Acute cardiovascular effects and pharmacokinetics of carvedilol in healthy dogs

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Objective—To determine acute cardiovascular effects and pharmacokinetics of carvedilol in healthy dogs.

Animals—14 mature healthy Beagles.

Procedure—12 dogs were anesthetized with morphine and α-chloralose. Catheters were placed in the aorta, left ventricle, and right atrium to record systemic and pulmonary pressures and determine vascular resistance and cardiac output. Electrocardiograms (leads I, aVF, and V_3) were recorded to determine electrocardiographic changes. Variables were measured before and after IV injection of incremental doses of carvedilol (cumulative doses, 10, 30, 70, 150, 310, and 630 µg/kg of body weight; n = 6) or vehicle alone (6). Pharmacokinetic analysis was performed, using 2 conscious dogs given 160 µg of carvedilol/kg as a single IV injection.

Results—Heart rate and velocity of fiber shortening at zero load (V_{max}) increased slightly but significantly from baseline values at doses of carvedilol ≥ 310 µg/kg and 10 µg/kg, respectively. Carvedilol did not affect systemic and pulmonary pressures or vascular resistances. Intravenous administration of approximately 150 µg of carvedilol/kg resulted in a plasma carvedilol concentration of approximately 100 ng/ml. Mean elimination half-life was 54 minutes, half-life of distribution was 3.5 minutes, and volume of distribution was 2,038 ml/kg.

Conclusions and Clinical Relevance—The therapeutic plasma concentration of carvedilol in humans is 100 ng/ml. At that plasma concentration in dogs, the reduction in afterload and positive inotropic effect that we observed would be beneficial for treating heart failure and minimizing the cardiotoxic effects of doxorubicin. (*Am J Vet Res* 2000;61:57–60)

Carvedilol is an arylethanolamine and has nonspecific β- and α_1-adrenergic blocking effects.[1] Carvedilol also reduces the release of endothelin and is a scavenger of free radicals of oxygen.[2] It is used for treatment of systemic arterial hypertension[3,4] and congestive heart failure[5] and has been purported to improve exercise capacity[6,7] and longevity in humans.[8] In a recent case report, carvedilol ameliorated heart failure caused by administration of doxorubicin to treat breast cancer in human patients.[9] Because carvedilol has an antioxidant effect, it may attenuate the progression of doxorubicin-induced myocardial damage. Carvedilol also decreases cardiac norepinephrine stores without inducing upregulation of β-receptors.[9] It decreases afterload and may be antiarrhythmic.[2] To our knowledge, there are no comprehensive studies investigating the cardiovascular effects and pharmacokinetics of carvedilol in dogs. The purpose of the study reported here was to determine the acute cardiovascular effects and pharmacokinetics of carvedilol in healthy adult dogs.

Received Nov 17, 1998.
Accepted Mar 2, 1999.
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The authors thank Dr. Duane Boyle for technical assistance.

Materials and Methods

Animals—This study was approved by the Institutional Laboratory Animal Care and Use Committee of The Ohio State University. Twelve mature healthy Beagles were used to determine cardiovascular effects of carvedilol, and 2 mature healthy Beagles were used to determine pharmacokinetics after IV administration of carvedilol.

Determination of cardiovascular effects—Food was withheld for 12 hours before dogs were anesthetized with morphine (2 mg/kg of body weight, IV) and α-chloralose (100 mg/kg, IV). This anesthetic regimen was used because it minimally affects cardiovascular function and autonomic control of the heart.[10] Dogs were intubated and ventilated with room air so that $Paco_2$ remained between 35 and 40 mm Hg. Electrocardiographic leads were placed for continuous recording of leads I, aVF, and V_3.[a] A jugular vein and a femoral and carotid artery of each dog were surgically exposed. To record aortic and left ventricular pressures, catheter-tip transducers[b] were introduced via the femoral and carotid arteries and positioned in the aorta and left ventricle, respectively. A fluid-filled catheter was introduced via the jugular vein and positioned in the right atrium to record right atrial pressure and measure cardiac output by use of thermodilution techniques.[c]

After baseline measurements were made for each of the cardiovascular variables, a baseline blood sample was collected for measurement of plasma carvedilol concentrations. Six dogs each were infused with vehicle (1 ml of dimethyl formamide added to 9 ml of saline [0.9% NaCl] solution, pH adjusted with 10 µl of 1*M* HCl) or carvedilol[d] (cumulative doses, 10, 30, 70, 150, 310, and 630 µg/kg). To achieve each cumulative dose of carvedilol, the following incremental doses were given every 15 minutes: 10, 20, 40, 80, 160, and 320 µg/kg. Control dogs received vehicle every 15 minutes. Volume and rate of vehicle or carvedilol infused at any time was 10 ml/min. Cardiovascular variables were measured, and plasma samples were obtained during the last minute of each plateau period following infusion. At the end of the experiments, dogs were euthanized with IV injections of 250 mg of sodium pentobarbital/kg.

Pharmacokinetics measurements—Two conscious dogs were given carvedilol (160 µg/kg, IV), and plasma samples for determination of carvedilol concentration were obtained 1, 2, 4, 8, 16, 32, 64, 128, 256, and 512 minutes after injection.

Determination of cardiovascular variables—Heart rate, interbeat interval (ms), and PQ, QRS, QT, and QTc (ie, QT interval/[RR interval]$^{1/3}$)[11] durations were calculated

from the lead-aVF ECG. **Maximal rate of rise and fall of left ventricular pressure** (dP/dt_{max} **and** dP/dt_{min}, respectively) **velocity of fiber shortening at zero load** (V_{max}),[12,13] and Tau (ie, time required for left ventricular pressure to decrease 63% of the distance between time of dP/dt_{min} and time ventricular pressure was 15 mm Hg greater than end diastolic pressure)[14] were calculated from the pressure tracings. Cardiac index and stroke volume index were calculated by dividing cardiac output by body surface area and heart rate, respectively. Systemic and pulmonary resistances were calculated by dividing mean arterial pressure minus either right atrial or left ventricular end diastolic pressures by cardiac output.

Determination of plasma carvedilol concentrations—Plasma samples were analyzed by on-line, solid-phase extraction followed by reverse-phase high-performance liquid chromatography. The lowest measurable concentration of carvedilol for which this test is accurate is 1.00 ng/ml in 0.1 ml of plasma.

Pharmacokinetic analysis—Plots were made of plasma carvedilol concentration versus cumulative dose. A pharmacokinetic analysis was performed, using nonlinear regression analysis.[c] A two-compartment model, defined by the equation $C_t = Ae^{-\alpha t} + Be^{-\alpha t}$, was used to describe the data. Elimination half-life was calculated as $0.693/\beta$. Half-life of distribution was calculated as $0.693/\alpha$. **Area under the curve** (**AUC**) was calculated as $A/\alpha + B/\beta$. Volume of distribution was calculated as dose/(AUC $\times$ β). Plasma clearance rate was calculated as dose/AUC.

Statistical analyses—Mean values determined for cardiovascular variables were compared by use of two-way ANOVA with repeated-measures design. Values obtained after dogs received each dose of carvedilol were compared with values obtained after dogs received each dose of vehicle. If a significant F-statistic was achieved ($P < 0.05$), specific means were compared by use of the contrast of multiple comparisons.[f] Means determined for the control group were compared with means determined at the same time for the treated group by use of unpaired *t*-tests. Differences were considered significant at $P < 0.05$.

Results

Cardiovascular effects—Baseline values for any variable did not differ between control and treated dogs. Heart rate of control dogs did not change from baseline value at any time. However, heart rates of treated dogs exceeded that of controls after administration of doses of carvedilol ≥ 30 μg/kg, and heart rates were significantly greater than the baseline value at doses ≥ 310 μg/kg (**Table 1**). Compared with baseline values, PQ duration shortened significantly after infusion of the third bolus of vehicle or the lowest dose of carvedilol. However, QRS and QTc duration did not change from baseline values in either group (control, 49 ± 2 ms and 280 ± 3 ms, respectively; treated, 49 ± 1 ms and 280 ± 3 ms, respectively). The QT duration decreased only in the controls after infusion of the last bolus of vehicle (baseline, 274 ± 10 ms; last bolus of vehicle, 258 ± 7 ms). Significant differences in the degree of QTc prolongation were not detected with increasing doses of carvedilol.

Compared with baseline values, cardiac index did not change in the control group but increased in the treated group in a dose-dependent manner at carvedilol doses ≥ 70 μg/kg (Table 1). Stroke volume index and Tau did not change from baseline values in either group (control, 37.1 ± 2.3 ml/m^2 and 33.5 ± 1.4 msec, respectively; treated, 34.3 ± 2.3 ml/m^2 and 30.8 ± 1.5 msec, respectively). However, dP/dt_{max} increased in control dogs after infusion of the fourth dose of vehicle and in treated dogs at carvedilol doses ≥ 150 μg/kg. Although V_{max} did not change from baseline value in the control group, in the treated group V_{max} increased beginning at a dose of 10 μg/kg. At carvedilol doses ≥ 70 μg/kg, V_{max} was greater in the treated dogs than in the control dogs. In the control group, dP/dt_{min} increased (ie, became more negative) from baseline value after infusion of the fourth vehicle bolus, and dP/dt_{min} decreased (ie, became less negative) in the treated group after infusion of the final dose of carvedilol.

Carvedilol did not affect systemic or pulmonary pressures. However, compared with baseline values, mean, systolic, and diastolic aortic pressures and mean and systolic pulmonary pressures did increase in the control group with increasing boluses of vehicle (**Table 2**). Systemic and pulmonary vascular resistances did not change from baseline values in either group (control, 4583 ± 244 dyn/sec/cm^{-5} and 824 ± 41 dyn/sec/cm^{-5}, respectively; treated, 4785 ± 269 dyn/sec/cm^{-5} and 866 ± 76 dyn/sec/cm^{-5}, respectively).

Pharmacokinetics—Plasma concentrations of carvedilol after IV administration of graded doses to 4 of the 6 anesthetized dogs were plotted linearly (**Fig 1**), and plasma concentrations of carvedilol versus time after IV admin-

Table 1—Mean (± SEM) values for cardiovascular variables measured in healthy anesthetized adult Beagles before and after IV injection of incremental doses of carvedilol (treated; n = 6) or equivalent volumes of vehicle* (control; 6)

	Heart rate (bpm)		PQ duration (ms)		CI (L/min/m^2)		dP/dt_{max} (mm Hg/s)		V_{max} (s^{-1})		dP/dt_{min} (mm Hg/s)	
Dose (volume)†	**Control**	**Treated**	**Control**	**Treated**	**Control**	**Treated**	**Control**	**Treated**	**Control**	**Treated**	**Control**	**Treated**
0‡	65 ± 3	76 ± 8	113 ± 7	111 ± 6	2.4 ± 0.2	2.6 ± 0.2	1,701 ± 78	1,898 ± 130	74.4 ± 3.0	80.3 ± 3.9	–2,788 ± 125	–2,624 ± 160
10 μg/kg (10 ml)	68 ± 4	90 ± 10	109 ± 6	102 ± 6[b]	2.4 ± 0.2	2.8 ± 0.2	1,739 ± 78	2,101 ± 182	74.7 ± 3.1	90.7 ± 6.3[c]	–2,750 ± 91	–2,586 ± 247
30 μg/kg (20 ml)	67 ± 4	84 ± 6[a]	108 ± 11	102 ± 4[b]	2.5 ± 0.2	2.9 ± 0.2	1,863 ± 161	2,157 ± 164	77.2 ± 3.9	91.3 ± 5.3[c]	–2,764 ± 108	–2,800 ± 345
70 μg/kg (30 ml)	66 ± 4	84 ± 4[a]	105 ± 8[b]	101 ± 4[b]	2.5 ± 0.2	3.0 ± 0.2[b]	1,928 ± 115	2,224 ± 192	74.7 ± 2.8	89.5 ± 4.8[a,c]	–2,879 ± 135	–2,821 ± 299
150 μg/kg (40 ml)	66 ± 4	87 ± 2[a]	106 ± 7[b]	99 ± 4[c]	2.5 ± 0.2	3.1 ± 0.2[c]	1,949 ± 104[b]	2,285 ± 196[b]	76.7 ± 4.2	93.1 ± 4.8[a,c]	–3,029 ± 170[b]	–2,833 ± 301
310 μg/kg (50 ml)	68 ± 4	95 ± 4[a,b]	100 ± 12[c]	95 ± 4[c]	2.5 ± 0.2	3.2 ± 0.3[c]	2,064 ± 205[c]	2,340 ± 192[c]	77.6 ± 7.3	95.1 ± 4.7[c]	–3,155 ± 149[c]	–2,708 ± 283
630 μg/kg (60 ml)	68 ± 3	106 ± 5[a,c]	101 ± 13[c]	91 ± 5[c]	2.6 ± 0.2	3.2 ± 0.3[c]	2,138 ± 261[c]	2,316 ± 159[c]	78.2 ± 5.4	97.9 ± 5.2[a,c]	–3,299 ± 139[c]	–2,511 ± 262[a]

*1 ml of dimethyl formamide added to 9 ml of saline (0.9% NaCl) solution; pH adjusted with 10 μl of 1 *M* HCl. †Cumulative dose of carvedilol and volume of vehicle infused. ‡Baseline values.

[a]Significantly ($P < 0.05$) different from control-group value determined at the same time. [b]Significantly ($P < 0.05$) different from baseline value determined for the same group. [c]Significantly ($P < 0.01$) different from baseline value determined for the same group.

bpm = Beats/min. CI = Cardiac index. dP/dt_{max} = Maximal rate of rise of left ventricular pressure. V_{max} = Velocity of fiber shortening at zero load. dP/dt_{min} = Maximal rate of fall of left ventricular pressure.

Table 2—Mean (± SEM) values for systemic and pulmonary pressures (mm Hg) measured in healthy anesthetized adult Beagles before and after IV injection of incremental doses of carvedilol (treated; n = 6) or equivalent volumes of vehicle* (control; 6)

	ASP		AMP		ADP		PSP		PMP		PDP	
Dose (volume)†	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated	Control	Treated
0‡	99.2 ± 4.4	98.1 ± 4.5	78.7 ± 4.3	76.1 ± 2.8	60.8 ± 4.1	56.7 ± 2.2	22.8 ± 1.2	20.9 ± 1.5	14.1 ± 0.4	13.8 ± 1.1	8.6 ± 0.4	8.6 ± 1.0
10 μg/kg (10 ml)	101.1 ± 4.5	98.8 ± 5.7	79.5 ± 4.0	75.3 ± 3.0	60.9 ± 4.1	55.7 ± 0.9	22.3 ± 1.8	19.3 ± 1.8	13.7 ± 0.6	13.2 ± 1.2	8.5 ± 0.6	8.4 ± 1.0
30 μg/kg (20 ml)	104.2 ± 5.1	104.2 ± 8.8	81.3 ± 3.6	80.7 ± 6.0	61.3 ± 3.6	59.6 ± 3.6	23.2 ± 2.0	20.3 ± 2.1	14.0 ± 0.5	13.7 ± 1.4	9.2 ± 0.3	8.6 ± 1.2
70 μg/kg (30 ml)	106.6 ± 5.3[c]	103.7 ± 7.2	83.2 ± 4.3	80.8 ± 4.7	62.7 ± 4.1	60.2 ± 2.5	24.4 ± 2.2[b]	20.3 ± 1.7	14.6 ± 0.7	13.9 ± 1.2	9.0 ± 0.9	8.7 ± 0.9
150 μg/kg (40 ml)	109.6 ± 5.7[c]	104.3 ± 7.2	87.2 ± 5.1[c]	81.8 ± 5.3	66.4 ± 4.8[b]	61.7 ± 3.4	24.5 ± 2.0[b]	19.0 ± 2.5[b]	14.8 ± 0.6	13.0 ± 1.7	8.9 ± 0.3	8.0 ± 1.2
310 μg/kg (50 ml)	115.2 ± 7.0[c]	100.3 ± 6.4	89.2 ± 5.4[c]	79.8 ± 5.0	68.6 ± 5.5[c]	61.5 ± 3.4	25.5 ± 2.1[c]	19.8 ± 1.3[a]	15.1 ± 0.6[b]	13.9 ± 0.9	8.9 ± 0.3	9.1 ± 0.7
630 μg/kg (60 ml)	117.8 ± 7.1[c]	94.5 ± 5.4[a]	92.0 ± 6.1[c]	74.9 ± 4.4	69.4 ± 6.0[c]	58.3 ± 3.6	26.5 ± 2.2[c]	17.7 ± 2.4[a,c]	15.6 ± 0.9[c]	12.5 ± 1.7	9.1 ± 0.4	7.9 ± 1.3

ASP = Aortic systemic pressure. AMP = Aortic mean pressure. ADP = Aortic diastolic pressure. PSP = Pulmonary systolic pressure. PMP = Pulmonary mean pressure. PDP = Pulmonary diastolic pressure.
See Table 1 for key.

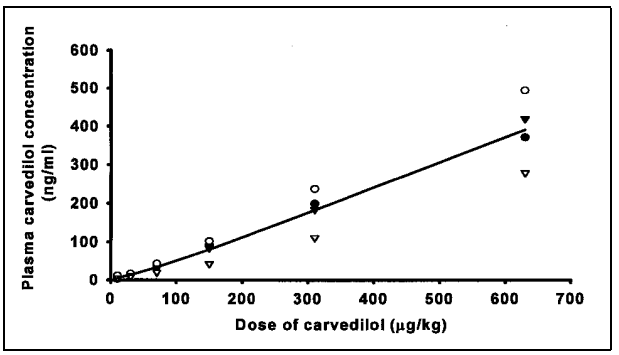

Figure 1—Plasma carvedilol concentrations measured 5 minutes after IV administration of incremental doses of carvedilol every 15 minutes to 4 healthy anesthetized adult Beagles. Doses listed on X axis are cumulative doses. Each symbol represent plasma concentrations determined for an individual dog.

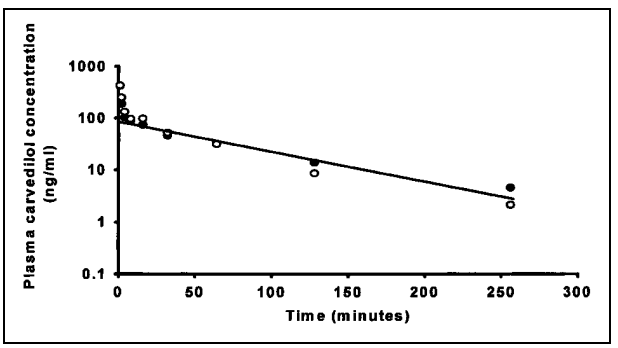

Figure 2—Plasma carvedilol concentrations in 2 healthy awake adult Beagles after IV administration of 160 μg of carvedilol/kg of body weight at time 0. Each symbol represents plasma concentrations determined for an individual dog.

istration of a single dose to 2 conscious dogs were plotted logarithmically (using a biexponential fit curve; **Fig 2**). Volumes of distribution for the 2 dogs were 2,207 ml/kg and 1,869 ml/kg (mean, 2,038 ml/kg). Half-lives for the terminal portions of the elimination curves were 58.24 minutes and 49.50 minutes (mean, 53.87 minutes). Plasma clearance rates were 26.27 ml/kg/min and 26.17 ml/kg/min (mean, 26.22 ml/kg/min). Half-lives for the distribution phase of the curves were 3.54 minutes and 3.59 minutes (mean, 3.57 minutes).

Discussion

Heart rate did not decrease in response to β-adrenergic blockade by carvedilol. Sponer et al[15,16] demonstrated an increase in heart rate after carvedilol administration to conscious dogs. They attributed the increase to a decrease in systemic vascular resistance and activation of the baroreceptor reflex. When heart rate was increased in these same dogs by infusion of isoproterenol to induce a high adrenergic state and cardioacceleration mimicking heart disease, the anticipated reduction in heart rate in response to carvedilol was observed. Sponer et al[15,16] also measured the percentage of attenuation of an isoproterenol challenge induced by carvedilol in unanesthetized dogs. They observed that IV administration of 1 mg of carvedilol/kg was necessary to completely block the increase in heart rate induced by 1 μg of isoproterenol/kg and that 630 μg of carvedilol/kg, which was equivalent to the maximal dose we gave, attenuated the increase in heart rate by almost 85%. Whether this relationship would hold in our dogs anesthetized with α-chloralose is not known.

The QT duration was corrected for heart rate by dividing the measured QT by the cube root of the RR interval. This method of correction is superior to the standard Bazet correction (division by the square root of the RR interval).[11] Carvedilol reduces the tendency for ventricular fibrillation associated with ischemia and reperfusion in cats.[17] This is consistent with properties of a class III antiarrhythmic drug. However, QTc duration was not prolonged in the present study.

Cardiac index, dP/dt_{max}, and V_{max} increased after administration of graded doses of carvedilol, but dP/dt_{max} also increased in control dogs. Such changes could be attributable to volume expansion that resulted from continuous infusion of 250 ml of α-chloralose during the experimental period and from the volume added during measurements of cardiac output via thermodilution. However, V_{max} is a primarily load-independent estimate of contractility, and it did not increase in the control dogs. Therefore, the positive inotropic effect of carvedilol reported by others[5,8] was confirmed by our results. Because stroke volume did not increase, the increase in cardiac index induced by carvedilol was attributable to the increase in heart rate. The load-dependent estimate of rate of relaxation (ie, dP/dt_{min}) increased in control dogs but did not change from baseline value in treated dogs. However, Tau, a primarily load-independent estimate of rate of relaxation, did not change in either group. Therefore, carvedilol appeared not to affect lusitropy.

Systemic and pulmonary arterial pressures increased in control dogs, an effect possibly attributable to volume expansion and increase in cardiac index. In treated dogs, however, pressures did not increase, and after administration of the final dose of carvedilol (cumulative dose, 630 μg/kg), systemic and pulmonary pressures were lower than in the controls. This result is consistent with the α_1-blocking property of carvedilol.

The preliminary pharmacokinetic analysis following IV administration of carvedilol to 2 dogs was performed, assuming a biexponential decay in a manner identical to that used by Louis et al.[18] Volume of distribution, clearance rate, and half-life determined for the distribution and elimination phases were similar in the 2 dogs. To our knowledge, there are no other reports indicating results of pharmacokinetic analysis of carvedilol in dogs. Carvedilol is converted to a glucuronide conjugate in the liver, with less than 2% of the drug excreted unchanged in urine.[19,20] Our pharmacokinetic analysis was performed in conscious, normally hydrated dogs; therefore, these results were not distorted by altered hepatic blood flow or abnormal hydration. In humans, the volume of distribution of carvedilol after IV administration is approximately 1.5 to 2.0 L/kg,[20] and the terminal half-life is approximately 2.4 hours.[19] The difference in rate of elimination between humans and dogs (ie, faster in dogs than in humans) was consistent with differences in rates of elimination of most protein-bound drugs that are conjugated by the liver (eg, diazepam, digitoxin).

In humans, the plasma concentration of carvedilol recommended for optimal therapy is approximately 100 ng/ml.[20] In our study, that concentration was achieved after IV infusion of between 150 and 310 μg of carvedilol/kg. At that plasma concentration, we observed slight but significant increases in heart rate and V_{max}, compared with baseline values.

We believe that carvedilol may have great potential for use in veterinary cardiology and oncology. There is little doubt that reduction in afterload (induced by the α_1-blocking property of carvedilol) would benefit patients with left-sided heart failure. There is less agreement that reduction in ventricular ectopia, which may be induced by the β_1-blocking property of carvedilol, could benefit the many large-breed dogs with dilated cardiomyopathy that die suddenly, presumably from ventricular arrhythmia. Doxorubicin is used frequently for its antineoplastic properties, but the dosage that can be used is limited because of the cardiotoxic effects of the drug, which are mediated via lipid peroxidation of membranes by free radicals of oxygen resulting in arrhythmic and negative inotropic effects. Carvedilol is a potent scavenger of free radicals of oxygen and reduces afterload. Both properties should be useful in minimizing the cardiotoxic effects of doxorubicin, thus allowing it to be used at higher and more potent dosages.

[a]Biopac (MP100), Biopac Systems Inc, Santa Barbara, Calif.
[b]Millar catheter (model SPC-350, 5F), Millar Instruments Inc, Houston, Tex.
[c]Baxtor (model COM-2), Baxtor Healthcare Corp, Santa Ana, Calif.
[d]SmithKline Beecham Pharmaceuticals, King of Prussia, Pa.
[e]Sigma Plot for windows, version 4.0, SPSS Inc, Chicago, Ill.
[f]SuperANOVA, version 1.11, Abacus Concepts Inc, Berkeley, Calif.

References

1. Bristow MR, Larrabee P, Minobe W, et al. Receptor pharmacology of carvedilol in the human heart. *J Cardiovasc Pharmacol* 1992;19(suppl 1):S68–S80.
2. Feuerstein GZ, Bril A, Ruffolo RR Jr. Protective effects of carvedilol in the myocardium. *Am J Cardiol* 1997;80:41L–45L.
3. Cournot A, Lim C, Duchier J, et al. Hemodynamic effects of carvedilol after acute oral administration in hypertensive and normal subjects. *J Cardiovasc Pharmacol* 1992;19(suppl 1):S35–S39.
4. Lund-Johansen P, Omvik P, Nordrehaug JE, et al. Carvedilol in hypertension: effects on hemodynamics and 24-hour blood pressure. *J Cardiovasc Pharmacol* 1992;19(suppl 1):S27–S34.
5. DasGupta P, Broadhurst P, Lahiri A. The effects of intravenous carvedilol, a new multiple action vasodilatory β-blocker, in congestive heart failure. *J Cardiovasc Pharmacol* 1991;18(suppl 4):S12–S16.
6. Hampton JR. Beta-blockers in heart failure—the evidence from clinical trials. *Eur Heart J* 1996;17(suppl B):17–20.
7. Cleland JGF, Bristow MR, Erdmann E, et al. Beta-blocking agents in heart failure. *Eur Heart J* 1996;17:1629–1639.
8. Bristow MR, Gilbert EM, Abraham WT, et al. Carvedilol produces dose-related improvements in left ventricular function and survival in subjects with chronic heart failure. *Circulation* 1996;94: 2807–2816.
9. Fazio S, Palmieri EA, Ferravante B, et al. Doxorubicin-induced cardiomyopathy treated with carvedilol. *Clin Cardiol* 1998;21: 777–779.
10. Rath DP, Little CM, Zhang H, et al. Sodium pentobarbital versus alpha chloralose anesthesia. *Circulation* 1995;91:471–475.
11. Spence S, Soper K, Hoe CM, et al. The heart rate-corrected QT interval of conscious beagle dogs: a formula based on analysis of covariance. *Toxicol Sci* 1998;45:247–258.
12. Mason DT, Spann JF, Selis R. Quantification of the contractile state of the intact human heart. *Am J Cardiol* 1970;26:248–257.
13. Katz AM. Indices of contractility and relaxation. In: Katz AM, ed. *Physiology of the heart*. 2nd ed. New York: Raven Press, 1992;403–405.
14. Weiss JL, Fredericksen JW, Weisfeldt ML. Hemodynamic determinant of the time course of fall in canine left ventricular pressure. *J Clin Invest* 1976;58:751–760.
15. Sponer G, Bartsch W, Strein K, et al. Pharmacological profile of carvedilol as a β-blocking agent with vasodilating and hypotensive properties. *J Cardiovasc Pharmacol* 1987;9:317–327.
16. Sponer G, Strein K, Bartsch W, et al. Vasodilatory action of carvedilol. *J Cardiovasc Pharmacol* 1992;19(suppl 1):S5–S11.
17. Brunvand H, Kvitting PM, Rynning SE, et al. Carvedilol protects against lethal reperfusion injury through antiadrenergic mechanisms. *J Cardiovasc Pharmacol* 1996;28:409–417.
18. Louis WJ, McNeil JJ, Workman BS, et al. A pharmacokinetic study of carvedilol (BM 14.190) in elderly subjects: preliminary report. *J Cardiovasc Pharmacol* 1987;10(suppl 11):S89–S93.
19. Neugebauer G, Akpan W, Möllendorff EV, et al. Pharmacokinetics and disposition of carvedilol in humans. *J Cardiovasc Pharmacol* 1987;10(suppl 11):S85–S88.
20. McTavish D, Campoli-Richards D, Sorkin EM. Carvedilol: a review of its pharmacodynamic and pharmacokinetic properties, and therapeutic efficacy. *Drugs* 1993;45:232–258.