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Pharmacokinetic evaluation of a sustained-release compounded procainamide preparation after 24-h (acute) administration in normal dogs

J.D. Thomason, DVM[a,b,*], D. Boothe, DVM[c], B. KuKanich, DVM, PhD[d], G. Rapoport, DVM[a]

[a] *Department of Small Animal Medicine and Surgery, College of Veterinary Medicine, University of Georgia, 501 DW Brooks Drive, Athens, GA, 30602, USA*
[b] *Department of Clinical Sciences, College of Veterinary Medicine, Kansas State University, 1800 Denison Avenue, Manhattan, KS, 66506, USA*
[c] *Department of Physiology and Pharmacology, College of Veterinary Medicine, Auburn University, 1220 Wire Road, Auburn, AL, 36849, USA*
[d] *Department of Anatomy and Physiology, College of Veterinary Medicine, Kansas State University, 1620 Denison Avenue, Manhattan, KS, 66506, USA*

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Methylcellulose;
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Abstract *Introduction:* The objective of the present study was to evaluate the pharmacokinetics of a compounded sustained-release procainamide formulation in normal dogs.
Animals: Six healthy, purpose-bred mixed-breed dogs participated in the study.
Methods: In phase I, two dogs were administered oral procainamide (30 mg/kg), and plasma was obtained to determine plasma concentration ranges and duration. In phase II, six dogs were administered procainamide (30 mg/kg by mouth every 12 hours) to determine the pharmacokinetics of sustained-release procainamide. Serum procainamide concentration was determined using an immunochemistry assay.
Results: No adverse clinical effects were noted in any of the dogs studied. The average maximum serum concentration, average serum concentration, and average minimum serum concentration were 10.17, 7.13, and 3.07 μg/mL, respectively. The average time over a 12-h period during which procainamide concentration exceeded 12 μg/mL was 2.35 h, was between 4 and 12 μg/mL was 7.19 h, and

* Corresponding author.
E-mail address: jthomason11@vet.k-state.edu (J.D. Thomason).

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was less than 4 μg/mL was 2.46 h. The average times at maximum concentration and minimum concentration were 18.67 and 12.25 h, respectively.
Conclusions: Administration of sustained-release procainamide twice daily achieved targeted plasma concentrations in most dogs. Evaluation of serum trough concentrations should be considered owing to interanimal variability to confirm that serum concentrations are within the reported therapeutic range for an individual patient.
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Introduction

Procainamide is a class IA antiarrhythmic medication [1—9]. As such, it exerts characteristic effects in excitable cardiac tissue. These include depression of the maximal rate of phase 0 depolarization, decreased speed of impulse conduction, and prolonged effective refractory period via delayed repolarization [1]. This activity is demonstrable in atrial myocytes, ventricular myocytes, and Purkinje fibers [2,3]. In addition, procainamide antagonizes the cardiac actions of vagally released acetylcholine [2,3]. As a result of this vagolytic effect, the tendency of acetylcholine to shorten the atrial refractory period is lessened. These actions make procainamide a suitable choice for the treatment of supraventricular and ventricular tachyarrhythmia [2—4].

Although there is a lack of studies correlating serum drug concentrations with antiarrhythmic effects in dogs, the reported therapeutic trough concentration for procainamide is 3—8 μg/mL [10]. This therapeutic concentration is similar to the effective concentration cited in people [11]. However, in people, a portion of the administered procainamide is metabolized by the liver to the metabolite, N-acetylprocainamide, which also contributes to the antiarrhythmic effects [11]. Dogs are unable to acetylate aromatic and hydrazine amino groups and are, therefore, unable to produce N-acetylprocainamide [11]. Because of this, it has been argued that dogs require higher serum concentrations of procainamide than people to control some cardiac arrhythmias [11]. Given the potential therapeutic benefit of procainamide at a trough concentration >4 μg/mL, we chose this target concentration in this study. However, clinical studies are needed to assess the true minimum effective concentrations in dogs.

Previously, a sustained-release procainamide (SRP) formulation was available and could be administered every 8 h to canine patients. This preparation is not currently commercially available, however, SRP is available through a compounding pharmacy.[e] Because an Food and Drug Administration (FDA)-approved product is not currently available, compounding SRP is considered appropriate. Compounded products are not subject to the same rigorous standards as commercially available products and can vary from batch to batch, which can affect a patient's response to therapy. Many veterinarians and clients may not choose a compounded procainamide option owing to the lack of proven stability, potency, efficacy, or bioequivalence studies. The purpose of this study was to evaluate the pharmacokinetics of this SRP formulation in normal dogs. The hypothesis was that this oral SRP would result in a trough serum concentration ≥4 μg/mL at 12 h in normal dogs.

Animals, materials, and methods

Animals

Six healthy, intact purpose-bred mixed-breed dogs participated in the study. All six dogs were determined to be healthy based on complete physical examinations and normal laboratory data (complete blood counts and serum chemistries). The study was approved by the Institutional Animal Care and Use Committee at the University of Georgia.

Study design

The study consisted of two phases: a pilot study (phase I) and a pharmacokinetic study (phase II). The purpose of phase I was to determine the appropriate dosage of SRP that achieved a target serum trough procainamide concentration of at least 4 μg/mL in two dogs. The purpose of phase II was used to determine the pharmacokinetics of the SRP formulation in six dogs.

[e] Wedgewood Pharmacy, Swedesboro, NJ.

Materials and methods

Two dogs were used for phase I of the study. Sustained-release procainamide was administered by mouth (30 mg/kg every 12 h beginning at time 0 h for one day) to fed animals. Serum samples (5 mL per sample) were collected using a jugular venous catheter at the following times: 0 (before drug administration), 0.5, 1, 2, 4, 6, 8, 10, 12 (before the second dose), 13, 14, 16, 18, 20, and 24 h (the total volume of blood collected from each dog was 2.5—4 mL/kg). Blood was allowed to clot for 10 min at room temperature in red-top tubes. The samples were centrifuged (3000 rotations per minutes for 5 min; G-force = 1509.3), and the serum was harvested and placed in plastic serum tubes, frozen (−80 C), and shipped to Auburn University for pharmacokinetic analysis after the 24-h collection period.

Using the data from these two dogs (Fig. 1), pharmacokinetic modeling was used to determine an appropriate oral dosage of SRP to achieve a trough concentration of at least 4 μg/mL. For phase II, a total of six dogs (the two dogs from phase I were used in phase II after a one-month washout period) were administered two oral doses of SRP (30 mg/kg PO q 12 h) at time 0 h and 12 h. The blood samples (5 mL) were obtained for pharmacokinetic analysis using jugular venous catheters at the following times: 0 (before drug administration), 0.5, 1, 2, 4, 6, 8, 10, 12 (before the second dose), 12.5, 13, 14, 16, 18, 20, and 24 h (the total volume of blood collected from each dog was 2.5—4 mL/kg).

Pharmacokinetic data were analyzed using noncompartmental methods.[f] A multiple-dosing plasma profile was simulated using compartmental methods. A one-compartment model with a lag time and first-order input and output was performed on the average plasma concentrations to determine absorption rate (K01), elimination rate (K10), volume of distribution per fraction of the dose absorbed (V/F), and lag time (TLAG).

For drug analysis, the serum samples were thawed and mixed to assure homogeneity. Procainamide was detected using a procainamide assay[g] on a chemistry analyzer.[h] The assay and methodology were validated for dog serum by the Clinical Pharmacology Laboratory of Auburn University. The upper and lower limits of quantitation were 20 and 0.5 μg/mL, respectively. The system was calibrated,[i] and the canine serum was spiked with known concentrations of procainamide HCl[j] and used as quality control samples. The coefficient of variation values were 11% in the low range (1.74 μg/mL) and less than 4% in the high range (15.7 μg/mL).

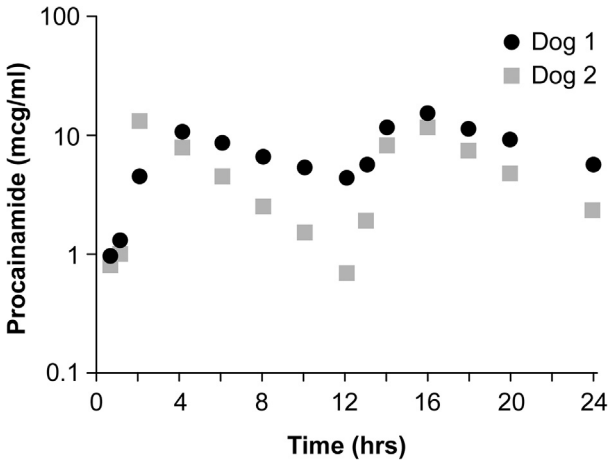

Fig. 1 Serum procainamide concentration in two dogs. Pharmacokinetic modeling was used to determine an appropriate oral dosage of SRP (30 mg/kg) to achieve at least 4 μg/mL. SRP, sustained-release procainamide.

Results

No adverse clinical effects were noted in any of the dogs in this study. There were three male and three female dogs. The average age was 7.5 years (range, 7—8 years). The average weight was 24.6 kg (range, 21.4—30 kg). The average maximum serum procainamide concentration, average serum procainamide concentration, and average minimum serum procainamide concentration were 10.17, 7.13, and 3.07 μg/mL, respectively. The average time over a 12-h period during which procainamide concentration exceeded 12 μg/mL was 2.35 h. The average time over a 12-h period during which procainamide concentration was between 4 and 12 μg/mL was 7.19 h. The average time over a 12-h period during which procainamide concentration was less than 4 μg/mL was 2.46 h. The maximum and minimum concentrations were achieved 18.67 and 12.25 h after dosing on average, respectively. At 12 h, the average procainamide concentration was 3.15 μg/mL (range,

[f] WinNonlin Professional v5.3, Pharsight Corp, Mountain View, CA.
[g] PROC Procainamide Assay, Siemens, New York, NY.
[h] Dimension Xpand Plus, Siemens, New York, NY.
[i] Drug Calibrator II, Siemens, New York, NY.
[j] VWR International, Radnor, PA.

1.0—4.5 μg/mL). At 24 h, the average procainamide concentration was 5.88 μg/mL (range, 3.4—8.7 μg/mL) (Fig. 2).

Multiple-dose administration was simulated using the following pharmacokinetic parameters: V/F = 5181 mL/kg, K01 = 0.9251 hr^{-1}, K10 = 0.04395, and TLAG = 0.657 h. At a steady state (approximately 4 days after therapy), the simulated maximum plasma concentration was 12.66 μg/mL, and the simulated minimum plasma concentration was 6.9 μg/mL for a dosage of 30 mg/kg PO every 12 h (Fig. 3).

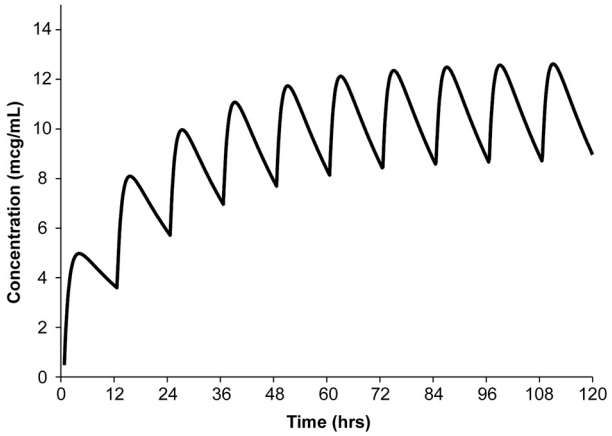

Fig. 3 Simulated serum concentrations for multiple-dose administration (30 mg/kg by mouth every 12 hours) based on the average plasma profiles of six healthy dogs.

Discussion

Procainamide is a class IA antiarrhythmic medication [1—9]. Although it is a suitable choice for the treatment of supraventricular and ventricular tachyarrhythmia, the short half-life of procainamide in the dog (approximately 3 h) makes administration problematic, necessitating dosing every six to 8 h [2]. This short dosing interval is likely to reduce client compliance and could result in therapeutic failure. Previously, SRP was available and could be administered every 8 h. The availability of SRP would provide a feasible therapeutic option in a subset of patients that may benefit from procainamide therapy and is an example of appropriate compounding.

Simulated multiple-dose administration of this formulation at 30 mg/kg PO q 12 h resulted in a maximum simulated plasma concentration of 12.66 μg/mL and a minimum simulated plasma concentration of 6.9 μg/mL, which is within a reasonable range of plasma concentrations. However, this simulation was based on the average plasma profile; therefore, it is important to remember that pharmacokinetic variability was observed between dogs, and an individual dog may not respond as this dosing simulation would predict. Therefore, these data and simulations should be used only as a guideline, and individual dosing adjustments should be based on an animal's response and adverse effects. Therapeutic drug monitoring will be necessary to optimize the dosing regimen for a specific animal.

The kinetics of drug release in this formulation is dependent on the solubility of the active moiety and the swelling and erosion properties of the polymer. Water-soluble drugs (such as procainamide) are released predominately by diffusion. There is also a limited contribution from matrix erosion and anomalous diffusion resulting from the

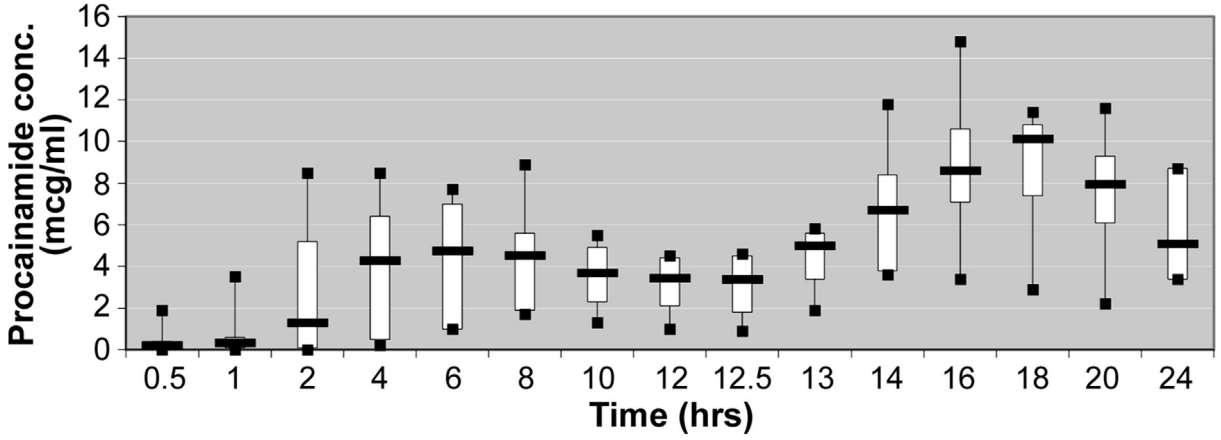

Fig. 2 A box and whisker plot demonstrating the serum procainamide concentrations in dogs at various times. The bold line indicates the median. The boxes contain the 25—75th centiles. The whiskers represent the minimum and maximum concentrations. Based on the data, administration twice daily can maintain serum concentration >4 μg/mL; in fact, some patients may maintain a concentration >4 μg/mL with dosing once daily.

relaxation of macromolecular polymer chains [12]. The release of water-soluble moieties typically follows first-order release kinetics [13]. Methylcellulose is widely used as a release rate control polymer for hydrophilic drugs owing to its regulatory acceptability, viscosity, and ability to be formulated into simple, robust, and easily fabricated dosage forms [13].

Typically, zero-order release kinetics is desirable for extended-release formulations to match the drug input rate with the rate of elimination, thereby maintaining steady-state plasma profiles [13]. However, first-order drug release resulting in the release rate (and subsequently absorption rate) being slower than the drug elimination rate can result in prolonged dosing intervals where the rate-limiting step for drug elimination is drug absorption. This is known as the flip-flop phenomenon. Procainamide-methylcellulose mixture allows an apparent first-order procainamide release at a rate to obtain and sustain serum levels, likely due to this phenomenon. However, because an immediate-release formulation was also not evaluated, this would need to be confirmed in future studies.

Given that compounded products are not subject to the same rigorous standards as commercially available products, many veterinarians and clients may not choose a compounded procainamide option owing to the lack of stability, potency, efficacy, or bioequivalence studies. However, based on the results of this study, administration of this SRP formulation twice daily may be a reasonable option for some dogs. However, further studies are needed using multiple batches tested in a blinded manner to ensure consistency of the current formulation.

Some limitations of this study are the small patient population, short duration of the study, the utilization of healthy dogs, the lack of evaluation of the stability and efficacy of this SRP formulation, and the inability to provide a recommended dosage for SRP in dogs. Dosage recommendations should be based on a pharmacodynamic investigation with a specifically determined physiologic response variable of interest.

Further studies are needed to evaluate multiple doses and determine the time until a steady state is achieved. The 24-h serum concentrations (trough second dose) were higher than the 12-h samples (trough first dose), indicating that accumulation was occurring. Because this product would be most useful for subacute and chronic management, it is important to know when the steady state occurs and what concentrations are achieved at the steady state.

Conclusions

In conclusion, although specific dosing recommendations cannot be made from this study owing to individual animal variability, it appears that administration of SRP twice daily could be efficacious for dogs. Owing to individual patient variability, evaluation of serum trough concentrations after at least four days of therapy should be considered to confirm concentrations within the reported therapeutic range. Future studies are required to determine appropriate dosage recommendations of SRP based on specific arrhythmia control.

Conflict of Interest Statement

The authors do not have any conflicts of interest to disclose.

Acknowledgments

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