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# Studies on the stereoisomers of β-adrenoceptor antagonists in conscious A-V blocked dogs

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**1** Atrial and ventricular chronotropic effects of the individual stereoisomers of propranolol, pindolol, metoprolol and penbutolol were studied in conscious dogs with chronic atrio-ventricular (A-V) block. Ventricular β-adrenoceptor blocking activity was assessed for all drugs against isoprenaline under the same experimental conditions.

**2** At low doses, the stereoisomers of propranolol and penbutolol decreased atrial rate, whereas those of pindolol and metoprolol produced an increase. At higher doses, all drugs increased atrial rate. All drugs decreased ventricular rate dose-dependently except (+)-pindolol.

**3** Relative ventricular β-blocking potencies of the (−)-isomers of propranolol, pindolol, metoprolol and penbutolol were respectively 38, 21, >43 and 31 times higher than those of their corresponding (+)-isomers. In addition, β-blocking potencies of (−)- and (+)-pindolol were respectively 60 and 120 times higher, those of (−)- and (+)-penbutolol 7 and 8 times higher and those of (−)- and (+)-metoprolol 4 and >4 times weaker than those of (−)- and (+)-propranolol.

**4** At comparable levels of ventricular β-adrenoceptor blockade, (−)-pindolol and (−)-metoprolol were more potent in producing ventricular bradycardia than their respective (+)-isomers, whereas (−)- and (+)-propranolol and (−)- and (+)-penbutolol were equiactive. In addition, regardless of which isomer was being studied, the order of ventricular bradycardiac potencies, at comparable levels of β-adrenoceptor blockade, was metoprolol > propranolol > penbutolol > pindolol.

**5** These results show that antagonism of β-adrenoceptors in the ventricle is at least partly responsible for the ventricular bradycardiac effect produced by these drugs, but also that some other factor, apparently distinct from the membrane stabilizing activity, is involved, suggesting the existence of some other as yet unknown pharmacological property of the β-adrenoceptor blocking drugs, especially evident in metoprolol. Finally, these results demonstrate that the intrinsic sympathomimetic activity exhibited by some of these drugs attenuate their bradycardiac effect.

## Introduction

In previous studies in the conscious dog with chronic atrio-ventricular (A-V) block (Boucher & Duchêne-Marullaz, 1980), we have shown that while the degree of ventricular bradycardia induced by an individual β-adrenoceptor blocking drug was proportional to the degree of ventricular β-adrenoceptor blockade produced by that drug, comparable ventricular β-adrenoceptor blocking doses of different drugs produced differing degrees of ventricular bradycardia. The known pharmacological properties of the β-adrenoceptor blocking agents involved, e.g. propranolol and metoprolol, failed to provide any rational explanation for these observations.

A large number of studies have clearly demonstrated that the β-adrenoceptor blocking activity of racemic β-adrenoceptor blocking drugs mainly resides in the (−)-isomer (Levy & Richards, 1966; Shanks & Dunlop, 1967; Whitsitt & Lucchesi, 1967; Barrett & Cullum, 1968; Toda *et al.*, 1978; Kaiser, 1980), whereas of those β-adrenoceptor blocking agents possessing membrane stabilizing activity, this is mainly associated with the (+)-isomer (Lucchesi *et al.*, 1967; Tremblay *et al.*, 1973; Kaiser, 1980; Iansmith *et al.*, 1983) or is equally shared between both isomers (Barrett & Cullum, 1968; Davis & Temte, 1968; Levy, 1968; Dohadwalla *et al.*, 1969; Pollen *et al.*, 1969; Tomlinson *et al.*, 1980). This latter activity is held responsible for all or some of the cardiodepressant side-effects observed with these agents, particularly depression of contractility and automaticity (Howe & Shanks, 1966; Lucchesi *et al.*, 1967; Parmley & Braunwald, 1967; Engelhardt & Traunecker, 1969;

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Fitzgerald *et al.*, 1972; Hellenbrecht *et al.*, 1974).

In the light of these results we set out to analyse the bradycardiac effects of certain β-adrenoceptor blocking drugs by investigating the individual effects of the (−)- and (+)-isomers of propranolol, pindolol, metoprolol and penbutolol, which possess different ancillary pharmacological properties. We measured, in the conscious dog with chronic A-V block, the atrial and ventricular chronotropic effects of both stereoisomers of each drug, and the intensities of the corresponding ventricular β-adrenoceptor blockade obtained, in order to determine whether, at the same level of β-adrenoceptor blockade, the ventricular bradycardia induced by the (−)- and (+)-isomers of the same drug was of similar magnitude. The experimental model used provides very high ventricular sensitivity to β-adrenoceptor blockade, as already shown in previous work involving various β-adrenoceptor blocking agents (Ruttenberg *et al.*, 1970; Duchêne-Marullaz *et al.*, 1975; Reynolds & Di Salvo, 1978; Boucher & Duchêne-Marullaz, 1980). High ventricular sensitivity of this type of model to membrane stabilizing activity has also been demonstrated in work on antiarrhythmic agents of Vaughan-Williams's class I type (Nye & Roberts, 1966; Baum *et al.*, 1975; Katoh *et al.*, 1982).

## Methods

Six mongrel dogs of either sex, weighing between 14 and 22 kg were used. They were housed in individual cages in a large colony room with food and water continuously available in their home cages.

### *Experimental procedure*

In these dogs, A-V block was induced at least 2 months earlier; this time lapse is sufficient for atrial and ventricular rates to become stable (Boucher *et al.*, 1982). A-V block was produced by crushing the bundle of His with forceps introduced through the open right atrium during temporary occlusion of the venae cavae (Fredericq's modified technique: Fredericq, 1904; Boucher & Duchêne-Marullaz, 1985). Two of these dogs were in addition fitted with a catheter, for long-term measurement of blood pressure, inserted into the left external iliac artery and connected to a valve fixed on the dog's neck according to a technique derived from that described by Bloomberg *et al.* (1970).

### *Measurements*

Electrocardiographic and blood pressure monitoring were carried out with a Cardiopan III T instrument (Massiot-Philips) and a Statham P23 Db transducer connected to the arterial valve and linked to the recorder via a pressure module. During recording, the dogs, which had been habituated to the experimentation procedure, were placed on a table and lightly restrained. A microcatheter was fitted before each test in a cephalic vein to allow painless drug administration.

### *Protocol*

(−)-Propranolol hydrochloride was administered intravenously at doses between 19.5 and 312 $\mu g\,kg^{-1}$; (+)-propranolol hydrochloride between 312 and 10000 $\mu g\,kg^{-1}$; (−)-pindolol base between 0.61 and 9.75 $\mu g\,kg^{-1}$; (+)-pindolol base between 1.22 and 312 $\mu g\,kg^{-1}$; (−)-metoprolol hydrochloride between 78 and 1250 $\mu g\,kg^{-1}$; (+)-metoprolol hydrochloride between 1250 and 10000 $\mu g\,kg^{-1}$; (−)-penbutolol sulphate between 4.87 and 78 $\mu g\,kg^{-1}$; (+)-penbutolol sulphate between 19.5 and 5000 $\mu g\,kg^{-1}$. These doses were selected in order to obtain levels of ventricular β-adrenoceptor blockade of comparable intensity with all drugs. The study was conducted in six prepared dogs. A control group comprised the same six dogs given 0.5 ml $kg^{-1}$ i.v. physiological saline (0.9% w/v NaCl solution). Each injection lasted 30 s and at least 4 days elapsed between successive tests performed on the same animal. This time lapse was found adequate for complete return to basal values of both spontaneous heart rates and those resulting from isoprenaline challenge. Atrial and ventricular rates, (determined over a 30 s period), and blood pressure were measured before and 1, 3 and 5 min after injection, and thereafter every 5 min for 1 h. In order to determine the intensity of the induced ventricular β-adrenoceptor blockade, the six dogs were in addition given two i.v. injections (lasting 15 s) of isoprenaline hydrochloride (1 $\mu g\,kg^{-1}$), the first 15 min before and the second 60 min after the administration of each dose of the eight drugs. Ventricular rate was measured before each injection of isoprenaline and at the time of maximal induced cardioacceleration (on average 30 s after the injection).

### *Drugs*

(−)- and (+)-Propranolol HCl were obtained from I.C.I. Pharma Laboratories (U.K.), (−)- and (+)-pindolol from Sandoz Laboratories (France), (−)- and (+)-metoprolol HCl from Ciba-Geigy Laboratories (Switzerland), (−)- and (+)-penbutolol sulphate from Hoechst Laboratories (France) and (±)-isoprenaline HCl from Winthrop Laboratories (France).

### *Statistical analysis*

Results were expressed as means ± s.e.mean for each

30 s measuring period, and also as mean maximal variations in rate and blood pressure ± s.e.mean. This parameter was calculated as follows: the period after which maximal or minimal mean rate or mean blood pressure had been attained was determined during the 30 min period following injection. The mean difference between corresponding individual rates or blood pressures and their basal values was calculated, giving mean maximal variations ± s.e.mean. The intensity of ventricular β-adrenoceptor blockade was assessed in terms of percentage reduction of control ventricular cardioacceleration by comparing for each animal the isoprenaline-induced ventricular cardioacceleration before and after each drug dose. The regression lines describing the relationships between the maximal decrease in ventricular rate and the dose administered, and between the percentage reduction of isoprenaline-induced ventricular cardioacceleration and the dose administered were determined, with their correlation coefficient, after having checked for the best linear fit (effect-log dose) by analysis of variance with testing for linearity. Effective doses $ED_{25}$ (the dose of drug producing a reduction of 25% of the isoprenaline-induced ventricular cardioacceleration) were calculated whenever possible. The correlation lines relating the intensities of the ventricular β-adrenoceptor blockade and the corresponding ventricular bradycardias were also computed for each drug and the significance of the correlation coefficient determined. Statistical analysis of the data was performed using analysis of variance in complete blocks without repeated measures, followed, when the $F$ value was significant, by multiple comparisons using Student's $t$ test, and for comparison of the ventricular bradycardias produced by two drugs at comparable β-adrenoceptor blockade, analysis of variance testing in particular for parallelism and difference in intensity was used.

## Results

### *Control series*

Mean basal atrial and ventricular rates for the 6 dogs were 84 ± 5 and 42 ± 2 beats $min^{-1}$, respectively. These rates were not significantly modified during the 60 min following administration of physiological

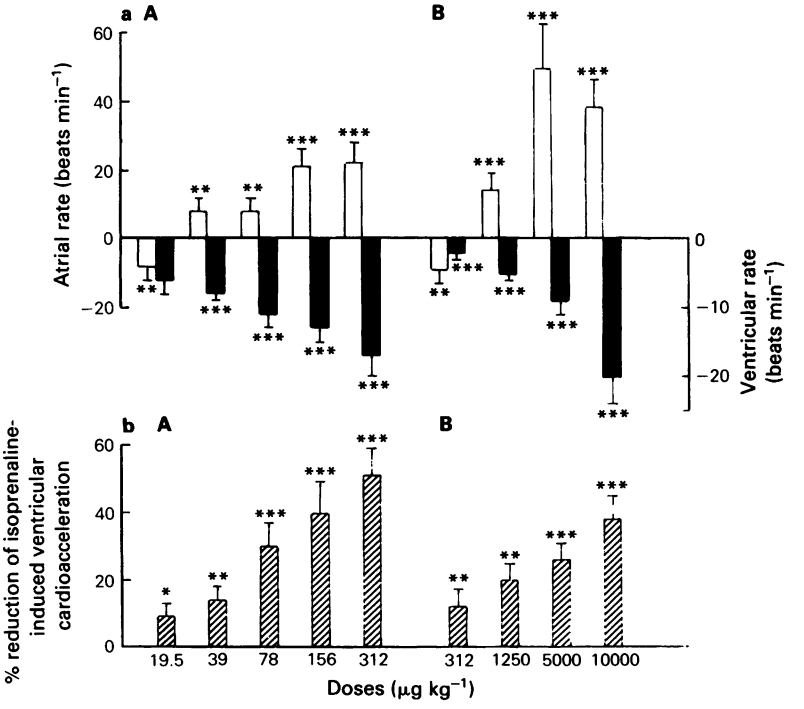


**Figure 1** Maximal effects on (a) atrial (open columns) and ventricular (solid columns) rates, and (b) percentage reduction of isoprenaline-induced ventricular cardioacceleration (hatched columns) by (−)-propranolol (A) and (+)-propranolol (B) in conscious dogs with chronic atrioventricular block. Values are means for groups of 6 dogs. Vertical lines show s.e.mean. *$0.01 < P < 0.05$, **$0.001 < P < 0.01$, ***$P < 0.001$ in comparison with control values.

saline. Mean atrial rate remained between 80 ± 6 and 89 ± 6 beats $min^{-1}$ and mean ventricular rate between 41 ± 3 and 44 ± 2 beats $min^{-1}$ throughout the measuring period.

*Effects on atrial rate*

At the lowest dose administered (19.5 and 312 $\mu g\ kg^{-1}$, respectively), (−)- and (+)-propranolol significantly decreased atrial rate ($P < 0.01$). At higher doses, both drugs increased atrial rate ($P < 0.01$) (Figure 1). Both (−)- and (+)-pindolol produced an increase in atrial rate, significant from 2.44 and 19.5 $\mu g\ kg^{-1}$ upwards, respectively ($P < 0.01$) (Figure 2); (−)- and (+)-metoprolol also increased atrial rate, and this change was significant from 625 and 5000 $\mu g\ kg^{-1}$, respectively ($P < 0.01$) (Figure 3). At the three lowest doses used, (−)- and (+)-penbutolol decreased atrial rate, significantly only at 9.75 $\mu g\ kg^{-1}$ for (−)-penbutolol and at the three doses for (+)-penbutolol ($P < 0.05$). At higher doses, both drugs increased atrial rate ($P < 0.01$) (Figure 4).

*Effects on ventricular rate*

At all doses used, (−)- and (+)-propranolol and (−)- and (+)-metoprolol brought about a significant decrease in ventricular rate ($P < 0.001$) (Figures 1 and 3). These effects, which appeared at the 1st min after injection and persisted throughout the 60 min observation period, were dose-related ($P < 0.05$). (−)-Pindolol decreased ventricular rate, and this change was significant from 1.22 $\mu g\ kg^{-1}$ ($P < 0.01$). This dose-related ($P < 0.001$) effect lasted only 10 to 30 min. (+)-Pindolol initially decreased ventricular rate at the two highest doses, but this was significant only at 312 $\mu g\ kg^{-1}$ ($P < 0.001$) (Figure 2). Thereafter, at all doses used, it increased ventricular rate ($P < 0.05$) from the 10th min until the end of the observation period. (−)- And (+)-penbutolol decreased ventricular rate, this was significant from 9.75 $\mu g\ kg^{-1}$ for the (−)-isomer and at all doses for the (+)-isomer ($P < 0.01$). These effects, which appeared between the 3rd and the 30th min and persisted throughout the whole observation period, were dose-related ($P < 0.001$) (Figure 4).

*Ventricular β-adrenoceptor blocking potencies*

The doses of the various drugs used produced ventricular β-adrenoceptor blockade, assessed in terms of percentage reduction of isoprenaline-induced ventricular cardioacceleration, of comparable intensity for all the drugs tested except for (+)-metoprolol for which higher toxic doses would have been necessary (Figures 1–4). For each particular drug, ventricular β-

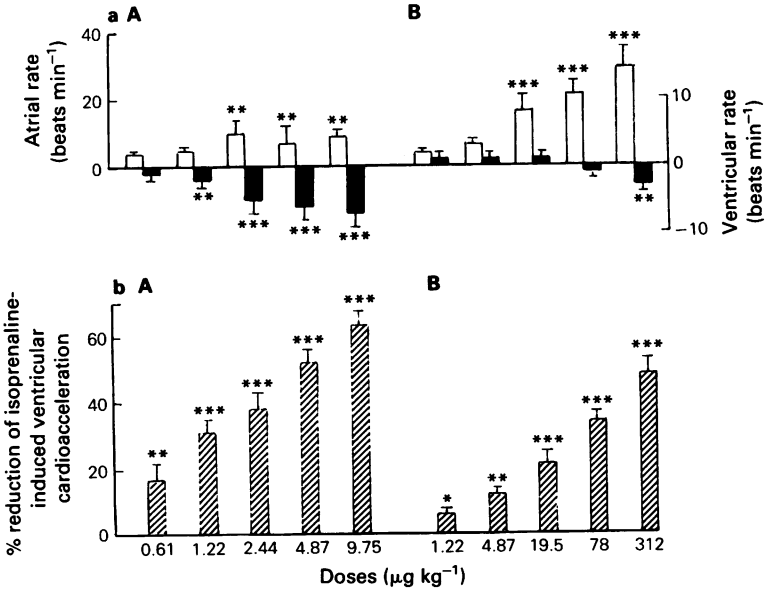


**Figure 2** Maximal effects on (a) atrial (open columns) and ventricular (solid columns) rates, and (b) percentage reduction of isoprenaline-induced ventricular cardioacceleration (hatched columns) by (−)-pindolol (A) and (+)-pindolol (B) in conscious dogs with chronic atrioventricular block. Values are means for groups of 6 dogs. Vertical lines show s.e.mean. *$0.01 < P < 0.05$, **$0.001 < P < 0.01$, ***$P < 0.001$ in comparison with control values.

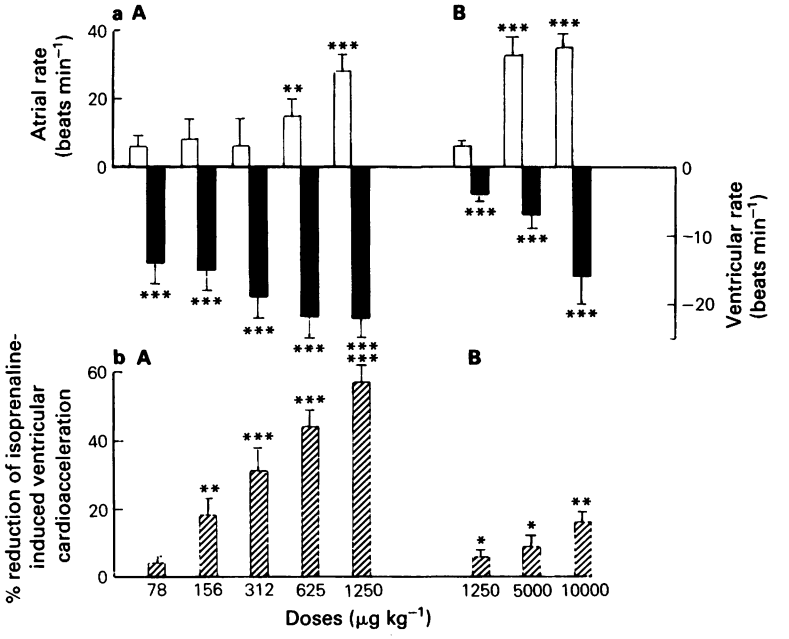


**Figure 3** Maximal effects on (a) atrial (open columns) and ventricular (solid columns) rates, and (b) percentage reduction of isoprenaline-induced ventricular cardioacceleration (hatched columns) by (−)-metoprolol (A) and (+)-metoprolol (B) in conscious dogs with chronic atrioventricular block. Values are means for groups of 6 dogs. Vertical lines show s.e.mean. *$0.01 < P < 0.05$, **$0.001 < P < 0.01$, ***$P < 0.001$ in comparison with control values.

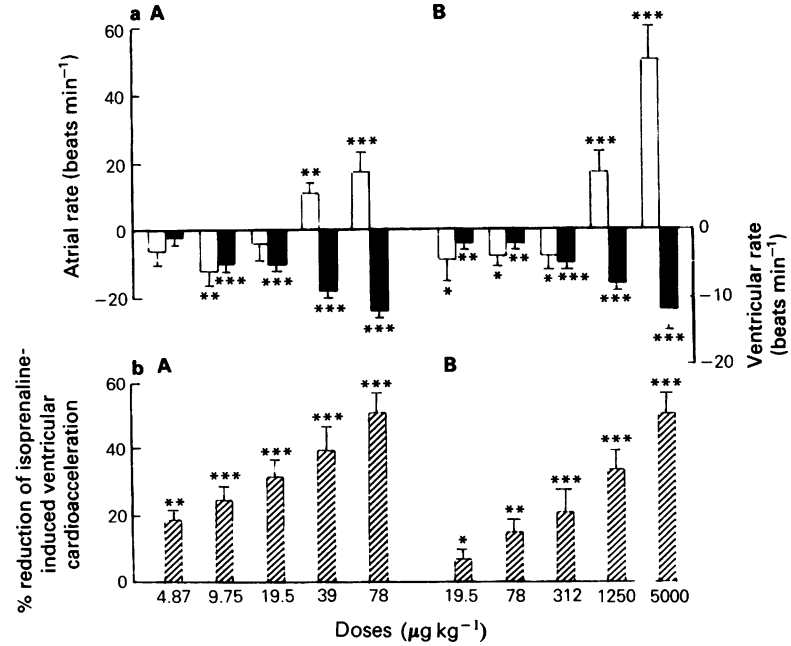


**Figure 4** Maximal effects on (a) atrial (open columns) and ventricular (solid columns) rates, and (b) percentage reduction of isoprenaline-induced ventricular cardioacceleration (hatched columns) by (−)-penbutolol (A) and (+)-penbutolol (B) in conscious dogs with chronic atrioventricular block. Values are means for groups of 6 dogs. Vertical lines show s.e.mean. *$0.01 < P < 0.05$, **$0.001 < P < 0.01$, ***$P < 0.001$ in comparison with control values.

adrenoceptor blocking potency was linearly log dose-related ($0.49 < r < 0.89$, $P < 0.005$). Table 1 shows the $ED_{25}$ values determined from the corresponding regression lines.

*Correlations between ventricular β-adrenoceptor blockade and ventricular bradycardia*

Both (−)- and (+)-propranolol and (−)- and (+)-metoprolol showed only weak correlations between the intensity of the induced ventricular β-adrenoceptor blockade and the amplitude of the corresponding ventricular bradycardia ($0.35 < r < 0.48$, $P < 0.05$), whereas both isomers of pindolol and penbutolol showed rather higher correlation coefficients ($0.40 < r < 0.61$, $P < 0.02$). In addition, (−)-pindolol and (−)-metoprolol, at doses producing identical ventricular β-adrenoceptor blockade, were more potent in producing ventricular bradycardia than the corresponding (+)-isomers ($P < 0.001$). Both isomers of propranolol and of penbutolol were shown to be statistically equipotent. For either isomer, the order of bradycardiac potencies at identical β-adrenoceptor blocking intensities was metoprolol > propranolol > penbutolol > pindolol.

*Effects on mean blood pressure*

At none of the doses used did (−)- and (+)-pindolol, (−)-metoprolol and (−)-penbutolol produce any effect on mean blood pressure, whereas (−)-propranolol from 78 μg kg$^{-1}$, (+)-propranolol from 5000 μg kg$^{-1}$, (+)-metoprolol from 1250 μg kg$^{-1}$ and (+)-penbutolol at 5000 μg kg$^{-1}$ lowered mean blood pressure by 20–30 mmHg. However, these effects on blood pressure were only transient (< 5 min).

## Discussion

In the conscious dog with chronic A-V block, low doses of (−)- or (+)-propranolol and (−)- or (+)-penbutolol lowered atrial rate whereas low doses of (−)- or (+)-pindolol and (−)- or (+)-metoprolol increased it. At higher doses, all these drugs increased atrial rate. These results are fully consistent with those obtained under the same conditions with (±)-propranolol and (±)-metoprolol (Boucher & Duchêne-Marullaz, 1980) and with (±)-pindolol (Duchêne-Marullaz *et al.*, 1975; Boucher *et al.*, 1984). Given the strong vagal tone and the weak adrenergic tone prevailing at the atrial level (Robinson *et al.*, 1973; Duchêne-Marullaz *et al.*, 1975; Reynolds & Di Salvo, 1978; Boucher *et al.*, 1979; Boucher & Duchêne-Marullaz, 1980), the cardioacceleration observed is undoubtedly of reflex origin through attenuation of the vagal tone in response to the simultaneously observed fall in the ventricular rate and to the slight hypotensive effect of these agents. The very high intrinsic sympathomimetic activity of pindolol (Barrett & Carter, 1970) must also be involved to some extent. The progressive reversal of the atrial chronotropic effects observed with propranolol and penbutolol can be ascribed to the association of dose-dependent attenuation of sympathetic tone by β-adrenoceptor blockade and progressive reflex suppression of vagal tone.

Except for (+)-pindolol, all the drugs lowered ventricular rate dose-dependently. This result is consistent with previous results obtained with (±)-propranolol and (±)-metoprolol (Ruttenberg *et al.*, 1970; Duchêne-Marullaz *et al.*, 1975; Reynolds & Di Salvo, 1978; Boucher & Duchêne-Marullaz, 1980). This bradycardiac effect is at least partly due to progressive suppression of sympathetic tone by β-adrenoceptor blockade, but the membrane stabilizing effect of some of the drugs would also be expected to be involved. The absence of ventricular bradycardia in the case of (+)-pindolol might be partly due to its intrinsic sympathomimetic activity, given the high doses administered.

As regards the intensity of ventricular β-adrenoceptor blockade obtained, the (−)-isomers proved to be much more potent than the corresponding (+)-isomers. Stereoisomer (−/+) potency ratios obtained from $ED_{25}$ values were respectively 38, 21, >43 and 31 for propranolol, pindolol, metoprolol and penbutolol, respectively. These values are consistent with those

**Table 1** Ventricular β-adrenoceptor blocking potencies of the optical isomers of propranolol, pindolol, metoprolol and penbutolol[1]

| *Isomers* | *Propranolol* | *Pindolol* | *Metoprolol* | *Penbutolol* |
|---|---|---|---|---|
| Laevo (−) | 62 ± 2 | 0.96 ± 0.03 | 233 ± 5 | 9.30 ± 0.44 |
| Dextro (+) | 2380 ± 210 | 21 ± 1 | >10000 | 293 ± 17 |

[1]These potencies were expressed as $ED_{25}$ (μg kg$^{-1}$) with respect to ventricular cardioacceleration induced by 1 μg kg$^{-1}$ isoprenaline. $ED_{25}$ values were determined from regression lines relating percentage reduction of cardioacceleration to doses of β-adrenoceptor blocking drugs. Values shown are means ± s.e.mean for groups of 6 dogs.

previously reported, i.e. 20–120 for propranolol (Howe & Shanks, 1966; Levy & Richards, 1966; Shanks & Dunlop, 1967; Barrett & Cullum, 1968), 20–380 for metoprolol (Toda *et al.*, 1978) and 50 for penbutolol (Kaiser, 1980). Comparable degrees of β-adrenoceptor blockade were obtained for (−)- and (+)-isomers by administering very high doses of the latter, except for (+)-metoprolol for which toxic high doses would have been required. In addition, the results showed (−)-pindolol to be about 60 times more potent, (−)-penbutolol 7 times more potent and (−)-metoprolol 4 times less potent than (−)-propranolol. Corresponding values for the (+)-isomers were 120, 8 and >4. Overall, these results are consistent with data from the literature which describe (±)-pindolol as being 3–40 times more potent (Giudicelli *et al.*, 1969; Hill & Turner, 1969; Aellig, 1976), (−)-penbutolol 4–26 times more potent (Boissier *et al.*, 1973; Giudicelli *et al.*, 1977; Sharma & Sapru, 1978) and (±)-metoprolol 2–4 times less potent (Åblad *et al.*, 1973; Boucher & Duchêne-Marullaz, 1980) than (±)-propranolol.

For comparable levels of β-adrenoceptor blockade, the (−)-isomers of pindolol and metoprolol had a stronger ventricular bradycardiac action than the corresponding (+)-isomers, whereas the (−)- and (+)-isomers of propranolol and penbutolol exhibited no such difference. Whichever the isomer, the order of ventricular bradycardiac potency for comparable β-adrenoceptor blockade was metoprolol>propranolol > penbutolol > pindolol, which entirely confirms the results obtained previously with (±)-propranolol and (±)-metoprolol (Boucher & Duchêne-Marullaz, 1980). The intrinsic sympathomimetic activity exerted by pindolol (Barrett & Carter, 1970) and to a lesser extent by penbutolol (Boissier *et al.*, 1973; Nyberg *et al.*, 1979; Kaiser *et al.*, 1980) may explain, at least in part, why these agents produced a weaker bradycardiac effect than did the other two drugs, and why (+)-pindolol, given the high doses used, had a weaker bradycardiac effect than (−)-pindolol for the same degree of β-adrenoceptor blockade. According to some authors (Giudicelli *et al.*, 1969; Laddu & Somani, 1972; Frishman & Kostis, 1982; Kostis *et al.*, 1982) this partial agonist activity can attenuate and even entirely offset the cardiodepressant effects of β-adrenoceptor blocking agents which possess it.

However, it is difficult to explain why (−)-metoprolol should have a stronger ventricular bradycardiac activity than (+)-metoprolol, or why (−)- and (+)-metoprolol should have a stronger bradycardiac activity than the other isomers tested. Some authors have considered that in addition to their β-adrenoceptor blocking effect, the membrane stabilizing activity exerted by certain β-adrenoceptor blocking drugs may be implicated in their cardiodepressant effects (especially bradycardia). However, it is widely accepted that metoprolol exerts a much lower membrane stabilizing activity than propranolol (Åblad *et al.*, 1973; Harada *et al.*, 1981) and that membrane stabilizing activity when it actually occurs is due either mainly to the (+)-isomer or to both isomers equally (Lucchesi *et al.*, 1967; Barrett & Cullum, 1968; Tomlinson *et al.*, 1980; Iansmith *et al.*, 1983). This suggests that some other as yet unknown pharmacological property of β-adrenoceptor blocking agents might explain these effects. This property would seem to be exhibited more markedly by the (−)-isomers, and be particularly evident with metoprolol.

In conclusion, the results presented here show that for comparable degrees of ventricular β-adrenoceptor blockade, the (−)-isomers of pindolol and metoprolol have a higher ventricular bradycardiac activity than the respective (+)-isomers, while the two isomers of propranolol and penbutolol are equiactive, and that whichever the isomer, metoprolol has a higher bradycardiac activity than the other three drugs. They further show that the isomers of the β-adrenoceptor blocking agents which exert an intrinsic sympathomimetic activity have a weaker ventricular bradycardiac activity than the others, confirming the protective role played by the intrinsic sympathomimetic activity with regard to induced bradycardia. Ventricular β-adrenoceptor blockade is at least partly responsible for the ventricular bradycardia, but some other factor is evidently also involved. This factor is apparently not the membrane stabilizing activity exhibited by certain β-adrenoceptor blocking agents, but might be some as yet unknown property of such drugs, particularly of metoprolol.

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## References

ÅBLAD, B., CARLSSON, E. & EK, L. (1973). Pharmacological studies of two new cardioselective adrenergic beta-receptor antagonists. *Life Sci.*, **12**, 107–119.

AELLIG, W.H. (1976). Beta-adrenoceptor blocking activity and duration of action of pindolol and propranolol in healthy volunteers. *Br. J. clin. Pharmac.*, **3**, 251–257.

BARRETT, A.M. & CARTER, J. (1970). Comparative chronotropic activity of beta-adrenoceptive antagonists. *Br. J. Pharmac.*, **40**, 373–381.

BARRETT, A.M. & CULLUM, V.A. (1968). The biological

properties of the optical isomers of propranolol and their effects on cardiac arrhythmias. *Br. J. Pharmac.*, **34**, 43–55.

BAUM, T., PETERS, J.R., BUTZ, F. & MUCH, D.R. (1975). Suppression of ventricular automaticity by antidysrrhythmic agents. *Eur. J. Pharmac.*, **33**, 363–369.

BLOOMBERG, M.L., BERGMAN, H. & SHEINER, N.M. (1970). A technique of chronic arterial catheterization in dogs. *J. cardiovasc. Surg.*, **11**, 137–140.

BOISSIER, J.R., COUTTE, R., ADVENIER, C. & GIUDICELLI, J.F. (1973). Activité bêta-adrénolytique et effets hémodynamiques du penbutolol. *Thérapie*, **28**, 1251–1265.

BOUCHER, M., DUBRAY, C. & DUCHÊNE-MARULLAZ, P. (1982). Long-term observation of atrial and ventricular rates in the unanaesthetized dog with complete atrioventricular block. *Pflügers Arch.*, **395**, 341–343.

BOUCHER, M., DUBRAY, C. & DUCHÊNE-MARULLAZ, P. (1984). Chronotropic effects of pindolol. Relation between ventricular effects and control resting ventricular rate values in conscious dogs with chronic A-V block. *Naunyn-Schmiedebergs Arch. Pharmac.*, **325**, 183–185.

BOUCHER, M. & DUCHÊNE-MARULLAZ, P. (1980). Acebutolol, metoprolol and propranolol in conscious dogs with chronic heart-block: chronotropic effects and relation between depression of ventricular activity and beta-adrenoceptor blocking potency. *Br. J. Pharmac.*, **70**, 335–340.

BOUCHER, M. & DUCHÊNE-MARULLAZ, P. (1985). Methods for producing experimental complete atrioventricular block in dogs. *J. Pharmac. Methods*, **13**, 95–107.

BOUCHER, M., DUCHÊNE-MARULLAZ, P. & LAVARENNE, J. (1979). Catecholamines and cardiac rhythms in the unanaesthetized dog with chronic A-V block. *Am. J. Physiol.*, **237**, H10–H17.

DAVIS, L.D. & TEMTE, J.V. (1968). Effects of propranolol on the transmembrane potentials of ventricular muscle and Purkinje fibers of the dog. *Circulation Res.*, **22**, 661–677.

DOHADWALLA, A.N., FREEDBERG, A.S. & VAUGHAN WILLIAMS, E.M. (1969). The relevance of β-receptor blockade to ouabain-induced cardiac arrhythmias. *Br. J. Pharmac.*, **36**, 257–267.

DUCHÊNE-MARULLAZ, P., COMBRE, A., LAVARENNE, J., LAPALUS, P. & SCHAFF, G. (1975). Comparaison des effets du propranolol, de l'alprénolol, du pindolol et du practolol sur les rythmes cardiaques de chiens non narcosés en dissociation auriculo-ventriculaire chronique. *J. Pharmac.*, **6**, 441–452.

ENGELHARDT, A. & TRAUNECKER, W. (1969). Pharmakologie einiger Phenoxypropanolamin-derivate mit beta-adrenolytischer Wirkung. *Arch. exp. Path. Pharmak.*, **263**, 203–204.

FITZGERALD, J.D., WALE, J.L. & AUSTIN, M. (1972). The haemodynamic effects of (±)-propranolol, dexpropranolol, oxprenolol, practolol and sotalol in anaesthetized dogs. *Eur. J. Pharmac.*, **17**, 123–134.

FREDERICQ, L. (1904). L'atriotomie temporaire, procédé nouveau d'exploration des fonctions du coeur. *Arch. int. Physiol.*, **1**, 83–85.

FRISHMAN, W.H. & KOSTIS, J. (1982). The significance of intrinsic sympathomimetic activity in beta-adrenoceptor blocking drugs. *Cardiovasc. Rev. Rep.*, **3**, 503–512.

GIUDICELLI, J.F., RICHER, C., CHAUVIN, M., IDRISSI, N. & BERDEAUX, A. (1977). Comparative beta-adrenoceptor blocking effects and pharmacokinetics of penbutolol and propranolol in man. *Br. J. clin. Pharmac.*, **4**, 135–140.

GIUDICELLI, J.F., SCHMITT, H. & BOISSIER, J.R. (1969). Studies on dl-4-(2-hydroxy-3-isopropylaminopropoxy)-indole (LB 46), a new potent beta-adrenergic blocking drug. *J. Pharmac. exp. Ther.*, **168**, 116–126.

HARADA, S., BAN, T., FUJITA, T. & KOSHIRO, A. (1981). Negative inotropic effects and the hydrophobicity of beta-adrenergic blocking agents. *Arch. int. Pharmacodyn. Ther.*, **252**, 262–271.

HELLENBRECHT, D., MÜLLER, K.F. & GROBECKER, H. (1974). Prediction of the non-specific cardiodepressant effects of beta-adrenoceptor blocking agents *in vitro* and *in vivo* by means of the Hansch analysis. *Eur. J. Pharmac.*, **29**, 223–235.

HILL, R.C. & TURNER, P. (1969). Preliminary investigations of a new beta-adrenoceptive receptor blocking drug, $LB_{46}$, in man. *Br. J. Pharmac.*, **36**, 368–372.

HOWE, R. & SHANKS, R.G. (1966). Optical isomers of propranolol. *Nature*, **210**, 1336–1338.

IANSMITH, D.H.S., NASH, C.B. & BANDURA, J.P. (1983). Biphasic nature of propranolol's microelectrophysiologic effects. *Am. J. Cardiol.*, **51**, 145–148.

KAISER, J. (1980). Untersuchungen zur Spezifität der Wirkungen von Penbutolol und Propranolol unter Berücksichtigung der optischen Isomeren. *Arzneim-Forsch. Drug Res.*, **30**, 427–432.

KAISER, J., HÄRTFELDER, G., LINDNER, E. & SCHÖLKENS, B. (1980). Pharmakologie der Beta-receptorblockers Penbutolol. *Arzneim-Forsch Drug Res.*, **30**, 420–426.

KATOH, T., KARAGUEUZIAN, H.S., PETER, T. SUGI, K., McCULLEN, A. & MANDEL, W.J. (1982). Comparative effects of antiarrhythmic drugs on canine idioventricular pacemakers. *In vivo* and *in vitro* correlation. *Jap. Heart J.*, **23** (suppl.) 87–89.

KOSTIS, J.B., FRISHMAN, W., HOSLER, M.H., THORSEN, N.L., GONASUN, L. & WEINSTEIN, J. (1982). Treatment of angina pectoris with pindolol: the significance of intrinsic sympathomimetic activity of beta-blockers. *Am. Heart J.*, **104**, 496–504.

LADDU, A.R. & SOMANI, P. (1972). Direct and beta-adrenoceptor blocking effects of 4-(2-hydroxy-3-isopropylaminopropoxy-)indole (LB 46) on myocardial hemodynamics. *Arch. int. Pharmacodyn. Ther.*, **196**, 5–15.

LEVY, J.V. (1968). Myocardial and local anesthetic actions of beta-adrenergic receptor blocking drugs: relationship to physico-chemical properties. *Eur. J. Pharmac.*, **2**, 250–257.

LEVY, J.V. & RICHARDS, V. (1966). Inotropic and chronotropic effects of a series of beta-adrenergic blocking drugs: some structure-activity relationships. *Proc. Soc. exp. Biol.*, **122**, 373–379.

LUCCHESI, B.R., WHITSITT, L.S. & STICKNEY, J.L. (1967). Antiarrhythmic effects of beta-adrenergic blocking agents. *A. New York Acad. Sci.*, **139**, 940–950.

NYBERG, G., WILHELMSSON, C. & VEDIN, A. (1979). Intrinsic sympathomimetic activity of penbutolol. *Eur. J. clin. Pharmac.*, **16**, 381–386.

NYE, C.E. & ROBERTS, J. (1966). The reactivity of atrial and ventricular pacemakers to quinidine. *J. Pharmac. exp. Ther.*, **152**, 67–74.

PARMLEY, W.W. & BRAUNWALD, E. (1967). Comparative myocardial depressant and antiarrhythmic properties of d-propranolol, dl-propranolol and quinidine. *J. Pharmac. exp. Ther.*, **158,** 11–21.

POLLEN, D.W., SCOTT, A.C. & WALLACE, W.F.M. (1969). A comparison of the direct effects and adrenergic blocking activity of d/l- and d-propranolol on the electrical and mechanical behaviour of isolated frog ventricle. *Cardiovasc. Res.*, **3,** 7–13.

REYNOLDS, R.D. & DI SALVO, J. (1978). Effects of dl-propranolol on atrial and ventricular rates in unanaesthetized atrioventricular blocked dogs. *J. Pharmac. exp. Ther.*, **205,** 374–381.

ROBINSON, J.L., FARR, W.C. & GRUPP, G. (1973). Atrial rate response to ventricular pacing in the unanaesthetized A-V blocked dog. *Am. J. Physiol.*, **224,** 40–45.

RUTTENBERG, H., HURWITZ, R., BLESA, M. & PAPPELBAUM, S. (1970). Effects of propranolol on myocardial automaticity in conscious dogs with chronic complete heart block. *UCLA Forum Med. Sci.*, **13,** 69–74.

SHANKS, R.G. & DUNLOP, D. (1967). Effect of propranolol on arrhythmias following coronary artery occlusion in dogs. *Cardiovasc. Res.*, **1,** 34–41.

SHARMA, P.L. & SAPRU, R.P. (1978). Comparative potency of intravenous penbutolol and propranolol in man. *Int. J. clin. Pharmac.*, **16,** 83–85.

TODA, N., HAYASHI, S., HATANO, Y., OKUNISHI, H. & MIYAZAKI, M. (1978). Selectivity and steric effects of metoprolol isomers on isolated rabbit atria, arteries and tracheal muscles. *J. Pharmac. exp. Ther.*, **207,** 311–319.

TOMLINSON, D.R., HAWORTH, S.C., HARMSWORTH, N.J. & ROSS, A.M. (1980). The effects of the optical isomers of propranolol on functional refractory period in rat isolated myocardium. *J. Pharm. Pharmac.*, **32,** 693–696.

TREMBLAY, G.M., DE CHAMPLAIN, J. & NADEAU, R.A. (1973). Effects of dl-propranolol, d-propranolol, l-propranolol and sotalol on myocardial contractility and coronary resistance. *Can. J. Physiol. Pharmac.*, **51,** 61–67.

WHITSITT, L.S. & LUCCHESI, B.R. (1967). The cardiac beta-adrenergic receptor blocking actions of propranolol and its stereoisomers. *Life Sci.*, **6,** 939–950.

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