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A COMPARISON OF THE BRONCHOCONSTRICTOR AND β-ADRENOCEPTOR BLOCKING ACTIVITY OF PROPRANOLOL AND ACEBUTOLOL

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The bronchoconstrictor and β-adrenoceptor blocking activity of (±)-propranolol, acebutolol and two of its analogues were compared in a group of littermate rats. Whilst the analogues of acebutolol had similar bronchoconstrictor potency to propranolol, acebutolol had considerably less activity. No correlation could be found between the degree of bronchoconstriction produced by the four drugs and their β-adrenoceptor blocking activity in the airway smooth muscle. Acebutolol and its analogues show a wide variation in lipid solubility and membrane stabilizing actions but neither of these properties could be related to the production of bronchospasm.

Introduction The ability of the β-adrenoceptor blocking drugs to cause bronchospasm has been widely reported in man (e.g. McNeill, 1964; Macdonald, Ingram & McNeill, 1967; Stone, Sarkar & Keltz, 1973). It has always been assumed that the bronchoconstriction was due to blockade of β-adrenoceptors in the airway smooth muscle and therefore it was expected that the cardioselective drugs, which cause relatively less blockade in the lungs, would be less likely to cause bronchospasm. However, there have been several clinical reports of bronchoconstriction induced by cardioselective β-adrenoceptor blocking drugs; for example, Powles, Shinebourne & Heimer (1969), Marlin, Kumana, Kaye, Smith & Turner (1975).

In animals, it is possible, by using a sensitive recording method, to demonstrate that bronchoconstriction is produced by the β-adrenoceptor blocking drugs (Maclagan & Ney, 1979). In the experiments to be described here, an attempt has been made to compare the effects in the lung of the non-selective β-adrenoceptor blocking drug, propranolol, with those of the cardioselective drug, acebutolol. Two analogues of acebutolol with widely varying physical properties (M&B 16942A and 19421) have also been included for comparison, since our earlier study had suggested that the bronchoconstrictor effects of this type of drug might be due to properties unrelated to β-adrenoceptor blockade (Maclagan & Ney, 1979).

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Method Guinea-pigs (600 to 800 g) of the Dunkin Hartley strain and a group of Sprague-Dawley littermate rats (300 to 500 g) were used. They were lightly anaesthetized with urethane (1.25 g/kg i.p.) and breathed spontaneously. Airways resistance (R_{aw}) and dynamic lung compliance (C_{dyn}) were measured by the method described by Maclagan & Ney (1979). The right carotid artery was cannulated for the measurement of blood pressure (BP) and this signal was integrated to give the heart rate (HR). The left jugular vein was cannulated for the intravenous injection of drugs.

The following drugs were used: isoprenaline sulphate (Burroughs Wellcome); (±)-propranolol (ICI); acebutolol and two of its analogues, M&B 16942A and 19421 (May and Baker). Details of the analogues of acebutolol are given in Table 1 of the paper by Basil, Clark, Coffee, Jordan, Loveless, Pain & Wooldridge (1976). The compounds chosen for the present experiments were Compound 1, M&B 16942A (1-(2-acetyl-4-acetylamino-phenoxy)-3-isopropylaminopropan-2-ol) and Compound 10, M&B 19421 (1-(2-*n*-butyryl-4-*n*-butyrylaminophenoxy)-3-isopropylaminopropan-2-ol). All drugs were made up in 0.9% w/v NaCl solution (saline), injected in a volume not exceeding 0.2 ml and washed in with 0.2 ml saline. Addition of ascorbic acid to the solutions of isoprenaline sulphate was not possible because this vehicle caused changes in the respiratory pattern. Consequently, every 60 min fresh isoprenaline solutions were prepared which were shown to be stable for this period of time as reproducible bronchodilator responses could be obtained to repeated test doses.

Results *Guinea-pigs* Injection of 2×10^{-7} and 4×10^{-7} mol/kg of propranolol to guinea-pigs resulted in increases in R_{aw} of 21 ± 6% ($n = 6$) and 39 ± 5% ($n = 6$) respectively. The same doses of acebutolol had no effect on R_{aw} but bronchoconstriction was seen with much larger doses e.g., 2×10^{-5} and 4×10^{-5} mol/kg of acebutolol caused increases in R_{aw} of 17 ± 4.6% ($n = 7$) and 36.5 ± 5.7% ($n = 7$) respectively. Thus, acebutolol was about 100 times less effective than propranolol in causing bronchoconstriction.

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Rats A similar difference in the bronchoconstrictor potency of propranolol and acebutolol was observed in rats. In this species an attempt was made to compare the bronchoconstrictor potency with β-adrenoceptor blocking activity for propranolol, acebutolol and its analogues M&B 16942A and M&B 19421.

Dose-response curves for isoprenaline-induced bronchodilatation and tachycardia were constructed from the percentage changes in R_{aw} and heart rate. The shift of the dose-response curve in the presence of the β-adrenoceptor blocking drug was used to assess the degree of β-adrenoceptor blockade. In an *in vivo* experiment of this type, complete dose-response curves could not be determined, so the shift of the curve was measured from an arbitrary point chosen as 50% of the maximal response obtained in the control period. A single dose level (4×10^{-7} mol/kg) of each antagonist was used in these experiments. The results are summarized in Table 1.

When the bronchoconstrictor effects of the drugs were compared (column 2 of the Table) it was found that, at a dose of 4×10^{-7} mol/kg, the analogues, M&B 16942A and 19421, were approximately equipotent to propranolol in causing bronchoconstriction whereas acebutolol was ineffective. However, at this dose, the degree of β-adrenoceptor blockade in the lungs produced by propranolol was about 4 times greater than that of M&B 19421 and twice that of acebutolol and M&B 16942A. Thus the bronchoconstrictor activity of the drugs did not correlate with their β-adrenoceptor blocking activity in the lungs.

Discussion Acebutolol was found to be a much weaker bronchoconstrictor agent than its two analogues, M&B 16942A and M&B 19421, and propranolol; in guinea-pigs, the bronchoconstrictor activity of acebutolol was about one hundred times less than that of propranolol.

We attempted to relate the drugs' ability to cause bronchospasm to their potency in causing blockade of the β_2-adrenoceptors in airway smooth muscle of rats. The experimental design for measuring β-blocking activity was necessarily simple but the data are in agreement with previously published *in vivo* work with these four drugs. Propranolol is considered to be a non-selective β-adrenoceptor blocker (Shanks, 1966) and this was confirmed in the present results. Comparison of the 3rd and 4th columns of Table 1 shows that acebutolol and M&B 19421 were more active antagonists at β_1- than β_2-adrenoceptors and that M&B 16942A was equally effective on both types of receptor. This confirms the findings of Basil *et al.* (1976). The present results also agree with those of Maxwell & Collins (1974); in both studies acebutolol was more selective for the cardiac β_1-receptors than the bronchial β_2-receptors. Thus our simple method for measuring β-adrenoceptor blockade appears to be a valid one.

The results show that M&B 16942A and M&B 19421 are much less potent β-blocking drugs than propranolol in the lung yet they cause an equal degeee of bronchoconstriction. Conversely, the two analogues are equipotent with acebutolol in blocking lung β_2-receptors, yet acebutolol is about 100 times less potent in causing bronchoconstriction. Thus there is no direct correlation between the ability of the drugs to cause bronchospasm and their ability to produce blockade of the β-adrenoceptors in the lung. This conclusion supports our earlier findings that the bronchoconstrictor and β-adrenoceptor blocking action of propranolol are unrelated (Maclagan & Ney, 1979). These results also suggest that the screening of drugs of this type for their relative lack of action on β_2-adrenoceptors may be an unreliable guide to their ability to cause bronchospasm.

Other properties of the compounds were then considered to see if they might contribute to the bronchoconstriction. The lipid solubility of the drugs was compared but no correlation with the bronchoconstrictor action could be found. The descending order of lipid solubility (measured as the partition coefficient in octanol/water at pH 7.4) was proprano-

Table 1 Comparison of effects of 4×10^{-7} mol/kg of antagonists as bronchoconstrictors and as β-adrenoceptor blocking agents

β-Adrenoceptor blocking drug	*Bronchoconstrictor action* ($\uparrow R_{aw}\ cmH_2O\ l^{-1}\ s^{-1}$)	*Antagonism of isoprenaline-induced bronchodilatation (arbitrary units)*	*Antagonism of isoprenaline-induced tachycardia (arbitrary units)*
(±)-Propranolol	16.3 ± 1.55	5.24 ± 1.56	5.1 ± 1.7
	(n = 3)	(3)	(3)
M&B 16942A	15.2 ± 6	1.86 ± 0.09	1.61 ± 0.11
	(n = 3)	(3)	(3)
M&B 19421	14.4 ± 1.2	1.18 ± 0.05	2.97 ± 0.26
	(n = 3)	(3)	(3)
Acebutolol	0	1.9 ± 0.7	8.53 ± 4.6
	(n = 2)	(2)	(2)

lol > M&B 19421 > acebutolol > M&B 16942A (K.R.H. Wooldridge, personal communication), while the descending order of bronchoconstrictor potency was propranolol ≥ M&B 16942A ≥ M&B 19421 ≫ acebutolol.

Since the compounds with higher lipid solubilities have relatively greater membrane stabilizing activity it may be concluded that the latter property is also unrelated to their bronchoconstrictor activity. There is at present no satisfactory explanation for the relative lack of bronchoconstrictor activity of acebutolol compared to the effects of the other tested drugs of this type.

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