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Cardiac vagal effects of rilmenidine in the dog: comparison with clonidine

M. Boucher[1,2], M. Dubar[3], E. Chapuy[1] & C. Chassaing[1]

[1]INSERM U.195, Faculty of Medicine, F-63001 Clermont-Ferrand Cedex 1, France; [2]Department of Physiology, Faculty of Pharmacy, F-63001 Clermont-Ferrand Cedex 1, France; and [3]IRI SERVIER, F-92415 Courbevoie Cedex, France

Correspondence: Prof. M. Boucher at Department of Physiology, Faculty of Pharmacy, F- 63001 Clermont-Ferrand Cedex 1, France

1 The cardiac vagal effects of rilmenidine (5 μg kg^{-1} min^{-1}) and clonidine (0.5 μg kg^{-1} min^{-1}) were studied in chloralose anaesthetized dogs.

2 Rilmenidine and clonidine progressively reduced the vagal stimulation-induced bradycardia. As indicated by the ED_{70}, rilmenidine was about 23 times less potent than clonidine in this respect. Concomitantly, both drugs dose-relatedly decreased heart rate and mean blood pressure with potency ratios of rilmenidine to clonidine of about 1:23 and 1:12, respectively.

3 Importantly, the heart rate values observed under vagal stimulation during drug infusion never exceeded the values under basal vagal stimulation, and with both drugs large interindividual variations occurred under vagal stimulation.

4 These results show that the vagal bradycardia inhibition produced by rilmenidine and clonidine results from their true bradycardic effects and not from actual cardiac vagolytic properties.

Introduction

Rilmenidine, (2 -(dicyclopropylmethyl)amino-2-oxazoline), is a centrally acting antihypertensive agent known to bind more selectively to imidazoline-preferring receptors than to α_2-adrenoceptors (Bricca *et al*., 1989; Gomez, Ernsberger, Feinland & Reis, 1991; Bricca *et al*., 1994) and only weakly to α_1-adrenoceptors (Van Zwieten, 1988; Verbeuren, Dinh Xuan, Koenig-Bérard & Vitou, 1990). Its blood pressure lowering effects, demonstrated in both animals and humans (Beau *et al*., 1988; Koenig-Bérard *et al*., 1988; Feldman *et al*., 1990; Gomez *et al*., 1991; Laurent & Safar, 1992), result mainly from an activation of the specific imidazoline binding sites located in the rostral ventrolateral medulla (Gomez *et al*., 1991; Dontenwill *et al*., 1994; Sannajust & Head, 1994). Rilmenidine and clonidine, the well-known centrally acting antihypertensive α_2-adrenoceptor agonist, have been shown to produce an initial short-lasting atrial bradycardia in conscious dogs with chronic atrioventricular block. This effect has been demonstrated to result from both an increase in cardiac cholinergic activity and a decrease in cardiac sympathetic tone for rilmenidine, and mainly from an enhancement of cardiac cholinergic activity for clonidine (Boucher, Dubar, Chapuy & Chassaing, 1996), in agreement with literature data (Hoefke & Kobinger, 1966; Schmitt & Fénard, 1970; Laubie *et al*., 1985). In addition, clonidine has already been shown to interfere with the vagal stimulation-induced bradycardia (Duchêne-Marullaz, Combre, Lapalus, Boucher & Lavarenne, 1971). Accordingly, the present study aimed to investigate and quantify the effects of rilmenidine on the bradycardia induced by vagal stimulation, in comparison with clonidine.

Methods

We studied seven mongrel dogs of either sex, weighing between 10 and 14 kg. They were housed in individual cages in a large colony room with food and water continuously available in their home cages. The study conformed to the NIH *Guidelines for Care and Use of Laboratory Animals*.

Surgical preparation and instrumentation

The seven dogs were anaesthetized with 100 mg kg^{-1} chloralose (i.e. 12.5 ml kg^{-1} of 0.8% α-chloralose in lukewarm 0.9% wt/vol NaCl physiological saline). They were ventilated via a tracheal tube with a Braun respirator. Body temperature was maintained at about 37°C with a thermostatically controlled heating table. Bipolar silver electrodes were placed at random on either the right or the left vagus nerve. Two microcatheters were fitted before each test, one in the saphenous artery to record blood pressure, and the other in the cephalic vein to allow drug administration.

Measurements

Electrocardiographic and blood pressure monitoring were carried out with a Beckman Dynograph

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instrument and a Statham P23 Db transducer. Nerve stimulation was applied in 2-ms rectangular pulses at 50 Hz in 15-s trains from a Janssen stimulator. Stimulation intensity was chosen for each dog so as to obtain a lowering of control heart rate (= vagal bradycardia) of about 50%. In all the experiments, the intensity was always between 0.3 and 3.0 mA.

Protocol

Each drug tested was administered to each dog in random order by continuous intravenous infusion (Braun perfusor, 0.5 ml min^{-1}, 120 min), and at least 15 days elapsed between successive tests performed on the same dog to allow it to recover from anaesthesia. Rilmenidine (as the dihydrogen phosphate) was administered at 5 μg kg^{-1} min^{-1}, a sufficiently high dose to produce significant chronotropic effects throughout the infusion period. Clonidine (as the hydrochloride) was infused at 0.5 μg kg^{-1} min^{-1}, a dose chosen to induce almost identical chronotropic effects. A control group was also set up, composed of the same seven dogs given 0.5 ml min^{-1} physiological saline. Vagal stimulation runs were performed before and repeatedly throughout the 120-min infusion period and heart rate, vagal bradycardia and mean blood pressure were measured concurrently.

Drugs

Rilmenidine dihydrogen phosphate was supplied by IRI Servier (Courbevoie, France) and clonidine HCl by Boehringer Ingelheim Laboratories (Rueil–Malmaison, France).

Statistical analysis

Results are arithmetic means ± SEM. The effect of each drug on the various parameters was established using analysis of variance in complete blocks without repeated measures, followed, when the *F*-value was significant, by multiple comparisons using Dunnett's test. The effects of the two drugs on the same parameter were compared using either effective dose values expressed in terms of base, i.e. ED_{40} and ED_{70}, calculated from the corresponding regression lines when possible or areas under the curves obtained by plotting the chosen parameter against time. ED_{40}, the dose which produced a 40 beats min^{-1} decrease in heart rate, was calculated for each dog from the corresponding regression line computed by plotting the decrease in heart rate against time (and thus dose) and averaged thereafter. ED_{70}, the dose producing a 70% inhibition of vagal bradycardia, was calculated as above by plotting the percent inhibition of basal vagal bradycardia against time (and thus dose).

Results

Control series

Basal heart rate, vagal bradycardia and mean blood pressure for the seven dogs used were 108 ± 6 beats min^{-1}, 55 ± 5 beats min^{-1}, and 148 ± 8 mmHg, respectively. These values were not significantly modified during the 120-min infusion of physiological saline.

Effects of rilmenidine and clonidine

Heart rate. Rilmenidine and clonidine dose-relatedly decreased heart rate from the third minute onward ($P < 0.001$) (Figs 1 and 3) and the first minute ($P < 0.01$) (Figs 2 and 3) of infusion. From the basal values of 107 ± 9 and 113 ± 5 beats min^{-1}, heart rate reached 46 ± 6 and 38 ± 5 beats min^{-1} at the 105th and 75th minute of the observation period, respectively. Assessed by the ED_{40}, the doses producing a 40 beats min^{-1} decrease in heart rate, which were 139.2 ± 33.0 μg kg^{-1} rilmenidine base and 6.0 ± 1.8 μg kg^{-1} clonidine base, the potency ratio of rilmenidine to clonidine was about 1:23.

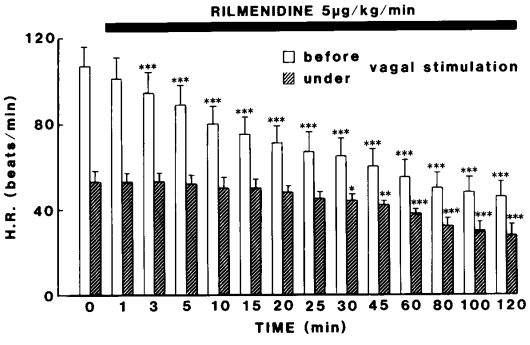

Figure 1 Changes in heart rate (HR) before and under vagal stimulation in chloralose anaesthetized dogs infused with 5 μg kg^{-1} min^{-1} rilmenidine. Values are means for seven dogs. Vertical lines show SEM. Significance: $^{*}P < 0.05$, $^{**}P < 0.01$, and $^{***}P < 0.001$ in comparison with time 0 values.

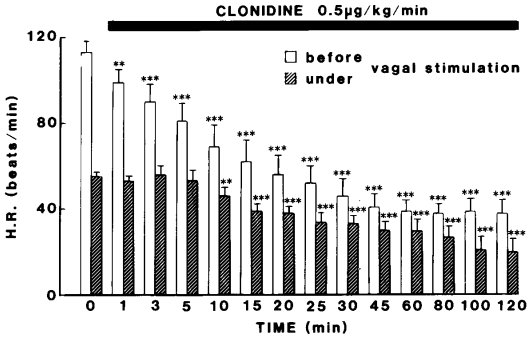

Figure 2 Changes in heart rate (HR) before and under vagal stimulation in chloralose anaesthetized dogs infused with 0.5 μg kg^{-1} min^{-1} clonidine. Values are means for seven dogs. Vertical lines show SEM. Significance: $^{**}P < 0.01$ and $^{***}P < 0.001$ in comparison with time 0 values.

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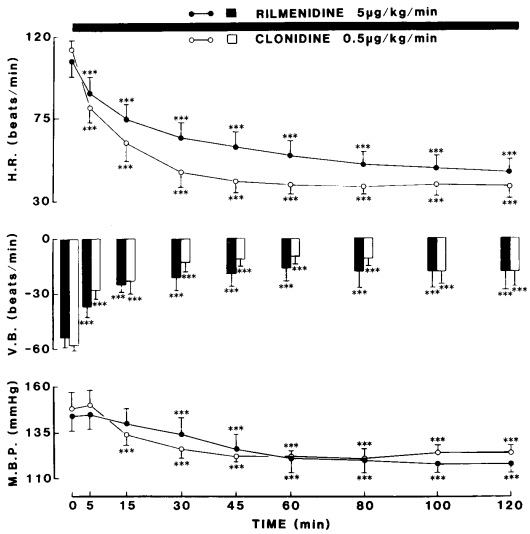

Figure 3 Changes in heart rate (HR), vagal bradycardia (VB), and mean blood pressure (MBP) in chloralose anaesthetized dogs infused with 5 µg kg^{-1} min^{-1} rilmenidine and 0.5 µg kg^{-1} min^{-1} clonidine. Control saline data have been omitted. Values are means for seven dogs. Vertical lines show SEM. Significance: *** $P < 0.001$ in comparison with time 0 values.

Vagal bradycardia. Basal vagal bradycardia was 54 ± 5 and 58 ± 3 beats min^{-1} in the rilmenidine and clonidine series. Both drugs progressively reduced vagal bradycardia. The effect of rilmenidine appeared from the third minute onward ($P < 0.01$) and reached $75 \pm 10\%$ inhibition of vagal bradycardia at the 70th minute of infusion (Figs 1 and 3). That of clonidine appeared from the first minute onward ($P < 0.05$) and reached $84 \pm 6\%$ inhibition of vagal bradycardia at the 75th minute of infusion (Figs 2 and 3). As a 100% inhibition of vagal bradycardia was never obtained, the doses producing a 70% inhibition of basal vagal bradycardia (ED_{70}) were calculated, indicating a potency ratio of the drugs of about 1:23. It is noteworthy that (i) heart rate observed under vagal stimulation during infusion never exceeded heart rate under basal vagal stimulation (Figs 1 and 2), and (ii) with both drugs large interindividual variations occurred, i.e. at the 120th minute, vagal stimulation produced a cardiac arrest in one (rilmenidine) and two dogs (clonidine), no bradycardic effect in five (rilmenidine) and three dogs (clonidine), and an intermediate effect in one (rilmenidine) and two dogs (clonidine).

Mean blood pressure. Rilmenidine and clonidine dose-relatedly lowered mean blood pressure from the 25th minute onward ($P < 0.01$) and the 15th minute ($P < 0.001$) (Fig. 3) of infusion. From the basal values of 144 ± 8 and 148 ± 9 mmHg, mean blood pressure reached its lowest values 118 ± 5 and 121 ± 4 mmHg at the 100th and 65th minute of the observation period, respectively. Assessed from the respective areas under the curves, the potency ratio of the drugs was about 1:12.

Discussion

In dogs anaesthetized with chloralose, rilmenidine induced a decrease in heart rate, the degree of which was related to the dose administered. This effect agrees with previous studies showing a slowing of heart rate after i.v. rilmenidine in animals (Laubie *et al*., 1985; Koenig-Bérard *et al*., 1988; Boucher, Dubar, Chassaing, Vivet & Duchêne-Marullaz, 1994; Sannajust & Head, 1994). Clonidine also decreased heart rate dose-relatedly, in full agreement with the literature data (Hoefke & Kobinger, 1966; Boissier, Giudicelli, Fichelle, Schmitt & Schmitt, 1968; Duchêne-Marullaz, Lavarenne, Lapalus, Boucher & Mongheal, 1974). Our study shows rilmenidine to be about 23 times less potent than clonidine, compared to 23–24 and 21 times as reported in previous work on sinus heart rate and ventricular rate in conscious dogs (Boucher *et al*., 1994, 1996). Rilmenidine lowered mean blood pressure with a potency 12 times less than clonidine, compared with 17 and 15 times in those two studies. This hypotensive effect has already been well-documented in different species and in various experimental conditions (Beau *et al*., 1988; Koenig-Bérard *et al*., 1988; Fiorentini, Guillet & Guazzi, 1989; Gomez *et al*., 1991).

Concomitantly, rilmenidine produced a reduction of the bradycardia induced by vagal stimulation, which was related to the dose administered. The effect of clonidine showed the same pattern. To interprete these results, which suggest cardiac vagolytic properties for both drugs, two points need to be stressed. First, the potency ratio of the drugs was about 1:23, i.e. exactly the same value as for the bradycardic effects. Second, the heart rate values observed under vagal stimulation during infusion of the drugs never exceeded the values under basal vagal stimulation. These facts suggest that the reduction of the vagal bradycardia produced by both drugs is in fact merely the result of their true bradycardic effects and not of actual vagolytic properties of these drugs. In addition, if such properties existed, then at some time, under some or other experimental conditions, an increase in heart rate would surely have been reported, which has never been the case. Another observation also needs to be stressed: large interindividual variations occurred after drug infusion. Thus, when the results are considered dog by dog, the vagal stimulation produced either no bradycardic effects at all in five and three dogs, which suggests apparent complete vagolytic effects, or in contrast a cardiac arrest in one and two dogs, which suggests apparent strong vagomimetic effects. However, in the second instance, the very low basal heart rate values counteracted these observations, leading in fact to a reduction of the vagal bradycardia. These data recall those previously reported with clonidine at doses ⩾

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66 μg kg^{-1} (Duchêne-Marullaz *et al.*, 1971), although no satisfactory explanation can be offered for these interindividual variations.

Overall, our results show that in the chloralose-anaesthetized dog rilmenidine and clonidine produce a reduction of the vagal stimulation-induced bradycardia, rilmenidine being 23 times less potent than clonidine. Both drugs also exert very similar bradycardic and hypotensive effects, rilmenidine being in this respect 23 and 12 times less potent than clonidine. The vagal bradycardia inhibition results from the true bradycardic effects of both drugs and not from actual cardiac vagolytic properties.

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*(Received 4 October 1996
Revised 5 December 1996
Accepted 9 January 1997)*