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European Journal of Pharmacology 355 (1998) 159–166

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Effects of the optical isomers of verapamil on electrophysiological properties of the heart in conscious dogs

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Received 27 May 1998; revised 23 June 1998; accepted 26 June 1998

Abstract

We compared the cumulative dose–response relations of verapamil (0.1, 0.2 and 0.4 mg kg^{-1}) in different R/S enantiomer ratios (100/0, 90/10, 80/20, 50/50 and 20/80) on the electrophysiological and hemodynamic characteristics of the heart using the conscious dogs. A reduction of mean arterial pressure occurred with $20R/80S$ producing a 3-times greater decrease than $100R/0S$, but an increase in heart rate occurred with $20R/80S$ producing a 9-times greater increase than $100R/0S$. Increased heart rate was concurrent with decreased mean arterial pressure most prevalent with a higher ratio of *S*-isomer that produced a greater reduction in mean arterial pressure and increase in heart rate at lower overall verapamil doses. Atrio-ventricular conduction time increased 3–5 min after each infusion, with $20R/80S$ producing a 4-times greater effect than $100R/0S$. These results indicate that the peripheral and cardiac electrophysiologic properties of various nonracemic verapamil mixtures are mainly attributable to the concentration of *S*-isomer.

Keywords: Ca^{2+} channel antagonist; Verapamil; Chemistry; Optical isomer; Heart; Electrophysiological effect

1. Introduction

Verapamil produces well recognized antianginal, antihypertensive, and antiarrhythmic effects (Ellrodt et al., 1980). Electrophysiologic experiments indicate that verapamil decreases the rate of sinus node discharge, atrioventricular conduction velocity, and lengthens atrioventricular nodal refractoriness by depressing the slow inward Ca^{2+} channel current (Fleckenstein, 1977; Zsoter and Church, 1983). Almost all of the effects of verapamil may be attributed to its Ca channel blocking action (Kaumann and Serur, 1975; Gloor and Urthaler, 1983).

The drug preparation available for clinical usage is a racemic mixture of equal amounts of *R*- and *S*-verapamil. *S*-verapamil is 6–10-times more potent than *R*-verapamil with regard to the Ca channel blocking effect (Bayer et al., 1975; Kaumann and Serur, 1975; Raschack, 1976; Satoh et al., 1979; Gloor and Urthaler, 1983; Echizen et al., 1985, 1988; van Amsterdam and Zaagsma, 1988). The *R*- and *S*-isomers of verapamil thus have different magnitudes of effect on hemodynamics and the atrioventricular conduction system (Satoh et al., 1979, 1980). The magnitude of the cardiac effects of a mixture of verapamil with a higher *R*-ratio may, therefore, be expected to be different than those of higher *S*-mixture. In the present study, we compared the effects of different ratios of *R*- and *S*-verapamil on cardiac electrophysiologic and hemodynamic characteristics in conscious dogs.

2. Materials and methods

All procedures and protocols used were reviewed and approved by the Animal Care and Use Committee of the Medical College of Wisconsin and they conformed to the guidelines set forth by the NIH and American Physiologic Society.

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0014-2999/98/$19.00
PII: S0014-2999(98)00480-4

2.1. Surgical preparation

A total of 14 adult mongrel dogs of either sex weighing between 19 and 25 kg were prepared for chronic electrophysiologic investigation by implanting epicardial electrodes and an indwelling aortic catheter. The dogs were fasted overnight and anesthetized with halothane at the dosage ≥ 1.5 of minimal alveolar concentration on the day of surgery. After tracheal intubation, anesthesia was maintained with isoflurane (1.0 to 1.5 minimal alveolar concentration) in oxygen administered via a positive pressure ventilation adjusted to maintain end tidal pCO_2 within the normal range (35 to 40 mmHg). Muscular relaxation was induced by 2 mg of pancuronium. A right, thoracotomy was performed within the fifth intercostal space and the heart suspended in a pericardial sling. Three bipolar electrode pairs were sutured to the epicardial surface of the right atrial appendage and on the right and left ventricular apex (Fig. 1). An additional bipolar electrode was sutured to the right atrium close to the anatomical region of the sinoatrial node. A bipolar plunge electrode was placed into base of the interventricular septum to record a His bundle electrogram. An indwelling arterial catheter was advanced into the aorta through the left femoral artery after surgical exposure of the artery at the inner side of the hind limb. All electrode leads were subcutaneously tunneled and exited through the skin between the scapulae. Incisions were closed in anatomic fashion and standard postoperative methods of analgesia were provided with 0.015 mg kg^{-1} of buprenorphine (Buprenex®, Reckitt & Colman, Hull, UK) and given 25 mg kg^{-1} cefazolin b.i.d. intramuscular (Cefazolin Sodium®, SoloPak Laboratories, Elk Grove Village, IL, USA). The dogs were allowed to recover from surgery prior to testing.

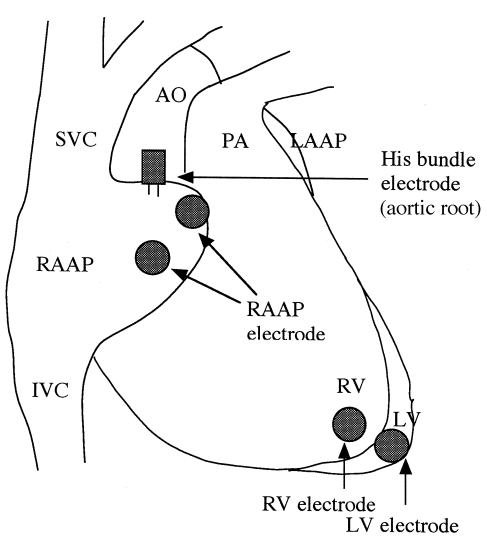

Fig. 1. Location of the electrode pairs sutured to the epicardial surface of the heart. AO = aorta, IVC = inferior vena cava, SVC = superior vena cava, PA = pulmonary artery, RAAP = right atrial appendage, LAAP = left atrial appendage, RV = right ventricle, LV = left ventricle. Bipolar needles of the His bundle electrode were advanced into the interventricular septum from the aortic root. Electrode lead wires are not shown.

2.2. Monitoring

Electrical signals from the bipolar electrodes were amplified using a custom built preamplifier (gain 1000) and filtered using a separate custom designed and built common mode rejection amplifier with a bandpass filter of 10–1000 Hz then individually adjusted for display (maximal gain 400). The signals were then sent to a desktop computer (Apple Macintosh Centris 650®, Cupertino, CA, USA), digitally converted with MacADIOS II A-D board (GW Instruments®, Somerville, MA, USA), displayed and stored for the subsequent analyses with SuperScope II (GW Instruments®, Somerville, MA, USA). The surface electrocardiogram was amplified (78213C, Hewlett-Packard®, Fort Collins, CO, USA), displayed, and the heart rate continuously measured (peak detector), using a separate monitor (model HP 78303A, Hewlett-Packard®). Right atrial appendage, right ventricular apex and His bundle electrograms were recorded, simultaneously. Cardiac pacing was performed with a programmed cardiac stimulator (model SEC3102, Nihon Kohden®, Tokyo, Japan). All measurements of conduction times were made during spontaneous sinus rhythm.

The His bundle electrode was advanced into the base of the interatrial septum from the aortic root. The electrode was advanced from a point located just behind and to the right of the origin of the right coronary artery. The His bundle electrode was slowly advanced parallel to the aorta, inferiorly and slightly anteriorly until a well-discernible His bundle was recorded. Atrioventricular conduction interval was measured as the time difference (ms) between the onset of the initial rapid deflection in the right atrial electrogram to the beginning of the His potential in the His bundle electrogram. His-ventricular conduction time interval (ms) was measured from the beginning of the His potential to the initial deflection of the QRS complex wave (earliest left ventricular activation) in a simultaneously recorded surface electrocardiogram lead II.

As an indicator of automaticity, sinus node recovery time was determined by pacing the right atrial appendage (30 s at 180 and 200 beats min^{-1} using 2 ms long pulses at 2 × threshold). Sinus node recovery time was measured from the last pacing spike to the first spontaneous atrial depolarization on the His bundle after cessation of pacing (ms).

To determine the effective refractory period of the ventricular myocardium, the ventricular excitation threshold was first determined by finding the minimum voltage required to produce a conducted ventricular complex with an extrastimulus 2 ms in duration and delivered 300 ms after the *R*-wave recorded in the lead II electrocardiogram. Using a twice threshold stimulus, the ventricle was paced

at 171 or 200 beats min^{-1}, depending on intrinsic rhythm. A timed extrastimulus (S2) was delivered 300 ms after the preceding pacing spike (S1). The S1–S2 coupling was decreased incrementally until the ventricle failed to produce a conducted response. The effective refractory period was thus defined as the longest S1–S2 interval which failed to produce a ventricular response.

Systolic and diastolic blood pressures were measured using a pressure transducer (Baxter Uniflow, Baxter®, Deerfield, IL, USA) and an amplifier (model HP 78205 D, Hewlett-Packard®), and they were subsequently digitized and recorded for calculation of mean arterial pressure. Pure *R*- or *S*-isomer of verapamil powder was dissolved in 5% dextrose and water (2.0 mg ml^{-1}) and filtered through 0.22-μm pore size membrane. After filtration, 100*R* and 100*S* verapamil solutions were mixed to make an appropriate *R*/*S* ratio mixture. A bolus dose was administered over 2 min using an infusion pump (model 5006100, Harvard®, South Natick, MA, USA).

2.3. Experimental protocol

Each dog was allowed to recover for a period of 7 days prior to experimentation. During the postoperative period, dogs were trained to stand quietly in a sling to allow electrophysiological monitoring. Prior to measurement, the electrocardiogram was examined to verify the absence of spontaneous arrhythmias other than normal respiratory sinus arrhythmias.

From the resting dog, five channel records were obtained at a sampling rate of 1 kHz per channel for 7 min to determine the following control parameters: Atrio-ventricular, His-ventricular, QRS, QT and heart rate. A corrected QT interval (QTc) was calculated from following equation; QTc = QT interval in ms/(*R*–*R* interval in s)$^{1/2}$. In addition, systolic and diastolic blood pressure were recorded, followed by the ventricular effective refractory period determination. Next, the heart was paced from the sinoatrial electrode pair to determine sinus node recovery time. After control measurement, cumulative dose–response relations of verapamil (0.1, 0.2 and 0.4 mg kg^{-1}) in different *R*/*S* ratios (100/0, 90/10, 80/20, 50/50 and 20/80) on hemodynamic and cardiovascular conduction system were established. Fifteen minutes were allowed between each injection. On each of 5 consecutive experimental days, a different *R*/*S* ratio of verapamil was randomly selected for study. On each study day, the dog was fasted overnight, transported to the laboratory and measurements were taken prior to and after each incremental dose of intravenous verapamil.

2.4. Statistical analysis

Data were processed and statistically analyzed, using an Apple Macintosh® desktop computer and standard statistics software package (Super two-way analysis of variance and Stat View, Abacus Concepts, Berkeley, CA, USA). Two-way analysis of variance with repeated measures were performed within each ratio, followed by the Fisher's protected least significant difference test (Fisher's PLSD) or the Scheffe test to determine the significance of differences between doses. Comparison between each ratio was determined using two-way analysis of variance followed by Newman–Keuls test. A χ^2 test of statistical independence was performed on data for atrioventricular block. Multiple linear regression analysis was used to compare the interactions between hemodynamic and conduction variables. All data are expressed as mean values ± S.E.M.,

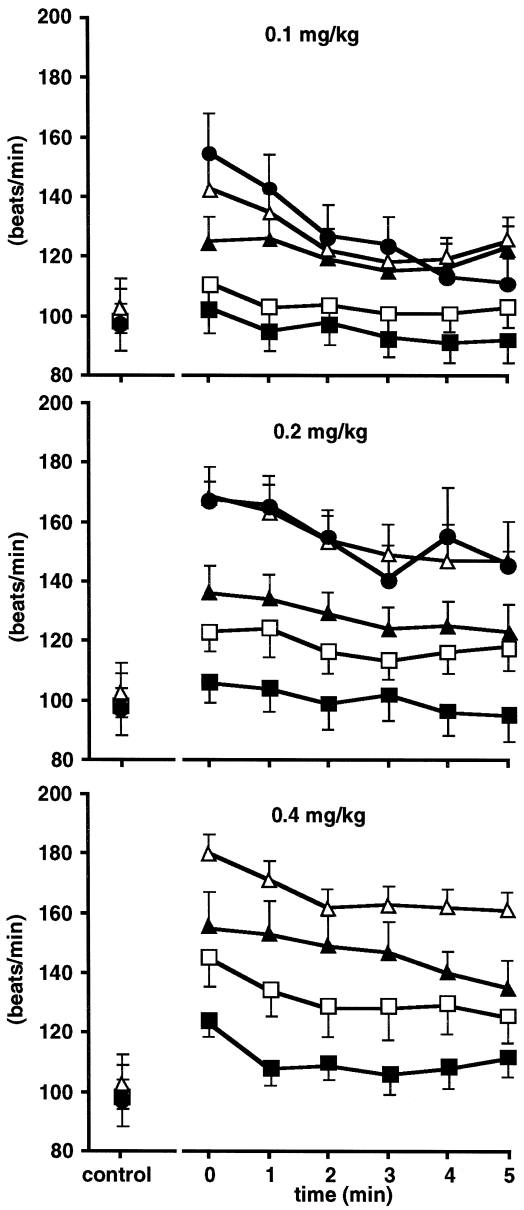

Fig. 2. The effect of different *R*/*S* verapamil ratios on heart rate (beats/min). Values are expressed as mean. Vertical lines show S.E.M. 0 min means just after injection of each drugs. Symbols: (■) 100*R*/0*S*, (□) 90*R*/10*S*, (▲) 80*R*/20*S*, (△) 50*R*/50*S* and (●) 20*R*/80*S* verapamil. Statistical significance symbols have been omitted for clarity.

and differences were considered as significant when $P < 0.05$.

3. Results

A total of 14 dogs were used in this study. Four dogs were excluded from data analysis because three dogs died following surgery before measurement could be obtained and one dog developed ventricular escape beats after surgery in the absence of any intervention.

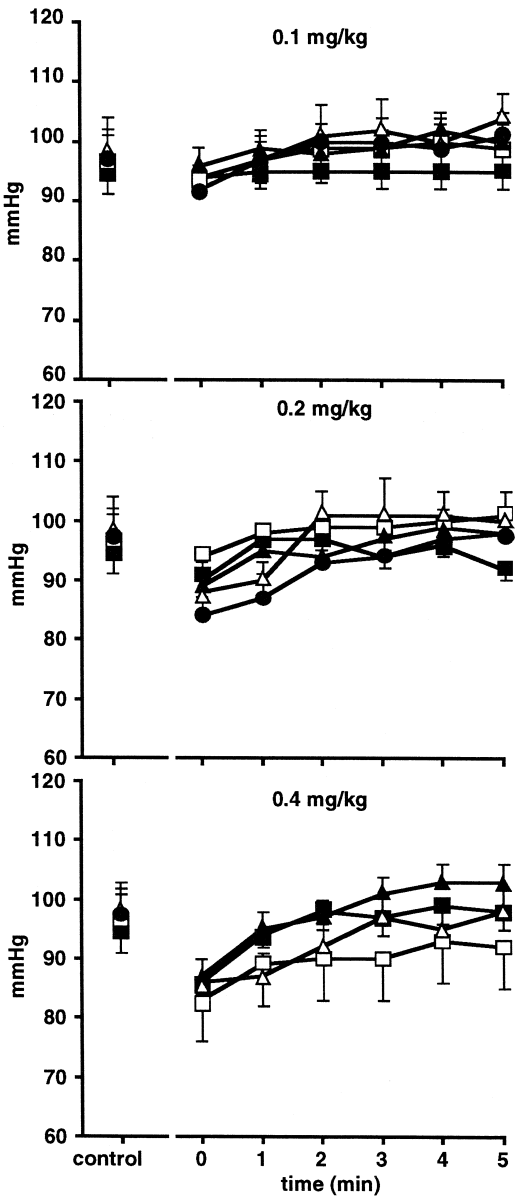

Fig. 3. The effect of different R/S verapamil ratios on mean arterial pressure (mmHg). Values are expressed as mean. Vertical lines show S.E.M. 0 min means just after injection of each drugs. Symbols: (■) $100R/0S$, (□) $90R/10S$, (▲) $80R/20S$, (△) $50R/50S$ and (●) $20R/80S$ verapamil. Statistical significance symbols have been omitted for clarity.

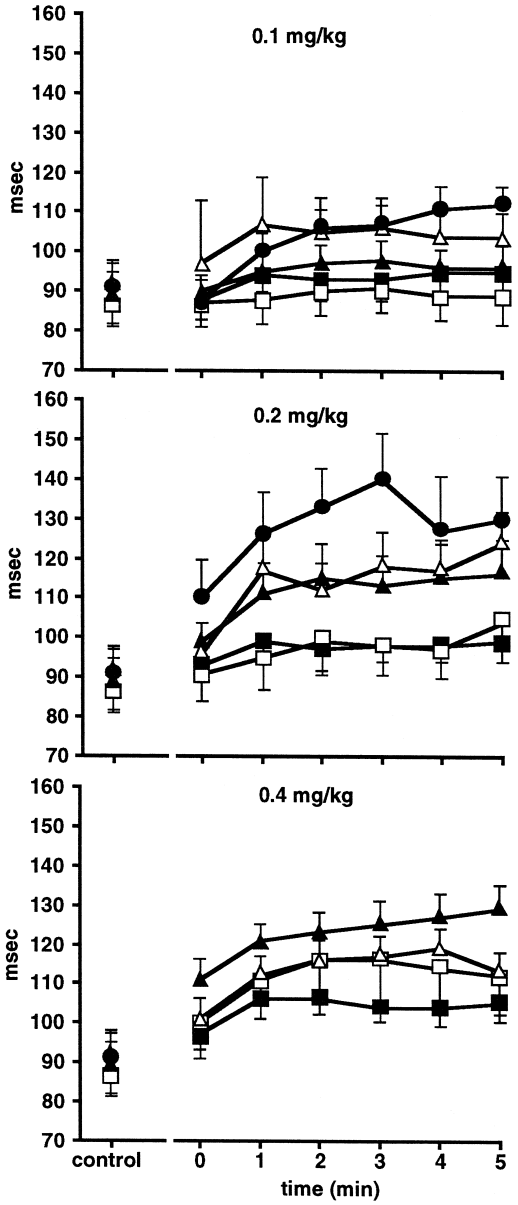

Fig. 4. The effect of different R/S verapamil ratios on atrio-ventricular time (ms). Values are expressed as mean. Vertical lines show S.E.M. 0 min means just after injection of each drugs. AH time = atrio-ventricular conduction time. Symbols: (■) $100R/0S$, (□) $90R/10S$, (▲) $80R/20S$, (△) $50R/50S$ and (●) $20R/80S$ verapamil. Statistical significance symbols have been omitted for clarity.

3.1. Effect of verapamil isomers on hemodynamics

Baseline heart rate was the same prior to administration of each mixture of verapamil. After infusion of verapamil, an initial increase in heart rate was observed. The increase in heart rate was qualitatively similar in each enantiomer ratio (Fig. 2) and the magnitude of the effect was dose-dependent. Just after injection of 0.2 mg kg^{-1}, the increase in heart rate in $20R/80S$-verapamil was 9-times greater than that observed in $100R/0S$-verapamil ($P < 0.01$).

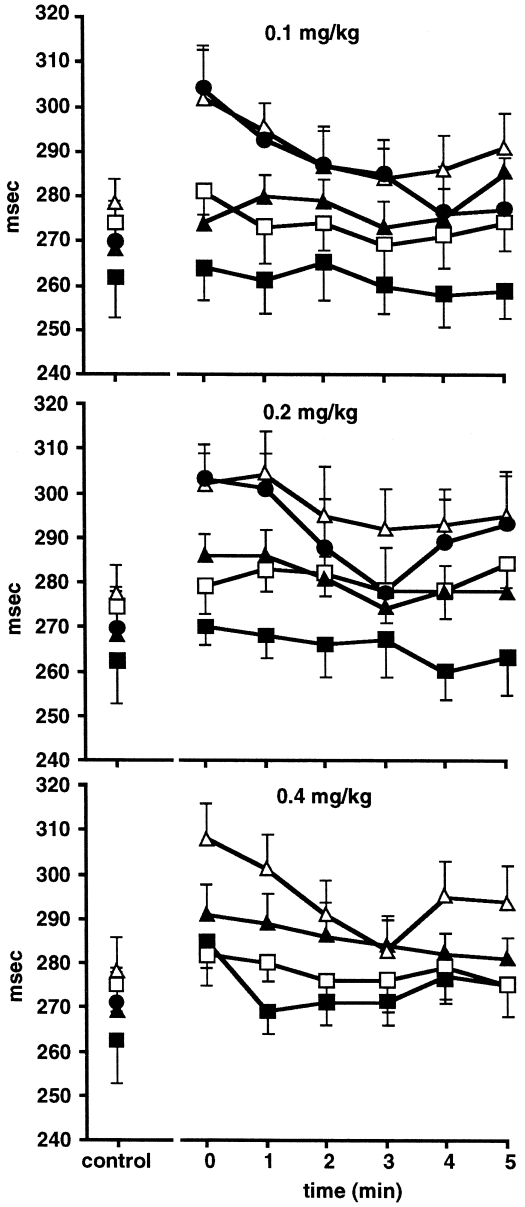

Fig. 5. The effect of different R/S verapamil ratios on QTc interval (ms). Values are expressed as mean. Vertical lines show S.E.M. 0 min means just after injection of each drugs. QTc = (QT interval in ms)/(R–R interval in s)$^{1/2}$. Symbols: (■) $100R/0S$, (□) $90R/10S$, (▲) $80R/20S$, (△) $50R/50S$ and (●) $20R/80S$ verapamil. Statistical significance symbols have been omitted for clarity.

The occurrence of second or third degree atrioventricular conduction block was observed in all animals receiving the $20R/80S$-verapamil, seven animals with $50R/50S$-verapamil, and three animals with $80R/20S$-verapamil at a dosage of 0.4 mg kg^{-1}. At the 0.2 mg kg^{-1} dose, five animals in the $20R/80S$-verapamil and three animals in $50R/50S$-verapamil groups exhibited atrioventricular conduction block. Data from those animals in which atrioventricular conduction block appeared were excluded from data analysis.

Baseline mean arterial pressure was 95–99 mmHg, and there was no significant difference between baseline values prior to administration of each mixture of verapamil (Fig. 3). After the injection of verapamil, there was an initial decrease in mean arterial pressure was reduced. The decline in mean arterial pressure occurred in a dose-dependent manner, 0.2 mg kg^{-1} of $20R/80S$-verapamil produced 3-times greater decrease than the same concentration of $100R/0S$-verapamil. Recovery of the decrease in mean arterial pressure was slower following $20R/80S$-verapamil compared to the other verapamil mixtures.

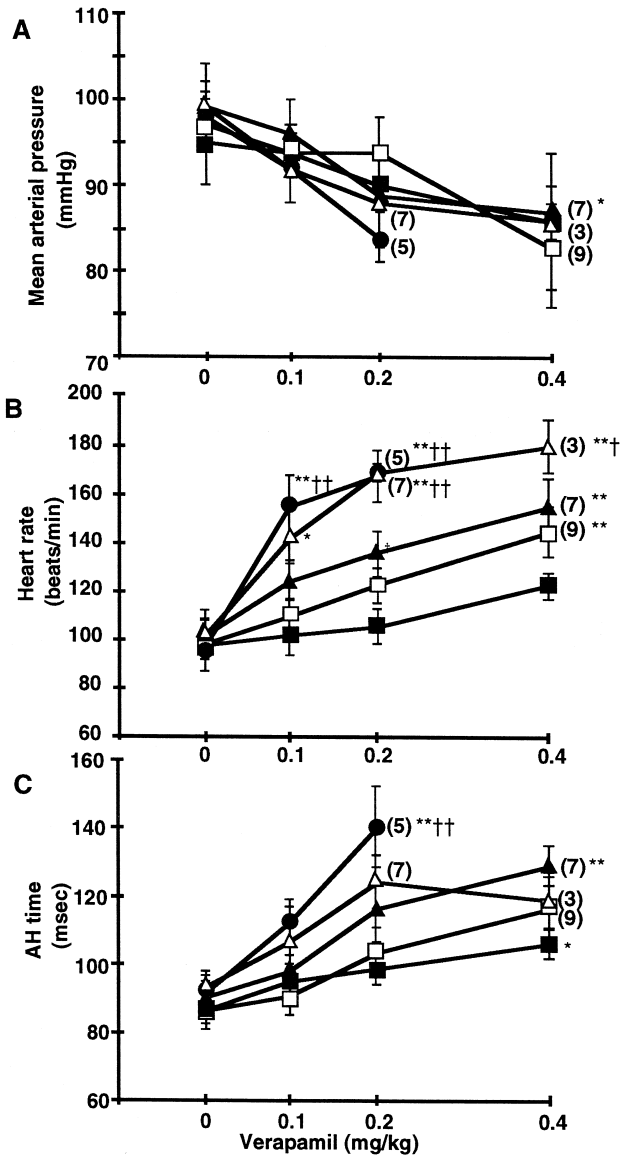

Fig. 6. Peak effect of different R/S verapamil ratios on hemodynamics parameters and atrio-ventricular time. Values are expressed as mean. Vertical lines show S.E.M. 0 min means just after injection of each drugs. Symbols: (■) $100R/0S$, (□) $90R/10S$, (▲) $80R/20S$, (△) $50R/50S$ and (●) $20R/80S$ verapamil. $*P < 0.05$, $**P < 0.01$, compared with no drug baseline within each ratio; $\dagger P < 0.05$, $\dagger\dagger P < 0.01$, compared with $100R/0S$-verapamil in the same dose; $n = 10$, except where noted by parentheses; AH time = atrio-ventricular conduction time.

3.2. Effect of verapamil isomers on conduction system

Baseline atrio-ventricular conduction times were not significantly different in each group of animals prior to drug administration (Fig. 4). The increase in atrio-ventricular time began 1–2 min after injection of 0.1 mg kg^{-1} verapamil, and the peak change in atrio-ventricular time occurred during a 3- to 5-min period following completion of the verapamil injection. The degree of change was larger in the higher *S* ratio drugs ($P < 0.05$), and the elongation of atrio-ventricular time did not return to control value in the higher *S* ratio groups. Atrio-ventricular prolongation was dose-dependent, peak change of atrio-ventricular time produced by 0.2 mg kg^{-1} of $20R/80S$-verapamil mixture was 4-times greater than the same dosage of $100R/0S$-verapamil.

Baseline His-ventricular times and QRS intervals in each group were 27.9–29.5 ms and 56–59 ms, respectively. The different *S*- and *R*-verapamil mixtures had no effect on these parameters (data not shown).

The effect of verapamil on QTc interval is shown in Fig. 5. After the 0.1 and 0.2 mg kg^{-1} doses of $20R/80S$-verapamil and $50R/50S$-verapamil, QTc interval was significantly increased compared with $100R/0S$-verapamil. However, QTc interval in each mixture did not change significantly compared to its baseline, control value, except for 0.1 mg kg^{-1} of $20R/80S$-verapamil.

Baseline ventricular effective refractory period ranged between 130–137 ms in all groups. With higher *S*-ratio verapamil the ventricular effective refractory period was shortened but these changes were not statistically significant (data not shown).

Control sinus node recovery time values at 180 and 200 beats min^{-1} were the same in each verapamil mixture. Sinus node recovery time was shortened by each ratio of verapamil paced at either 180 or 200 beats min^{-1} in a dose-dependent manner, and shortening was greater following administration of mixtures with higher *S*-isomer ratio. The shortened sinus node recovery time was only significant following $90R/10S$-verapamil and $50R/50S$-verapamil paced at 200 beats min^{-1} (data not shown).

3.3. Peak effect comparison of hemodynamics and the conduction system between each ratio group

The time-course for onset of the hemodynamic effects and electrophysiologic effects were different (Figs. 2–4). To clarify the effect of different mixtures of verapamil on each parameter, we therefore compared the effect of each mixture at the time of its peak effect using the absolute value of the response.

Fig. 6 shows the peak effects of all concentrations and all dosages on hemodynamic variables and atrio-ventricular conduction time. The effect of verapamil on mean arterial pressure showed no significant difference between mixtures (Fig. 6A). Concerning the different *R*/*S* ratio of verapamil on heart rate, the higher *S*-verapamil affected heart rate to a greater extent at a lower dosages. There was a dramatic increase in heart rate following administration of the $20R/80S$-verapamil and $50R/50S$-verapamil mixtures compared with that after $100R/0S$-verapamil (Fig. 6B). The effect of different *R*/*S* ratio verapamil on atrio-ventricular time is shown in Fig. 6C. Higher *S*-verapamil was more effective in lengthening the atrio-ventricular time.

Multiple linear regression analyses demonstrated that the interaction between mean arterial pressure and heart rate with $100R/0S$-verapamil was associated with the

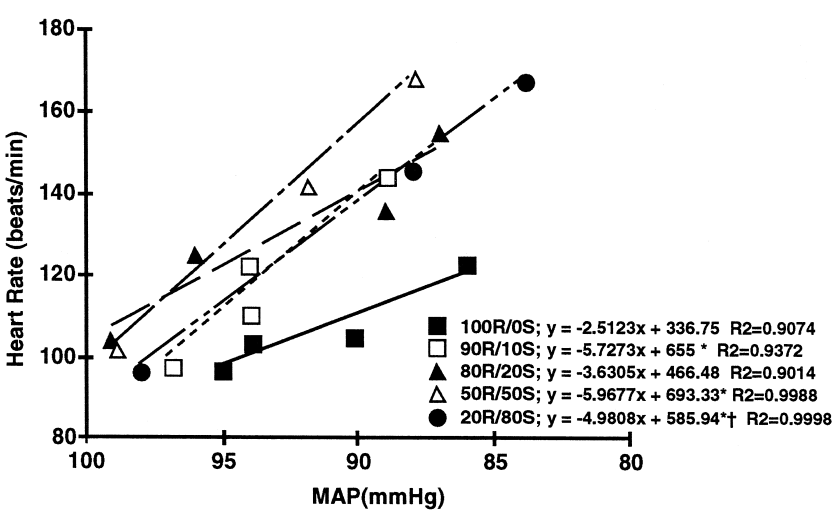

Fig. 7. Correlation between mean arterial pressure and heart rate. Symbols: (■) $100R/0S$, (□) $90R/10S$, (▲) $80R/20S$, (△) $50R/50S$ and (●) $20R/80S$ verapamil. $*\ P < 0.05$, compared with slope in $100R/0S$-verapamil; $\dagger P < 0.05$, compared with slope in $50R/50S$-verapamil; During the high $50R/50S$-verapamil and $20R/80S$-verapamil doses, atrioventricular conduction block occurred and those two regression lines, therefore, consist of only three points.

least increase in heart rate measured against a drop in blood pressure (Fig. 7). Ratios of 50*R*/50*S*-verapamil, 90*R*/10*S*-verapamil and 20*R*/80*S*-verapamil produced a greater rate of heart rate increase as opposed to a drop in mean arterial pressure than that following 100*R*/0*S*-verapamil. For the relations between atrio-ventricular time vs. either mean arterial pressure or heart rate, multiple regression analyses failed to show any significant differences in the slope factor between ratios (data not shown).

4. Discussion

Our results indicate that all *R*/*S* mixtures of verapamil produced hypotension and baroreceptor mediated reflex tachycardia and QTc prolongation, followed by increases in atrio-ventricular interval. A higher *R*-verapamil produced a smaller increase in the heart rate for a given drop in mean arterial pressure, while higher *S*-verapamil produced a greater increase in heart rate and atrio-ventricular time for a given drop in blood pressure and a greater incidence of atrioventricular block. Recovery from changes in heart rate, mean arterial pressure and atrio-ventricular conduction time were delayed following the higher *S*-verapamil mixtures when compared to higher *R*-verapamil.

Almost all verapamil effects are attributable to its Ca channel blocking activity (Kaumann and Serur, 1975; Gloor and Urthaler, 1983). Satoh et al. have reported that in anesthetized dog, *S*-verapamil was only 1.5–3-times as potent as *R*-verapamil in producing the hemodynamic effects, though it was about 5–10-times more potent in producing a negative chronotropic and dromotropic effect compared to *R*-verapamil (Satoh et al., 1979, 1980). In our present study, using a conscious dog model, there was a greater change in heart rate with a higher *S*-isomer ratio mixture of verapamil. It has been reported that the direct inhibitory action of verapamil on sinus node automaticity is masked by baroreflex tachycardia and that anesthesia masks this response (Vasquez et al., 1984). Therefore, we used conscious, unsedated dogs, a situation believed to provide a better model to study drugs effects on electrical activity, ventricular function, baroreceptor activation, and systemic circulation (Seagard et al., 1985; Pagel et al., 1998). The heart rate increase observed following all *R*/*S* verapamil mixtures just after infusion is attributable to baroreceptor activation secondary to peripheral vasodilation. These heart rate changes were observed in previous reports using racemic verapamil in conscious state studies (Walsh et al., 1981; Millard et al., 1982; Nakaya et al., 1983; Vasquez et al., 1984; Schmieder et al., 1987).

Class III antiarrhythmic drugs increase QTc and the ventricular effective refractory period (Olsson, 1989). During the higher *S*-verapamil infusion, an increase in QTc interval was observed from the time after injection of each ratio of verapamil, but the ventricular effective refractory period did not change. Verapamil has been reported to block the potassium current in different cells using the voltage-clamp technique (Jacobs and DeCoursey, 1990; Galietta et al., 1991). Repolarization of ventricular myocardium is dependent mainly on various potassium currents (Opie, 1991). Therefore, it is reasonable to hypothesize that the blockade of potassium currents caused by verapamil is responsible for the longer depolarization phase of the action potential leading to an increase in QTc interval.

Linear regression analysis of the peak effects on hemodynamics and atrioventricular conduction system failed to indicate any significant difference in the slope factor between each ratio. These results are difficult to interpret because the peak effects on hemodynamics and atrioventricular time occurred at different times with respect to each drug infusion. Furthermore, a complete atrioventricular block in all animals at the high 20*R*/80*S*-verapamil dose prevented subsequent calculation of conduction times.

The different enantiomer ratios of verapamil do not have the same degree of effects on hemodynamics and atrioventricular conduction. The higher *R*-verapamil had a smaller effect on reflex tachycardia and atrioventricular conduction block while preserving mean arterial pressure as compared with those of the higher *S*-mixture. The increase in potency of Ca^{2+} channel antagonist activity caused by high extracellular potassium have been reported to be different between *R* and *S* isomer of verapamil (Curtis and Walker, 1986; Curtis, 1990). The Ca^{2+} channel antagonist activity of *R*-enantiomer is potentiated by high potassium more than that of *S*-enantiomer. This may explain the variation in differences between *R* and *S* isomer of verapamil on heart rate, mean arterial pressure and atrio-ventricular time.

5. Conclusion

The peripheral and cardiac electrophysiologic properties of various nonracemic verapamil mixtures are mainly attributable to the level of *S*-isomer. Due to possible species differences, our results must be extrapolated cautiously to the management of patients with nonracemic verapamil mixtures. If applicable to humans, our findings suggest that there would be a greater effect of the *S*-enantiomer on the reflex increases in the heart rate and the atrioventricular block. Furthermore, it is likely that the *R*-enantiomer would have only limited effects on the heart rate increases and the atrio-ventricular interval while retaining systemic vasodilating properties.

Acknowledgements

The authors thank G.D. Searle, St. Louis, MO for their generous support and a supply of *R*- and *S*-verapamil.

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