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Pharmacokinetics of oseltamivir carboxylate in critically ill patients: each patient is unique

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Dear Editor,

Patients infected with the 2009 H1N1 pandemic influenza virus often develop severe viral pneumonia with acute respiratory distress syndrome (ARDS) and multiple organ failure. High-dose oseltamivir (≥150 mg twice daily) has been advocated as optimal treatment [1]. However, the scientific evidence for this advice is lacking thus far [2]. Therefore, we explored the pharmacokinetics of oseltamivir and its active metabolite oseltamivir carboxylate in critically ill patients with H1N1 pandemic influenza following different dosing regimens.

All patients with H1N1 pandemic influenza admitted to the ICU of the University Medical Center Utrecht were eligible for inclusion. Patients received oseltamivir at a dose determined by their treating physician, and blood samples were drawn at $t = 0$, 1, 2, 3, 4 and 8 h on day three of treatment. Oseltamivir and oseltamivir carboxylate plasma concentrations were determined by HPLC–MS/MS [3]. The area under the concentration–time curve from 0 to 8 h ($AUC_{0–8}$) was estimated using non-compartmental analysis. Patient characteristics were obtained from the patient files.

Six patients were included in the analysis (Table 1). All patients had ARDS due to H1N1 pneumonitis. Additionally, patient 1 had a pulmonary embolism, patient 2 had kidney failure caused by multiple renal cysts and received continuous venovenous hemofiltration (CVVH; blood flow 200 mL/min, ultrafiltrate flow 2 L/h), patient 3 had received stem cell transplantation and suffered from pulmonary aspergillosis, patient 4 was 29 weeks pregnant (a cesarean section was performed a few hours before sampling), patient 5 was on extracorporeal membrane oxygenation, and patient 6 had newly diagnosed hairy cell leukemia and renal failure for which CVVH was started the day after sampling. The pharmacokinetic parameters, as well as the prescribed dose, were widely variable (Table 1). No relationship was observed between dose and $AUC_{0–8}$.

Thus far, no concentration–response relationship has been established for oseltamivir. However, a carboxylate AUC of >2,270 ng h/mL is considered adequate [4]. Despite a high variability, all carboxylate $AUC_{0–8}$ in this study were >2,270 ng h/mL. In line with

Table 1 Patient characteristics and pharmacokinetics of oseltamivir and oseltamivir carboxylate on day 3 of oseltamivir treatment

	Patient ID					
	1	2	3	4	5	6
Sex	F	F	M	F	M	M
Age (years)	51	69	60	29	50	35
Height (cm)	165	166	175	165	176	198
Weight (kg)	65	62	65	70	75	95
BMI (kg/m^2)	23.9	22.5	21.2	25.7	24.2	24.2
APACHE IV	56	109	61	54	74	134
Creatinine (μmol/L)	104	123	109	48	76	299
Cumulative fluid retention days 1–3 (L)	1.8	3.1	4.5	7.0	7.7	8.8
Oseltamivir dose (mg)	150 twice daily	75 once daily	150 twice daily	150 twice daily	75 twice daily	Day 1 150 mg twice daily, days 2 and 3 75 mg twice daily
Extracorporeal therapy	–	CVVH	–	–	ECMO	–
Oseltamivir C_{max} (ng/mL)	140	115	77	51	86	39
Oseltamivir AUC[a] (ng h/mL)	481	405	431	216	265	107
Oseltamivir carboxylate C_{max} (ng/mL)	1,875	601	1,607	613	588	3,824
Oseltamivir carboxylate AUC[a] (ng h/mL)	13,454	3,766	10,089	3,784	4,708	27,286

CVVH continuous venovenous hemofiltration, *ECMO* extracorporeal membrane oxygenation
[a] Patients 1, 2, 3 and 6 0–8 h; patient 4 0–8.4 h; patient 5 0–9 h

previous studies, tremendous carboxylate levels were found in a patient with decreased renal function, and doubling of the dose resulted in doubling of the exposure [2, 4]. However, if the standard dose of 75 mg twice daily had been administered to patient 4, exposure might have been below the previously established target AUC. This might be caused by an increased apparent distribution volume and an increased clearance during pregnancy, since the glomerular filtration rate may be increased by 50 % [5]. Additionally, a dose of 75 mg once daily resulted in adequate carboxylate exposure during CVVH (patient 2) in which up to fivefold increased AUCs have previously been observed [2].

This study showed conclusively that in critically ill patients dosing should be based upon the characteristics and knowledge of organ function in the individual patient: a oseltamivir dose of 150 mg twice daily is required during pregnancy, while 75 mg once daily results in adequate carboxylate exposure in patients with renal failure receiving CVVH. Monitoring oseltamivir carboxylate AUCs may optimize therapy in critically ill patients in whom pharmacokinetics are highly variable and unpredictable.

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