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CASE REPORT

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Hemodialysis as emergency treatment of a severe baclofen intoxication in a 3 kg dog

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Objective: To describe the clinical efficacy and drug removal kinetics of hemodialysis (HD) as emergency treatment in a small size dog with severe baclofen intoxication.

Case description: A 2-year-old dog was presented in stupor to the emergency service a few hours after ingestion of up to 25 mg of baclofen. Medical stabilisation was attempted but was unsuccessful in improving the neurological condition and the patient rapidly progressed to coma. A 4-h session of HD was performed in emergency with near complete resolution of neurological signs and only mild disorientation by the end of the treatment. No adverse side effects occurred during HD. Baclofen concentration was measured serially during the session. Drug extraction ratio, clearance and mass removal by the dialyser were calculated. Dialytic elimination rate constant (K_d) was seven times higher than the intrinsic elimination rate constant (K_{intr}) and the half-life ($t½$) during HD was nearly nine times shorter than the endogenous one.

New or unique information provided: This is the first case report providing pharmacokinetic data associated with HD treatment of severe baclofen intoxication in a dog.

KEYWORDS
baclofen, canine, extracorporeal therapy, intoxication, neurological signs

1 | CASE DESCRIPTION

A 2-year-old, female neutered Prague Ratter dog weighing 2.9 kg was presented to the Emergency Service of the University of Zurich Small Animal Hospital with neurological signs following the accidental ingestion of up to 25 mg (9 mg/kg) baclofen[a] 1–5 h prior to presentation.

On presentation, the dog was in lateral recumbency, with stuporous mentation, hypersalivating, with bilaterally myotic pupils and weak gag reflex. On physical examination, the dog was normothermic, with a rectal temperature of 36.7°C (98.06°F) and hemodynamically stable with a heart rate of 116/min and a noninvasive mean arterial pressure of 80 mmHg (The SunTech Vet20; SunTech Medical, Inc., Morrisville, NC), respiratory rate of 28/min and a pulse oximetry of 100% on room air.

Venous blood gas analysis revealed mild hypercapnia, PvCO2 (47.9 mmHg, 29–43 mmHg), with a normal pH (7.36, RI, 7.30–7.48), normoglycemia (7mmol/l, RI, > 4.5 mmol/l) and increased lactate (3.7 mmol/L, RI, 0.42–2.13 mmol/L). A urine drug test[b] was negative for illicit drugs.

An intravenous fluid bolus of 20 ml/kg of isotonic balanced crystalloid was administered to correct the hyperlactatemia. The dog also received an intravenous bolus of lipid emulsion[c] at 2 ml/kg. Flow-by oxygen (4 L/min) was provided via a face mask during stabilisation. Over the following 2 h, the dog's neurological condition worsened to

[a] Lioresal 25 mg, Novartis Pharmaceuticals, East Hanover, NJ.

[b] Willi Fox Multidrogen test, Willi Fox GmbH CH-4001 Basel.
[c] SMOFlipid 20%, Fresenius Kabi, Uppsala, Sweden.

coma with delayed pupillary light reflex despite therapy. Gag reflex was still present.

Following discussion with the owner regarding the deterioration of the neurological signs, extracorporeal therapy was chosen as rescue treatment to possibly increase baclofen elimination. An 8-Fr × 12 cm dual-lumen dialysis catheter[d] was placed in the right jugular vein percutaneously using a modified Seldinger technique under sterile conditions.

Based on the pharmacokinetic characteristics of baclofen, a single 240-min session of conventional hemodialysis (HD) was performed using an AK98 HD device[e], with a high-flux dialyser 2H[f] of a priming volume of 17 ml and effective membrane area of 0.2 m^2. A neonatal extracorporeal circuit[g] with a priming volume of 32 ml was used. The total extracorporeal circuit volume was equal to 49 ml. The dialysate flow rate during the session was maintained at 500 ml/min. The dialysis machine was programmed to maintain the minimum ultrafiltration rate of 100 ml/h. In compensation for the minimum ultrafiltration rate, to maintain a constant fluid balance and prevent hypovolemia, intravenous fluid administration with balanced crystalloid solution at 100 ml/h was administered during the session. The extracorporeal circuit was primed with 50 ml of pRBC due to the small patient's body size in order to prevent anemia following connection to the extracorporeal circuit.

Standard heparinisation[h] was used targeting an aPTT[i] between 180 and 250 s during the session. A total of 22.5 l (7.5 l/kg) of blood was processed over 240 min with an average flow rate (Qb) of 94 ml/min.

During the session the patient was monitored with continuous ECG, blood pressure monitoring and repeated neurological assessments. No intervention was required to maintain the patient's hemodynamic stability.

Neurologically the dog rapidly improved with progressive return of cranial nerve reflexes. At 120 min of the session, the dog became dysphoric and required mild sedation with dexmedetomidine[j] (1 mcg/kg) IV. The dog remained sedated and returned to a mild disorientation by the end of the HD treatment.

The baseline serum baclofen plasma concentration (C_p bacl) at the beginning of the session was 1269 µg/l (RI, 100–600 ug/l) and at the end of the session 4 h later was 132 µg/l. During the HD session, the C_p bacl dropped by 89% equal to an average reduction of 22.25% per hour. Over a15-h period following the HD session, the plasma baclofen concentration further dropped from 132 to 44 µg/l, equal to a reduction of 66% (3.3% per hour).

During the HD treatment, blood samples pre and post dialyser were collected at 120 min to determine the extraction ratio (ER) and instantaneous clearance (k_i) of the dialyser. The ER (%) was calculated using the formula: [(Pre $C_p$bacl – Post $C_p$bacl)/Pre $C_p$bacl]. The measured ER of baclofen was 54%. The k_i of the dialyser was calculated by multiplying the ER by the instantaneous blood flow rate (Qb): Clearance (k_i [ml/min]) = ER (%) × Qb (ml/min) (Milanov, 1992). The calculated k_i was 54 ml/min (18.6 ml/kg/min).

In order to determine the actual efficiency in baclofen removal by HD alone compared to the physiologic elimination by the dog, we calculated the elimination rate constants during and after the HD session, namely the total elimination rate constant (K_{tot}) and the intrinsic elimination rate constant (K_{intr}) using the following equation (Depner, 1990; Wu et al., 2005):

$$C_t = C_0 e^{-Kt}$$

where C_t and C_0 are the plasma concentrations at time t and at time 0, respectively; K is the elimination rate constant; and t represents the time (h). During HD, K_{tot} is the sum of K_{intr} and the dialytic elimination rate constant (K_d). This is due to the fact that during HD the physiologic elimination of the drug is ongoing and contributes to the overall decrease in C_p bacl. K_{intr} was directly determined over 15 h following the dialysis treatment. By subtracting K_{intr} from K_{tot} is then possible to establish K_d, which represents the clearance of baclofen solely due to HD. K_{tot} was 0.565/h, while the patient's K_{intr} was only 0.066/h. K_d 0.499/h. Based on these results, the clearance of baclofen by HD is seven times higher than the physiologic clearance of the dog.

Using the formula $t½$ = Ln2/K, where Ln indicates the natural logarithm, the half-life during and post dialysis was also calculated, resulting, respectively, in a $t½$ of 1.2 and 10.5 h.

During HD, the patient progressively returned to a normal state of consciousness, passing from comatose to spontaneous vocalisations and disorientation within 120 min of session. Dexmedetomidine[m] (1 mcg/kg) was given IV to sedate the patient; after that, the dog was able to lift her head and maintain a sternal posture.

At the end of the treatment, the dog was disoriented but awake and responsive. By the morning, 9 hours later, the patient was neurologically normal, was eating and drinking and no relapse of neurological signs was observed.

The dog was discharged fully recovered less than 24 h after the HD treatment.

2 | DISCUSSION

Our case report provides a unique set of information: HD has been shown to be a rapid and effective method for the treatment of severe baclofen intoxication; additionally, we demonstrated the feasibility of performing HD alone with a high flux dialyser without the need for coupling it to hemoperfusion (HP), saving costs and avoiding the potential complications associated with a larger extracorporeal circuit.

Baclofen is a neurotropic drug that inhibits the release of the excitatory neurotransmitters glutamate and aspartate (Milanov, 1992). Baclofen is approved in human medicine for the treatment of muscular spasticity associated with various neurological disorders (Jones & Lance, 1976).

[d] 8×12cm double lumen Hemo-Cath, medCOMP, Braunfels,Germany
[e] Baxter Ak98, Gambro, Deerfield, IL
[f] Polyflux2H dialyzer, Gambro dialysatoren GmbH, Gemany.
[g] Tubing sets for hemodialysis BL 120 N, Novaline, Vital healthcare SND.BHD, Malaysia.
[h] Heparin sulfate, Hospira, Lake Forest, IL
[i] Coag Dx Analyzer, One IDEXX Drive, Westbrook, ME
[j] Dexdomitor 0.5 mg/ml, Orion Corporation, Finland.

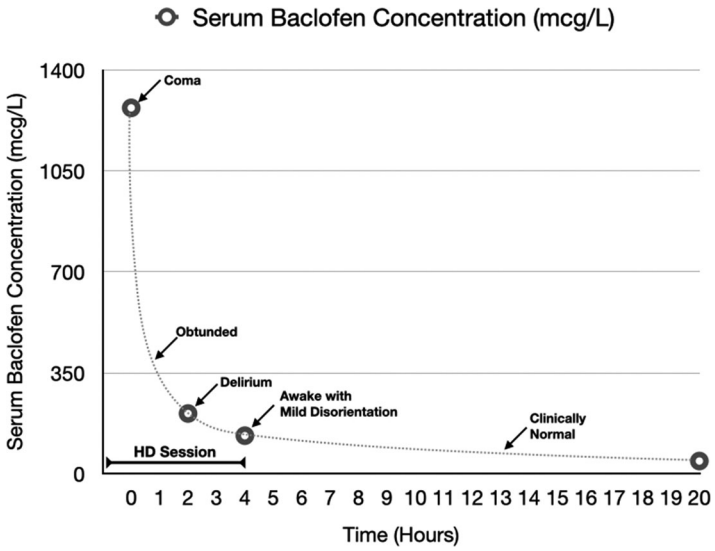

FIGURE 1 Serum baclofen concentration during and following hemodialysis session; arrows indicate time point of changes in clinical condition

After oral administration, baclofen is rapidly absorbed from the gastrointestinal tract reaching peak plasma concentrations within 2–3 h (Faigle & Keberle, 1972; Wuis et al., 1989). The half-life in human is 3.5–8.6 h, whereas in dogs it has not yet been formally established (Scott et al., 2007). Cases of intoxications from accidental ingestion have already been reported in dogs (Fox & Daly, 2016; Hecht & Allenspach, 1998; Scott et al., 2007). Although the lethal dose is unknown, occurrence of clinical signs has been reported at doses as low as 1.3 mg/kg, while severe neurological signs, coma and death have been observed at doses above 8 mg/kg (Wismer, 2004). In the case report by Scott et al., a baclofen plasma concentration of 170 000 µg/l was associated with persistent coma and required prolonged mechanical ventilation (Scott et al., 2007). In our case, the plasma concentration of 1269 µg/l at the time of presentation was already associated with refractory coma, showing that doses far lower than those reported before can be associated with severe neurological signs in dogs.

Our patient was presented within 5 h of ingestion, in a stuporous state and progressed within 2 h to coma. Lipid emulsion therapy was administered as an initial bolus at 2 ml/kg over 15 min. The initial bolus was not followed by the classic constant rate infusion. This decision was based on the lack of clinical response, the rapid deterioration of the neurological condition and the high ingested dose that was unlikely to be managed with lipid infusion alone, although we cannot exclude that a higher dose of lipid emulsion or more prolonged administration could have palliated the clinical signs, as described in previous reports (Bates et al., 2013).

Since there is no available specific antidote, current treatment recommendations of baclofen intoxication rely on early gastric decontamination to prevent intestinal absorption, lipid emulsion therapy and symptomatic therapy for the management of neurological signs (Bates et al., 2013; Khorzad et al., 2012; Wismer, 2004). In an already neurologically impaired patient, gastric decontamination is largely ineffective and possibly dangerous. Once absorption from the gastrointestinal tract has occurred, intravenous lipid therapy has been used with the aim of binding the circulating baclofen (Fox & Daly, 2016). The symptomatic treatment of neurological signs includes seizure control and mechanical ventilation to manage the comatose patients (Dias et al., 2011; Torre et al., 2008).

The use of extracorporeal therapy has already been described as a strategy to actively remove absorbed baclofen and decrease the duration of intoxication in both human and veterinary medicine (Bates et al., 2013; Dias et al., 2011; Fox & Daly, 2016; Khorzad et al., 2012; Scott et al., 2007; Torre et al., 2008; Wismer, 2004; Wu et al., 2005). Although baclofen pharmacokinetics is not well established in dogs, the low protein binding (31%), low molecular weight (213 Da) and moderate volume of distribution (in humans 2.5 l/kg) suggest that baclofen is a suitable drug for removal by HD (Faigle & Keberle, 1972; Scott et al., 2007; Wu et al., 2005).

Scott et al. demonstrated that the use of in series HD/HP was an effective strategy for baclofen removal. They determined that combined HD/HP shortened the elimination half-life from 5 to 1.5 h in the initial 2 h of therapy. Although the use of HD/HP has shown excellent results in baclofen removal as reported above, this requires not only the availability of an HD machine but also the use of a special HP filter which would be associated with a larger extracorporeal volume and special consideration peculiar to HP.

Based on the drug-kinetic data and the patient's small body size, we elected to use HD alone as extracorporeal drug removal therapy.

The calculated half-life of baclofen ($t½$) during and after HD, based on the relationship $t½ = Ln2/K$, was 1.2 and 10.5 h, respectively, reflecting a nearly nine times higher elimination rate of baclofen during HD compared to the endogenous elimination of the dog.

The clinical condition of our patient already improved 120 min into the HD session and the complete remission of the initial neurological signs was obtained by the end of the treatment. No recurrence of signs of intoxication was noted following the HD session (Figure 1), leading to the conclusion that there was no significant rebound of plasma concentration of baclofen.

The rapid resolution of clinical signs significantly decreased the need for nursing care. The dog was comatose on admission and was

transferred to the ICU at the end of the session with mild signs of disorientation which resolved within a few hours. The dog was able to be discharged less than 1 day after presentation, saving costs and with a much lower need of intensive care than a similarly intoxicated patient managed with mechanical ventilation.

The limitation of the use of HD as a treatment for baclofen intoxication is the lack of widespread availability and the cost, which although more affordable than the management of a ventilated patient in an ICU can be still prohibitive for some owners.

Our recommendation in case of severe baclofen intoxication is to consider referring the patient early to a centre where HD treatment is available, given the rapid absorption of the drug from the GI tract and the likelihood of rapid progression to severe neurological deficits.

AUTHOR CONTRIBUTIONS

Formal analysis; resources; writing-original draft; and writing–review and editing: Linda Gabba. *Resources; supervision; writing-original draft; and writing–review and editing*: Claudia Iannucci. Visualisation; resources; supervision; writing–original draft; and writing–review and editing: Alessio Vigani.

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CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

ETHICS STATEMENT

The authors confirm that the ethical policies of the journal, as noted on the journal's author guidelines page, have been adhered to. No ethical approval was required as this is a review article with no original research data.

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