Investigation of the short-term effects of a transdermal formulation of atenolol in healthy cats

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OBJECTIVE

To investigate associations between short-term treatment with a previously described compounded transdermal formulation of atenolol and heart rate in cats.

ANIMALS

11 healthy adult cats.

PROCEDURES

Cats received the atenolol gel formulation (gradually increased from 12.5 mg/cat, q 24 h to 25 mg/cat, q 12 h) by application to the pinnae at home over a 10-day period in a prospective, experimental study. On day 10, cats were hospitalized for measurement of serum atenolol concentrations 3, 6, and 12 hours after the morning treatment. Mean heart rate measured at the 3- and 6-hour time points was compared with a baseline value (measured at enrollment).

RESULTS

All cats completed the study; 4 were excluded from analyses after an apparent formulation error was detected in 1 batch. Two cats had minor adverse effects (localized erythema of the pinna). Five of 7 cats had serum atenolol concentrations ≥ 260 ng/mL (considered therapeutic) at ≥ 1 time point. Heart rate had a strong negative correlation ($r = -0.87$) with serum atenolol concentration. A 90-day drug stability investigation of 4 formulations (identical to the intended study treatment except for pH [range, 6.5 to 7.7]) revealed an apparent decrease in atenolol concentration at a pH of 7.7.

CONCLUSIONS AND CLINICAL RELEVANCE

Topical administration of the formulation as described resulted in targeted serum atenolol concentrations in most cats, with attendant HR reduction. Validation of these preliminary results in a larger sample and investigation of the treatment in cats with structural heart disease is needed. Verification of appropriate pH (target, 7.0) is likely essential for the compound's stability.

Cats affected with hypertrophic cardiomyopathy are frequently prescribed atenolol, a selective β_1-adrenergic receptor antagonist. Although atenolol treatment has not been conclusively shown to increase survival rates in affected cats, some veterinary cardiologists prescribe atenolol on the basis of the theoretical benefits of β_1-adrenergic receptor blockade and extrapolation of improved survival rates in people with hypertrophic cardiomyopathy that receive atenolol.[1] Adequate β_1-adrenergic receptor blockade results in decreased contractility and lower HR with a longer diastolic phase and reduced myocardial oxygen demand.[2]

For cats, atenolol is administered orally in tablet form at a dosage of 6.25 to 12.5 mg every 12 to 24 hours; this formulation is highly bioavailable in cats (mean ± SD, 90 ± 9%) and has a half-life of 3.66 hours, with peak atenolol concentration occurring 1 to 2 hours after administration.[3–5] However, owner compliance may be poor for long-term oral treatment.[6] For animals such as cats that can be difficult to routinely pill at home, alternate routes of administration are advantageous. Transdermal applications may potentially improve patient-owner interactions, and this route avoids gastrointestinal degradation and hepatic first-pass metabolism of products. The physicochemical properties of atenolol make it suitable for development as a transdermal formulation.[7]

Little information has been published on the effects of transdermal formulations of atenolol in cats. One group previously evaluated the pharmacokinetics and pharmacodynamic effects of atenolol administered as a single dose IV (1 mg/kg) or orally (3 mg/kg) to 9 healthy purpose-bred cats that underwent challenge with isoproterenol.[5] In that study,[5] the HR of cats that had plasma atenolol concentrations ≥ 260 ng/mL was significantly reduced, compared with baseline (pretreatment) measurements, 6 and

ABBREVIATIONS

HR	Heart rate
HPLC	High-performance liquid chromatography
IQR	Interquartile (25th to 75th percentile) range

12 hours after drug administration. Another group compared pharmacodynamic variables after administration of equivalent doses (6.25 mg/cat, q 12 h) of oral and transdermal formulations of atenolol for 1 week to 7 healthy cats in a crossover-design study and found that 6 cats had serum atenolol concentrations > 260 ng/mL 2 hours after receiving the final dose of the oral formulation, whereas only 2 cats had this result after receiving the final dose of the transdermal formulation.[3] Plasma atenolol concentrations > 260 ng/mL were detected 12 hours after drug administration in 3 of the 7 cats after oral treatment but in none after transdermal treatment,[3] raising questions regarding the equivalence of treatments when the same dose is delivered by transdermal versus oral routes and the potential for variable results when the medication is compounded.

Recently, authors of our group generated and tested various atenolol gel formulations for topical administration to cats in a collaborative research effort between the College of Pharmacy and the College of Veterinary Medicine at Oregon State University.[8] That investigation[8] was the first part of a 2-part study, in which the effects of various penetration enhancers and polymer concentrations on the release profile of atenolol compounded from commercially available tablets into a gel formulation were determined, and a formulation optimized for transdermal drug delivery was selected for testing in healthy cats. The details of that investigation, including the summary pharmacokinetics data determined for 7 cats of the present study, have been reported elsewhere.[8] The purpose of the second part of the study, which is reported here, was to evaluate the pharmacodynamic effects of the selected transdermal atenolol formulation in the same sample of healthy cats. We hypothesized that this atenolol formulation, administered every 12 hours at a dose higher than that used in the aforementioned comparison of oral and transdermal formulations,[3] would result in serum atenolol concentrations > 260 ng/mL (considered therapeutic)[5] in individual cats and be associated with decreases in HR measured after phlebotomy, compared with pretreatment values for the same cats.

Materials and Methods

Cats

A convenience sample of healthy adult mixed-breed cats owned by staff and students of the Oregon State University College of Veterinary medicine was enrolled in the study. Participation was recruited through an electronic mail list message seeking healthy cats > 1 year of age that were receiving no medications other than antiparasitic agents administered on a monthly basis. The number of included cats reflected budgetary constraints and logistic concerns. The cats were classified as healthy on the basis of results of a physical examination, CBC and serum biochemical analysis, blood pressure measurement, ECG, and echocardiography. Informed owner consent was obtained prior to study inclusion, and the study was approved by the Institutional Animal Care and Use Committee of Oregon State University.

Procedures

Three batches of a previously described atenolol gel formulation[8] (125 mg/mL) optimized for transdermal delivery and created with commercially available atenolol tablets,[a] propylene glycol,[b] glycerol,[c] polysorbate 80,[d] dimethyl isosorbide,[e] US Pharmacopeia–grade 95% ethanol,[f] carbomer 934,[g] triethanolamine,[b] and US Pharmacopeia–grade purified water were used in the study. The methods for replicating the formulation administered to cats in the study are provided **(Supplementary Appendix S1)**. Each batch was tested prior to use to ensure that the measured atenolol concentration was within 10% of the targeted concentration of 125 mg/mL. Briefly, 1 g of the prepared product (a clear, colorless gel) was diluted in 1 L of water and mixed thoroughly for 20 minutes, then filtered through a 0.45-µm filter to produce a nominal 12.5 µg/mL solution of atenolol. One milliliter of this solution was centrifuged for 10 minutes at 3,500 × *g*. The supernatant was removed, and a 20-µL aliquot was analyzed by means of HPLC.[8] All batches had results within 1% of the targeted value, and final products were stored at room temperature (22 to 25 °C) for ≤ 5 days prior to being dispensed for use in the study.

Initially, a maximum transdermal dosage of 12.5 mg every 12 hours was planned for use in the study; however, early results (data for the first 2 treated cats) indicated that this dosage was likely to result in drug concentrations less than the targeted value of 260 ng/mL (not shown), and a maximum dosage of 25 mg every 12 hours was selected instead. The dose administered was gradually escalated to reach this target over time according to the following schedule: 12.5 mg every 24 hours for 2 days, then 12.5 mg every 12 hours for 2 days, then 25 mg in the morning followed by 12.5 mg 12 hours later for 2 days, and finally 25 mg every 12 hours for 3 days, with the last dose for study purposes given on the morning of day 10.[8] This timeline was selected so that the dose was slowly titrated upward as a safety precaution and time was allowed for the dermal barriers to soften before applying the maximum dose. After sample collection on day 10, cats were discharged from the hospital, and the treatment was tapered and discontinued.[8]

The atenolol formulation was packaged in syringes and provided to the owners with instructions for administration.[8] Briefly, owners were provided disposable gloves and instructed that residual material from previous doses was to be cleaned from the surface of the ear with sensitive skin wipes, doses were to be given in the described order and alternated between the left and right ears, and the specified amount was to be applied as an even layer of gel over the inner surface of the pinna. Owners

were asked to report any adverse effects potentially associated with the medication, including signs of illness, weakness, or local effects (eg, erythema or excessive grooming of the ears). On day 10 of treatment, cats were admitted to the hospital for serial collection of blood samples after the morning dose of atenolol was administered.

Blood samples (approx 3 mL) were obtained by venipuncture 3, 6, and 12 hours after drug administration on day 10 for measurement of serum atenolol concentration.[8] Blood samples were allowed to clot at room temperature, then centrifuged at 3,000 × *g* for 5 minutes. Collected serum was refrigerated at 5 °C for up to 12 hours before submittal to a commercial laboratory[h] for measurement of atenolol concentrations with HPLC–tandem mass spectrometry.[8]

At baseline (the time of initial screening, prior to phlebotomy) and immediately after blood sample collection at the 3- and 6-hour time points on day 10, a 7-lead ECG was obtained for each cat. The ECGs were analyzed to determine HR following the catecholaminergic stimulus associated with handling and blood sample collection and its potential association with circulating atenolol concentrations. Mean HR was measured from a 30-second ECG recording.

Statistical analysis

Statistical analysis was performed with a commercially available software package.[i] Given the small sample size, data were considered nonparametric and reported as median and IQR unless otherwise indicated. The relationship between HR (mean value during the 30-second recording) and plasma atenolol concentration at the same time points was evaluated with a repeated-measures correlation in the package.[j] Histograms and Q-Q plots of conditional mixed model residuals were examined to evaluate the assumption of normality. The difference between baseline HRs and those measured 3 and 6 hours after atenolol administration on day 10 was assessed with the Wilcoxon signed rank test. Values of $P < 0.05$ were considered significant.

Results

Seventeen cats were screened for study enrollment, and 11 cats met the inclusion criteria. There were 5 males and 6 females (median body weight, 4.6 kg [range, 3.7 to 5.7 kg]; median age, 4.5 years [range, 1.3 to 9 years]). Reasons for exclusion included frequent ventricular ectopy (n = 1), occult renal dysfunction (2), and equivocal or mild structural heart disease (3). All enrolled cats successfully completed the drug trial, and no cats were reported to have clinically important adverse effects (eg, signs of hypotension, lethargy, syncope, or weakness). Two cats had localized erythema of the pinna that was well tolerated and resolved without treatment.

The first 2 cats that participated in the study received the initially planned maximum atenolol dosage of 12.5 mg, every 12 hours, and had serum atenolol concentrations < 260 ng/mL 3, 6, and 12 hours after administration of the drug on day 10. Data from those experiments were excluded from the final analysis, and with the maximum dosage increased to 25 mg every 12 hours, the same 2 cats were reenrolled in the study after a 4-week washout period. All other cats enrolled in the study received atenolol according to the revised dosage protocol. The median atenolol dose for the 11 cats, once the target of 25 mg/cat was reached, was 5.4 mg/kg (IQR, 5.2 to 6.6 mg/kg).

The 11 cats were assigned to 3 cohorts, each receiving atenolol gel from a separate batch. The second cohort of cats (n = 4) had day-10 serum atenolol concentrations < 260 ng/mL (at all time points for 3 of 4 cats), and marked discoloration of the gel was observed by the study authors after an owner commented on formulation discoloration; the results for these 4 cats were excluded from all data analyses because of a presumed formulation error when that batch was created.

Of the remaining 7 cats, 5 had serum atenolol concentrations > 260 ng/mL at ≥ 1 time point after drug administration on day 10 **(Figure 1)**. Four cats had atenolol concentrations greater than this cutoff 3 hours after the treatment, and 1 additional cat had an atenolol concentration of 255 ng/mL at this time point. Atenolol concentration was greater than the targeted value for 1 cat at the 6-hour time point and for 4 cats at the 12-hour time point after this treatment.

The median HR at baseline (the time of screening for study enrollment) for the 7 cats retained in the analysis was 200 beats/min (IQR, 180 to 220 beats/min). Af-

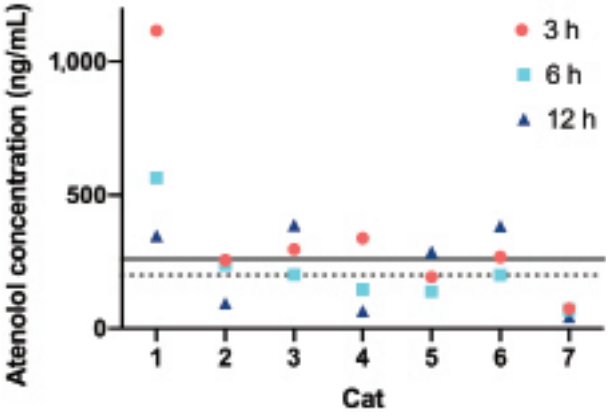

Figure 1—Serum atenolol concentrations for 7 healthy cats 3, 6, and 12 hours after drug administration (time 0 for this analysis) on day 10 of a prospective, experimental study to investigate associations between treatment with a previously described[8] nonpatented gel formulation of atenolol for transdermal delivery and heart rate in cats. On days 1 to 9, owners applied the gel to the inner surface of their cat's pinna (dosage gradually increased from 12.5 mg/cat, q 24 h, to 25 mg/cat, q 12 h). After the morning drug administration (25 mg) on day 10, blood samples were collected for assessment of atenolol concentrations at the time points shown; pharmacokinetic data are reported elsewhere.[8] The solid and dotted horizontal lines represent serum atenolol concentrations of 260 and 200 ng/mL, respectively.

ter drug administration on day 10, the median HR was 175 beats/min (IQR, 140 to 180 beats/min) at the 3-hour time point and 180 beats/min (IQR, 163 to 185 beats/min) at the 6-hour time point (each immediately following sample collection [presumed catecholaminergic stimulus]). There was a significant ($P < 0.001$) negative correlation ($r = -0.87$) between HR (mean value for the 30-second recording for each cat) and serum atenolol concentration **(Figure 2)**. The median HR for the study sample at the 3-hour time point was significantly ($P = 0.03$) lower than the baseline value, whereas median HR at the 6-hour time point was not significantly ($P = 0.06$) different from the baseline value.

Because a formulation error was suspected for the batch of atenolol gel provided for cats of the second study cohort, an investigation was undertaken to determine whether various pH and light conditions had degradation effects on atenolol in the formulation over 90 days. The pharmacologists suspected that there were technical issues with the pipette used during the compounding of this batch of atenolol gel and that a miniscule increase (0.02 mL) in the concentration of triethanolamine (used to neutralize the carbomer gel foundation of the formulation) in this batch increased the pH of the gel and catalyzed accelerated degradation of atenolol.

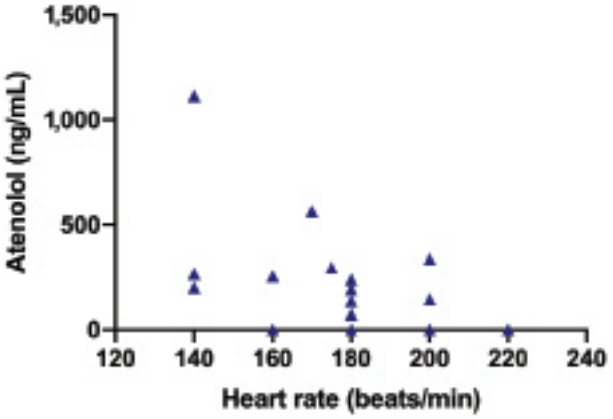

Figure 2—Scatterplot depicting heart rate verus serum atenolol concentration for the 7 cats in Figure 1. Results are shown for 3 sampling time points (baseline [the time of initial screening for study enrollment, prior to phlebotomy] and 3 and 6 hours after transdermal drug administration on day 10 [immediately after blood sample collection at each time point]). The baseline atenolol concentration was presumed to be 0. Twenty data points are present; however, some data points with identical values overlap.

Four atenolol formulations were created to replicate the compound used for in vivo testing, except that the pH was varied by titration with glacial acetic acid in a final step. This adjustment was made to atenolol gel in the beaker before it was allocated into syringes so that a drop of glacial acetic acid would not affect the overall atenolol volume or concentration. The atenolol gels (21 syringes/pH/light condition) had pH levels of 6.5, 7.0, 7.4, and 7.7 at the time of compounding (day 0). Atenolol concentrations and pH values were determined on day 0 and 7, 14, 21, 28, 60, and 90 days later for gels stored with light exposure or light restriction. For samples that underwent light exposure, syringes were placed under a lamp with an incandescent light bulb left on continuously throughout this part of the study. Samples with light restriction were placed in a sealed drawer with no light exposure for the same period. Drug concentrations were measured by HPLC as previously described; descriptive results are reported as the mean of 3 replicates/time point under each of the tested conditions.

The analysis results indicated that atenolol content of each formulation with a pH ≤ 7.4 on day 0 was generally stable over 90 days, regardless of the light exposure conditions **(Figure 3)**. For samples in the light exposure group, the measured atenolol concen-

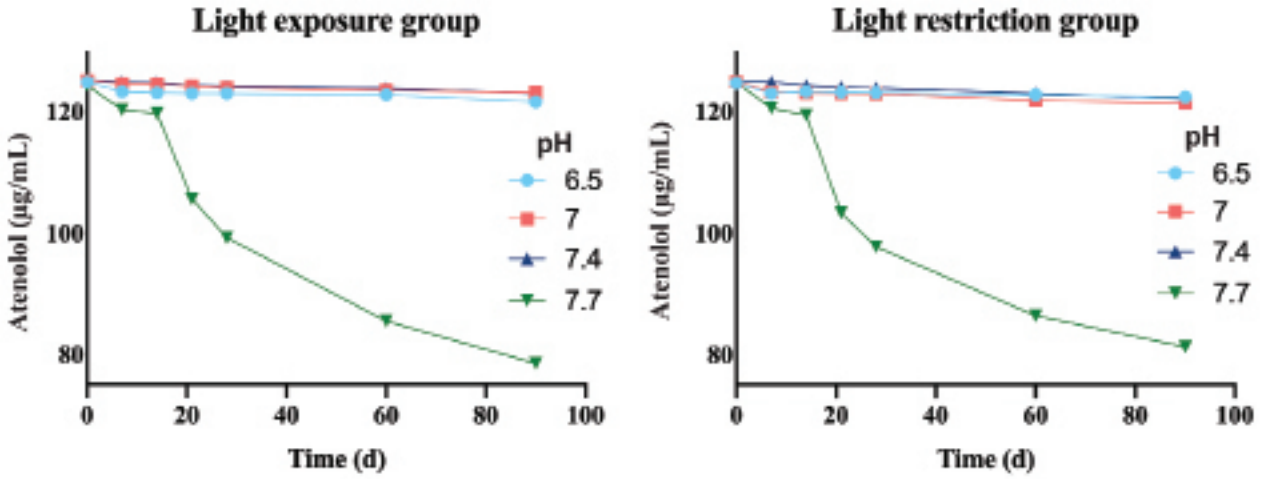

Figure 3—Concentrations of atenolol measured by HPLC in 4 transdermal gel formulations (125 mg of atenolol/mL) over 90 days under conditions of light exposure and light restriction. The formulations were created to replicate the product tested in cats of the present study, except that the pH (targeted as 7.0 for in vivo testing) of the compounds shown was adjusted to range from 6.5 to 7.7 on day 0 (the day of compounding). Data points represent the mean of 3 replicates/pH/time point for each of the light conditions.

trations ranged from 125.2 µg/mL (day 0) to 123.0 µg/mL (day 90) at a pH of 7.4, from 125.1 µg/mL (day 0) to 123.2 µg/mL (day 90) at a pH of 7.0, and from 124.9 µg/mL (day 0) to 121.6 µg/mL (day 90) at a pH of 6.5. When the pH was 7.7 on day 0, the atenolol content declined substantially over the same interval (from 124.3 µg/mL [day 0] to 78.5 µg/mL [day 90]). The results were similar for samples in the light restriction group. All samples appeared clear and translucent at all time points with no apparent color change at pH levels ≤ 7.4; the samples that had a pH of 7.7 changed to a light yellow in both the light exposure and light restriction groups.

Discussion

In the present study, the described transdermal formulation of atenolol administered at a dosage of 25 mg/cat (approx 5.4 mg/kg), topically, every 12 hours, provided serum atenolol concentrations deemed therapeutic (≥ 260 ng/mL) at ≥ 1 time point in 5 of the 7 healthy cats for which data were analyzed and an attendant reduction in the median heart rate 3 hours after drug administration (immediately following blood sample collection for that time point), compared with the result at baseline. These results were encouraging, as many medications administered transdermally are known to have substantial variability, compared with formulations created for oral or IV administration. Given the small number of cats in the study and the variable serum atenolol concentrations measured, these results require validation in a larger cohort of cats.

Interestingly, 3 of 7 cats had numerically higher serum atenolol concentrations at the 12-hour time point than at the 6-hour time point. One explanation for the apparently greater concentration in some cats at the later time point is that the circulating concentration was affected by different phases of drug absorption; an initial burst of atenolol diffusion resulted in high serum atenolol concentrations at the 3-hour time point, followed by relatively rapid elimination of the absorbed atenolol, causing a decrease in its concentration at the 6-hour time point. The major barrier to drug absorption via the transdermal route during the initial burst phase is skin penetration; however, the skin barrier eventually weakens so diffusion across the dermis is subsequently accelerated and more drug is absorbed, resulting in another increase in circulating drug concentration.

Compared with a previous study[3] in which 2 of 7 healthy cats developed serum atenolol concentrations that were considered therapeutic after application of a transdermal formulation of the drug, the present study differed in its design and in the drug formulation that was used. Building on the information published from that study,[3] penetration enhancers (dimethyl isosorbide and ethanol) were added, and a different surfactant (polysorbate 80) was used for the formulation[8] in our investigations. There was a slightly longer time between the titration of the atenolol up to the desired dose and sample collection to theoretically allow for more softening of the stratum corneum layer by hydrating the epidermis to increase its permeability, as the stratum corneum is the primary physical barrier to chemical penetration.[9] Our targeted dosage was also higher at 25 mg/cat every 12 hours, compared with 6.25 mg/cat every 12 hours in the previous study,[3] as was the concentration of atenolol in the transdermal gel formulation in our study.

We did use the previously described cutoff for serum atenolol concentration of 260 ng/mL as an estimate of therapeutic circulating drug concentration[3,8]; however, as indicated in the aforementioned report,[3] an exact therapeutic cutoff is not known. A previous study[5] performed to evaluate the β-adrenergic receptor blocking effects of orally administered atenolol (3 mg/kg, PO, q 24 h for 3 consecutive days) in cats that underwent isoproterenol challenge found that the lowest circulating atenolol concentration associated with adequate β-adrenergic receptor blockade as assessed by attenuated HR was 260 ng/mL, and serum atenolol concentrations of 42 ng/mL did not yield a significant clinical effect. This suggests that the cutoff for a therapeutic circulating drug concentration falls within the range between 42 and 260 ng/mL.[3] The therapeutic circulating concentration of atenolol in people is reported to be 200 µg/mL,[10] and with an analogous cutoff, 6 of 7 cats in the present study would have had therapeutic circulating concentrations of the drug at ≥ 1 of the assessed time points (5/7 cats at 3 hours and 4/7 cats at 6 and 12 hours). On visual evaluation of HR data for individual cats with serum atenolol concentrations between 200 and 260 ng/mL, a consistent numeric reduction in HR of 20 to 40 beats/min was observed, compared with the baseline values (data not shown); this suggested that a cutoff of 200 ng/mL may be more appropriate, although the sample size was small and there is presently no consensus among veterinary cardiologists regarding an optimal change in HR for cats requiring this treatment.

We encountered several dosage and formulation issues in this pharmacologic investigation. First, the initial dosage of 12.5 mg/cat, every 12 hours, did not result in the targeted serum atenolol concentrations. This was not surprising, as administering the equivalent of oral dosages in transdermal formulations has been shown to result in less consistent and lower plasma drug concentrations.[3,11] Although transdermal formulations are appealing in that they avoid hepatic first-pass metabolism and can be technically easier to administer than oral formulations for many cats, the issues encountered in the present study highlighted one of the attendant challenges associated with topical treatment. Other notable issues that can be encountered are related to drug characteristics such as molecular weight, solubility, molecular interactions with skin components, and the degree of ionization.[3,9] A high degree of interindividual variability in peak serum atenolol concentrations has been observed in people,[12] and this effect was considered a possible cause for the marked range in serum atenolol concen-

trations in our study sample, particularly at the 3-hour time point. We also could not verify that owner or patient compliance related to treatments was optimal, as the treatments were administered in the home environment. Finally, different rates of metabolism could have contributed to the wide variation in circulating atenolol concentrations in cats that received the stable atenolol formulation.

Subjectively assessed results of drug stability testing at various pH levels performed after the in vivo experiments of the present study suggested that pH is critically important to stability of the transdermal formulation described in this report. Another group of researchers previously found that changes in pH and light exposure accelerated the degradation of atenolol under experimental conditions,[13] whereas our findings suggested that pH was the major determinant of atenolol degradation, independent of light exposure, for ≤ 90 days. Under normal circumstances, atenolol is broken down by an oxidation-reduction chemical reaction. Oxidation-reduction chemical reactions are pH dependent, with a range of pH values that generally attenuate the reaction. Raising or lowering the pH will alter the proton or hydroxyl concentration in the product, increasing the rate of the reaction. The data from our study suggested that a pH of 7 to 7.4 is adequate to minimize atenolol degradation in the formulation over a 3-month period. Considering that pH is likely a critical component of formulation stability, it is important that the pH be verified as a final step in compounding this gel.

The study reported here had several limitations. A small number of healthy cats were enrolled in the study, and the findings should be verified in a larger sample of cats, as well as in cats with structural heart disease. As previously mentioned, application of the medication in the home environment created the potential for problems related to compliance, which could have introduced variability in the doses administered, frequency of administration, or duration of treatment before testing. We measured serum atenolol concentrations in healthy cats that were likely experiencing stress related to transport and hospitalization, which theoretically could have affected transdermal absorption of the treatments administered on the morning of day 10, as stress-induced vasoconstriction can cause drug trapping through decreased dermal perfusion and lead to drug accumulation in the epidermis rather than systemic absorption.[9] Conversely, vasodilation can promote systemic drug accumulation, and changes in blood pressure that result from stress are among the challenges associated with medical research involving cats.[9] The baseline HRs of cats in our study were obtained by means of ECG during the initial screening appointment, and ideally, this measurement would have been performed immediately after phlebotomy to mirror the order of events on day 10. A final ECG for each cat after the 12-hour blood sample collection would also have provided additional information about the duration of drug effects. Finally, a greater number of sampling time points would have provided more precise pharmacokinetic and pharmacodynamic data; however, this would have required sedation and placement of catheters for sample collection in healthy cats of a research colony, and our study relied on the voluntary enrollment of cats privately owned by individuals in our local veterinary community.

Overall, our results suggested that the described transdermal formulation of atenolol, administered topically on the inner surface of the pinna at 25 mg/cat (approx 5.4 mg/kg), every 12 hours, can provide circulating atenolol concentrations that are considered therapeutic, although some variability in these values was observed. Attendant HR reductions in our small sample of healthy cats supported that the treatment can yield desired β-adrenergic receptor blocking effects; however, investigation in a larger cohort of cats is needed, and the pharmacokinetics and clinical effects of the treatment in cats with structural heart disease have yet to be investigated. We found that the appropriate pH is a critical component for the stability of this formulation, and a targeted pH of 7.0 to 7.4 should be confirmed when the compound is created.

Acknowledgments

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The authors declare that there were no conflicts of interest.

Footnotes

a. Teva, Gardena, Calif.
b. JT Baker Inc, Phillipsburg, NJ.
c. EMD Chemicals Inc, Port Wentworth, Ga.
d. Acumedia, Lansing, Mich.
e. Croda Healthcare, Edison, NJ.
f. Pharmaco, Brookfield, Conn.
g. Spectrum, Gardena, Calif.
h. MedTox Laboratories, Saint Paul, Minn.
i. Prism 8, GraphPad Software, San Diego, Calif.
j. RMCORR, version 0.4.1 (2017), R Core Team, R Foundation for Statistical Computing, Vienna, Austria.

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Supplementary Materials

Supplementary materials are available online at: avmajournals.avma.org/doi/suppl/10.2460/ajvr.82.10.811.