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Supratherapeutic oseltamivir levels during continuous dialysis: an expected risk

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Dear Editor,
We read with interest the recent correspondence by Lemaitre and colleagues. The authors describe the case of a patient treated with high-dose oseltamivir (150 mg BID) for severe infection due to influenza A/H1N1. Despite receiving simultaneous extracorporeal membrane oxygenation (ECMO) and continuous veno-venous hemodiafiltration (CVVHDF), oseltamivir carboxylate (OC) $C_{\max}$ and AUC_{0-12} were five-fold higher in comparison to data from healthy volunteers [1]. We offer a possible explanation for their findings.

After oral administration, oseltamivir phosphate (an inactive prodrug) is rapidly converted to OC, the active metabolite. OC is primarily (60–70%) eliminated renally as unchanged drug through a combination of glomerular filtration and tubular secretion. The mean total renal clearance of OC in healthy volunteers is 18.8 L/h. This vastly exceeds glomerular filtration rate ($\sim 125 \text{ ml/min} = 7.5 \text{ L/h}$), which suggests a significant degree of clearance via tubular secretion. Indeed, tubular secretion of OC

occurs via the anionic transport process and inhibition of secretion by probenecid results in an approximate twofold increase in $C_{\max}$, 2.5-fold increase in AUC, and a 50% decrease in renal clearance [2].

OC is readily dialyzable through continuous renal replacement therapy (CRRT). The effects of continuous veno-venous hemofiltration (CVVHF) on the clearance of OC were investigated in an in vitro study. The authors found a minimal amount of adsorption to the hemofilters ($\sim 1\%$) and a sieving coefficient of ~ 1 [3]. This would suggest that clearance during hemodiafiltration should approximate the sum of dialysate and ultrafiltrate flow rates [4]. In the case by Lemaitre and colleagues, the patient was initiated on CVVHDF with flow rates of 1.5 L/h dialysate and 1.5 L/h ultrafiltration. We assume that there was minimal tubular secretion of drug since the patient was anuric. Therefore, the maximum extracorporeal clearance rate generated by CVVHDF would be 3 L/h. Although Lemaitre and colleagues point out that adhesion of drugs to the ECMO circuit may occur, it is unlikely that this would significantly contribute to the overall drug clearance [5]. Given the above data, the clearance of OC in this patient would be expected to be ~ 6 times lower than that in healthy volunteers (3 L/h vs. 18.8 L/h), which is in line with their findings.

Oseltamivir is well-tolerated to doses up to 1,000 mg, with the main adverse effect being transient gastrointestinal upset [2]. Understandably, many clinicians prefer to dose oseltamivir aggressively when treating critically ill patients with influenza (especially that due to H1N1). Given the paucity of data, it is difficult to

make firm dosing recommendations at this time. However, investigators and clinicians should be aware that supratherapeutic levels should be expected when high-dose oseltamivir is given to patients receiving CRRT.

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