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ACEBUTOLOL, METOPROLOL AND PROPRANOLOL IN CONSCIOUS DOGS WITH CHRONIC HEART-BLOCK: CHRONOTROPIC EFFECTS AND RELATION BETWEEN DEPRESSION OF VENTRICULAR ACTIVITY AND β-ADRENOCEPTOR BLOCKING POTENCY

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1 Atrial and ventricular chronotropic effects of acebutolol, metoprolol and propranolol were studied in conscious dogs with chronic heart-block. Ventricular β-adrenoceptor blocking activity was assessed for the three drugs against isoprenaline (1 μg/kg) under the same experimental conditions.

2 Acebutolol and metoprolol significantly increased atrial rate. The effect was proportional to the dose for acebutolol, independent for metoprolol. Propranolol had no significant effect on atrial rate. All three drugs significantly lowered ventricular rate in proportion to the dose.

3 Ventricular β-blocking potencies of metoprolol and acebutolol were respectively 2 and 3 times weaker than that of propranolol as indicated by ED_{50} values.

4 The ventricular depressor effect observed was proportional to the degree of ventricular β-blockade present, although this may not be the only factor involved.

Introduction

In the conscious dog with heart-block, propranolol depresses ventricular rate (Ruttenberg, Hurwitz, Blesa & Pappelbaum, 1970; Robinson, Farr & Grupp, 1973; Duchêne-Marullaz, Combre, Lavarenne, Lapalus & Schaff, 1975; Reynolds & Di Salvo, 1978). Depressed His bundle automaticity has also been observed under similar experimental conditions for alprenolol and practolol (Duchêne-Marullaz *et al.*, 1975) and for sotalol and practolol (Reynolds & Di Salvo, 1978). Pindolol appears to cause no significant ventricular depression (Duchêne-Marullaz *et al.*, 1975).

The present work compares the effects of acebutolol, metoprolol and propranolol, in a canine model in which the bundle of His had been crushed, with particular reference to the relationship between ventricular depressor activity of these drugs and their ability to block ventricular β-adrenoceptors.

Methods

Ten mongrel dogs of either sex weighing between 10 and 21 kg were used. Atrioventricular block had been produced in these animals, between 3 months to 6 years earlier, by crushing the bundle of His with forceps introduced through the right atrium. Cardiac electrical activity was recorded from the three standard leads. The animals, which were already used to the experimental conditions, were lightly restrained and placed on a table. A catheter was inserted into a cephalic vein before each test to enable drugs to be administered without spurious effects due to injection stress.

Drugs were administered in the following doses: acebutolol (hydrochloride): 0.3125, 0.625, 1.25, 2.5 and 5 mg/kg; metoprolol (hydrochloride): 0.15625, 0.3125 and 0.625 mg/kg; propranolol (hydrochloride): 0.07812, 0.15625 and 0.3125 mg/kg.

Chronotropic effects

Each dose of each of the three drugs was administered intravenously to a group of eight animals selected at random. A control group of eight animals was given saline (0.9% w/v NaCl solution) 0.5 ml/kg. Injections took 30 s and an interval of 3 to 4 days always elapsed between successive injections performed on the same animal. Atrial and ventricular rates were measured for a 30 s period, at the following times: 15, 10 and 5 min before injection, 1, 3 and 5 min after the injection and thereafter every 5 min for 1 h.

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Results are expressed in terms of (a) mean rates for each 30 s measuring period, and (b) mean maximal variations in rate. These were calculated from individual variations measured when mean rates were either minimal or maximal during the first 30 min following injection. Statistical analysis of the results was performed by Student's t test for paired series. The degree of dose-response proportionality was assessed for both atrial and ventricular rate variations for each drug in terms of significance of correlation coefficients.

Ventricular β-blocking potencies and effects on arterial pressure

Four representative animals were given two injections of isoprenaline hydrochloride (1 μg/kg). The first injection was given 15 min before, and the second 15 min after the administration of each of the three drugs. Ventricular rates were measured before each injection of isoprenaline and 0.5, 1 and 2 min afterwards. The degree of isoprenaline-induced ventricular tachycardia was compared before and after an administration of each of the three drugs, and their β-blocking potency assessed in terms of percentage inhibition of this isoprenaline-indexed tachycardia. Regression lines relating percentage inhibition of tachycardia to dose were computed for each drug and effective dose values (ED_{50}) calculated.

The effects on arterial pressure of 1 μg/kg of isoprenaline before and after the administration of 2.5 mg/kg of acebutolol, 0.625 mg/kg of metoprolol or 0.3125 mg/kg of propranolol were also investigated. A catheter was inserted into the right saphenous artery under local anaesthesia and blood-pressure monitored with a Statham P23 Db transducer connected to a Cardiopan III T electrocardiograph via a pressure module.

Results

Effects on atrial and ventricular rates

In animals with chronic heart-block, atrial and ventricular rates were between 31 and 120 beats/min (mean ± s.e. = 72 ± 3 beats/min; $n = 96$) and between 20 and 52 beats/min (mean ± s.e. = 37 ± 1 beats/min; $n = 96$) respectively. These rates were unaffected for up to 1 h by the administration of 0.5 ml/kg of physiological saline (Figure 1). The atrial rate at different times after saline administration remained between 56 ± 6 and 65 ± 5 beats/min (from the pre-injection control value of 63 ± 5 beats/min) and ventricular rate stayed between 37 ± 3 and 39 ± 4 beats/min (from a control value of 38 ± 3 beats/min).

Effect of acebutolol. Acebutolol significantly increased atrial rate (Figures 1 and 4) and this effect was dose-related ($P < 0.01$). Atrial tachycardia was evident within the first min and declined towards control over the 1 h period of observation. In contrast, acebutolol significantly lowered ventricular rate ($P < 0.01$), e.g. by 18% with a dose of 0.312 mg/kg and by 41% at 5 mg/kg (Figures 1 and 4). This effect was dose-related ($P < 0.05$). The ventricular bradycardia always appeared within the first min of injection and persisted throughout the subsequent 1 h of observation.

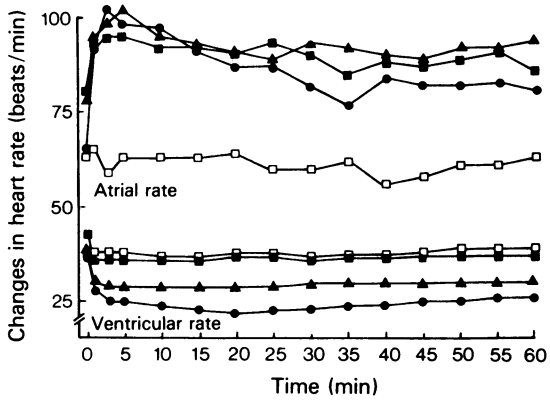

Figure 1 Changes in atrial and ventricular rates in conscious dogs with chronic heart-block after injection of acebutolol: 0.312 mg/kg (■); 1.25 mg/kg (▲); 5 mg/kg (●); and saline (□). Values are means for groups of 8 dogs. For reasons of clarity standard errors have been omitted in this figure and Figures 2 and 3.

Effect of metoprolol. Although metoprolol also significantly increased atrial rate ($P < 0.05$; Figures 2 and 4) no dose-response relationship could be demonstrated. However, metoprolol did significantly reduce ventricular rate ($P < 0.001$; Figures 2 and 4), an effect which was dose-related ($P < 0.02$). As with acebutolol, ventricular bradycardia appeared immediately after the injection and persisted throughout the 1 h observation period.

Effect of propranolol. Propranolol raised the atrial rate only slightly, and non-significantly, at all doses (Figures 3 and 4), but caused significant ventricular bradycardia ($P < 0.01$; Figures 3 and 4). As with acebutolol and metoprolol, ventricular bradycardia was related to dose ($P < 0.05$), appeared immediately after injection and lasted throughout the 1 h observation period.

Ventricular β-adrenoceptor blocking potencies of acebutolol, metoprolol and propranolol and their effects on arterial pressure

For each of the three drugs, a relationship between dose administered and percentage inhibition of ven-

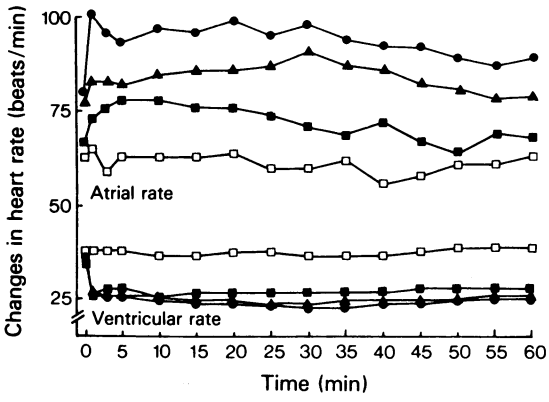

Figure 2 Changes in atrial and ventricular rate in conscious dogs with chronic heart-block after injection of metoprolol: 0.156 mg/kg (■); 0.312 mg/kg (▲); 0.625 mg/kg (●); and saline (□). Values are means for groups of 8 dogs.

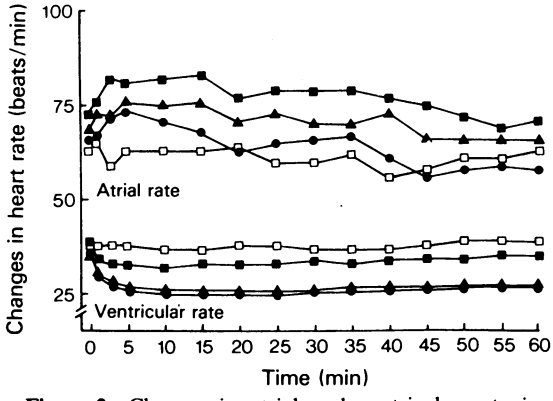

Figure 3 Changes in atrial and ventricular rate in conscious dogs with chronic heart-block after injection of propranolol: 0.078 mg/kg (■); 0.156 mg/kg (▲); 0.312 mg/kg (●); and saline (□). Values are means for groups of 8 dogs.

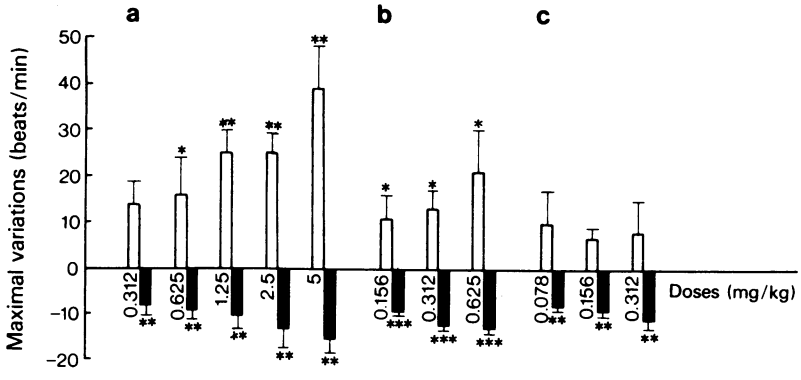

Figure 4 Comparative effects of acebutolol (a), metoprolol (b) and propranolol (c) on atrial (open columns) and ventricular (solid columns) rates, in the conscious dog with chronic heart-block. The figure shows the maximal variations occurring during the first 30 min after the injections. Values are means for groups of 8 dogs; vertical lines show s.e. mean. *$0.01 < P \leq 0.05$; **$0.001 < P \leq 0.01$; ***$P \leq 0.001$.

tricular tachycardia induced by isoprenaline (1 μg/kg) could be demonstrated (correlation coefficients of 0.84, 0.88 and 0.74 for acebutolol, metoprolol and propranolol respectively). ED_{50} values calculated from the regression lines obtained were 643 ± 168, 430 ± 39 and 217 ± 35 μg/kg for acebutolol, metoprolol and propranolol respectively.

All three drugs had a comparable but weak hypotensive effect (5 to 10 mmHg) at the doses used (2.5, 0.625 and 0.312 mg/kg for acebutolol, metoprolol and propranolol respectively). Acebutolol and metoprolol did not modify the hypotensive action of isoprenaline, whereas propranolol almost entirely suppressed it (Figure 5).

Discussion

The evaluation of the β_1-adrenoceptor blocking potency of acebutolol and metoprolol relative to propranolol has yielded results which vary widely depending on the experimental conditions. Thus *in vitro*, acebutolol has a pA_2 of 7 as compared with 8.4 for propranolol (Baird & Linnel, 1972; Spach, Miesch & Schwartz, 1975). In the anaesthetized animal, the β_1-blocking activity of acebutolol has been found to be between 3 and 20% of that of propranolol (Cuthbert & Owusu-Ankomah, 1971; Baird & Linnel, 1972; Basil, Jordan, Loveless & Maxwell, 1973), whereas in the conscious dog the β_1-blocking activity ratio is 7%

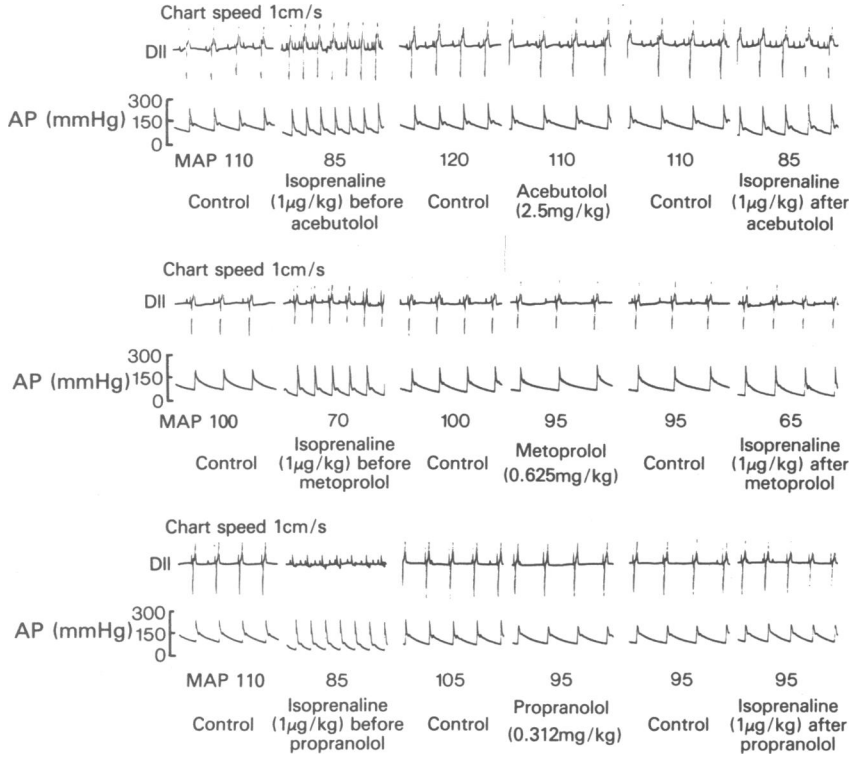

Figure 5 Effects of isoprenaline before and after the three drugs acebutolol, metoprolol and propranolol, on arterial pressure (AP), in the conscious dog with chronic heart-block. The mean arterial pressure (MAP) was determined by integration.

(Basil *et al.*, 1973). Our experiments indicate a β_1-blocking activity ratio of 33%, i.e. somewhat higher than those previously reported.

As far as metoprolol is concerned, K_B values *in vitro* indicate a β_1-blocking activity 14% of that of propranolol (Johansson, 1973). *In vivo*, evaluations are widely divergent, ranging from 20 to 200% relative to propranolol (Åblad, Carlsson & Ek, 1973; Åblad, Borg, Carlsson, Ek, Johnsson, Malmfors & Regårdh, 1975; Johnsson, 1975; Johnsson, Nyberg & Sölvell, 1975). Our results indicate an activity 50% that of propranolol, which lies within the range of values previously reported.

The method used by us to evaluate β_1-blocking activity does not claim to do any more than supplement the large number of techniques already employed. To begin with, there is no reason to suppose that the β_1-blocking activity of a particular drug is the same in both atrium and ventricle. In addition, the values obtained here take into account the cardioselectivity exhibited by acebutolol and metoprolol (Basil *et al.*, 1973; Åblad *et al.*, 1973; Harms and Spoelstra, 1978). This is clearly demonstrated in our experiments since neither drug modified the hypotensive action of isoprenaline, whereas propranolol suppressed it. This hypotension may reflexly trigger the cardioaccelerator innervation which still acts on the ventricle in heart-block (Vassalle, Levine & Stuckey, 1968). Moreover, cardioselective drugs, and particularly metoprolol, inhibit the effects of cardiac sympathetic nerve stimulation more readily than they do those of isoprenaline; with propranolol the inhibition is of the same order of magnitude for both types of stimulus (Åblad, Brändström, Ek & Sjölander, 1971; Åblad *et al.*, 1973). It is thus likely that in our tests the β_1-blocking potencies of acebutolol and metoprolol have been somewhat underestimated relative to propranolol.

Acebutolol caused significant atrial tachycardia which reached 39 ± 9 beats/min at the highest dose used, (5 mg/kg). It is likely that the intrinsic sympathomimetic activity of the drug is involved (Khambatta, 1972; Basil *et al.*, 1973) although it would seem to be too weak to be solely responsible for such a marked elevation in heart-rate. A more likely explanation would be a reduction of vagal tone concomitant with hypotension. Several months after the creation of the

heart-block, atrial cardiomoderator tone is effectively strong; functional denervation of the heart with atropine and propranolol raises the atrial rate to 150 ± 6 beats/min (Duchêne-Marullaz, Combre and Chassaing, 1974) whereas in the present experiments the mean atrial rate was 72 ± 3 beats/min. Metoprolol, which possesses no intrinsic sympathomimetic activity (Åblad *et al.*, 1973) also raised atrial rate, though less markedly than acebutolol. As previously reported (Duchêne-Marullaz *et al.*, 1975; Reynolds & Di Salvo, 1978) propranolol, though it lowered arterial pressure to about the same extent as acebutolol and metoprolol, did not significantly alter atrial rate.

All three drugs, at all doses administered, caused a significant decrease in ventricular rate. Now, in the conscious dog in sinus rhythm, provided the animals are accustomed to the experimental procedures, as in the present study, the administration of propranolol (up to 2 mg/kg) and of acebutolol (up to 5 mg/kg) does not affect heart-rate (Duchêne-Marullaz, Schaff, Delort & Billaud, 1967; Bergamaschi, Shanks, Caravaggi & Mandelli, 1971; Kantelip, Gueorguiev & Duchêne-Marullaz, unpublished). In this study, the ventricular bradycardia observed was considerable (18 to 41% of the spontaneous ventricular rate for acebutolol, 25 to 37% for metoprolol and 20 to 30% for propranolol). This ventricular depressor effect is dose-related and parallels the degree of the β_1-blocking activities of the drugs. These results agree with those of Reynolds & Di Salvo (1978) with propranolol. It may thus be that the particular haemodynamic conditions brought about by heart-block, trigger the cardioaccelerator system which to some extent corrects an excessive ventricular bradycardia. Such a corrective action would be suppressed to a degree proportional to the β_1-blocking activity of the drug administered. However, although we cannot at this stage offer any other explanation, the above mechanism may not be the only one involved. Thus comparable degrees of ventricular bradycardia (9 beats/min) were obtained with all three drugs with widely differing β_1-blocking activities (acebutolol 50 ± 3%; metoprolol 27 ± 5%; propranolol 41 ± 5%). This indicates that metoprolol has a higher ventricular depressor activity for a given β_1-blocking potency than the other two drugs. This difference cannot be explained by any of the known properties of these drugs. At the doses used, membrane stabilizing activity does not seem to be involved, since with propranolol this effect measured on ventricular muscle and Purkinje fibres appears significant only from the dose of 3 mg/l (Davis & Temte, 1968). Moreover, metoprolol is practically devoid of such activity (Åblad *et al.*, 1973) and acebutolol has only 20% of that of propranolol (Basil *et al.*, 1973).

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