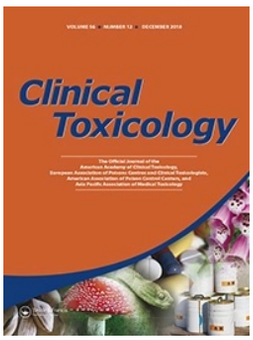

Clinical Toxicology

ISSN: 1556-3650 (Print) 1556-9519 (Online) Journal homepage: https://www.tandfonline.com/loi/ictx20

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To cite this article: Philippe Hantson, Claire Wuidart & Vincent Haufroid (2019): Severe and prolonged flecainide intoxication treated by extracorporeal life support: possible role of cytochrome P450 2D6 polymorphism?, Clinical Toxicology

To link to this article: https://doi.org/10.1080/15563650.2018.1542703

Published online: 13 Feb 2019.

CLINICAL TOXICOLOGY
https://doi.org/10.1080/15563650.2018.1542703

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LETTER TO THE EDITOR

Severe and prolonged flecainide intoxication treated by extracorporeal life support: possible role of cytochrome P450 2D6 polymorphism?

Dear Editor,

An 18-year-old woman was admitted six hours after the ingestion of a maximal estimated dose of 18,000 mg of extend-release flecainide that was her chronic treatment for supraventricular tachycardia. On arrival, she had a Glasgow Coma Scale score 3 that progressed from 3 to 6/15. Arterial blood pressure was 96/79 mm Hg, heart rhythm was 63/min, irregular. The electrocardiogram (ECG) revealed irregular rhythm with broad QRS complexes (220 ms). The initial laboratory investigation has revealed: arterial pH 7.21, bicarbonate 14 mmol/L, lactate 10.6 mmol/L, creatinine 1.4 mg/dL. The patient received 100 mmol of intravenous sodium bicarbonate and 1000 mL of fluids. After the development of a refractory shock, advanced cardiac life support was commenced with epinephrine and norepinephrine, external cardiac massage, and electric shocks for ventricular tachycardia and ventricular fibrillation. An additional dose of 300 mmol of sodium bicarbonate was administered without any change on the ECG. A single dose of activated charcoal had also been administered after intubation, even if the delay from ingestion was probably too long. Intravenous lipid emulsion (ILE) therapy was also given according to the following regimen: 1.5 mL/kg as a bolus, followed by 0.25 mL/kg/min over 30 min; there was no change in hemodynamic conditions. Extracorporeal cardiac life support (ECLS) was initiated less than 35 min after the failure of pharmacological resuscitation. Cardiac echography showed a depressed left ventricular function (ejection fraction 35%). The complete intensive care management is detailed in Figure 1.

Under ECLS therapy, there was a correction of metabolic acidosis with a progressive decrease of arterial lactate concentration and a shortening of QRS duration. Epinephrine infusion was weaned after a few hours. Urine output was maintained. On day 2, the patient developed acute ischemia of the lower limb, and the femoral catheter and ECLS had to be removed. After 48 h of ECLS withdrawal, numerous episodes of ventricular arrhythmias were recorded with hemodynamic instability with the need of ECLS reintroduction; again sodium bicarbonate (300 mmol) and ILE infusion were found ineffective. At this time, the flecainide plasma concentration was still 2386 μg/L. Intestinal transit time was slow. Esophagogastroscopy failed to reveal gastric bezoars. The complete weaning of ECLS was possible on day 8. Liver and renal function was preserved over the clinical course. The patient was extubated one day later and was discharged from the ICU with a normal ECG and echocardiography. We calculated a terminal elimination half-life of flecainide at 100 h. Therefore, the patient was also investigated for cytochrome P450 2D6 genetic polymorphism. The patient genotype was confirmed to be CYP2D6 * 2/* 5 (* 5 allele corresponding to a complete allele deletion).

Management of severe flecainide poisoning by ECLS has been occasionally reported, with a delay for weaning ranging from 26 to 72 h [1–3]. Flecainide has a high volume of distribution (9 L/kg) and a relatively long terminal elimination half-life of 7–22 h after a therapeutic dose, but a longer half-life (23–73 h) may be noted after flecainide overdose [4]. Flecainide is mainly metabolized into the liver by the 2D6 isoform of cytochrome P450 (CYP2D6) [5]. Our patient possessed a loss of function allele for CYP2D6 (* 5 allele corresponding to a complete allele deletion) and should be, therefore, classified as CYP2D6 "intermediate metabolizer" (IM), based on genotype analysis. While the biotransformation of a therapeutic dose would not be theoretically significantly reduced by the loss of a single function allele, we cannot exclude that the rate of flecainide metabolism could have been reduced in the presence of a large drug overdose. It should be noted that the Royal Dutch Pharmacist Association-Pharmacogenetics Working Group (DPWG) still recommends a dose reduction of 25% for CYP2D6 intermediate metabolizers even for a therapeutic dose of flecainide [6]. Other explanations for sustained symptoms and prolonged elimination should be the delayed absorption of an extend-release preparation, with ileus as an aggravating factor, and saturation of CYP2D6 metabolism. Finally, even if flecainide has not been a high hepatic extraction coefficient, changes in hepatic blood flow may have occurred during the ECLS period.

Disclosure statement

No potential conflict of interest was reported by the authors.

Informed consent

A written consent was obtained from the patient.

References

[1] Corkeron MA, van Heerden PV, Newman SM, et al. Extracorporeal circulatory support in near-fatal flecainide overdose. Anaesth Intensive Care. 1999;27:405–408.
[2] Auzinger GM, Scheinkestel CD. Successful extracorporeal life support in a case of severe flecainide intoxication. Crit Care Med. 2001;29:887–890.

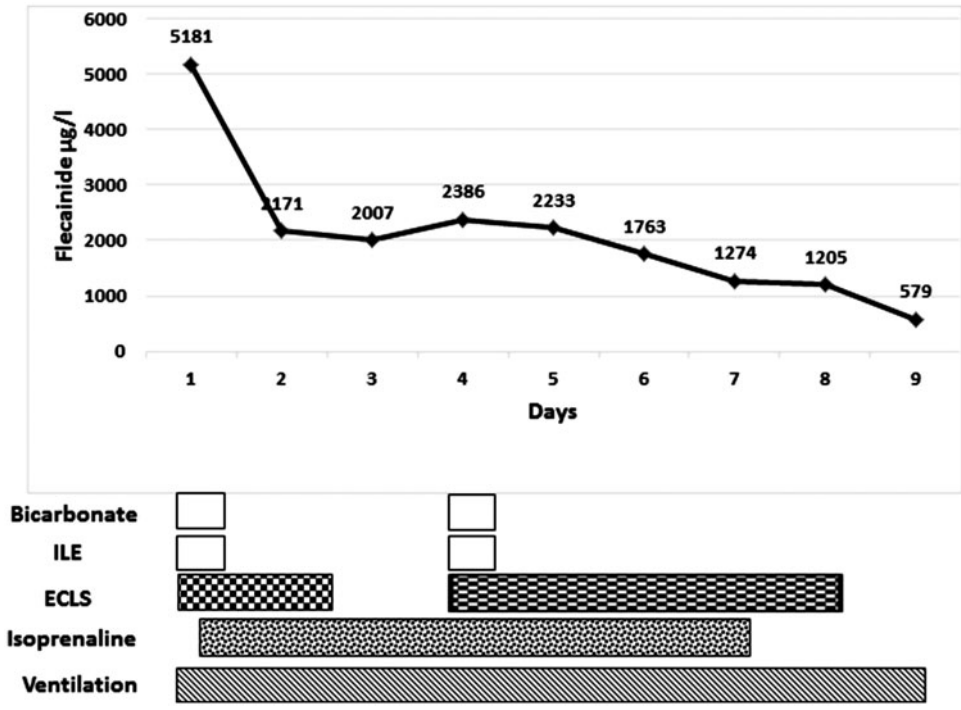

Figure 1. Evolution of flecainide plasma concentration over time and time course of the different strategies applied. ILE, intravenous lipid emulsion. ECLS, extracorporeal life support.

[3] Mandawat A, McCullough SA, Gilstrap LG, et al. Successful treatment of flecainide overdose with sustained mechanical circulatory support. Heart Rhythm Case Rep. 2015;1:137–140.
[4] Boriani G, Strocchi E, Capucci R, et al. Flecainide: evidence of non-linear kinetics. Eur J Clin Pharmacol. 1991;41:57–59.
[5] Doki K, Homma M, Kuga K, et al. Effect of CYP2D6 genotype on flecainide pharmacokinetics in Japanese patients with supraventricular tachyarrhythmia. Eur J Clin Pharmacol. 2006;62:919–926.
[6] Swen JJ, Nijenhuis M, de Boer A, et al. Pharmacogenetics: from bench to byte–an update of guidelines. *Clin Pharmacol Ther*. 2011;89:662-673. Available from: https://www.pharmgkb.org/guidelineAnnotation/PA166104969 (Accessed October 2, 2018).

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Received 7 August 2018; revised 5 October 2018; accepted 25 October 2018

https://doi.org/10.1080/15563650.2018.1542703