

Pharmacokinetics of carvedilol after intravenous and oral administration in conscious healthy dogs

Wendy G. Arsenault, DVM; Dawn M. Boothe, DVM, PhD; Sonya G. Gordon, DVM, DVSc; Matthew W. Miller, DVM, MSc; Jeffrey R. Chalkley, DVM; Ilona Petrikovics, PhD

Objective—To determine the pharmacokinetics of carvedilol administered IV and orally and determine the dose of carvedilol required to maintain plasma concentrations associated with anticipated therapeutic efficacy when administered orally to dogs.

Animals—8 healthy dogs.

Procedures—Blood samples were collected for 24 hours after single doses of carvedilol were administered IV (175 µg/kg) or PO (1.5 mg/kg) by use of a crossover nonrandomized design. Carvedilol concentrations were detected in plasma by use of high-performance liquid chromatography. Plasma drug concentration versus time curves were subjected to non-compartmental pharmacokinetic analysis.

Results—The median peak concentration (extrapolated) of carvedilol after IV administration was 476 ng/mL (range, 203 to 1,920 ng/mL), elimination half-life ($t_{1/2}$) was 282 minutes (range, 19 to 1,021 minutes), and mean residence time (MRT) was 360 minutes (range, 19 to 819 minutes). Volume of distribution at steady state was 2.0 L/kg (range, 0.7 to 4.3 L/kg). After oral administration of carvedilol, the median peak concentration was 24 µg/mL (range, 9 to 173 µg/mL), time to maximum concentration was 90 minutes (range, 60 to 180 minutes), $t_{1/2}$ was 82 minutes (range, 64 to 138 minutes), and MRT was 182 minutes (range, 112 to 254 minutes). Median bioavailability after oral administration of carvedilol was 2.1% (range, 0.4% to 54%).

Conclusions and Clinical Relevance—Although results suggested a 3-hour dosing interval on the basis of MRT, pharmacodynamic studies investigating the duration of β -adrenoreceptor blockade provide a more accurate basis for determining the dosing interval of carvedilol. (*Am J Vet Res* 2005;66:2172–2176)

Carvedilol^a is a third-generation nonselective β -adrenoreceptor blocking agent with unique ancillary α_1 -adrenoreceptor blocking and antioxidant properties presently licensed for treatment of essential hypertension and congestive heart failure in humans.

Similar to other β -adrenoreceptor blocking agents, carvedilol has consistently been found to improve left ventricular function and survival in humans with heart

failure secondary to systolic dysfunction.¹ Although the mechanism of improvement is not completely understood, the deleterious effects of chronic excessive adrenergic stimulation of cardiomyocytes are limited by treatment with β -adrenoreceptor blockers. Carvedilol also has antioxidant effects that may decrease oxidant stress and apoptosis of cardiomyocytes associated with progressive heart failure.²

Chronic blockade of β -adrenoreceptors is useful in ameliorating systolic dysfunction that develops in an experimental model of mitral insufficiency in dogs.³ Mitral insufficiency resulting from spontaneous chronic degenerative valvular disease is the leading cause of congestive heart failure in dogs and represents > 75% of all cardiovascular disease in dogs.^{4,5} Presently, there is no known treatment available to delay the progression of nonclinical chronic degenerative valvular disease to congestive heart failure. Yet, the beneficial pharmacologic properties of carvedilol may be useful in this regard. Studies indicating therapeutic efficacy of carvedilol are warranted; however, there have been no studies to determine the dose in dogs without heart failure. The purposes of the study reported here were to determine the pharmacokinetics of carvedilol administered IV and orally and determine the dose of carvedilol required to maintain plasma concentrations associated with anticipated therapeutic efficacy when administered orally to dogs. Efficacy and duration of β -adrenoreceptor blockade were determined by a concurrent pharmacodynamic study performed in the same dogs.⁶

Materials and Methods

Dogs—The study was approved by the University Laboratory Animal Care Committee of Texas A&M University. Eight mature healthy hound dogs (4 sexually intact males, 3 sexually intact females, and 1 spayed female) from 2 to 5 years old and weighing approximately 20 to 25 kg were studied by use of a nonrandomized crossover design.

Preliminary data—Two dogs were used to determine the optimal dose of carvedilol necessary to attain targeted pharmacodynamic effects.⁶ On the basis of results from that study, carvedilol was administered PO at a dose of 1.5 mg/kg in the study reported here.

Received December 9, 2004.

Accepted February 8, 2005.

From the Departments of Small Animal Medicine and Surgery (Arsenault, Gordon, Miller, Chalkley) and Veterinary Physiology and Pharmacology (Boothe, Petrikovics), College of Veterinary Medicine, Texas A&M University, College Station, TX 77843-4474. Dr. Arsenault's present address is Southwest Florida Veterinary Cardiology, 27223 Barefoot Ln, Bonita Springs, FL 34135. Dr. Boothe's present address is Department of Anatomy, Physiology and Pharmacology, College of Veterinary Medicine, Auburn University, Auburn, AL 36849. Dr. Chalkley's present address is Department of Clinical Science, College of Veterinary Medicine, Kansas State University, Manhattan, KS 66506. Dr. Petrikovics' present address is 142 McAdory Hall, Auburn University, Auburn, AL 36849.

Supported by the Morris Animal Foundation, Cavalier King Charles Spaniel Health Foundation, and Texas A&M Signature Program.

Presented as an abstract at the 21st Annual Forum of the American College of Veterinary Internal Medicine, Charlotte, NC, June 2003.

Address correspondence to Dr. Boothe.

Preparation of dogs—All dogs received an opioid and anticholinergic premedication, and anesthesia was induced with propofol and maintained with isoflurane. A vascular access port^b was surgically placed in the left femoral vein to facilitate repeated blood sampling for pharmacokinetic analysis. A telemetry unit^c was surgically implanted in the right flank with a telemetry catheter inserted into the right femoral artery for invasive pharmacodynamic data collection.

Pharmacokinetic evaluation—Pure carvedilol powder^d was supplied by the manufacturer. Immediately prior to the study, the powder was solubilized in 90% dimethyl sulfoxide for IV injection to a concentration of approximately 2 mg/mL and sterilized by use of a 0.2- μ m filter.^e Dimethyl sulfoxide was determined to be the only vehicle in which the drug could be solubilized and safely administered IV to dogs. After collection of a baseline plasma sample, carvedilol (175 μ g/kg) was administered over 1 minute via a catheter placed in a cephalic vein, and blood samples were collected at 0.5, 1.5, 3, 5, 7, 9, 15, 20, 25, 30, 35, 45, 60, 90, 120, 150, 180, 240, 300, 360, 720, and 1,440 minutes from which plasma was obtained. For experiments in which carvedilol was administered orally, food was withheld from all dogs for 12 hours prior to administration of carvedilol (1.5 mg/kg) in a small meatball of canned dog food. Blood samples were collected at time 0 (prior to oral administration of carvedilol) and at 15, 30, 45, 60, 75, 90, 105, 120, 135, 150, 165, 180, 195, 210, 240, 300, 360, 720, and 1,440 minutes.

Sample analysis—Plasma was obtained from blood samples and frozen at -20°C within 2 hours of collection; lithium heparin was used as the anticoagulant. Plasma samples were prepared by solid-phase extraction by use of a C8 column^f and 90% methanol and 10% potassium monophosphate (KH_2PO_4) solution as the eluant. The eluant was subjected to reverse-phase high-performance liquid chromatography (HPLC) according to previously described methods⁷ with slight modifications. Briefly, carvedilol was separated from the eluant by use of a C18, 5 μ m, 250 \times 4.6-mm column.⁸ Carvedilol was eluted with a mobile phase comprised of 40% 50mM KH_2PO_4 adjusted to a pH of 2.5 and 60% methanol at a flow rate of 1.0 mL/min. Carvedilol was detected by use of fluorescence spectrophotometry set for an excitation wavelength of 47 nm and an emission wavelength of 344 nm.

The assay was validated in canine plasma; the lower and upper limits of quantitation were 2.0 and 800 ng/mL, respectively, and were based on the lowest and highest concentrations that could be accurately detected within 15%, with the exception of the lowest control for which 20% variability was accepted.

Data analysis—Plasma concentrations obtained after IV administration of carvedilol (log vs time curves) were analyzed by use of noncompartmental linear regression analysis^h with area under the curve (AUC) determined to infinity by the trapezoidal method. For IV administration, peak plasma concentrations were extrapolated to the Y intercept (C_0), whereas for oral administration, the actual maximum concentration (C_{max}) was reported at the time to maximum concentration (T_{max}). Other parameters determined were elimination half-life ($t_{1/2}$; calculated as harmonic mean \pm pseudostandard deviation); mean residence time (MRT); and, after IV administration, clearance and volume of distribution at steady state (V_{dss}). Bioavailability (F) after oral administration of carvedilol was determined from the following equation:

$$(\text{Dose}_{\text{IV}} \times \text{AUC}_{\text{PO}}) / (\text{Dose}_{\text{PO}} \times \text{AUC}_{\text{IV}}) \times 100$$

Statistical analysis—Descriptive statistics were determined by use of commercially available software.^h Variables are reported as median and range. Differences between sexes were compared by use of paired *t* tests.

Results

Intravenous and oral administration of carvedilol was well tolerated by all dogs. After IV administration of carvedilol, dogs had a brief period of mild sedation (< 2 hours). Mild hemolysis that was attributed to the dimethyl sulfoxide vehicle was detected in plasma samples after IV administration of carvedilol. The PCV, which was evaluated at the beginning and end of each experiment, was unaffected by this degree of hemolysis. After oral administration, various levels of light sedation were seen. One dog developed a cough after oral and IV administration of carvedilol. This was a repeatable finding in this dog and was considered to possibly represent a bronchoconstrictive effect of the β_2 -adrenoreceptor blocking effects of carvedilol.

After IV administration of carvedilol, median peak concentration (extrapolated) was 476 ng/mL (range, 203 to 1,920 ng/mL), median $t_{1/2}$ was 282 minutes (range, 19 to 1,021 minutes), and median MRT was 360 minutes (range, 19 to 819 minutes; Table 1; Figure 1). Volume of distribution at steady state was 2.0 L/kg (range, 0.7 to 4.3 L/kg). Median F after oral administration of carvedilol was 2.1% (range, 0.4% to 54%; Table 2). Bioavailability in 1 dog was higher than the others, which was confirmed during repeated experiments in which carvedilol was administered orally. When data from this dog were removed from the analysis, median F was 1.6%.

After oral administration of carvedilol, the median C_{max} was 24 μ g/mL (range, 9 to 173 μ g/mL), median T_{max} was 90 minutes (range, 60 to 180 minutes), median $t_{1/2}$ was 82 minutes (range, 64 to 138 minutes), and median MRT was 182 minutes (range, 112 to 254 minutes; Table 2; Figure 2).

Analysis of data obtained after IV and oral administration of carvedilol revealed higher plasma concentrations of carvedilol in male dogs, compared with female dogs. This was attributed, in part, to the large V_{dss} detected in female dogs.

The retention time for carvedilol was 8 minutes. A second peak was identified in both male and female dogs after oral and IV administration of carvedilol; however,

Table 1—Pharmacokinetics of carvedilol in plasma after IV administration of a single dose of carvedilol (175 μ g/kg) in 8 dogs.

Variable	Mean \pm SD	Median (range)
C_{max} (μ g/mL)	770 \pm 626	476 (203–1,920)
Males	1,101 \pm 766	1,019 (447–1,920)
Females	440 \pm 188	453 (203–650)
AUC (min \cdot ng/mL)	32,031 \pm 21,729	32,141 (3,994–70,878)
Males	40,650 \pm 27,669	43,864 (3,994–70,878)
Females	23,411 \pm 11,747	23,405 (9,464–37,372)
$t_{1/2}$ (min)	415 \pm 376	6282 (19–1,021)
Males	455 \pm 466	390 (19–1,021)
Females	375 \pm 330	282 (104–833)
MRT (min)	402 \pm 306	360 (19–819)
Males	390 \pm 355	360 (19–819)
Females	415 \pm 304	420 (129–689)
Cl (L/min/kg)	11.6 \pm 14	5.6 (2.5–44)
Males	13.6 \pm 20.2	4.0 (2.5–44)
Females	9.6 \pm 6.1	7.7 (5–19)
V_{dss} (mL/kg)	2.2 \pm 1.3	2.0 (0.7–4.3)
Males	1.6 \pm 1.3	1.1 (0.7–3.5)
Females	2.9 \pm 1.2	2.8 (1.5–4.3)

C_{max} = Maximum concentration in plasma. AUC = Area under the curve. $t_{1/2}$ = Elimination half-life. MRT = Mean residence time. Cl = Clearance. V_{dss} = Volume of distribution at steady state.

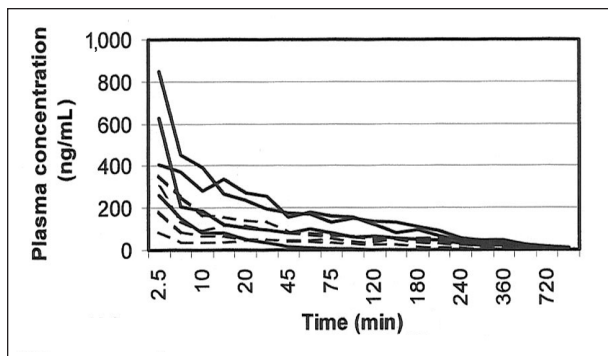


Figure 1—Plasma concentrations over time in 8 dogs receiving carvedilol (175 µg/kg, IV). Solid line = Males. Dashed line = Females.

Table 2—Pharmacokinetics of carvedilol in plasma after PO administration of a single dose of carvedilol (1.5 µg/kg) in 8 dogs.

Variable	Mean ± SD	Median (range)
C_{max} (µg/mL)	66 ± 69	24 (9–173)
Males*	111 ± 74	131 (9–173)
Females	21 ± 6	20 (15–29)
T_{max} (min)	98 ± 45	90 (60–180)
Males	120 ± 49	120 (60–180)
Females	75 ± 30	60 (60–120)
AUC (min·ng/mL)	8,577 ± 8,303	4,149 (1,265–21,211)
Males*	14,076 ± 8,861	16,915 (1,265–21,211)
Females	3,077 ± 1,299	2,989 (1,764–4,566)
$t_{1/2}$ (min)	92 ± 26	82 (64–138)
Males	96 ± 19	94 (77–118)
Females	88 ± 34	76 (64–138)
MRT (min)	177 ± 47	182 (112–254)
Males	204 ± 43	206 (149–254)
Females	151 ± 37	154 (112–184)
F (%)	8.9 ± 18.2	2.1 (0.4–54)
Males	15.5 ± 25.6	3.9 (0.4–54)
Females	2.3 ± 2.3	1.5 (0.6–5.6)

*Significantly ($P = 0.05$) different from value for females.
 T_{max} = Time to C_{max} ; F = Bioavailability.
 See Table 1 for remainder of key.

the magnitude of this peak, compared with the carvedilol peak, was greater in female dogs, compared with male dogs, with the exception of 1 male dog. It is believed that this peak may have represented an active metabolite that was present primarily in female dogs.

Discussion

Preliminary pharmacokinetics of IV administration of carvedilol (160 µg/kg) in 2 clinically normal, conscious dogs has been reported.⁸ Additionally, plasma carvedilol concentrations of 0.2, 0.4, and 0.8 mg/kg, every 24 hours, have been reported⁹ in dogs with iatrogenic mitral regurgitation. To the authors' knowledge, no study has evaluated the kinetics of carvedilol after oral and IV administration in healthy conscious dogs with the intent of determining the appropriate dose and dosing interval for oral administration of carvedilol in dogs.

In our study, the disposition of carvedilol varied in healthy dogs after IV and oral administration. Among the most dramatic differences was the C_{max} . Extrapolated peak plasma concentrations (C_0) of carvedilol varied approximately 10-fold after IV administration and 20-fold after oral administration. Concentrations were consistently higher after IV and oral administration of carvedilol in male dogs, com-

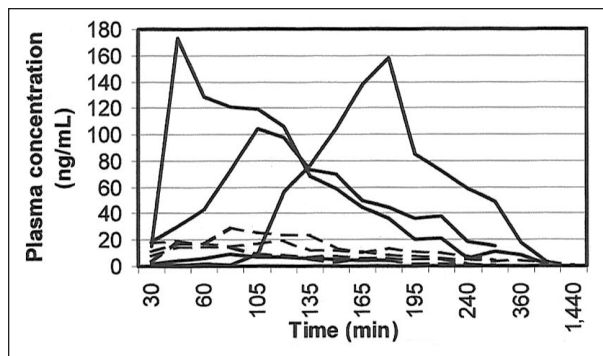


Figure 2—Plasma concentrations over time in 8 dogs receiving carvedilol (1.5 mg/kg, PO). Solid line = Males. Dashed line = Females.

pared with female dogs, with the exception of 1 male in which the disposition of carvedilol was similar to female dogs. Differences between sexes are often not considered in the disposition of drugs but have been reported for selected drugs. Because plasma drug concentrations vary with time, $Vdss$ may potentially explain differences in the disposition of drugs between sexes. In dogs, the $Vdss$ of carvedilol was similar to, although more variable than, that reported¹⁰ in humans (median $Vdss$, 1.5 to 2.0 L/kg). In our study, significant differences in $Vdss$ could not be detected between sexes (range in females, 1.5 to 4.3 L/kg; range in males, 0.7 to 3.5 L/kg), although this may reflect the small sample size. However, differences in $Vdss$ alone probably are not sufficient to explain the marked variability in drug concentrations. Differences in elimination may also contribute to differences in drug concentrations between sexes, although again, small sample size precluded detection of differences in $t_{1/2}$ (a hybrid parameter dependent on clearance and $Vdss$), MRT (a physiologically more appropriate indicator of $t_{1/2}$), or clearance. Contributing to the inability to detect significant differences between sexes was 1 male dog for which carvedilol disposition was similar to females.

In the study reported here, a median MRT of approximately 3 hours (range, 112 to 254 minutes) suggested a 3-hour dosing interval for oral administration of carvedilol in healthy dogs. The inconvenience of a dosing interval of this frequency would severely limit the clinical use of carvedilol when administered orally. However, pharmacodynamic evaluation of oral administration of carvedilol detected at least a 12-hour pharmacodynamic response, suggesting that oral administration of carvedilol twice daily is adequate.⁶

As with other parameters, F of carvedilol after oral administration varied markedly (median, 2.1%; range, 0.4% to 54%). The wide range was attributable to 1 dog with a high F. When data from this dog were removed from the analyses, the upper limit of the range was 5.6% (adjusted median, 1.6%). The F of carvedilol after oral administration was much lower in dogs in our study, compared with the F (25%) reported^{10,11} in humans. Presently, the recommended target dosage in humans with heart failure is 25 mg twice daily¹²; on the basis of a weight of 70 kg, the dosage on a milligram per kilogram basis would be 0.36 mg/kg twice daily. However, 1.5 mg/kg twice daily was necessary to

achieve a similar concentration of carvedilol in plasma in dogs, attributable in part to low *F* after oral administration.

The range of dosages used in humans for oral administration of carvedilol depends on its clinical indication (congestive heart failure vs hypertension), and reported plasma concentrations of carvedilol are associated with the population of patients evaluated. Dosages of 25 mg twice daily represent the target dosage for humans with heart failure, but clinical efficacy, albeit decreased, is present at dosages as low as 6.25 mg twice daily. Median peak plasma concentration of carvedilol in healthy humans receiving 25 mg twice daily is 21 ng/mL.¹¹ Peak plasma concentration may be increased by 50% to 100% in human patients with advanced heart failure receiving the same dose, attributable to a combination of impaired renal clearance and hepatic metabolism. In the study reported here, when this therapeutic target dose was extrapolated to dogs, although there was wide variability, therapeutic concentrations of carvedilol in plasma were not reached in 3 females and 1 male. Yet, pharmacodynamically (heart rate and blood pressure), all dogs responded similarly to the same carvedilol dosage.⁶ One possibility for the uniform pharmacodynamic response in the face of such large variations (20-fold) in peak plasma carvedilol concentrations may be explained by differences in metabolism among dogs and particularly between sexes. This theory is supported by the presence of what appears to be a carvedilol metabolite that had a much higher peak than the parent compound in all female dogs and 1 male dog. An advantage of the use of HPLC for those drugs that undergo elimination by metabolism is separation of the parent drug from its metabolites. Identification of a chemical compound (drug) by use of HPLC is based on the chemical structure of the drug and its interaction with particles in a column. The known chemical (the standard) is carried through the column by use of a mobile phase. The column type is chosen on the basis of its ability to interact with the drug of interest. Interaction between the drug and column causes the drug to be retained rather than travel through the column along with the mobile phase. The greater the interaction, which is dependent on the chemical characteristics of the drug, the longer the retention time of the drug in the column. Generally, even subtle differences in chemical structures will alter the interaction between drug and column and thus lead to different retention times. The time at which the compound finally passes through the column, the retention time, is characteristic for that compound and can be used to identify (and quantify) the compound in unknown samples. Occasionally, 1 compound will be so similar to another compound that the retention times will be the same. This would be true for enantiomers (isomers that are mirror images of one another) and occasionally is true for a drug and its metabolite or different metabolites of the same drug. Because conjugation (phase II metabolism) reactions result in the addition of a large molecule (eg, glucuronic acid, glutathione, or sulfate), the change in chemical structure generally is too great to permit detection of the parent compound

and its metabolite under the same conditions. Thus, simultaneous detection of the compound and its metabolites tends to be limited to phase I metabolites because these reactions (eg, oxidation, hydrolysis, and reduction) generally produce metabolites that are extremely similar to the parent compound. The metabolites generally are more polar than the parent compound.

Reverse-phase HPLC separates compounds by use of a nonpolar (C18) column. With such a column, compounds that are nonpolar tend to be attracted to the column and thus are retained, whereas less polar compounds are eluted first (ie, have a shorter retention time). In the study reported here, the retention time for carvedilol was 8 minutes. However, a second peak characterized by a shorter retention time (6 minutes) was detected in all dogs. Its shorter retention time suggested that it was a metabolite of carvedilol. The magnitude of this earlier peak was much greater than that of carvedilol in female (and 1 male) dogs. The magnitude of the presumed metabolite peak was sufficiently great to suggest that it was a major metabolite. Because standards were not available for each of the carvedilol metabolites, identifying which potential metabolite the 6-minute peak may represent was not possible. However, by use of mass spectrometry, Schaefer et al¹³ have proposed a chemical structure of > 32 metabolites of carvedilol in several species. Only 5 metabolites are sufficiently structurally similar to carvedilol to warrant their consideration as possible candidates in the dogs in our study (the other metabolites being either glucuronidated and sulfated phase II metabolites or much smaller metabolites resulting from oxidative cleavage). Each of the remaining 5 metabolites (M2, M4, M5, M14, and M16) is a hydroxylated version of carvedilol. Should the 6-minute peak represent an active carvedilol metabolite (which is more likely for phase I vs phase II metabolites), those dogs for which the presumed metabolite predominated may be expected to have a similar pharmacodynamic reaction to carvedilol as those dogs in which carvedilol was the predominant peak. Interestingly, in the study by Schaefer et al,¹³ none of the phase I metabolites were identified as being notable in the plasma of intact female dogs by use of mass spectrometry. In that study, the cleaved and directly glucurone-conjugated (at nitrogen) metabolites of carvedilol predominated in plasma of dogs. However, because these metabolites are structurally different from carvedilol, it is unlikely that they appeared in our study.

Statistical analysis of concurrent pharmacokinetic and pharmacodynamic data indicated a significant correlation between peak concentration of carvedilol in plasma and pharmacodynamic parameters. This correlation suggests that monitoring of plasma drug concentrations may be valuable for assessment of therapeutic peak plasma drug concentrations and assist in clinical decision-making regarding administration of appropriate dosages to individual dogs.⁶ This becomes important when administering a drug with such a variable plasma drug concentration among dogs. Additionally, this would be of clinical benefit with drugs such as β -adrenoreceptor blocking agents, which can have detrimental effects when administered exces-

sively. In the study reported here, median T_{\max} in dogs was 90 minutes (range, 60 to 180 minutes), suggesting that this may represent an optimal sampling time for assessing therapeutic concentrations of carvedilol.

Results of our study indicated that IV (175 $\mu\text{g}/\text{kg}$) and oral (1.5 mg/kg) administration of carvedilol is well tolerated in conscious healthy dogs. Additionally, carvedilol administered at a dosage of 1.5 mg/kg , PO, twice daily appears to attain a therapeutic peak plasma concentration of carvedilol in most healthy dogs. Marked variability in peak plasma carvedilol concentrations was evident among dogs receiving the same dosage in an identical manner. Subgroup analyses revealed that the variability may have been attributed to sex; however, the small number of dogs in this study precluded statistical significance. Additionally, important metabolites appear to be present, primarily in female dogs. Analyses of pharmacodynamic data from a parallel study⁶ suggest that these may be active metabolites, given the similarity and significance of the heart rate and blood pressure effects detected in all dogs, despite the lower peak concentrations of carvedilol in plasma in females. Further investigation into metabolite identification is warranted.

-
- a. Coreg, GlaxoSmithKline, Philadelphia, Pa.
 - b. Titanium SoloPort Max, MAXA-CBAS-C70, Access Technologies Inc, Skokie, Ill.
 - c. TA11PA-D70, Data Sciences International Inc, Saint Paul, Minn.
 - d. Carvedilol powder, GlaxoSmithKline, Philadelphia, Pa.
 - e. Nalgene, 0.2- μm PES 25-mm disposable syringe filter, Nalge Nunc International, Rochester, NY.
 - f. C8 column No. 1210-2059, Varian Inc, Palo Alto, Calif.

- g. Prevail C18 column No. 99211, Alltech, Smithtown, NY.
- h. WinNonLin, version 4.0, Pharsight, Mountainview, Calif.

References

1. Lechat P, Packer M, Chalon S, et al. Clinical effects of β -adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials. *Circulation* 1998;98:1184-1191.
2. Rossig L, Haendeler J, Mallat Z, et al. Congestive heart failure induces endothelial cell apoptosis: protective role of carvedilol. *J Am Coll Cardiol* 2000;36:2081-2089.
3. Tsutsui H, Spinale FG, Nagatsu M, et al. Effects of chronic β -adrenergic blockade on the left ventricular and cardiocyte abnormalities of chronic canine mitral regurgitation. *J Clin Invest* 1994;93:2639-2648.
4. Das KM, Tashjian RJ. Chronic mitral valve disease in the dog. *Vet Med Small Anim Clin* 1965;60:1209-1216.
5. Detweiler DK, Patterson DF. The prevalence and types of cardiovascular disease in dogs. *Ann N Y Acad Sci* 1965;127:481-516.
6. Gordon SG, Arsenault WG, Longnecker M, et al. Pharmacodynamics of carvedilol in conscious, healthy dogs. *J Vet Intern Med* 2006;in press.
7. Hokama N, Hobaru N, Kameya H, et al. Rapid and simple micro-determination of carvedilol in rat plasma by high-performance liquid chromatography. *J Chromatogr B Biomed Sci Appl* 1999;732:233-238.
8. Sawangkoon S, Miyamoto M, Nakayama T, et al. Acute cardiovascular effects and pharmacokinetics of carvedilol in healthy dogs. *Am J Vet Res* 2000;61:57-60.
9. Uechi M, Sasaki T, Ueno K, et al. Cardiovascular and renal effects of carvedilol in dogs with heart failure. *J Vet Med Sci* 2002;64:469-475.
10. McTavish D, Campoli-Richards D, Sorokin EM. Carvedilol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1993;45:232-258.
11. Neugebauer G, Akpan W, von Mollendorff E, et al. Pharmacokinetics and disposition of carvedilol in humans. *J Cardiovasc Pharmacol* 1987;10:S85-S88.
12. Coreg [product monograph]. Mississauga, ON, Canada: SmithKline Beecham Pharma Inc, 1996.
13. Schaefer WM, Politowski J, Hwang B, et al. Metabolism of carvedilol in dogs, rats, and mice. *Drug Metab Dispos* 1998;26:958-969.