ESC European Society of Cardiology
European Heart Journal - Case Reports (2023) **7**, 1
https://doi.org/10.1093/ehjcr/ytad241

Reply to the letter to the editor

We appreciate the interest shown in our article 'Loperamide-induced cardiogenic syncope: a case report of a life-threatening presentation of an over-the-counter drug[1]'

In his letter,[2] Dr. Sohn raises an important point; lipid emulsion therapy likely has more than one mechanism of action. Dr. Sohn describes the lipid shuttle hypothesis in his letter. While the initial scavenging of toxic metabolites can be explained by the lipid sink hypothesis,[3] the small bolus of lipid emulsion would not remove enough to cause a reversal of toxicity. Indeed, lipid emulsion has been shown to facilitate the redistribution of the toxin away from the heart to the liver, skeletal muscles acting as a lipid shuttle.[4] It also leads to the alteration of the pharmacokinetic properties leading to a reduction in the distribution half-life and a shortening of the elimination half-life.[5]

In addition to the scavenging effects of lipid emulsion therapy, experimental evidence has shown cardiotonic and vasoconstrictive effects.[6] Several studies have shown that lipid emulsion therapy produces positive cardiovascular effects via increasing preload and by direct mechanisms.[7] In animal models, lipid emulsion has been shown to produce positive inotropic and lusitropic effects.[8] Post-conditioning effects attributable to inhibition of the opening of the mitochondrial permeability transition pore (mPTP) and activation of the reperfusion injury salvage kinase (RISK) pathway have been well described in models of bupivacaine toxicity.[9] While one could theorize a similar benefit in the setting of loperamide-induced cardiogenic shock, more work is needed in the setting of loperamide toxicity. Direct channel-based effects, calcium signalling, and reversal of mitochondrial block have also been mentioned as additional mechanisms; more recent work has shown these theories lack robust evidence.[10] Overall, we would like to thank Dr. Sohn for highlighting the lipid shuttle hypothesis and the multimodal mechanisms of lipid emulsion therapy. We wholeheartedly agree that further research examining the effects of lipid emulsion therapy in the setting of loperamide toxicity is required.

We thank Ollitrault *et al*. for their interest in our paper. The pharmacovigilance report sheds additional light on the incidence of various cardiovascular adverse drug events associated with loperamide.[11] We concur that this paper along with the paper by Ollitrault *et al*. raises public awareness regarding this issue.

Conflict of interest: All authors have no conflicts of interest to disclose.

Funding: None.

Data availability

Data that is referenced is publicly available.

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Handling Editor: David Duncker