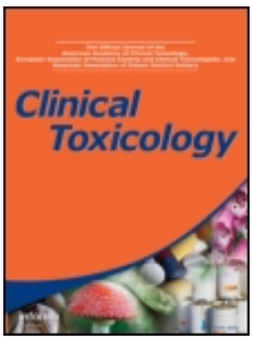

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LETTER TO THE EDITOR

Usefulness of plasma drug monitoring in severe baclofen poisoning

To the Editor:

High-doses of baclofen, a β-(ρ-chlorophenyl)-derivative of γ-aminobutyric acid indicated to treat spasticity of spinal cord origin, are increasingly used to manage alcohol dependence despite the absence of high-level evidence. Baclofen poisoning may be responsible for encephalopathy, coma, respiratory depression, seizures, and hypothermia.[1] Regarding its pharmacokinetics, baclofen is almost completely eliminated from the body by renal filtration and tubular secretion, whereas only a minor pathway involves liver metabolism.[2] Since baclofen is a small water-soluble molecule with limited volume of distribution (~1 L/kg) and binding rate to plasma proteins (~30%), hemodialysis may be useful for enhancing its elimination;[3–5] however, the definitive evidence of hemodialysis clinical usefulness is lacking.

A 29-year-old woman, suffering from neonatal spastic hemiplegia, was admitted to our intensive care unit (ICU), ~16 hours after ingesting 3,500 mg baclofen, 150 mg desloratadine, and 84 mg esomeprazole. On admission, she was comatose (Glasgow Coma Score: 3) with pinpoint myosis but no other remarkable signs (blood pressure: 99/57 mmHg, heart rate: 67/min, respiratory rate: 18/min, and temperature: 36°C). She was intubated and mechanically ventilated. Electrocardiogram was normal; biochemical tests unremarkable and routine toxicological screening tests negative. Seizure activity was evidenced using continuous electroencephalogram monitoring and required multiple treatments including midazolam, phenytoin, phenobarbital, and thiopental. Hemodialysis (Fresenius 5008; Polysulfone membrane; blood flow: 250 mL/min; dialysate flow: 500 mL/min; 13 Fr-femoral catheter) was initiated with four 6-hour sessions guided by plasma baclofen concentrations, measured from 16 to 440 hours post-ingestion by liquid chromatography coupled to mass spectrometry in tandem developed with a Quantum Ultra apparatus (Thermo Fisher Scientific) and electrospray source ionization in positive mode (limit of quantification: 5 ng/mL).

The first plasma baclofen concentration measured 16 h post-ingestion was 2,060 ng/mL (therapeutic range: 60–400 ng/mL; Fig. 1). Based on the first four time points and assuming first-order elimination kinetics with neglected absorption and distribution phases at these times, peak baclofen concentration 3 h after the ingestion was estimated at ~8,000 ng/mL close to concentrations reported in fatalities[6] and the elimination half-life was ~7 h, roughly similar to the observed values at therapeutic doses (mean: 3.5 h, range: 2–6 h).[2,7] After each hemodialysis session, plasma baclofen concentrations significantly decreased by a mean of $50 \pm 2\%$ with a mean elimination half-life of 5.0 ± 1.8 h, close to the value found in this patient with preserved renal function before hemodialysis and to the values previously determined in patients with normal renal function,[2] thus questioning the exact benefit of hemodialysis in enhancing baclofen elimination in the absence of renal failure. Interestingly, after each hemodialysis cessation, concentrations re-increased, until doubled 10 hours later. To explain this observation, we hypothesized baclofen redistribution from the red blood cells or peripheral tissues into the plasma, a well-known phenomenon with several other drugs.

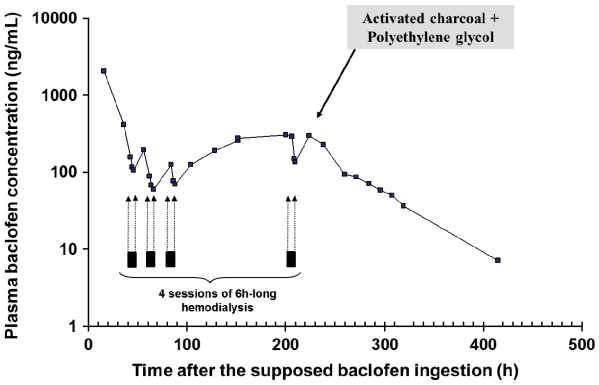

Fig. 1. Time course of plasma baclofen concentrations.

On day 4, thiopental was stopped when plasma baclofen concentrations significantly decreased (69 ng/mL). However, seizures recurred on day 8, concomitantly with a remarkable elevation in plasma baclofen concentrations (peak: 306 ng/mL) after a prolonged rebound from day 5 to day 9, justifying the fourth hemodialysis session as decided by the physicians in charge. Additionally, polyethylene glycol and activated charcoal (two 50 g doses at 8-h intervals) were administered, resulting in the decrease in baclofen concentrations with a prolonged apparent elimination half-life of 39 h, as also previously reported.[7] Our data supported the persistent prolonged intestinal absorption possibly related to sedation-related reduced GI motility or pharmacobezoar rather than delayed clearance in our patient with normal renal function. The late rebound in days 5–9 and the successful prevention of further rebound after administration of activated charcoal made delayed absorption more likely. In contrast, tissue rebound seemed a less likely explanation for rebound since baclofen is water-soluble with low protein binding and limited volume of distribution. The electroencephalographic epileptic activity disappeared on day 11 (plasma baclofen: 92 ng/mL) allowing the stopping of all antiepileptic drugs. The patient woke up on day 13 (plasma baclofen: 50 ng/mL) and was extubated on day 15 (plasma baclofen: 22 ng/mL). She was discharged to the psychiatric ward and baclofen was reintroduced to prevent spasticity.

In conclusion, severe baclofen poisoning may result in a delayed rebound in plasma concentrations together with recurrence of toxicity. Monitoring plasma baclofen concentrations appears beneficial for guiding appropriate patient management including GI decontamination and hemodialysis. However, hemodialysis is of no benefit to increasing baclofen elimination, if the patient has normal renal function.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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