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Effects of Diltiazem on Hemodynamic Variables and Ventricular Function in Healthy Horses

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Quinidine is effective for treatment of atrial fibrillation (AF) in horses, but often accelerates ventricular response rate. Diltiazem effectively controls heart rate response to AF in other species. This investigation determined the effects of diltiazem on cardiac rate and rhythm, left ventricular (LV) function, central hemodynamics, and peripheral blood flow in normal, standing, nonsedated horses. A dose-finding study was performed. Afterward, 8 healthy horses were treated with diltiazem IV every 30 minutes to achieve cumulative dosages of 0 (saline control), 1, 1.5, and 2 mg/kg. Plasma diltiazem concentration, heart rate and rhythm (by electrocardiography), LV function and central hemodynamics (by cardiac catheterization), LV dimensions (by echocardiography), and forelimb blood flow (by Doppler sonography) were determined during each treatment period. Diltiazem plasma concentrations between 390 and 910 ng/mL were achieved, with considerable variation among horses. Cardiac effects of diltiazem included intermittent depression of the sinus and atrioventricular (AV) nodes and mild impairment of systolic and diastolic LV function. Vascular effects of diltiazem included arterial vasodilatation, increased limb blood flow, and decreased systemic vascular resistance. Baroreceptor reflex-mediated sympathetic activation increased sinus node rate and presumably blunted the depressive effects of diltiazem on myocardial and nodal tissues. Two horses developed transient high-grade sinus arrest with severe systemic hypotension. Diltiazem appears relatively safe in healthy horses, but dosage may be limited by hypotension from vasodilatation and direct suppression of sinus node discharge. Because of its inhibitory effects on AV nodal conduction, diltiazem may prove useful for heart rate control in horses with AF.

Key words: Arrhythmia; Atrial fibrillation; AV nodal conduction; Calcium-channel blocker; Heart rate control; Ventricular response rate.

Atrial fibrillation (AF) is the most common arrhythmia affecting performance in horses.[1] Quinidine sulfate is the drug of choice for conversion of AF to sinus rhythm.[1] However, anticholinergic effects of quinidine facilitate impulse conduction across the atrioventricular (AV) node independent of plasma concentration. This action often results in an increased ventricular response rate in horses with AF.[1–3] Sustained, rapid supraventricular tachycardia is the most common severe adverse effect of quinidine therapy, affecting over 50% of all treated horses.[1,3] Digoxin can be administered IV for heart rate control in horses with high pretreatment heart rate or when tachycardia develops during quinidine treatment.[1] Digoxin exerts a parasympathetic action that increases the functional refractory period of the AV node, decreases AV nodal conduction, and reduces ventricular response rate.[4] However, the value of digoxin treatment in the conversion of AF to sinus rhythm in horses is undetermined.[1] Heart rate control with digoxin may fail during stress or excitement, when high sympathethic tone overrides the vagomimetic effect of digoxin.[5,6] Furthermore, digoxin may not be optimal for the acute control of heart rate in patients with AF, because this drug has a delayed onset of action, carries a low toxic-to-therapeutic ratio, can precipitate ventricular ectopy, and may delay recovery from tachycardia-induced atrial remodeling.[4,7–11]

Diltiazem is a calcium-channel blocker, which is used in humans and dogs for the treatment of supraventricular arrhythmias and for heart rate control in the treatment of AF, atrial flutter, AV nodal reentry, and atrioventricular reciprocating tachycardia.[4,12] Diltiazem inhibits AV nodal conduction regardless of the level of sympathetic tone[6,7,13] and results in a faster and more efficacious ventricular rate control compared to digoxin.[8,9,14] The cardiovascular effects of diltiazem have not been reported in horses.

The aim of the present study was to investigate the effects of graded doses of diltiazem on cardiac rate and rhythm, AV nodal conduction, systolic and diastolic left ventricular (LV) function, central hemodynamics, and peripheral blood flow in normal, standing, nonsedated horses.

Materials and Methods

Horses

Ten Standardbred horses (5 geldings, 5 mares) with a mean age of 12.5 years (range, 6–23 years) and mean body weight of 485 kg (range, 426–531 kg) were used. Six horses were used for both the initial dose-finding study and the hemodynamic study that followed, allowing a drug-free time interval of at least 2 weeks between the 2 studies. Two horses were used for the dose-finding study only, and 2 horses were used for the hemodynamic study only. All horses were considered healthy based on physical examination, cardiac auscultation, electrocardiogram, echocardiographic examination, CBC, serum chemistry, and plasma fibrinogen concentration. The left carotid artery of each horse was surgically elevated to a subcutaneous location at least 3 weeks before beginning the experiments.[15] All diltiazem experiments, including instrumentation, were performed under local anesthesia[a] in nonsedated horses standing in stocks. The studies were approved by the Institutional Laboratory Animal Care and Use Committee of The Ohio State University.

Dose-Finding Study

The aim of this first part of the investigation was to determine a diltiazem dose that produced a decrease of mean carotid artery pres-

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sure of at least 10 mmHg, prolongation of the PR interval, and consistent 2nd-degree AV block. Considering the frequency-dependent effects diltiazem exerts in other species, these end-points may not be appropriate measures for the therapeutic effects of diltiazem during rapid supraventricular arrhythmias, such as AF in horses. However, they were considered adequate to assess the effects of diltiazem in healthy horses in sinus rhythm. Eight horses were used for the dose-finding study. Two 14G catheters[b] were aseptically placed under local anesthesia[a] in either jugular vein for drug administration and blood sampling, respectively. A 19G catheter[c] was placed aseptically under local anesthesia[a] in the elevated carotid artery for measurement of arterial blood pressure with a fluid-filled system.[d] A base-apex electrocardiogram (ECG) was used to determine the atrial rate (AR), ventricular rate (VR), cardiac rhythm, and PR interval. Diltiazem[e] (5 mg/mL) was administered IV over 2 minutes at dosages of 0.05, 0.125, 0.25, 0.5, and 1.0 mg/kg every 15 minutes, in order to achieve cumulative dosages of 0.0 (baseline), 0.05, 0.175, 0.425, 0.925, and 1.925 mg/kg. The dose regimen was chosen based on published data in dogs.[6] All physiologic data were recorded simultaneously at a sampling rate of 200 Hz by a digital data acquisition system[f] and stored in a raw-format computer file for later offline analysis. Data were analyzed before drug administration (baseline) and at the midpoint of each treatment period (7.5 minutes after each dose of diltiazem). The ECG tracing and pressure wave forms were analyzed by visual inspection and by the computer software of the data acquisition system.[f] Systolic, diastolic, and mean arterial blood pressure and PR interval were averaged over 10 consecutive beats. The AR and VR were averaged from a 1-minute recording interval. Blood samples were collected at the beginning of each data collection period for later determination of diltiazem plasma concentrations.

Hemodynamic Study

Eight horses were used to assess the effects of IV diltiazem. Two 8F catheter introducers[g] were aseptically placed under local anesthesia[a] in the right jugular vein approximately 20 cm apart. A Swan-Ganz thermodilution catheter[h] was inserted through the proximal introducer and advanced until the tip of the catheter was positioned in the pulmonary artery. A polyethylene catheter[i] was inserted through the distal introducer and advanced into the right atrium. These 2 catheters were used for measurement of right atrial and pulmonary artery pressures and for determination of the cardiac output. A 9F catheter introducer[j] was aseptically placed under local anesthesia[a] in the elevated left carotid artery. A custom-made dual-tipped pressure-sensing catheter[k] then was inserted into the introducer and advanced until the proximal sensor was positioned in the aorta and the distal sensor was positioned in the left ventricle. This catheter allowed simultaneous recording of aortic and LV pressures. Catheter placement was guided by observation of characteristic pressure waveforms during continuous pressure monitoring.[f,l] The zero-pressure reference point for the fluid-filled catheters was the point of the shoulder. Both transducers[d] were calibrated to 0 and 50 mmHg with a mercury manometer. A base-apex ECG was monitored. Prebaseline measurements were obtained (time −40 minutes) after an equilibration period of 30 minutes, followed by administration of a 50-mL bolus of 0.9% sodium chloride[m] over 5 minutes (time −25 to −20 minutes). Baseline measurements were obtained 5 minutes after completion of the saline administration (time −15 minutes). The saline bolus allowed steady baseline values to be established and ruled out any influence on the measured variables of instrumentation, physiologic changes over time, and drug administration procedures. After baseline recordings, diltiazem[e] (5 mg/mL) was administered IV at a dosage of 1 mg/kg over 5 minutes (time 0–5 minutes), followed by 2 additional doses of 0.5 mg/kg administered over 5 minutes every 30 minutes (time 30–35 minutes and 60–65 minutes), in order to achieve cumulative dosages of 1 mg/kg, 1.5 mg/kg, and 2 mg/kg, respectively. These dosages were based on the results of the dose-finding study. All drugs were injected into the jugular vein through the side-port of the proximal catheter introducer. A programmable infusion pump[o] was used for controlled drug delivery.

All physiologic data were acquired simultaneously at a sampling rate of 200 Hz by a digital data acquisition system[f] and stored for later offline analysis. Hemodynamic data were analyzed for the following time periods: prebaseline (PB; −40 minutes), baseline (B; −15 minutes), diltiazem 1 mg/kg (D1; 15 minutes), diltiazem 1.5 mg/kg (D1.5; 45 minutes), and diltiazem 2 mg/kg (D2; 75 minutes). At the beginning of each data collection period, blood samples were collected for later determination of plasma drug concentrations. Analysis of the ECG recordings was performed by visual analysis and with the computer software of the data acquisition system.[f] The rate of sinus node discharge (AR), VR, the number of 2nd-degree AV blocks, and the occurrence of sinus arrhythmia were determined by visual inspection during a 1-minute period. The duration of the PR interval was averaged over 10 consecutive beats. All pressure measurements and derived variables were averaged over a 1-minute interval for each time period. Systolic, diastolic, and mean aortic pressures (SAP, DAP, MAP), left ventricular end-diastolic pressure (LVEDP), mean right atrial pressure (RAP), and mean pulmonary arterial pressure (PAP) were determined. The maximal rate of increase ($+dp/dt_{max}$) and decrease ($-dp/dt_{max}$) in LV pressure, and the time constant of isovolumetric relaxation (*tau*) were derived from the LV pressure recordings. *Tau* was calculated by a semilogarithmic model during the initial 40 ms of isovolumetric relaxation starting at $t_0 = t(-dp/dt_{max})$.[16] Cardiac output (CO) was determined by thermodilution.[1,17] Five thermodilution determinations were made at each time period. Quality of the recordings was assessed by visual evaluation of the thermodilution curves. The 4 closest values then were averaged to give the final value for that time period. Stroke volume (SV = CO/heart rate) and systemic vascular resistance (SVR = [MAP − RAP] × 80/CO) were calculated. Pulmonary vascular resistance (PVR) was estimated as PVR = (PAP − LVEDP) × 80/CO, using LVEDP as a surrogate for pulmonary capillary wedge pressure, assuming unrestricted pulmonary venous and mitral blood flow. Echocardiographic and vascular ultrasonographic examinations were performed at the end of each data collection period and recorded on videotape for offline analysis.[p] All echo measurements were performed on 3 individual cardiac cycles and averaged for each time point. The first beats after sinus or atrioventricular block were excluded from the analysis. The fractional shortening (FS) of the left ventricle was determined by standard 2-dimensional (2-D) and M-mode echocardiographic techniques.[18] The junction between the brachial and the median artery with the branching common interosseus artery was imaged from the medial aspect of the right forelimb at the level of the proximal radius. Measurements were performed in 2 distinct vessels in order to obtain optimal axial resolution for 2D measurements and optimal alignment of blood flow with the ultrasound beam for Doppler measurements. The diameter (D) of the brachial artery was determined immediately proximal to the common interosseus artery. Peripheral vascular blood flow was measured in the common interosseus artery by pulsed-wave Doppler technique.[19] The instantaneous pulse rate (PR) and the velocity-time integral (VTI), mean velocity (MV), peak systolic velocity (PSV), and end-diastolic velocity (EDV) of the spectral Doppler tracing were determined. The pulsatility index (PI = [PSV − EDV]/MV) and the resistive index (RI = [PSV − EDV]/PSV) were calculated.[19] Blood flow is commonly calculated as Flow = $\pi(D/2)^2 \times VTI \times PR$. However, in this study, the product of VTI and PR (VTI × PR) was calculated as a surrogate of vascular blood flow; the vascular diameter (D) was not included in this calculation and was assessed separately, because D was measured in a different vessel. Blood collection, pressure and ECG recordings, determination of cardiac output, echocardiography, and vascular ultrasonography were performed in consecutive order at each data collection period.

Adverse Effects

In both experiments, the horses were monitored for potential adverse effects during drug administration periods and for a duration of 8 hours

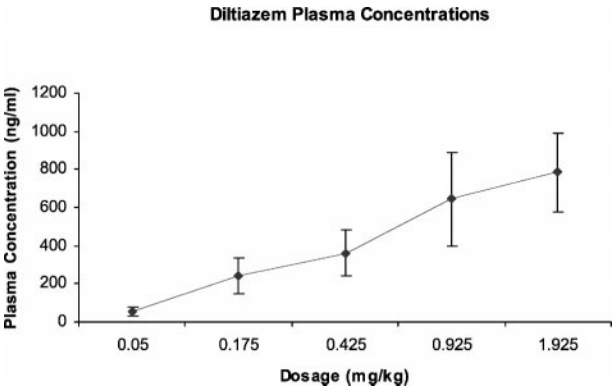

Fig 1. In the dose-finding study, plasma diltiazem concentrations increased linearly with geometrical dosing (mean ± SD).

after the last dose of diltiazem. Attention was focused on the development of bradycardia and other cardiac rhythm disturbances, hypotension, peripheral edema, coughing, increase in respiratory rate and signs of respiratory distress, colic, diarrhea, neurologic abnormalities, and laminitis. A serum chemistry profile[q] was performed before and 24 hours after the dose-finding study.

Determination of Plasma Drug Concentrations (Cp)

Blood samples were collected into evacuated glass tubes containing EDTA[r]. All samples were centrifuged at 4,000 × *g* for 15 minutes. Plasma then was transferred into cryovials[s], frozen, and stored at −80°C until analysis. Plasma diltiazem concentrations were determined by a commercial laboratory[t] by gas chromatography.[20] The lower limit of detection was 5.0 ng/mL.

Statistical Analysis

One-way repeated-measures analysis of variance (ANOVA) with Dunnett's post-hoc test was used to compare variables across treatment periods to baseline.[u] Friedman repeated-measure ANOVA on ranks was used for nonparametric variables. The serum biochemical results before and after diltiazem treatment were compared by means of a paired *t*-test.[u] The relationships between Cp and drug dosage, PR interval, and MAP, respectively, were examined by regression analyses by means of linear mixed-model techniques with random intercept and random slope.[v] The 1st-order autoregressive structure was identified as the best fitting covariance structure by using the likelihood methodology. The level of significance was $P < .05$.

Results

Dose-Finding Study

A significant quadratic relationship was identified between drug dosage and plasma concentration, Cp (Cp = 29.96 + [899.58 × dose] + [−268.58 × dose^2]; Fig 1). Considerable individual variation in plasma concentrations was noted, especially at the 2 highest doses. Diltiazem caused a significant dose-dependent decrease in mean arterial blood pressure (Fig 2a) and slight but not significant prolongation in PR interval (repeated-measures ANOVA with Dunnett's test, $1 - \beta = 0.5$, with $\alpha = .05$). Mean arterial blood pressure (MABP) was inversely and linearly related to plasma diltiazem concentrations, with a mean decrease in MABP of 0.0304 mmHg for every 1 ng/mL increase in Cp (MABP = −0.0304 Cp + 109.15; $P < .0001$). The relationship between PR interval and Cp was not statistically significant. The AR and VR increased with increasing dosages of diltiazem from 0.05 mg/kg to 0.925 mg/kg, and the frequency of AV blocks decreased (Fig 2b). At higher diltiazem dosages (1.425 mg/kg and 1.925 mg/kg), the frequency of AV blocks increased again (leading to a decrease in VR). Sinus arrhythmia was observed in 3 horses. At the 2 highest doses, plasma diltiazem concentrations averaged 720 ± 43 ng/mL and 874 ± 113 ng/mL, respectively. The desired effects of diltiazem (decrease of mean carotid blood pressure of at least 10 mmHg, prolongation of PR interval, 2nd-degree AV block) were achieved at doses above 0.925 mg/kg, corresponding to plasma diltiazem concentrations higher than 646 ± 246 ng/mL.

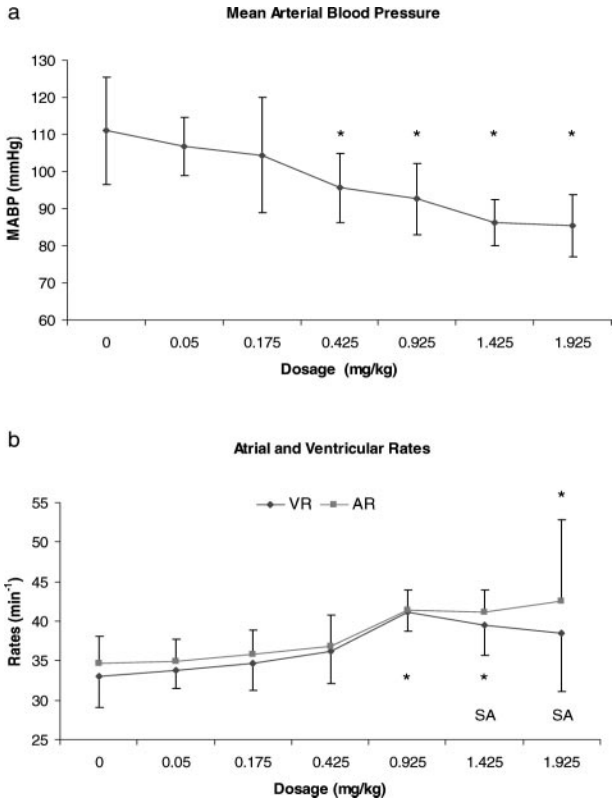

Fig 2. (a) Diltiazem produced a dose-dependent decrease in mean arterial blood pressure (MABP) (dose-finding study; mean ± SD; * significantly different from baseline, repeated-measures ANOVA with Dunnett's test, $P < .05$). **(b)** A dose-dependent increase in atrial rate (AR) and ventricular rate (VR) was observed with increasing doses of diltiazem. The difference between AR and VR equals the frequency of 2nd-degree AV blocks. SA indicates the occurrence of sinus arrhythmia in 3 horses (dose-finding study; mean ± SD; * significantly different from baseline, repeated-measures ANOVA with Dunnett's test, $P < .05$).

Hemodynamic Study

Plasma diltiazem concentrations did not differ significantly among the treatment periods D1, D1.5, and D2, respectively (Table 1). The PR interval was significantly higher during treatment periods D1 and D1.5 (Fig 3a). The VR increased insignificantly after diltiazem administration (versus baseline). The rise in AR was more pronounced, consistent with the increased frequency of AV block after

Table 1. The effects of diltiazem on hemodynamic parameters and indices of left ventricular function (hemodynamic study; all values reported as mean ± SD).

					Diltiazem (cumulative dose)		
		N	Prebaseline	Baseline	1 mg/kg	1.5 mg/kg	2 mg/kg
Time	Minutes		−45	−15	15	45	75
Diltiazem concentration	ng/mL	7	—	—	714 ± 185[a]	706 ± 133[a]	711 ± 188[a]
HR (LV)	$Minutes^{-1}$	6	33.96 ± 3.54	35.10 ± 3.15	43.28 ± 8.02	40.52 ± 9.99	40.08 ± 7.90
SAP	mmHg	7	115.76 ± 11.62	117.50 ± 13.25	105.40 ± 11.02[b]	106.24 ± 12.61[b]	105.98 ± 11.40[b]
MAP	mmHg	7	94.35 ± 11.15	94.84 ± 11.60	83.55 ± 10.42[b]	83.93 ± 10.87[b]	83.45 ± 10.07[b]
DAP	mmHg	7	76.12 ± 10.13	75.76 ± 10.13	64.08 ± 9.73[b]	64.88 ± 9.43[b]	63.87 ± 8.94[b]
PAP	mmHg	7	22.83 ± 3.17	23.41 ± 4.01	25.72 ± 4.66[b]	25.74 ± 4.58[b]	26.07 ± 5.22[b]
RAP	mmHg	7	4.48 ± 2.66	5.04 ± 3.43	8.31 ± 3.11[b]	10.96 ± 2.71[b]	10.83 ± 3.64[b]
LVEDP	mmHg	6	18.05 ± 4.10	16.78 ± 7.25	21.97 ± 7.03[b]	24.85 ± 6.13[b]	25.73 ± 6.69[b]
$+dp/dt_{max}$	mmHg/sec	6	1,212 ± 228	1,241 ± 224	1,143 ± 294	1,091 ± 278[b]	1,121 ± 248
FS	%	7	40.4 ± 4.3	39.4 ± 4.5	36.4 ± 5.0	35.9 ± 6.3	36.1 ± 6.9
$-dp/dt_{max}$	mmHg/sec	6	1,691 ± 176	1,756 ± 200	1,442 ± 143[b]	1,429 ± 276[b]	1,427 ± 209[b]
Tau	msec	6	43.39 ± 9.99	41.23 ± 12.47	47.64 ± 15.45	48.18 ± 16.04[b]	50.46 ± 16.68[b]
CO	L/min	7	28.5 ± 5.4	28.1 ± 4.3	32.4 ± 5.2	32.8 ± 7.2	27.3 ± 5.0
SV	mL	7	892 ± 159	854 ± 160	853 ± 139	874 ± 170	764 ± 90
SVR	$Dynes \times s \times cm^{-3}$	7	259.5 ± 77.9	262.4 ± 63.4	186.4 ± 40.5[b]	175.3 ± 43.5[b]	201.7 ± 27.9[b]
PVR	$Dynes \times s \times cm^{-3}$	6	14.7 ± 14.2[b]	21.2 ± 21.0	10.9 ± 13.4[b]	5.1 ± 11.8[b]	5.3 ± 13.5[b]

[a] Values followed by the same letter do not differ significantly (Friedman repeated-measures ANOVA on ranks, $P = .964$).
[b] Significantly different from baseline values (one-way repeated-measures ANOVA, Dunnett's posthoc, $P < .05$).

administration of diltiazem (Fig 3b). Both frequency of 2nd-degree AV block and the degree of sinus arrhythmia increased during administration of diltiazem. Sinus arrhythmia was most pronounced during D1.5 and D2. However, considerable individual variation was observed in the effects on the sinus node and AV node among horses. Diltiazem caused high-degree sinus arrhythmia in 2 horses, whereas 2nd-degree AV block was predominant in 3 horses. One horse developed a large number of AV blocks during D1 and D1.5 and developed predominantly sinus arrhythmia during D2. In one horse neither sinus arrhythmia nor 2nd-degree AV block was noted.

The effects of diltiazem on hemodynamic parameters and indices of LV function are summarized in Table 1. Diltiazem caused SAP, DAP, and MAP to decrease, whereas PAP, RAP, and LVEDP increased significantly compared to baseline. The LV $+dp/dt_{max}$ and $-dp/dt_{max}$ decreased, FS decreased, and *tau* increased. Significant decreases in SVR and PVR were detected. Changes in CO and SV were not significant throughout the study, but SV revealed a tendency to decrease during D2. Statistical power was inadequate to detect small changes in these values ($1 - \beta = 0.31$ for CO and 0.05 for SV, with $\alpha = .05$). The diameter of the brachial artery and VTI × PR in the common interosseus artery increased significantly during all treatment periods (Fig 4a,b), whereas RI and PI decreased (Fig 4c). These findings were compatible with peripheral vasodilatation and increased limb blood flow.

Adverse Effects

Two horses developed bouts of high-grade sinus arrest with severe hypotension and clinical signs of near-syncope during the diltiazem administration period. In the first horse, these effects occurred in both the dose-finding and the hemodynamic study at cumulative dosages of 1.8 mg/kg and 1 mg/kg, leading to plasma diltiazem concentrations of 1,500 ng/mL and 760 ng/mL, respectively. On both occasions, drug administration was discontinued immediately, and treatment with lactated Ringer's solution, calcium gluconate, and dobutamine was initiated. This horse was excluded from final data analysis in both studies due to incomplete data. The second horse was used in the hemodynamic study only. It revealed similar but somewhat milder adverse effects at a diltiazem dosage of 2 mg/kg and a plasma diltiazem concentration of 930 ng/mL. No emergency treatment was necessary, and data collection was not affected by the event. Therefore, this horse was included in the final data analysis. Both horses developed marked sinus tachycardia immediately after the events, and the clinical signs of hypotension resolved within 1 minute. No signs of bradycardia or tachycardia, rhythm disturbances, or hypotension occurred during the 8-hour monitoring period after the end of the trial. No signs of laminitis, respiratory, gastrointestinal, or neurologic compromise were noted during or after drug administration. No behavioral changes were observed.

Significant increases in liver enzyme activities were not detected 24 hours after the dose-finding study. Statistically significant decreases were found in alkaline phosphatase activity (from 133 ± 14 U/L to 128 ± 14 U/L; $P = .022$, paired *t*-test [normal range: 80–187 U/L]), gamma-glutamyltransferase (from 11 ± 3 U/L to 9 ± 2 U/L; $P = .005$, paired *t*-test [normal range: 9–24 U/L]), and serum urea nitrogen concentration (from 22 ± 4 mg/dL to 19 ± 2 mg/dL; $P = .014$, paired *t*-test [normal range: 13–27 mg/dL]). A statistically significant increase in serum phosphate concentration was detected (from 2.3 ± 1.0 mg/dL to 3.4 ± 0.5 mg/dL; $P < .001$, paired *t*-test [normal range: 1.2–4.8 mg/dL]).

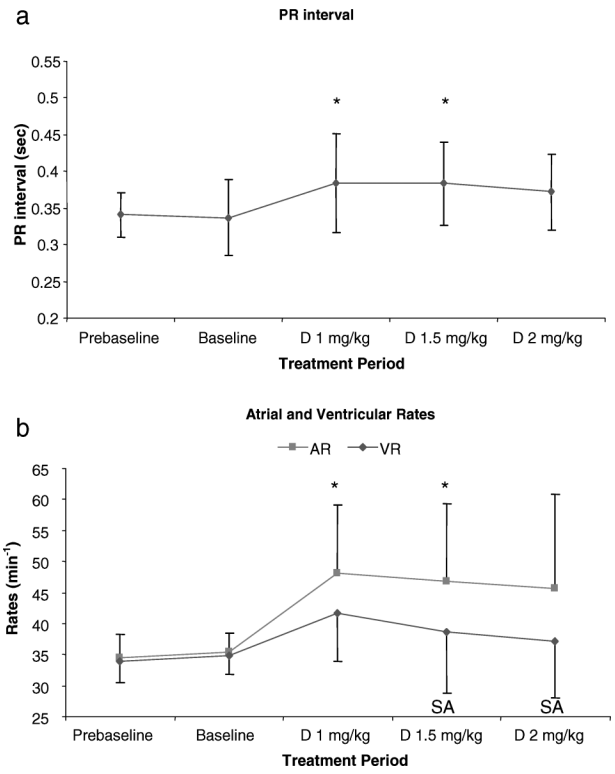

Fig 3. (a) In the hemodynamic study, diltiazem produced a slight but significant increase in PR interval. (mean ± SD; * significantly different from baseline, repeated-measures ANOVA with Dunnett's test, $P < .05$). **(b)** In the hemodynamic study, similar to the dose-finding study, the atrial rate (AR) and, to a lesser extent, the ventricular rate (VR) increased after administration of diltiazem. Considerable individual variation in AR and VR was present during the diltiazem treatment periods. The difference between AR and VR represents the frequency of atrioventricular (AV) blocks observed at each treatment period. SA indicates the occurrence of pronounced sinus arrhythmia in 3 horses (mean ± SD; * significantly different from baseline, repeated-measures ANOVA with Dunnett's test, $P < .05$).

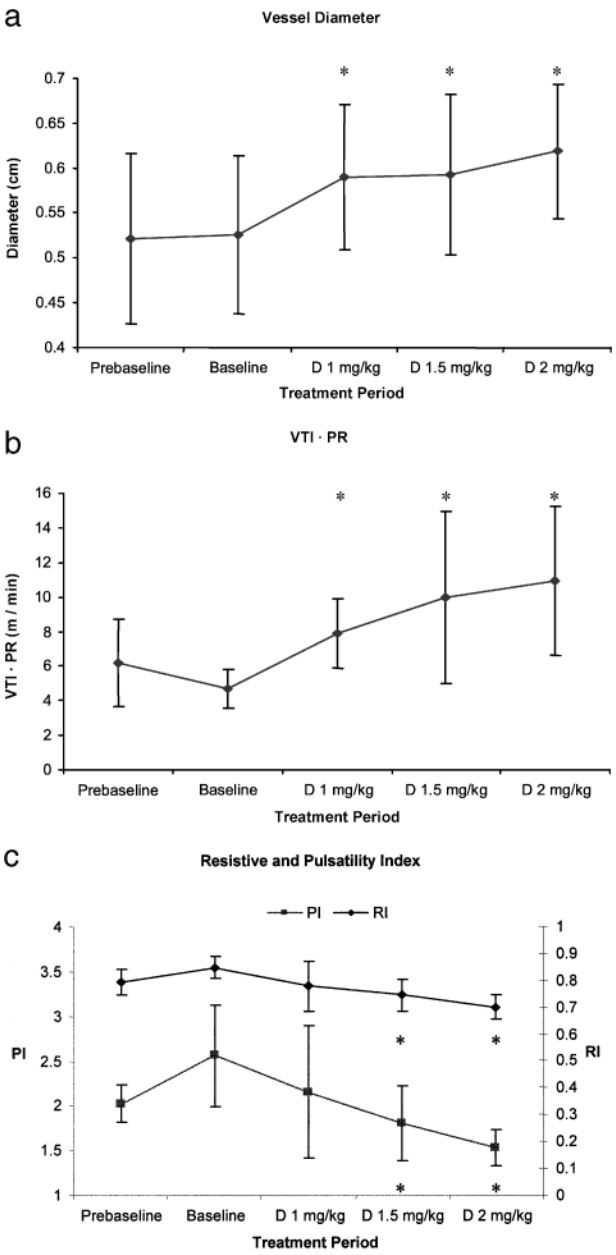

Fig 4. (a) The diameter of the brachial artery was significantly increased during all treatment periods (mean ± SD; * significantly different from baseline, repeated-measures ANOVA with Dunnett's test, $P < .05$). **(b)** The product of velocity-time integral (VTI) and pulse rate (PR), a surrogate of the blood flow in the common interosseus artery, increased significantly during treatment periods (mean ± SD; * significantly different from baseline, repeated-measures ANOVA with Dunnett's test, $P < .05$). **(c)** Diltiazem caused a significant decrease in resistive index (RI) and pulsatility index (PI) of blood flow in the common interosseus artery (mean ± SD; repeated-measures ANOVA with Dunnett's test, $P < .05$).

Discussion

Diltiazem is a selective inhibitor of voltage-sensitive L-type calcium channels that control calcium influx into vascular smooth muscle cells and cardiac myocytes and play a major role in excitation-contraction coupling, control of sinoatrial pacemaker activity, and regulation of AV conduction in the AV node.[4,21,22] Vascular effects of diltiazem include vasodilatation and reduction of systemic vascular resistance with subsequent lowering of systemic blood pressure.[4,12,21,22] In the present study, the expected decrease in arterial blood pressure was shown to be dose-dependent and was inversely related in a linear fashion to plasma diltiazem concentrations. Dilatation of the brachial artery and decreased RI and PI in the common interosseus artery clearly demonstrated the vasodilatory effects of diltiazem. Because the vascular diameter and the indices of blood flow were determined in 2 distinct (but adjacent) vessels, a surrogate of peripheral blood flow (VTI × PR) was calculated, thereby ignoring changes in the vascular diameter. However, assuming that the vascular effects of diltiazem were similar in both vessels, and considering the concomitant increase in D and VTI × PR, we inferred that the peripheral blood flow (flow = $\pi(D/2)^2 \times VTI \times PR$) to the limb increased following administration of diltiazem. Effects on other peripheral arterial beds were not examined, but likely are similar.

In the intact animal, the net effects of diltiazem on car-

diac function are dictated by the sum of the direct cardiac effects and the opposing indirect effects resulting from baroreceptor reflexes triggered by a decrease in systemic blood pressure.[4,12,21–25] In the present study, increase in atrial rate, and to a lesser degree in ventricular rate, were consistent with increased sympathetic drive due to baroreceptor reflex activation, similar to findings in normal dogs and humans.[23,26–28] The direct effects on sinus node and AV node varied among horses and were expressed by the occurrence of sinus arrhythmia, high-degree sinus arrest, slight prolongation of the PR interval, and 2nd-degree AV block, despite the presence of increased sympathetic tone. The inhibitory effect on AV nodal conduction is the basis for the use of calcium channel blockers in the treatment of supraventricular arrhythmia. Diltiazem typically acts in a frequency-dependent manner; hence, the effects of diltiazem on the AV node are more pronounced at faster pacing rates, and the slowing of AV conduction is enhanced in the presence of supraventricular arrhythmias.[22,29] Our study does not allow any conclusions to be made about the frequency-dependent effects of diltiazem in horses. However, it is likely that effective dosages for heart rate control in horses with AF will be lower than those used in the present study in normal horses. The dosages used in this study are considerably higher than those used clinically in dogs and humans with supraventricular arrhythmias. For acute heart rate control in humans with AF, an initial dose of 0.25 mg/kg IV over 2 minutes is recommended, followed by a second dose of 0.35 mg/kg IV or an infusion of 5 to 15 mg/h for up to 24 hours to effect.[4,30,31] Mean plasma diltiazem concentrations between 80 and 290 ng/mL are required to produce a 20–40% reduction in heart rate in these patients.[31] In dogs with supraventricular arrhythmias, multiple boluses of 0.05 to 0.25 mg/kg IV are administered every 5 minutes to effect.[5,12] Total cumulative doses of 0.44 to 0.94 mg/kg leading to mean plasma concentrations of 60 to 120 ng/mL were found to be optimal for treatment of iatrogenic AF in dogs.[6]

The effects of calcium channel blockers on systolic and diastolic ventricular performance in intact animals are complex and depend on the specific drug, the dose, the experimental design, existing pathological conditions, concomitant effects of other cardiovascular drugs or anesthetics, adrenergic tone, and changes in loading conditions.[23] Diltiazem exhibits negative inotropic actions on isolated myocardial tissue in vitro[32,33] and after intracoronary administration in vivo.[23] The slight decreases in $+dp/dt_{max}$ and FS found in the present study were consistent with decreased LV systolic function under direct influence of diltiazem. Reflex increase in adrenergic tone and changes in ventricular loading probably attenuated the direct negative inotropic effects of diltiazem.[23] The degree of these effects was considered clinically irrelevant in the present study. However, decreased LV systolic function may be more pronounced in the presence of chronic volume overload and heart failure and might therefore have important clinical implications.[28,34] The use of calcium channel blockers generally is contraindicated in patients with untreated heart failure. However, effective treatment of AF in patients with congestive heart failure is clinically important, and rate control with diltiazem or a combination of digoxin and diltiazem was shown to be beneficial and relatively safe in humans with heart failure associated with AF and high ventricular response rate.[9,35] In this context, the negative inotropic effects of diltiazem may be offset by reductions in heart rate and peripheral vascular resistance, leading to increased coronary perfusion, reduced myocardial oxygen consumption, improved ventricular performance, and often to a reduction of clinical signs.[9,35]

Diltiazem also is used for treatment of patients with diastolic heart failure caused by LV hypertrophy, hypertension, or ischemic heart disease.[4, 36–40] In the diseased ventricle, calcium channel blockers enhance ventricular relaxation, most likely as a result of improved myocardial blood flow and favorable effects on ventricular loading conditions.[36–40] Conversely, calcium entry blockade directly impairs LV relaxation in conscious dogs and humans with normal ventricular function.[41,42] This direct effect is closely linked to the negative inotropy of calcium channel blockers.[41] It may be attenuated or even reversed during systemic administration because of concomitant reflex sympathetic stimulation,[41,43] changes in inotropic state,[43,44] effects on ventricular loading conditions,[45–47] and alterations in loading sequence.[47–49] The variables used to evaluate LV relaxation in the present study, $-dp/dt_{max}$ and *tau*,[50–52] indicated that diltiazem caused a slight, but clinically irrelevant, decrease in ventricular relaxation in horses with normal ventricular function.

The increases in RAP and LVEDP indicated increased left and right heart filling pressures. Similar increases were reported in dogs, swine, and humans after IV administration of calcium channel blockers.[42,53,54] Although calcium channel blockers relax arterial smooth muscle, they seem to have little effect on most venous beds and do not affect preload significantly.[21,55] Conversely, baroreceptor reflex-mediated sympathetic constriction of venous capacitance vessels may lead to an increase in venous return. Concurrent impairment of ventricular contractile function and relaxation, tachycardia, and the resulting incomplete emptying of the ventricles may cause an increase in filling pressures.[42]

The elimination half-life of diltiazem is approximately 3 hours (2.2–4 hours) in dogs[56–58] and 2–6 hours in humans.[4,22,31] The pharmacokinetic properties of diltiazem in horses were unknown at the time during which our study was conducted. Assuming a half-life similar to that of dogs and humans, the cumulative dosing regimen used in the hemodynamic study was expected to produce increasing plasma diltiazem concentrations, because the amount of diltiazem eliminated over the time of drug administration would be minimal.[6] However, plasma diltiazem concentrations did not increase significantly between the time points D1, D1.5, and D2 of the hemodynamic study. This finding indicates that the plasma half-life of diltiazem may be considerably shorter in horses than was reported in dogs and humans, either because of a higher rate of elimination or redistribution into extravascular compartments. These findings are consistent with results of an ongoing pharmacokinetic study performed by the authors, indicating that diltiazem after IV administration to healthy horses has a median terminal half-life of 1.5 hours (Schwarzwald et al, unpublished observations). Differences in drug effects

between the dose-finding and the hemodynamic study, and among D1, D1.5, and D2, respectively, may be explained by differences in dosing intervals, time-dependent actions, presence of active metabolites, or redistribution of the drug. Metabolite concentrations were not determined in the present study.

Diltiazem is considered a safe and effective drug to rapidly lower heart rate in humans with AF and atrial flutter. SA or AV nodal disturbances, preexisting hypotension, and most forms of ventricular tachycardia are considered contraindications for the use of calcium channel blockers.[4,7,21,22] Although heart rate control is important in patients with supraventricular tachyarrhythmia and heart failure, diltiazem should be used with caution in patients with severe ventricular systolic dysfunction. The most prominent adverse effects of calcium antagonists in humans, dogs, and cats are bradycardia, hypotension, and rhythm disturbances.[21,59] Whereas similar adverse effects also were found in the present study, other known adverse effects, such as gastrointestinal distress, constipation, central nervous system effects, peripheral edema, coughing, wheezing, pulmonary edema, or increases in liver enzyme activities were not observed after short-term administration of diltiazem. The decrease in serum alkaline phosphatase, gamma-glutamyl transferase, and serum urea nitrogen concentration as well as the increase in serum phosphate concentration in the present study were not considered clinically relevant. The IV use of diltiazem in healthy horses therefore is considered relatively safe, but the dosage is critical, and its use may be limited by hypotension because of vasodilatation and transient high-degree sinus arrest leading to severe bradycardia. As a result of the frequency-dependence of diltiazem's effects, effective dosages for heart rate control in horses with AF may be considerably lower than those used in this study, and reduced dosages may lower the risk of adverse effects. Diltiazem should be administered to effect under ECG and blood pressure monitoring. No inferences can be made regarding the long-term use of diltiazem in horses. Specific diltiazem antagonists are not available. Treatment of adverse effects consists of correction of hypotension and arrhythmia by IV administration of fluids, calcium gluconate or calcium chloride, inotropic agents (dobutamine), and vasopressors (norepinephrine).[4]

In conclusion, the results of this study in normal horses in sinus rhythm show that the cardiac effects of diltiazem, at dosages between 1 and 2 mg/kg IV, include intermittent depression of the sinus and AV nodes and mild impairment of systolic and diastolic LV function. Vascular effects of diltiazem include arterial vasodilatation and decreased systemic vascular resistance leading to reduced afterload. The decrease in arterial blood pressure seemingly invokes the baroreceptor reflex, causing sympathetic activation that increases sinus node rate and presumably blunts the depressive effects of diltiazem on myocardial and nodal tissues. Because of its inhibitory effects on AV nodal conduction, diltiazem is likely to prove useful for heart rate control in horses with AF, presumably at dosages lower than those used in our study. Additional studies are required to determine the pharmacokinetic profile of diltiazem, the potential frequency-dependence of diltiazem effects on nodal tissues, and the effects and safety of combined treatment with diltiazem and quinidine in horses with AF.

Footnotes

[a] Bupivacaine HCl, Sensorcaine®, AstraZeneca LP, Wilmington, DE
[b] Angiocath 14G IV catheter, Becton Dickinson, Sandy, UT
[c] Intracath 19G/30.5 cm IV catheter, Becton Dickinson, Sandy, UT
[d] Pressure Monitoring Kit (PX36N), Edwards Lifesciences LCC, Irvine, CA
[e] Diltiazem HCl, D-2521, Sigma Chemical Co, St. Louis, MO; in Sterile Water for Injection, Vedco Inc, St. Joseph, MO
[f] Ponemah Physiology Platform, Gould Instrument Systems Inc, Valley View, OH
[g] 8F Percutaneous catheter introducer, Maxxim Medical, Athens, TX
[h] 7F 110 cm Swan-Ganz thermodilution catheter (141HF7), Edwards Lifesciences, Irvine, CA
[i] Intramedic polyethylene 240 tubing (90 cm), Clay Adams, Parsippany, NJ
[j] 9F Percutaneous catheter introducer, Maxxim Medical, Athens, TX
[k] 8F 180-cm Millar Mikro-Tip catheter (Model SPR-872), Millar Instruments Inc, Houston, TX
[l] Marquette Series 7010 Monitor, Marquette Electronics Inc, Milwaukee, WI
[m] 0.9% Sodium Chloride Injection USP, Baxter, Deerfield, IL
[n] Quinidine Gluconate Q-5001, Sigma Chemical Co, St Louis, MO
[o] PHD2000 Infusion Pump, Harvard Apparatus Inc, Holliston, MA
[p] Megas ES, Biosound Esaote, Indianapolis, IN
[q] Roche/Hitachi 911, Roche Diagnostics Corporation, Indianapolis, IN
[r] BD Vacutainer K3 EDTA, 10 mL, Becton Dickinson, Franklin Lakes, NJ
[s] Fisherbrand Cryovial 4.0 mL, Fisher Scientific, Pittsburgh, PA
[t] National Medical Services, Willow Grove, PA
[u] SigmaStat Version 3.0, SPSS Inc, Chicago, IL
[v] R Version 1.8.0, Free Software, www.r-project.org

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