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The β-adrenoceptor blocking properties of the α-methyl analogues of propranolol and practolol in the anaesthetized dog

B. LEVY

Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas 77550, U.S.A.

Summary

1. The β-adrenoceptor blocking properties of α-methyl propranolol and α-methyl practolol were determined in anaesthetized dogs according to their abilities to modify the isoprenaline-induced effects on diastolic pressure, heart rate, myocardial contractile force, femoral arterial blood flow and pulmonary airway resistance.

2. α-Methyl propranolol shifted the isoprenaline dose-response curves for the fall in diastolic pressure and the positive inotropic and chronotropic responses to the right in a parallel manner yielding pA_2 and slope values of 6·66 (0·92), 6·34 (0·77) and 6·59 (0·61) respectively. The slopes of the graphs for determining pA_2 values for the cardiac β-adrenoceptor blocking properties of α-methyl propranolol were significantly less than 1 and indicated a mechanism other than simple, competitive, reversible antagonism.

3. α-Methyl propranolol exerted a much weaker blockade of respiratory smooth muscle β-adrenoceptors than has been reported for propranolol.

4. α-Methyl practolol exerted a weaker blocking effect on myocardial β-adrenoceptors than has been reported for practolol. No significant blockade of vascular or respiratory smooth muscle β-adrenoceptors occurred after a total cumulative dose of 10 μg/kg of α-methyl practolol.

5. α-Methyl substitution of propranolol and practolol reduces the potency but increases the selectivity of their β-adrenoceptor blocking properties.

6. The β-adrenoceptors subserving cardiac stimulation, vasodilatation and bronchodilatation are representative of three different β-adrenoceptor sub-types in the dog.

Introduction

β-Adrenoceptor antagonists are structurally related to each other as well as to isoprenaline. Relatively minor structural changes may modify the potency, the intrinsic activity, the presence or absence of local anaesthetic activity and the selectivity of the β-adrenoceptor blockade.

Butoxamine has been classified as a vascular-selective β-adrenoceptor antagonist because of its ability to produce a relatively greater blockade of vascular than cardiac β-adrenoceptors in the anaesthetized dog (Levy, 1966a). Butoxamine is the prototype of a group of vascular-selective β-adrenoceptor antagonists which also

includes dimethyl isopropylmethoxamine (Levy, 1966b) and 1-(4'-methylphenyl)-2-isopropylamino-propanol (H 35/25), (Levy, 1967). All of these compounds possess an α-methyl group on the ethanolamine side chain and this substituent group appears to be of some significance in the selectivity of β-adrenoceptor blockade produced by butoxamine and the other members of this group. The significance of the α-methyl substitution is further indicated by the observation that 1-(4'-methylphenyl)-2-isopropylamino ethanol (H 29/50), an agent which differs from H 35/25 in that it does not possess the α-methyl group, is a non-selective β-adrenoceptor antagonist (Levy & Wilkenfeld, 1969). A similar relationship has been reported for dichloroisoprenaline and its α-methyl analogue (Van Deripe & Moran, 1965).

The purpose of this study was to determine the effects of α-methyl substitution on the β-adrenoceptor blocking properties of propranolol (Black, Crowther, Shanks & Dornhorst, 1964) and practolol (Dunlop & Shanks, 1968) in the anaesthetized dog.

Methods

Twenty mongrel dogs of either sex, weighing between 10–16 kg, were anaesthetized with 220 mg/kg of barbitone sodium and 20 mg/kg of pentobarbitone sodium given together intravenously.

Cardiovascular studies

Six dogs per group were used to study the effects of each antagonist. The trachea, a carotid artery and a jugular vein were cannulated. All dogs in this series only were bilaterally vagotomized. Arterial blood pressure (mmHg, 1 mmHg = 1·333 mbar) was recorded from a carotid artery by means of a Statham transducer (Model P23-AA). Heart rate (beats/min) was recorded continuously with a linear electronic tachometer (Electronics for Medicine, Inc.) triggered by the arterial pulse. Cardiac contractile force (g) was measured with animals under positive pressure artificial respiration. The heart was exposed by a thoractomy and a calibrated strain-gauge arch (Boniface, Brodie & Walton, 1953; Cotten & Bay, 1956) was sutured to the right ventricle. The dogs were respired with a tidal volume of approximately 13 ml/kg at a frequency of 20 times per minute. Femoral arterial blood flow (ml/min) was also recorded by means of a square wave electromagnetic flowmeter (model 301, Carolina Medical Electronics, Inc.). Non-cannulating flow probes with a circumference of 5, 7 or 10 mm were used depending on the size of the vessel. A small branch of the femoral artery was cannulated with a fine polyethylene catheter for the intra-arterial injection of drugs. Responses to isoprenaline injected intravenously and intra-arterially were determined before and after pretreatment with cumulative doses of each antagonist which were only given intravenously. Consecutive doses of isoprenaline were given at 5 min intervals. Each dose of antagonist was infused over a 10 min period in a total volume of 6 ml. Ten min then elapsed before administering isoprenaline.

Quantitative evaluation for isoprenaline antagonism included comparison of mean changes in responses to initial control changes by Student's paired t test with a level of significance of $P<0{\cdot}05$ (Snedecor, 1950). The calculation of pA_2 values was according to the method of Arunlakshana & Schild (1959). pA_2 is defined as the negative logarithm of the molar concentration of antagonist which increases the agonist dose-ratio two-fold. All pA_2 and slope values (from the Arunlakshana-Schild plots) were determined in the following manner. Regression lines were

calculated by the method of least squares with the pooled results obtained from 6 dogs. For each concentration of antagonist (mol/kg) the ratio of the equiactive dose of agonist in the presence and absence of antagonist (dose-ratio) was calculated. Dose-ratios were determined at the approximate mid-point of the agonist dose-response curves. Log (dose-ratio−1) was plotted against log dose of antagonist in mol/kg.

The effective concentration of the blocking drug *in vivo* was calculated on the assumption of uniform distribution of the injected dose in the body volume. This assumption is necessarily an approximation since plasma binding, drug elimination and other factors causing non-uniform distribution are neglected. In spite of these limitations the calculation of pA_2 values for the whole animal was considered to be a valid procedure which could provide comparative data for different blocking drugs as well as providing a basis for analysing log dose-response curves obtained with different concentrations of the same blocking drug.

Mean changes in resting cardiovascular parameters due to the intrinsic effects of both antagonists were determined. Changes in all parameters were determined 10 min after each dose of antagonist and prior to challenge with isoprenaline and were compared to pre-injection control levels.

Pulmonary airway resistance studies

Eight dogs in all were used in this study. Arterial pressure, recorded from a femoral artery, and heart rate were recorded continuously as described above. A cuffed endotracheal tube was inserted into the trachea and connected in series to a pneumotachograph to record flow rate (0–40 litres/min, Electronics for Medicine). The dogs were breathing spontaneously. The pressure difference across the screen was measured by a differential pressure transducer (Statham Model PM-15 $\pm$0·04–350). The tidal volume was obtained by electrical integration of the flow rate signal (model IRD, Electronics for Medicine, Inc.). Calibration of tidal volume (ml) was obtained by passing 50 ml of air through the pneumotachograph screen. An 18 gauge, 1·5 inch hypodermic needle was inserted through one of the intercostal spaces into the pleural cavity. A second needle was inserted into the rubber tubing between the endotracheal tube and the pneumotachograph. The pressure difference between the pleural cavity and trachea was measured by a second differential pressure transducer (Statham, model PM 5 $\pm$0·2–350). A water manometer was used to calibrate this system (cm H_2O). These measurements formed the basis for measuring pulmonary airway resistance ((cm H_2O/litre)/s) by the isovolume method of Diamond (1967). Histamine, in a single standard dose of 10 μg/kg, was used to produce an increase in pulmonary airway resistance over control resting levels. The change in pulmonary airway resistance induced by histamine given 30 s after a standard dose, 1 μg/kg, of isoprenaline, was measured before and after increasing cumulative doses of each antagonist. This dose of isoprenaline usually abolished the increase in pulmonary airway resistance evoked by the standard dose of histamine (Wasserman & Levy, 1973). A standard dose of histamine was injected at the end of each experiment to determine the effect, if any, of the antagonist on the responsiveness of histamine itself. A second injection of isoprenaline (1 μg/kg) alone was given before and after pretreatment with antagonist to demonstrate the effects of the antagonist treatment on the fall in

diastolic pressure and the increase in heart rate evoked by isoprenaline in these groups of dogs. All drug injections were made into a femoral vein.

The effects of the antagonists on the β-adrenoceptors involved in airway resistance were quantitated by comparing their abilities to inhibit the isoprenaline-induced inhibition of the histamine-induced increase in airway resistance. All responses were compared to the initial control responses by Student's *t* test for paired data with a level of significance of $P<0.05$.

Drugs

Racemic isoprenaline and histamine phosphate were both prepared as solutions of 1 mg/ml in saline (0·9% w/v NaCl solution). The isoprenaline solution also contained 100 μg/ml of ascorbic acid as a preservative. Appropriate dilutions were prepared fresh daily and kept on ice. α-Methyl propranolol and α-methyl practolol were both prepared as 10 mg/ml solutions in saline containing 0·1 N HCl. Both antagonists were in the form of acetates. Doses of all drugs are expressed in terms of their salts.

Results

Effects of α-methyl propranolol on the cardiovascular responses to isoprenaline

Dose-response curves for the effects of isoprenaline on diastolic pressure, heart rate and myocardial contractile force were determined before and after treatment with cumulative doses of 0·1, 0·3, 1 and 3 mg/kg of α-methyl propranolol. The isoprenaline dosage was increased following this treatment as required in order to maintain the same approximate maximal response throughout. Isoprenaline was administered in a total dose range of 0·1–30 μg/kg. Following α-methyl propranolol pretreatment the dose-response curves for isoprenaline on all three parameters were shifted to the right in a parallel manner. Figures 1A and 1B show that the dose-response curves for isoprenaline on heart rate and contractile force were shifted to the right in a more uniform manner following doses of 0·3 mg/kg and higher. The dose-response curves for the isoprenaline-induced fall in diastolic pressure were shifted to the right in a parallel and more uniform manner after all doses of α-methyl propranolol (Figure 1C). These apparent differences in the degree of shifting of the isoprenaline dose-response curves become more obvious when the pA_2 and slope values for α-methyl propranolol are calculated and compared to those obtained with propranolol under similar experimental conditions in a previous study (Table 1; Wasserman & Levy, 1973). A comparison of the pA_2 values for α-methyl propranolol would suggest that an equivalent β-adrenoceptor blocking effect was obtained on all three parameters. Propranolol also exerted an equivalent β-adrenoceptor blocking effect on all 3 parameters but was approximately four times more potent than the α-methyl analogue. However, the slopes for propranolol were all equivalent to a value of 1, thus suggesting a typical competitive, reversible blocking effect. The slope for the pA_2 value of α-methyl propranolol on diastolic pressure of 0·92 was not significantly different from 1 while the slope values for its effects on heart rate and contractile force of 0·61 and 0·77 respectively were both significantly less than 1. These results suggest that α-methyl propranolol resembles propranolol in blocking vascular β-adrenoceptors but differs from it in the nature of its β-adrenoceptor blocking effect in cardiac tissue.

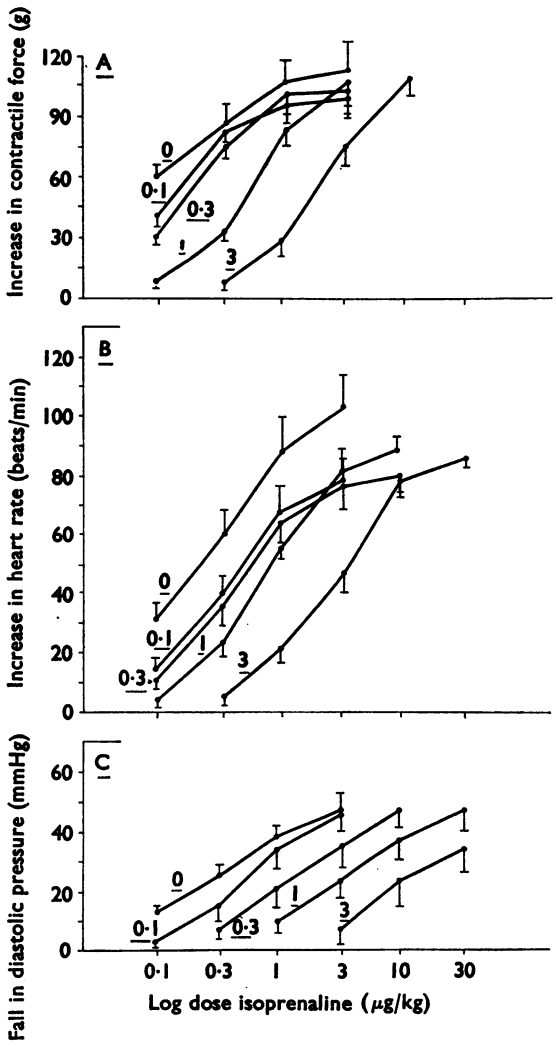

FIG. 1. Shifts produced by α-methyl propranolol in the dose response curves of the positive inotropic responses (A), the positive chronotropic responses (B) and the fall in diastolic pressure (C) induced by isoprenaline. Each point represents the mean value ± standard error obtained from 6 dogs.

Figure 2 further confirms the ability of α-methyl propranolol to block β-adrenoceptors in the femoral vascular bed. The increase in femoral arterial blood-flow induced by a standard dose of 0·1 μg/kg of isoprenaline given intraarterially was significantly reduced following a cumulative, i.v. dose of 0·1 mg/kg of α-methyl propranolol. These results were obtained in 5 of the dogs used in the cardiovascular studies cited above.

α-Methyl propranolol produced significant reductions in basal levels of myocardial contractile force and heart rate after cumulative doses of 0·1 and 0·3 mg/kg respectively (Figures 3A and 3B). No significant reduction in resting levels for diastolic pressure was noted even after the maximum cumulative dose of 3 mg/kg (Figure 3C).

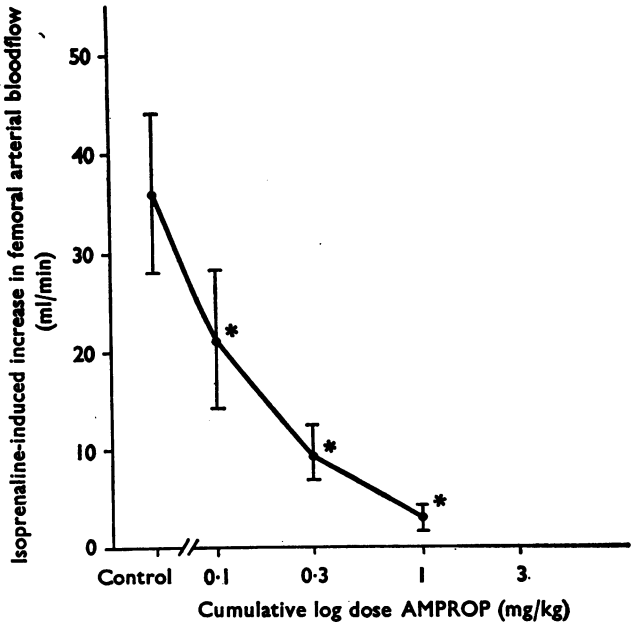

FIG. 2. Effects of α-methyl propranolol (AMPROP) on the isoprenaline-induced (0·1 mg/kg, i.a.) increase in femoral arterial blood flow. Each point represents mean value±standard error obtained from 5 dogs. Asterisk indicates significant difference from initial control response, $P<0.05$.

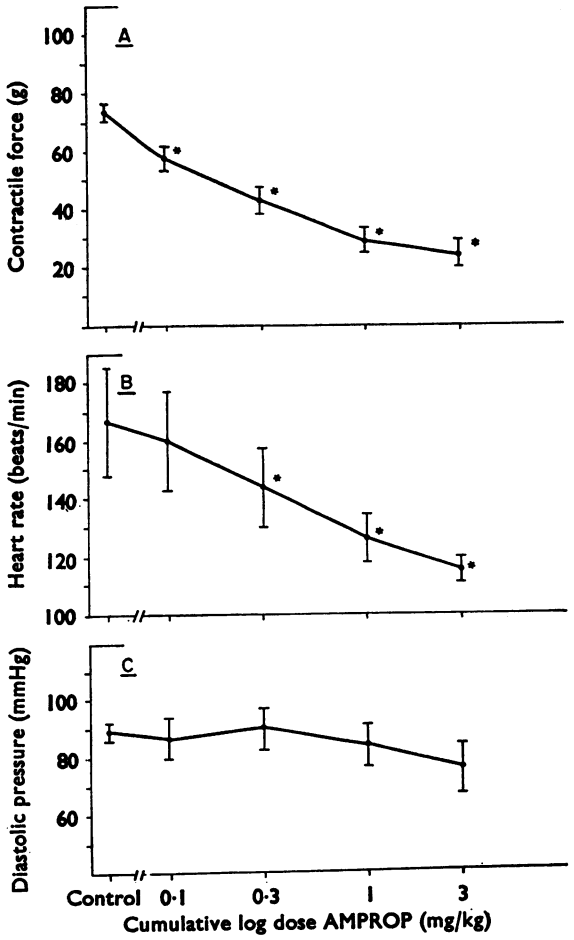

FIG. 3. Effects of α-methyl propranolol (AMPROP) on basal levels of myocardial contractile force (A), heart rate (B) and diastolic pressure (C). Each point represents the mean value± standard error obtained from 6 dogs. Asterisk indicates significant difference from initial control levels, $P<0.05$.

Effects of α-methyl propranolol on the isoprenaline-induced changes in airway resistance The ability of isoprenaline (1 μg/kg, i.v.) to inhibit the increase in airway resistance produced by histamine (10 μg/kg, i.v.) was determined in 5 dogs before and after treatment with cumulative doses of 0·1–3 mg/kg of α-methyl propranolol. Wasserman & Levy (1973) previously showed that 1 μg/kg of isoprenaline will prevent the increase in airway resistance produced by 10 μg/kg of histamine. Figure 4C shows that a significant inhibition of the isoprenaline response occurred only after a cumulative dose of 3 mg/kg of α-methyl propranolol. Such treatment also produced a gradual but marked increase in resting airway resistance that was significant after 1 mg/kg. The increase in airway resistance produced by histamine was somewhat increased after the last dose of α-methyl propranolol. However, this post-experimental histamine response did not differ significantly

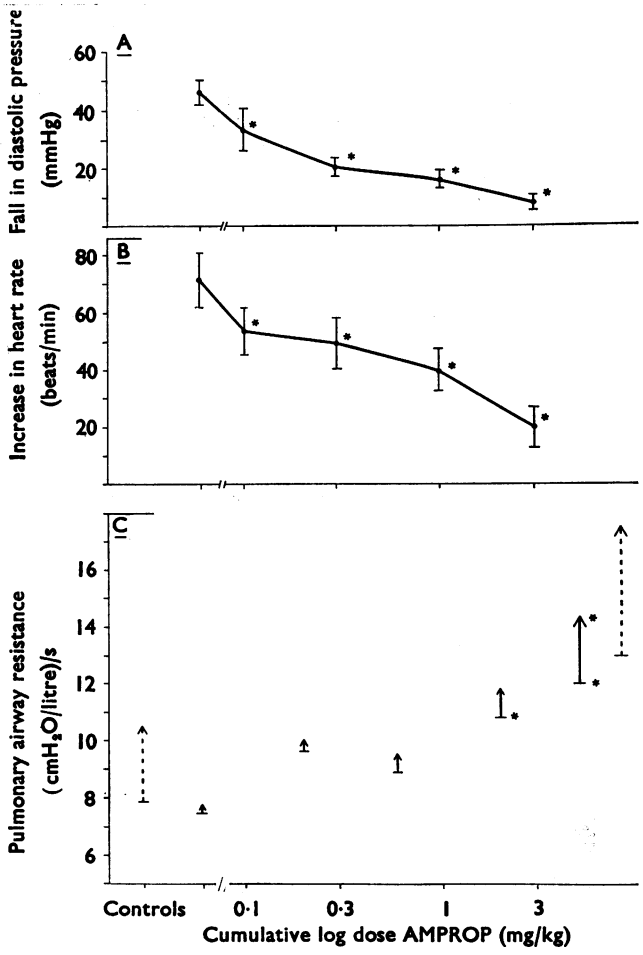

FIG. 4. Effects of α-methyl propranolol (AMPROP) on the isoprenaline-induced (1 μg/kg) fall in diastolic pressure (A), increase in heart rate (B) and reduction in pulmonary airway resistance (C). Resting pulmonary airway resistance is indicated by the horizontal bar and peak responses are represented by the arrows. Two broken lines represent responses to histamine alone (10 μg/kg, i.v.). All other lines represent responses to histamine injected 30 s after isoprenaline (1 μg/kg, i.v.). Each point represents the mean value ± standard error obtained from 5 dogs. Asterisk indicates significant difference from initial control values, $P<0.05$.

from the initial control value. Figures 4A and 4B show that the increase in heart rate and fall in diastolic pressure evoked by isoprenaline alone, in this group of animals, was reduced significantly following 0·1 mg/kg of α-methyl propranolol.

These results indicate that α-methyl propranolol blocks vascular β-adrenoceptors and cardiac β-adrenoceptors possibly through different mechanisms. It is clearly much less effective in blocking respiratory β-adrenoceptors than it is in blocking either cardiac or vascular β-adrenoceptors.

Effects of α-methyl practolol on the cardiovascular responses to isoprenaline. Isoprenaline was injected in a group of 6 dogs in doses of 0·3 and 1·0 μg/kg before and after pretreatment with cumulative doses of 1, 3 and 10 mg/kg of α-methyl practolol. Figure 5A shows that the positive inotropic response to 0·3 μg/kg of isoprenaline was significantly reduced following 3 mg/kg of α-methyl practolol and the same response to 1 μg/kg was significantly reduced after 10 mg/kg α-methyl practolol. The positive chronotropic responses to both doses of isoprenaline were

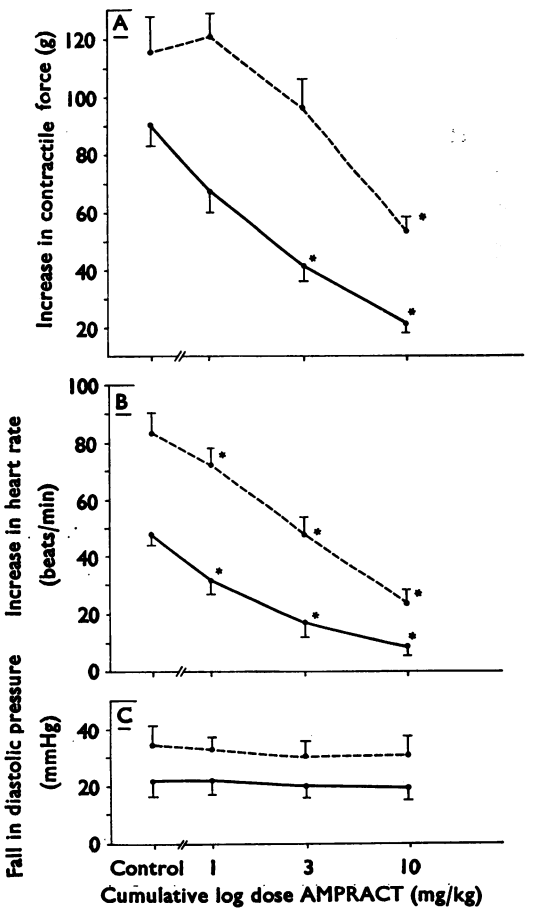

FIG. 5. Effects of α-methyl practolol (AMPRACT) on the positive inotropic (A), positive chronotropic (B) and fall in diastolic pressure (C) responses induced by isoprenaline. Solid line represents responses to 0·3 μg/kg and dashed line represents responses to 1 μg/kg of isoprenaline respectively. Each point represents the mean value ± standard error obtained from 6 dogs. Asterisk indicates significant difference from initial control values, $P<0.05$.

reduced after 1 mg/kg of α-methyl practolol (Figure 5B). No significant reductions in the isoprenaline-induced falls in diastolic pressure were seen even after a cumulative dose of 10 mg/kg of α-methyl practolol. Figure 6 summarizes the effects of α-methyl practolol treatment on resting levels of heart rate, contractile force and diastolic pressure. Significant reductions in heart rate and contractile force were evident following 1 mg/kg of α-methyl practolol (Figures 6A and 6B); no significant reduction in resting diastolic pressure was evident after 10 mg/kg of the drug.

Effects of α-methyl practolol on the isoprenaline-induced changes in airway resistance. The isoprenaline-induced (1 μg/kg) fall in diastolic pressure, increase in heart rate and inhibition of the histamine-induced increase in airway resistance were determined in 3 dogs before and after pre-treatment with α-methyl practolol (1–10 mg/kg) as described above. The small group was due to the low supply of available drug. However, the results obtained were clear. Figure 7 summarizes these results and shows that the isoprenaline-induced increase in heart rate was inhibited in a dose-dependent manner by α-methyl practolol pretreatment (Figure 7B). The isoprenaline-induced fall in diastolic pressure was not reduced following

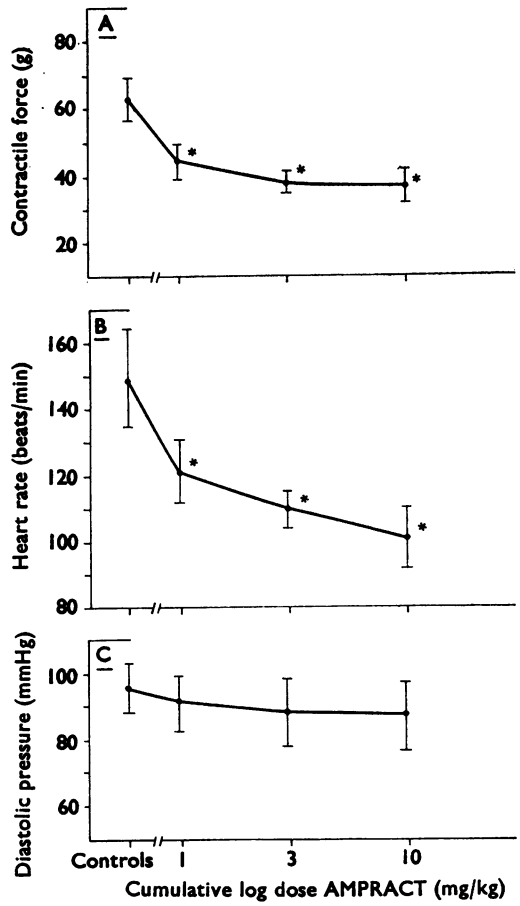

FIG. 6. Effects of α-methyl practolol (AMPRACT) on basal levels of myocardial contractile force (A), heart rate (B) and diastolic pressure (C). Each point represents the mean value ±standard error obtained from 6 dogs. Asterisk indicates significant difference from initial control levels, $P<0{\cdot}05$.

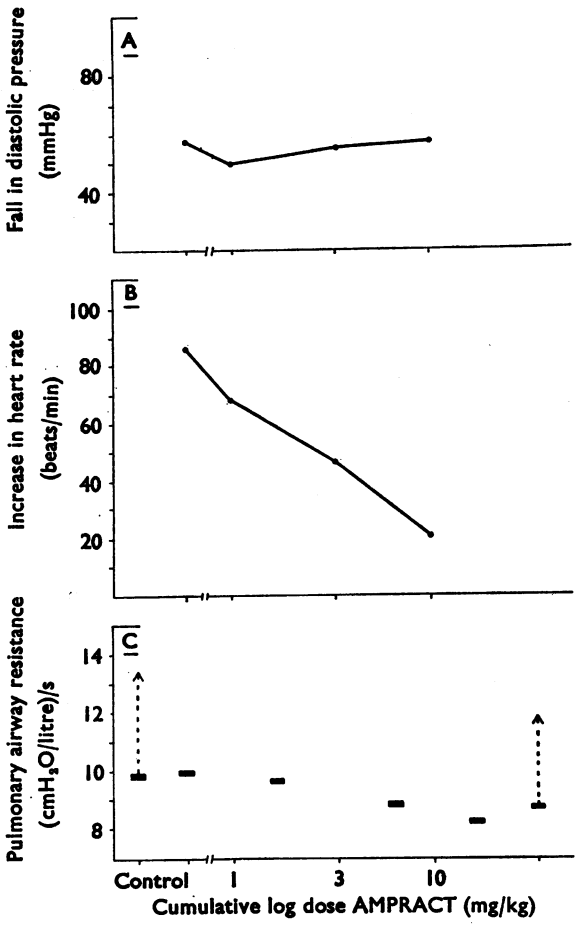

FIG. 7. Effects of α-methyl practolol (AMPRACT) on the isoprenaline-induced (1 μg/kg) fall in diastolic pressure (panel A), increase in heart rate (panel B) and reduction of pulmonary airway resistance (panel C). Resting pulmonary airway resistance is indicated by the horizontal bar and peak responses are represented by the arrows. Two broken lines represent responses to histamine alone (10 μg/kg, i.v.). All other lines represent responses to histamine injected 30 s after isoprenaline (1 μg/kg, i.v.). Each point represents the mean value from 3 dogs.

α-methyl practolol treatment in any dose (Figure 7A). No significant blockade of the isoprenaline-induced effect on airway resistance even after a cumulative dose of 10 mg/kg α-methyl practolol. This treatment also exerted no significant effect on either the resting levels of airway resistance or histamine responsiveness (Figure 7C).

These results with α-methyl practolol indicate that a maximal cumulative dose of 10 mg/kg will only produce a significant reduction of the isoprenaline-induced cardiac stimulant effects. No significant blockade of β-adrenoceptors in either vascular or respiratory smooth muscle in this dose range could be demonstrated.

Discussion

Levy & Wilkenfeld (1969) suggested that β-adrenoceptor antagonists might be classified into three types. One type is capable of selectively blocking vascular

β-adrenoceptors to a relatively greater extent than myocardial β-adrenoceptors; examples are butoxamine (Levy, 1966a), dimethyl isopropyl methoxamine (Levy, 1966b) and H 35/25 (Levy, 1967). The second type is capable of selectively blocking myocardial β-adrenoceptors to a relatively greater extent than vascular β-adrenoceptors; examples are practolol (Dunlop & Shanks, 1968) and 1-(*p*-allylphenoxy)-3-isopropylamino-2-propanol HCl (H 64/52, Levy, 1973). The third type is capable of exerting a non-selective blockade of β-adrenoceptors in all tissues in the same dose range; examples include all of the classical β-adrenoceptor antagonists such as propranolol, dichloroisoprenaline, pronethalol, sotalol, alprenolol and many others.

Those agents that are classified as vascular-selective β-adrenoceptor antagonists all possess an α-methyl substituent group on the ethanolamine side chain. Introduction of an α-methyl group to dichloroisoprenaline, a non-selective β-adrenoceptor antagonist, resulted in an agent that exerted vascular-selective β-adrenoceptor blocking properties (Van Deripe & Moran, 1965). Similar results occurred when an α-methyl group was added to the ethanolamine side chain of INPEA (Somani, 1969). Results cited in this study deal with the effects of methyl substitution on the α-carbon of propranolol and practolol. It should also be pointed out that propranolol and practolol both have an oxymethylene group inserted between the ethanolamine side chain and the aryl group. This type of substitution increases the potency of β-adrenoceptor blockade as is indicated by the fact that propranolol is approximately 10 times more potent than pronethalol, an agent devoid of the oxymethylene group.

α-Methyl propranolol appeared to produce a competitive reversible blockade of β-adrenoceptors in cardiac and vascular smooth muscle as is shown in Figure 1. A cumulative dose range of 0·1–3 mg/kg of α-methyl propranolol resulted in a parallel shifting to the right of the isoprenaline dose-response curves. A comparison of the pA_2 and slope values calculated for α-methyl propranolol and compared to similar experiments performed with propranolol (Wasserman & Levy, 1973) indicated the following results (Table 1). α-Methyl propranolol produced equivalent pA_2 values when calculated from the inhibition of the isoprenaline-induced effects on diastolic pressure, heart rate and contractile force. Compared to propranolol, it appeared to be about 1/10 as potent as a β-adrenoceptor antagonist. The slope values calculated for propranolol on all 3 parameters were all equivalent to 1. These data would support the classification of propranolol as a non-selective, reversible competitive β-adrenoceptor antagonist. α-Methyl propranolol yielded a slope value equivalent to 1 (0·92) only on the isoprenaline-induced drop in diastolic pressure; the slope values of 0·77 and 0·61 for the positive inotropic and

TABLE 1. *pA_2 and regression line slope values for α-methyl propranolol and propranolol in the anaesthetized dog*

Drug	Parameter			Reference
	Fall in diastolic pressure	Positive Chronotropic effect	Positive Inotropic effect	
α-Methyl propranolol	6·66* (0·92)	6·59 (0·61)	6·34 (0·77)	This study
Propranolol †	7·58 (1·17)	7·14 (0·85)	7·26 (1·1)	Wasserman & Levy, 1973

* Each pA_2 value and slope, in parentheses, represents pooled results obtained from 6 dogs. † These results are part of a Ph.D. dissertation completed by M. A. Wasserman (1972).

chronotropic responses to isoprenaline were clearly less than 1. These results would suggest that α-methyl propranolol produces a blockade of vascular β-adrenoceptors that resembled that produced by propranolol and other non-selective β-adrenoceptor antagonists. The blocking effect of α-methyl propranolol on cardiac β-adrenoceptors was clearly different from that evoked by propranolol and related agents.

α-Methyl propranolol exerted a relatively weak blockade of respiratory β-adrenoceptors as shown in Figure 4C. A cumulative dose of 0·1 g/kg significantly reduced the isoprenaline-induced fall in diastolic pressure. A total cumulative dose of 3 mg/kg of α-methyl propranolol was required before any significant blockade of respiratory smooth muscle β-adrenoceptor was apparent. In a previous study it was found that the ED_{50} value for propranolol based upon its ability to reduce the isoprenaline-induced (1 μg/kg) inhibition of the increase in airway resistance due to histamine (10 μg/kg) was 106 μg/kg (C.I. $P=0{\cdot}05$ 80–140; Wasserman & Levy, 1973). α-Methyl propranolol treatment also resulted in a gradual but marked increase in resting airway resistance (Figure 4C). This response did not occur with either propranolol (Wasserman & Levy, 1973) or α-methyl practolol.

α-Methyl substitution of propranolol yields a compound that differs from propranolol in being more selective and less potent as a β-adrenoceptor antagonist. α-Methyl propranolol clearly exerts a different ratio of effects on the myocardial and respiratory β-adrenoceptors than does propranolol.

α-Methyl substitution of practolol, a cardiac-selective β-adrenoceptor antagonist, resulted in a compound that was an even more selective β-adrenoceptor antagonist. It exerted no significant blocking effect on the isoprenaline-induced fall in diastolic pressure (Fig. 5C) but reduced the positive inotropic and chronotropic responses to isoprenaline in a cumulative dose range of 1–3 mg/kg (Figures 5A and 5B). Wasserman & Levy (1973) previously found that practolol, under identical experimental conditions, yielded ED_{50} values of 195 μg/kg (C.I. $P=0{\cdot}05$ 93–393) and 227 μg/kg (C.I. $P=0{\cdot}05$ 127–408) according to its ability to inhibit the isoprenaline-induced (1 μg/kg) positive inotropic and chronotropic effects respectively. Finally, α-methyl practolol exerted no significant blocking effect on the isoprenaline-induced changes in airway resistance (Figure 7C). Practolol has been shown to exert a significant blockade of this effect of isoprenaline on aiway resistance yielding an ED_{50} value of 609 μg/kg (C.I. $P=0{\cdot}05$ 262–1410) (Wasserman & Levy, 1973). α-Methyl substitution of practolol results in a compound that exerts a weaker blocking effect on cardiac β-adrenoceptors than practolol and which produces no significant blockade of either vascular or respiratory smooth muscle β-adrenoceptors.

These results indicate that α-methyl substitution of propranolol and practolol differentially reduces the β-adrenoceptor blocking potencies of the parent substances, resulting in compounds that are more selective in action. Results obtained in this study, particularly with α-methyl propranolol, add further support to the observation that the β-adrenoceptors subserving cardiac stimulation, vasodilatation and bronchodilatation represent three different β-adrenoceptor subtypes in the dog.

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Please send reprint requests to: Dr. Sydney Ellis, Department of Pharmacology and Toxicology, University of Texas Medical Branch, Galveston, Texas 77550, U.S.A.

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