as the Recovery Trial (<https://www.recoverytrial.net/>) to perform large platform trials, so that we may create a robust evidence base for new treatments of paracetamol poisoning. Candidate treatments for paracetamol poisoning include high dose acetylcysteine and fomepizole. Performing such trials is the hard thing to do; the easier option is to recommend treatment without a robust evidence base.

Yours faithfully,

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Declarations of interest: All authors have worked on studies of paracetamol poisoning. DNB, ME and JAV have no other conflicts of interest. JWD was the Chief Investigator on the POP Trial of calmagofodipir in paracetamol overdose.

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