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LETTER

Paracetamol absorption test to detect poor enteric absorption of oseltamivir in intensive care unit patients with severe influenza: a pilot study

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Dear Editor,

Pandemic and seasonal influenza epidemics can be associated with a high degree of morbidity and mortality, especially in patients developing severe influenza pneumonitis with the acute respiratory distress syndrome (ARDS) or the less frequent fulminant myocarditis. Early administration of the neuraminidase inhibitor oseltamivir has been shown to reduce the duration of respiratory illness for patients infected with both influenza A and B viruses [1] and was associated with a reduction in hospital mortality in patients with severe influenza. Since the 2009 influenza pandemics, early oseltamivir administration, which can only be given orally (or through a nasogastric tube), is thus recommended by the World Health Organization in patients hospitalized for severe influenza, including those requiring intensive care (ICU) admission. Indeed, pharmacokinetic data obtained in healthy volunteers, as well as in critically ill patients [2], showed that oseltamivir phosphate (OP), the inactive prodrug, is well absorbed and rapidly converted by intestinal and hepatic esterases to the active metabolite oseltamivir carboxylate (OC), which is renally eliminated. However, enteric absorption can be compromised in critically ill patients [3] due to impaired gut function, particularly in patients with cardiovascular failure. Unfortunately, plasma OC measurements are not routinely performed in most hospitals, precluding close monitoring of OC pharmacokinetics. Using the paracetamol absorption test (PAT), Jahns et al. [4] recently demonstrated enteral drug malabsorption in two patients with fulminant influenza myocarditis and cardiogenic shock, prompting a switch to parenteral therapy. The current pilot study aimed at assessing the diagnostic performances of the PAT for detecting oseltamivir absorption failure in critically ill patients with severe influenza. The study reported on a prospective cohort of 15 patients admitted to the ICU for severe influenza during the 2018/2019 influenza epidemics. Oseltamivir was routinely prescribed at a standard dose of 75 mg twice daily (an oral suspension of oseltamivir 6 mg/mL was given orally or through a nasogastric tube, which was then flushed with water) within the first 24 h and then adjusted to creatinine clearance when it was < 60 mL/min. A PAT was performed in all patients within 72 h of ICU admission, consisting in the measurement of plasma paracetamol concentration (homogeneous immunoassay with a limit of quantification (LOQ) of 5 mg/L) 60 min after enteral loading with 1000 mg of paracetamol [2, 3]. The PAT was considered positive for a plasma paracetamol concentration ≥ 10 mg/L [4]. The pharmacokinetics of oseltamivir and its metabolites were subsequently explored by measuring OP and OC trough plasma concentrations, using ultra-performance liquid chromatography with tandem mass spectrometry with LOQ < 1 ng/mL and < 10 ng/mL, respectively [5]. Based on pharmacokinetics data obtained in healthy subjects loaded orally with 75 mg of oseltamivir bi-daily,

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adequate OC trough plasma concentration was 158 ng/mL (i.e., approximately 35% of the maximal concentration value) [5]. Fifteen patients (12 males/three females), aged 62 ± 17 years, were included (Table E1, online supplement). Among them, seven (47%) required vasopressors, eight (53%) invasive mechanical ventilation and four (27%) extracorporeal membrane oxygenation support. All patients had influenza A infection except one patient who had an influenza B virus infection. Seven patients fulfilled the criteria for the ARDS, and four patients had myocarditis. Two patients died in the hospital. Eleven patients (73%) had a positive PAT (median [range] plasma concentration of paracetamol was 13 mg/L [10–36]), and all had OC trough plasma concentrations above the predefined threshold value (651 ng/mL [201–3789]), corresponding thus to a positive predictive value of the PAT of 100% for detecting sufficient oseltamivir absorption. Among four patients who had a negative PAT, two patients—who were under extracorporeal membrane oxygenation support (ECMO)—showed undetectable OC trough plasma concentrations (< 10 ng/mL), while two others had concentrations above the predefined adequate concentrations. Overall, patients having a negative PAT had significantly lower OC plasma trough concentrations than others (Fig. 1) and there was a significant and strong correlation between plasma concentrations of paracetamol measured at 60 min of enteral loading and oseltamivir plasma trough concentrations (Spearman's $r = 0.66$, $p = 0.009$). Two patients with negative PAT were switched to intravenous zanamivir.

Our data suggest that the PAT can be useful for early detection of enteric absorption failure in patients with severe influenza under oral oseltamivir treatment, particularly in those under ECMO. Until confirmatory studies are done, we suggest performing a PAT when therapeutic drug monitoring of oseltamivir is not available. If negative, switching to parenteral zanamivir therapy should be considered.

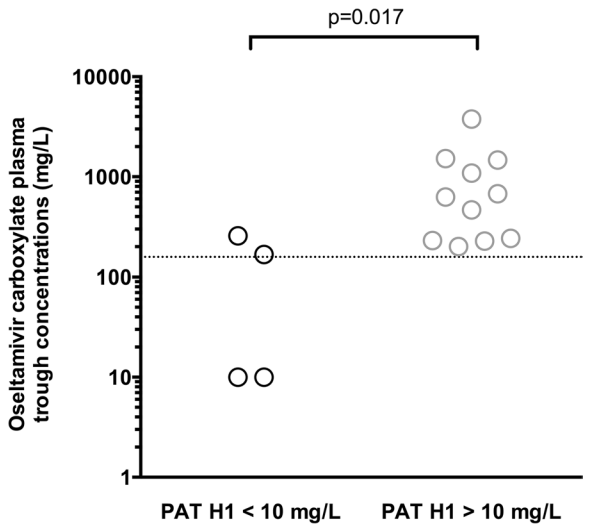

Fig. 1 Oseltamivir carboxylate trough plasma concentration in patients with positive or negative paracetamol absorption test. The dotted line indicates the predefined oseltamivir carboxylate trough concentration threshold value (i.e., 158 ng/mL); note that the *y*-axis is a logarithmic scale; *OC* oseltamivir carboxylate, *PAT* paracetamol absorption test; the *p* value comes from the Mann–Whitney test

Electronic supplementary material
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Compliance with ethical standards

Conflicts of interest
The authors declare that they have no conflicts of interest.

Ethical approval
All patients received information that the data abstracted from their medical charts would be used for research purposes. This study has been performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments. Data were anonymized and compiled according to the requirements of the ***Commission Nationale Informatique et Liberté***.

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