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THE POISON PEN

In Reply to "Hydroxychloroquine Overdose: What Are the Exact Roles of Diazepam and Potassium Infusion?"

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We thank Drs. Megarbane and Schicchi for their thoughtful comments and highlights regarding recent animal models suggesting the importance of mechanical ventilation and vasopressor support in the setting of acute hydroxychloroquine poisoning [1, 2]. We agree that although the literature on hydroxychloroquine poisoning is scarce, it is reasonable to infer treatment strategies from clinical experience with chloroquine ingestions.

Drs. Megarbane and Schicchi make valid points on the consideration of initiation of intravenous diazepam compared with epinephrine infusions in moderately and severely poisoned patients. The writers point to in vitro and in vivo data suggesting that the use of diazepam does not impact cardiac performance nor do its attributable cardioprotective effects contribute to significant recovery of cardiac function in poisoned rats [1, 3]. These investigations do suggest that diazepam may have some effect in augmenting the inotropy imparted through concomitant administration of vasopressors. It does, however, highlight the challenge in developing data-driven treatment algorithms for acutely poisoned patients given the lack of ethical mechanisms through which to conduct adequately powered human clinical trials. Clinically, one confounding factor frequently encountered is the unknown dose of hydroxychloroquine taken and the time of ingestion, as well as coingestants. While hydroxychloroquine (HCQ) levels might suggest the severity of ingestion, if we extrapolate from data surrounding chloroquine, these concentrations do not result in real time and are rarely clinically relevant once obtained. We therefore think that in some cases, diazepam may still be of value, especially in critically ill individuals who are mechanically ventilated, supported hemodynamically with vasopressors, and continue to manifest signs of HCQ toxicity. Unlike animal studies that have defined doses and controlled times to intervention, the condition of human intentional and unintentional ingestion is widely variable, often associated with chronic toxicity, coingestants, and underlying disease states, thereby requiring elasticity around direct extrapolation of animal data. In individuals who have moderate HQC toxicity (acute doses of 2–4 g), diazepam may be less effective, assuming that the dose ingested is known [2].

We also thank Drs. Megarbane and Schicchi for reminding us that correcting hydroxychloroquine-induced hypokalemia should be a careful intervention as aggressive over-correction can result in hyperkalemia. Depending of the degree of cardiac conduction abnormalities seen after acute hydroxychloroquine overdose, infusion of potassium may help eliminate the confounding factor of hypokalemia contributing to dysrhythmias. As medical and clinical toxicologists, we frequently manage the effects of drug-induced hypokalemia due to intracellular sequestration of potassium ions. Ensuring correction of this electrolyte abnormality and

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understanding the potential for rebound hyperkalemia is critical in the safe management of hydroxychloroquine poisoning.

Overall, in a critically ill individual suffering from acute hydroxychloroquine overdose, the use of vasopressors, mechanical ventilation, and possibly diazepam are features of management that should be considered during the clinical course [3]. The management of hydroxychloroquine-induced dysrhythmias may need to include correction of hypokalemia and in the setting of a prolonged QRS complex and consideration of sodium loading agents like hypertonic saline and sodium bicarbonate. There is clearly a need for additional investigations, both in animals and potentially on human subjects to understand the impact of these various treatment options to better address this potentially life-threatening poisoning that has become increasingly relevant during the COVID-19 pandemic [4].

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Compliance with Ethical Standards

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