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Population pharmacokinetics of a single oral dose of gabapentin identifies rapid plasma clearance in rehabilitated Pacific harbor seal pups (*Phoca vitulina richardii*)

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Objective
Determine the pharmacokinetic parameters of a single dose of gabapentin administered orally in healthy weaned Pacific harbor seal (HS) pups (*Phoca vitulina richardii*).

Methods
In the spring of 2023, rehabilitated HS pups were enrolled in this pharmacokinetic study. Seals were administered 10 mg/kg of gabapentin orally in a fish. A sparse sampling model was employed to collect blood samples from 0.25 to 48 hours after drug administration. Plasma drug concentrations were determined using liquid chromatography-tandem mass spectrometry. Pharmacokinetic parameters were determined using noncompartmental analysis for sparse data.

Results
15 HSs were included in this study. The mean peak plasma concentration was 7,669.4 ng/mL, the mean time to peak plasma concentration was 1 hour, the mean area under the concentration-versus-time curve from time 0 to infinity was 23,811.8 h·ng/mL, and the mean terminal half-life was 1.9 hours. No adverse effects were observed in any HSs.

Conclusions
The plasma concentration of gabapentin that confers analgesia is not known in veterinary species. During this study, mean gabapentin concentrations exceeded the concentration estimated to treat neuropathic pain in humans only at 1 hour.

Clinical Relevance
Gabapentin was rapidly absorbed and eliminated in HSs, indicating that higher dosages and/or frequent dosing of gabapentin may be needed to maintain targeted plasma concentrations in young HSs. Additional studies to investigate the clinical efficacy of gabapentin in veterinary species are warranted, and clinical discretion should be used when applying these results to patients outside of the specific demographic group studied here.

Keywords: analgesia, gabapentin, harbor seal, pharmacokinetics, *Phoca vitulina*

Harbor seals (HSs; *Phoca vitulina*) and other pinnipeds are commonly treated in rehabilitation centers and in zoological institutions worldwide for a variety of conditions that warrant analgesic or anticonvulsant intervention. These painful or abnormal neurologic conditions include acute and chronic musculoskeletal and nerve injury/trauma, epilepsy, renal disease, petroleum exposure, and postoperative care, among other health concerns. To date, only 3 pharmacokinetic studies[1–3] have been conducted in pinnipeds to assess analgesic medications, and only 1 study[3] was in HSs. Two of the studied medications, tramadol and buprenorphine, are opioids with potential undesirable side effects including respiratory depression, constipation, nausea, and sedation.[4,5] In marine mammals specifically, opioids are known

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to cause significant sedation.[6] The other studied analgesic, meloxicam, is an NSAID. Meloxicam has a narrow therapeutic dosing range with the possibility of significant gastrointestinal and renal adverse effects.[3,7] Investigation of other classes of analgesics is warranted to find alternatives to undesirable side effects and to better characterize options for multimodal analgesia.[8] Studies of anticonvulsants in pinnipeds are even more limited, with levetiracetam and phenobarbital levels reported for only a few individual pinnipeds.[9]

Gabapentin is a GABA analog that was originally developed as an antiepileptic drug.[5,10] In humans, gabapentin is now 1 of 3 drug classes that are recommended as first-line medications for the treatment of neuropathic pain in addition to the antiseizure effects.[10,11] Gabapentin has a wide safety margin with relatively few reported side effects. While drugs such as NSAIDs may not be appropriate for use in patients with renal compromise or gastric ulceration, gabapentin would be considered a safe alternative analgesic medication for some types of pain.[8]

The pharmacokinetics of gabapentin have been published in other species[12–21] but never in a marine mammal. The studies in mammals have investigated dosages ranging from 10 to 120 mg/kg with recommended dosing intervals ranging from 6 to 12 hours.[15–20] Due to interspecies variation in pharmacokinetics and pharmacodynamics, establishing the pharmacokinetics on a species-specific basis is important to guarantee a given drug's safety and efficacy.[22]

The objective of this study was to determine the pharmacokinetic profile of gabapentin in healthy HSs (area under the curve, rate of absorption, maximum plasma concentration [C_{max}], time to C_{max}, and terminal half-life). An understanding of the pharmacokinetics of gabapentin in HSs will provide objective data for prescribing an appropriate gabapentin dose and frequency in this species. These results will improve clinicians' ability to adequately treat painful and seizurogenic conditions in this widely treated species.

Methods

Animals

Fifteen weaned HS pups were enrolled in this study. Inclusion criteria included the provisions that all enrolled HSs had undergone rehabilitation at The Marine Mammal Center (TMMC) due to maternal separation, malnutrition, and/or other mild health concerns and had been deemed clinically healthy enough following rehabilitation for return to the wild and that none of the HSs had been administered any pharmacologic agents within 14 days of time point 0. The HSs were rescued and cared for under National Oceanic and Atmospheric Administration permit No. 26532. The study protocol was approved by the TMMC IACUC (No. 2023-1-1). Each HS received an initial and subsequent examination by an experienced, qualified veterinarian. Seals were housed outdoors in pens with full-time access to saltwater pools and were fed thawed herring (*Clupea* spp) 3 to 4 times each day as previously described.[3]

Study design

Each HS enrolled was in the study based on their normal health status and approval for release to the wild at their required prerelease examinations, which occurred 5 to 12 days before the actual release date. Approval for release was contingent upon a normal physical examination, a weight threshold deemed appropriate for prerelease examination, and unremarkable blood work (CBC, chemistry panel, and serum amyloid A). Baseline (time point 0) pharmacokinetic samples were obtained for all enrolled HSs from the blood collected at these release examinations. All HSs were manually restrained for release examinations and for venipuncture for subsequent pharmacokinetic samples during the study. Manual restraint and venipuncture were performed according to previously described methods.[23]

Each HS was administered a single dose of oral gabapentin at a dosage of 10 mg/kg, rounded to the nearest capsule size. The gabapentin was fed to the HS in a single fish (frozen-thawed herring), and each HS was monitored to ensure that they consumed the fish in its entirety before the rest of the diet was provided. A sparse sampling protocol was employed; in addition to the baseline samples, each HS was sampled at 2 designated time points, determined at random, for a total of 3 samples collected per seal and per time point.

Blood samples were obtained from the epidural intervertebral vein using a 1.5-inch 20-gauge needle at 0.25, 0.5, 1, 3, 5, 8, 12, 24, 36, and 48 hours for a total of 11 time points including the baseline (time 0) sample. Approximately 3 mL of blood was collected per venipuncture, and the blood sample was collected directly into vacutainer 1-mL lithium heparin tubes.

Within 30 minutes of sample acquisition, samples were centrifuged for 10 minutes at 1,000 X *g*, and the resulting supernatant plasma was transferred into cryogenic vials and stored at −80 °C until analysis (5 to 6 months). Samples were transported on ice to the Analytical Chemistry Laboratory at the School of Veterinary Medicine at the University of California-Davis.

Determination of plasma gabapentin concentrations

Gabapentin calibration curves and negative control samples were prepared fresh for each quantitative assay. Plasma calibrators were prepared by dilution of the gabapentin working standard solutions (Cerilliant) with drug-free plasma to concentrations ranging from 0.5 to 50,000 ng/mL. Quality control samples (plasma fortified with analyte at 2 concentrations within the standard curve) were included as a check of accuracy.

Before analysis, 100 µL of plasma was diluted with 150 µL of acetonitrile (ACN):1 M acetic acid (9:1 [vol:vol]) containing 0.1 ng/µL of d10-gabapentin internal standard (Cerilliant) to precipitate proteins. The samples were vortexed for 2 minutes to mix, refrigerated for 20 minutes, vortexed for an additional 1 minute, and centrifuged (4,300 rpm/3,102 *g*) for 10 minutes at 4 °C.

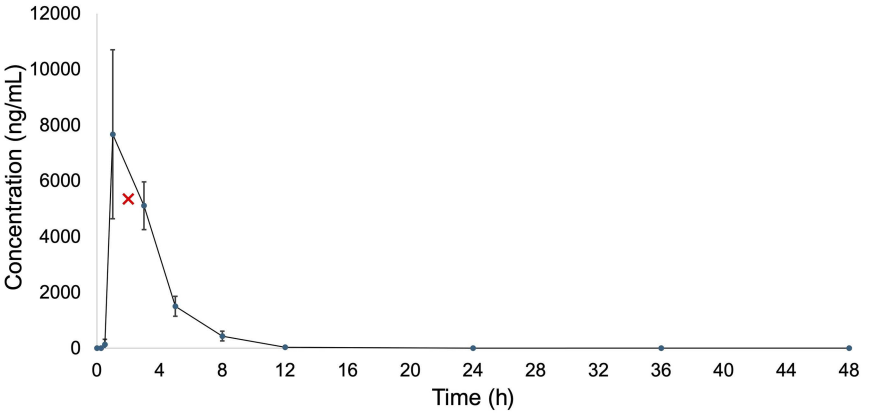

Figure 1—Mean plasma concentrations of gabapentin from 0.25 to 48 hours in 15 clinically normal, rehabilitated Pacific harbor seal pups (*Phoca vitulina richardii*) following a single oral dose of gabapentin at 10 mg/kg in a fish between June 6 and June 25, 2023. Time 0 was before gabapentin administration. The red "x" indicates the concentration estimated to treat neuropathic pain in humans.

The concentration of gabapentin was measured in plasma by liquid chromatography tandem mass spectrometry (LC-MS/MS) using positive heated electrospray ionization. An aliquot (20 µL) of the sample was injected into the LC-MS/MS system. Quantitative analysis was performed on a TSQ Altis triple quadrupole mass spectrometer coupled with a Vanquish liquid chromatography system (Thermo Scientific). Product masses and collision energies of each analyte were optimized by infusing the standards into the TSQ Altis. Chromatography employed an ACE 3 C18 10-cm X 2.1-mm 3-µm column (Mac-Mod Analytical) and a linear gradient of ACN in water with a constant 0.2% formic acid at a flow rate of 0.35 mL/min. The initial ACN concentration was held at 1% for 0.2 minutes, ramped to 95% over 5.4 minutes, and held at that concentration for 0.1 minutes before re-equilibrating for 3.9 minutes at initial conditions.

Detection and quantification were conducted using selective reaction monitoring of the initial precursor ion for gabapentin (m/z, 172.1) and the internal standard d10-gabapentin (m/z, 182.2). The responses for the product ions for gabapentin (m/z, 95.1 and 137.1) and the internal standard (m/z, 104.1, 147.2, and 164.2) were plotted, and the peaks at the proper retention time were integrated, using Quanbrowser software (Thermo Scientific). Quanbrowser software was used to generate calibration curves and quantitate analytes in all samples by linear regression analysis. A weighting factor of 1/X was used for all calibration curves.

Pharmacokinetic analysis

Pharmacokinetic parameters were calculated using a commercially available software program (Phoenix Winnonlin, version 8.2; Certara Inc) by noncompartmental analysis of sparse data, in which the plasma drug concentrations from all HSs at a unique time point are averaged and the mean concentrations are used to calculate pharmacokinetic parameters. Estimation of the SEs for concentration to C_{max} was calculated as previously described, using a modification, and accounting for any correlations in the data resulting from repeated sampling of individual animals.[24,25]

Results

Nine male and 6 female weaned HSs were enrolled in the study (body weight, 18 to 25 kg; average, 20.4 kg; 3 to 5 months of age). Each HS was administered a single dose of oral gabapentin at a dosage of 10 mg/kg, rounded to the nearest capsule size (dose, 200 or 300 mg gabapentin; average dose, 10.1 mg/kg). All enrolled HSs had undergone rehabilitation at TMMC due to maternal separation, malnutrition, and/or other mild health concerns and had been deemed clinically healthy enough for return to the wild.

For the LC-MS/MS analytical method, the instrument response was linear and gave correlation coefficients of 0.99 or better. The precision and accuracy of the assay were determined by assaying quality control samples in replicates (n = 6). Accuracy was reported as percent nominal concentration, and precision was reported as percent relative standard. For gabapentin, accuracy was 94% for 6 ng/mL and 93% for 10,000 ng/mL. Precision was 1% for 6 ng/mL and 2% for 10,000 ng/mL. The technique was optimized to provide a limit of quantitation of 0.5 ng/mL and a limit of detection of approximately 0.25 ng mL for gabapentin.

Gabapentin was successfully administered to all HSs and was detected in plasma samples through 24 hours postdrug administration **(Figure 1 and Table 1)**. Pharmacokinetic parameters are reported

Table 1—Mean plasma concentration of gabapentin for each time point in 15 clinically normal, rehabilitated Pacific harbor seal pups (*Phoca vitulina richardii*) following a single oral dose of gabapentin at 10 mg/kg in a fish between June 6 and June 25, 2023.

Time (h)	Mean (ng/mL)	SD	No. of samples
0	ND	0	15
0.25	1.0	0	3
0.5	136.1	180.7	3
1	7,669.4	3,027.2	3
3	5,110.1	854.3	3
5	1,504.1	356.3	3
8	434.3	175.1	3
12	31.9	3.8	3
24	1.2	2.1	3
36	ND	ND	3
48	ND	ND	3

ND = Not detected.

in **Table 2**. No adverse effects were observed in any of the HSs, and no sedation was noted in any animal at any time point postadministration. All animals were released to the wild upon completion of sample collection; release was not delayed by participation in this study.

Table 2—Pharmacokinetic parameters for gabapentin following administration of a single oral dose of gabapentin at 10 mg/kg in a fish to 15 clinically normal, rehabilitated Pacific harbor seal pups (*Phoca vitulina*) between June 6 and June 25, 2023.

Parameter	Value
C_{max} (ng/mL)	7,669.4 (1,747.8)*
t_{max} (h)	1.0
$AUC_{0-\infty}$ (h·ng/mL)	23,811.8
AUC_{extrap} (%)	0.03
λ_z (1/h)	0.364
$t_{1/2\lambda}$ (h)	1.9

Data are presented as geometric mean. Parameters were generated using noncompartmental analysis.

*The SE for maximum plasma concentration (C_{max}).

λ_z = Terminal slope of the concentration-versus-time curve. $AUC_{0-\infty}$ = Area under the concentration-versus-time curve from time 0 to infinity. AUC_{extrap} = Extrapolated portion of the area under the curve. $t_{1/2\lambda}$ = Terminal half-life. t_{max} = Time to C_{max}.

Discussion

Gabapentin has a variety of clinical uses in human medicine, and accordingly, the targeted therapeutic dose changes depending on the clinical application. In humans, a serum concentration > 2,000 ng/mL resulted in a lower frequency of seizures.[26] Some previous pharmacokinetic studies[14,16,19] on gabapentin in veterinary species provided dose recommendations based on a target plasma threshold of 2,000 ng/mL. However, the plasma concentration of gabapentin associated with analgesic effects is unknown in most species. Studies in mice suggest that plasma concentrations associated with analgesia for inflammatory hyperalgesia range from 1,400 to 16,700 ng/mL.[27–29] To the authors' knowledge, there are no pharmacokinetic/pharmacodynamic studies in humans that determine a threshold plasma concentration for analgesia, but a prospective pharmacodynamic study[30] used previously published pharmacokinetic data to perform a clinical trial simulation. Based on these models, the authors estimated that the effective concentration for treating neuropathic pain in humans is approximately 5,350 ng/mL.[30]

Compared with dogs and cats administered a single dose of gabapentin at 10 mg/kg orally, HSs had a lower time to C_{max}, C_{max}, and terminal half-life.[16,19] In our study, mean plasma concentrations were above 1,400 ng/mL at 1, 3, and 5 hours; above 2,000 ng/mL at 1 and 3 hours; above 54,000 ng/mL at 1 hour; and never above 167,000 ng/mL. Regardless of the target threshold employed, gabapentin was rapidly absorbed and eliminated in HSs relative to other studied mammals, indicating that higher dosages and/or frequent dosing is likely warranted to achieve and maintain concentrations reported to be effective in other species.

The subjects in the present study were exclusively HS pups (weaned, but less than 1 year of age). Gabapentin pharmacokinetics in human children and infants demonstrated that younger patients had lower area under the concentration-versus-time curve from time 0 to infinity and C_{max} and faster clearance rates, suggesting that younger children may require 30% higher doses of gabapentin compared with older children.[31] Because gabapentin is highly water soluble, these authors postulated that the presumably higher body water content in younger children may lead to a higher volume of distribution and (and thus, lower C_{max}) of gabapentin relative to older children. Similar logic (high body water content and rapid creatinine clearance leading to comparatively low C_{max} and terminal half-life in young animals compared with other studies in mammals) may be applicable to the exclusively weaned pup population of HSs in our study.

The HSs were fed according to their normal feeding schedule, and gabapentin was administered in a fish so that the generated pharmacokinetic profile is representative of clinically realistic scenarios for gabapentin dosing. Previous studies[32] in humans have suggested that gabapentin absorption may occur more rapidly with consumption of a high-protein meal compared with fasting. Fed a piscivorous diet consistent with the species' natural history, it is possible that the protein content may have facilitated rapid gabapentin absorption. Additionally, the average reported gastrointestinal transit time for young HSs fed primarily herring was 3 hours and 50 minutes,[33] which is markedly faster than postfeeding total transit time in adult dogs and cats (average of 27 hours and 51 minutes and 50 hours and 9 minutes, respectively).[34] These differences may be in part due to the high water content in the HS diet and their younger age and also may bear relevance for the described pharmacokinetic profile.

Mean gabapentin concentrations exceeded the concentration estimated to treat neuropathic pain in humans (5,350 ng/mL) only at 1 hour. Rapid elimination of gabapentin has been described in other species; in dogs, gabapentin exceeded the therapeutic threshold (defined as 2,000 ng/mL in that study) for up to 8 to 12 hours, depending on the dose used (10 or 20 mg/kg). Gabapentin exceeded 2,000 ng/mL for less than 5 hours in this study. Regardless of the target threshold, the excretion rate of gabapentin in weaned HS pups was more rapid than expected. Gabapentin may be useful in multimodal analgesia regimens and/or as alternatives to NSAIDs or opioids. Due to opioid use disorder in humans, the CDC recommends nonopioid therapy as first-line treatment for chronic pain.[35] Due to the potential for human dependency and abuse, opioids are controlled, which may lead to difficulty in obtaining these drugs as well as a high level of oversight with their use. Gabapentin is also dosed orally, which has some advantages over injectable medication. Subcutaneous administration of drugs can be challenging in some pinniped species due to their thick

blubber layer.[36] Due to the lipophilic nature and vascularization of blubber compared with SC tissue or muscle, drugs inadvertently injected into the blubber may result in dramatically different absorption of the drug or may not be systemically distributed at all.[6] A study[2] on SC sustained-release buprenorphine in northern elephant seals found that 23% of study subjects developed cellulitis or abscesses at the injection site. There is no such risk of these adverse effects with oral medication administration. Oral dosing also allows analgesic administration without manual restraint or injection-associated discomfort. Limiting the number of times an animal is restrained, whether wild or in managed care, may reduce stress and is safer for the patient and the human handlers.

This study implemented a sparse-sampling model, which is recommended for pharmacokinetic studies with small sample sizes[36–38] and has been employed in several recent pharmacokinetic studies in nondomestic species.[3,39–41] This strategy also minimizes the handling stress for individual patients while allowing sufficient samples to be collected to establish a statistically valid profile for the drug.

The limitations of this study include a small sample size of only young animals, single-dose administration, and a lack of paired IV pharmacokinetics, which are needed for oral bioavailability assessment. Studies assessing the pharmacodynamics of gabapentin for treating different conditions in veterinary species and multidose regimens would provide additional clinical insights. These results may be useful in determining appropriate dosing of gabapentin in this HS age class; extrapolation to other pinnipeds and marine mammals, especially of different age groups, should be performed with caution.

In conclusion, a single dose of gabapentin at 10 mg/kg orally in a fish was rapidly absorbed and eliminated in rehabilitated, weaned HS pups, suggesting that higher dosages or more frequent dosing may be required to maintain target plasma concentrations within this specific demographic.

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Disclosures

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