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Comparative study of six β-adrenoceptive antagonists on airway resistance and heart rate in the guinea-pig

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Summary

1. The effects of six β-adrenoceptive antagonists [(±)-propranolol, (+)-propranolol, (±)-sotalol, (±)-practolol, (±)-pindolol and (±)-procinolol] were studied on airway resistance and heart rate in guinea-pigs and dose-response curves constructed.

2. All β-adrenoceptive antagonists decreased heart rate and increased airway resistance. A significant correlation was found between the increase in airway resistance and the degree of bradycardia induced by all drugs except practolol. The orders of activity of the six drugs in inducing significant variations of the two parameters were respectively, for airway resistance: (±)-procinolol>(±)-pindolol>(±)-propranolol>(±)-sotalol>(+)-propranolol>(±)-practolol, and for heart rate: (±)-pindolol>(±)-procinolol>(±)-propranolol>(±)-sotalol>(+)-propranolol>(±)-practolol.

3. (±)-Sotalol, (±)-pindolol and (±)-procinolol-induced changes in airway resistance and heart rate reached plateau values, which were not modified by increasing the dose. Since sotalol and procinolol have only very weak partial agonist and cardiac depressant properties, it appears that these changes can mainly be accounted for by the suppression of sympathetic tone. It is probable that this is also the case with pindolol.

4. On the other hand, (±)-propranolol and (+)-propranolol induced dose-related changes in airway resistance and heart rate. Thus, a direct and non-specific effect of both drugs on the bronchial muscle, similar to that observed on the heart appears to be implicated, together with sympathetic tone suppression in these variations.

5. (±)-Practolol-induced effects on airway resistance and heart rate were different from those observed with the five other β-adrenoceptive antagonists.

Introduction

Intravenous administration of propranolol to asthmatic subjects has been shown to induce a reduction in forced expiratory volume (FEV_1) (McNeill, 1964). This result was confirmed when propranolol was administered orally (Von Meier, Lydtin & Zöllner, 1966) or by aerosol (Langer, 1967). Similarly, Herxheimer (1967) has shown that exposure to an aerosol of propranolol induced severe dyspnoea in guinea-pigs.

The effects of i.v. propranolol on airway resistance have recently been investigated in normal subjects (McNeill & Ingram, 1966; Macdonald, Ingram & McNeill,

1967) and in dogs (Oskoui & Aviado, 1969), and in both cases an increase in airway resistance has been observed. In asthmatic patients, propranolol was shown to be a much stronger bronchoconstrictor agent than practolol when both drugs were administered intravenously (Macdonald & McNeill, 1968) and stronger than alprenolol and oxprenolol, when all drugs were given by aerosol (Beumer, 1969).

In the present work, the effects of six different β-adrenoceptor blocking agents have been investigated on airway resistance in guinea-pigs. These agents, which were chosen because they differed widely from each other in their respective β-adrenoceptor antagonism, partial agonist and quinidine-like properties, were (±)-propranolol, (+)-propranolol, (±)-sotalol, (±)-pindolol, (±)-practolol and (±)-procinolol [1-(o-cyclopropylphenoxy)-3-isopropylamino-2-propanol]. In an attempt to elucidate their mechanisms of action at the bronchopulmonary level, the effects of the six drugs on airway resistance were compared to those exerted simultaneously on heart rate.

Methods

Male guinea-pigs, weighing from 0·4 to 0·6 kg were anaesthetized with urethane (1·25 g/kg, i.p.). A cannula was inserted into the trachea and the animals were allowed to breathe spontaneously.

Transpulmonary pressure was determined by means of a Hewlett Packard 268 B differential pressure transducer. One port of this transducer was connected to an intrapleural catheter inserted into the 6th or 7th intercostal space. The catheter was of polyethylene tubing, 1·2 mm in inner diameter and 20 cm long. The other port of the differential transducer was connected to the endotracheal cannula.

Air flow and tidal volume were determined according to the method described by Ito & Aviado (1968). The guinea-pig was placed in supine position in a body plethysmograph made of wood and plexiglas. A Sanborn pneumotachometer was connected to one open end of the chamber. The tracheal cannula was passed through another hole to the outside of the body plethysmograph. Thus, the respiratory movement of the guinea-pig caused a continuous flow of air in and out of the plethysmograph via the pneumotachometer. The air flow arising from chest motion in the body plethysmograph was integrated (Hewlett Packard 350–5000 B unit) to derive tidal volume. Heart rate was measured by means of a Hewlett Packard 350–3400 cardiotachometer and all parameters (transpulmonary pressure, air flow, tidal volume and heart rate) were continuously recorded on a 7700 series Hewlett Packard recorder.

In this study, the mean airway resistance values include the intrathoracic (alveoli to trachea) and tissue viscous resistance components. Mean airway resistance is expressed as the ratio of the pressure change to flow change occurring at two points of equal volume during inspiration and expiration. Since at these two points of equal lung volume the compliance is the same, this factor does not need to be involved in mean airway resistance calculation. This method provided values which represent the average inspiratory and expiratory resistance near peak inspiratory and expiratory flow. Thus, these values closely approximate to the average resistance during the respiratory cycle (Amdur & Mead, 1958 ; Colgan, 1964 ; Diamond, 1967, 1969).

All β-adrenoceptor blocking drugs have been studied in groups of seven guinea-pigs. All drugs were injected into the cannulated left jugular vein. The effects of five to seven increasing doses of each drug were studied in each guinea-pig. The values of the four parameters were measured when the maximal effects on airway resistance and heart rate were observed, i.e. 2 min after each injection and also 15 and 30 min after the last injection. All injections were spaced 2·5 min apart.

The following drugs, exclusive of anaesthetic agent, were used: (±)- and (+)-propranolol hydrochlorides, (±)-sotalol hydrochloride, (±)-pindolol, (±)-practolol hydrochloride and (±)-procinolol [1-(o-cyclopropylphenoxy)-3-isopropylamino-2-propanol] hydrochloride, a new potent β-adrenoceptor blocking drug (Boissier, Ratouis, Dumont, Derible & Lavaux, 1970; Boissier, Giudicelli, Viars, Advenier, Mouillé & Larno, 1971b). (±)-Pindolol was dissolved at the required concentrations in saline containing an equimolar quantity of tartaric acid. All other drugs were dissolved in 0·9% sodium chloride at the required concentrations. Doses are expressed in terms of the base for all drugs.

Results

Airway resistance

The effect of increasing doses of each of the six β-adrenoceptor blocking drugs in enhancing airway resistance is shown in Fig. 1, and Table 1 indicates airway resistance basic values in the control situation. With all drugs, the maximum increase in airway resistance was observed 2 min after their administration. The increase induced by the highest dose of the six drugs lasted at least 30 min with (±)-propranolol, sotalol, pindolol and practolol, but was reduced to about half that time with procinolol and (+)-propranolol (Table 2).

As can be seen from Fig. 2, three different types of dose-response curves to the β-adrenoceptor blocking drugs on airway resistance can be distinguished. The increases in airway resistance induced by pindolol, sotalol and procinolol are not dose-dependent and quickly reach, although at different doses, plateau values of 8 to 16% which do not differ significantly from each other. Higher doses of pindolol and procinolol could not be used, since they induced cardiovascular failure and were lethal in guinea-pigs. On the other hand, (±)-propranolol and (+)-propranolol induced dose-related increases in airway resistance. Finally, practolol had only moderate effects on airway resistance over a wide range of doses.

The order of activity of the six drugs in inducing a significant increase in airway resistance is procinolol>pindolol>(±)-propranolol>sotalol>(+)-propranolol>practolol.

Heart rate

The effect of increasing doses of each of the six β-adrenoceptor blocking drugs in reducing heart rate is shown in Figure 1. The control heart rates are shown in Table 1. With all drugs the maximum decrease in heart rate was observed 2 min after their administration. The bradycardia induced by the highest dose of the six drugs lasted over 30 min with sotalol and pindolol, but decreased in intensity earlier with the four other agents (Table 2).

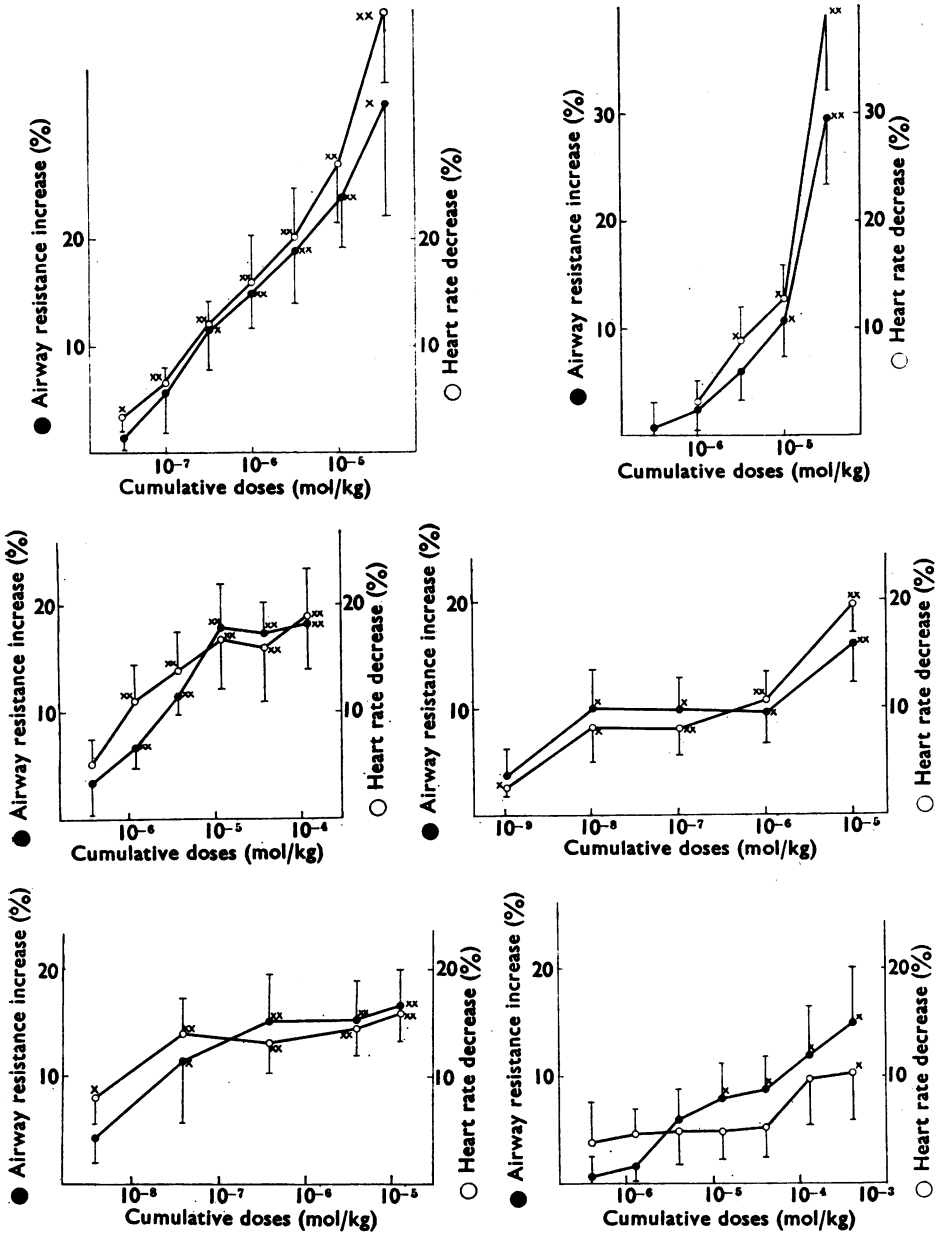

FIG. 1. Individual effects (mean±S.E.M.) of increasing and cumulative doses of (±)-propranolol, (+)-propranolol, (±)-sotalol, (±)-procinolol, (±)-pindolol and (±)-practolol on airway resistance and heart rate in guinea-pigs. X ($P<0.05$) and XX ($P<0.01$) indicate significant increases in airway resistance or decreases in heart rate.

TABLE 1. *Control values (mean±S.E.M.) for airway resistance and heart rate in the six groups of guinea-pigs before receiving the drugs indicated*

Group	Airway resistance ((cm H_2O/ml)/s)	Heart rate (beats/min)
(±)-Propranolol	0·47±0·06	256±12
(+)-Propranolol	0·43±0·03	260±13
Sotalol	0·41±0·08	260±12
Pindolol	0·37±0·04	260±11
Practolol	0·36±0·02	219±18
Procinolol	0·34±0·04	256± 8

Figure 3 shows that three different types of response to the six β-adrenoceptor blocking drugs on heart rate can again be distinguished. The reductions in heart rate induced by pindolol, procinolol and sotalol are not dose-dependent and quickly reach (at different doses) plateau values of 8 to 16%, which do not differ significantly from each other. (±)-Propranolol and (+)-propranolol induced dose-related decreases in heart rate. Finally, practolol had significant negative chronotropic effects only at the dose of 100 mg/kg ($4{\cdot}1 \times 10^{-4}$ mol/kg).

The order of activity of the six drugs in inducing a significant bradycardia is pindolol>procinolol>(±)-propranolol>sotalol>(+)-propranolol>practolol.

Figure 1 and Table 3 show that with (±)-propranolol, (+)-propranolol, sotalol, pindolol and procinolol there is a linear regression and a significant correlation between drug-induced increases in airway resistance and decreases in heart rate. No correlation was found with practolol.

Discussion

Our results show that all six β-adrenoceptor blocking drugs induce in guinea-pigs a decrease in heart rate and an increase in airway resistance. If the former effect

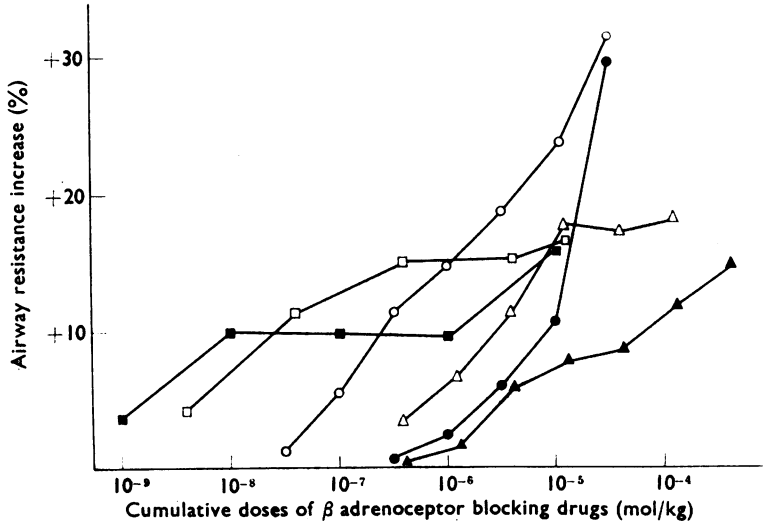

FIG. 2. Variations in airway resistance induced in guinea-pigs by (±)-propranolol (○), (+)-propranolol (●), (±)-sotalol (△), (±)-practolol (▲), (±)-pindolol (□) and (±)-procinolol (■).

TABLE 2. *Percentage* (±S.E.M.) *variations in airway resistance and heart rate induced by the highest dose of the six β-adrenoceptor blocking drugs measured* 2 *and* 30 *min after administration*

β-Adrenoceptor blocking drug	mg/kg	mol/kg	Airway resistance Percentage increase after 2 min	Airway resistance Percentage increase after 30 min	Heart rate Percentage decrease after 2 min	Heart rate Percentage decrease after 30 min
(±)-Propranolol	2·6	1×10^{-5}	24·7†± 5·8	23·3†±4·3	−22·7†±4·4	−17·2†±3·2
(+)-Propranolol	8·7	$3{\cdot}4\times10^{-5}$	31·3*±10·4	13·2*±4·6	−43·6†±5·9	−32·5†±5·8
Sotalol	26	$1{\cdot}1\times10^{-4}$	19·0†± 6·0	16·7†±3·6	−17·6†±5·1	−16·0†±7·7
Pindolol	3	$1{\cdot}2\times10^{-5}$	18·5†± 4·8	17·0*±4·9	−16·5†±2·9	−13·9*±4·1
Practolol	100	$4{\cdot}1\times10^{-4}$	14·6*± 4·8	13·3 ±7·6	−10·3*±4·1	− 5·9 ±4·2
Procinolol	2·6	1×10^{-5}	15·6†± 3·7	9·0*±3·0	−19·6†±2·6	− 5·4 ±4·3

* Significant variation $P<0{\cdot}05$. † Significant variation $P<0{\cdot}01$.

is rather well documented, the latter, which has already been described with propranolol (Macdonald & McNeill, 1968; Oskoui & Aviado, 1969) appears to be a general property of the six drugs studied. However, it must be observed that practolol and procinolol cause only slight increases in airway resistance over a wide range of doses. This finding is less surprising for practolol, which is known to have a selective affinity for β_1-(cardiac) adrenoceptors (Dunlop & Shanks, 1968) and weak bronchoconstrictor effects (Macdonald & McNeill, 1968) than it is for procinolol, which is a non-selective β-adrenoceptor blocking agent (Boissier *et al.*, 1971b).

The effects of sotalol, procinolol and pindolol on airway resistance and heart rate are not dose-dependent and, within the range of doses studied, the changes in both parameters reach plateau values of 8 to 16%. Sotalol is known to have neither partial β-adrenoceptor agonist activity (Barrett & Carter, 1970), nor myocardial depressant effects, unless very high doses are used (Singh & Vaughan-Williams, 1970). This is also the case with procinolol which, with doses up to 1 mg/kg ($3{\cdot}5 \times 10^{-6}$ mol/kg), has no intrinsic β-adrenoceptor stimulant activity and

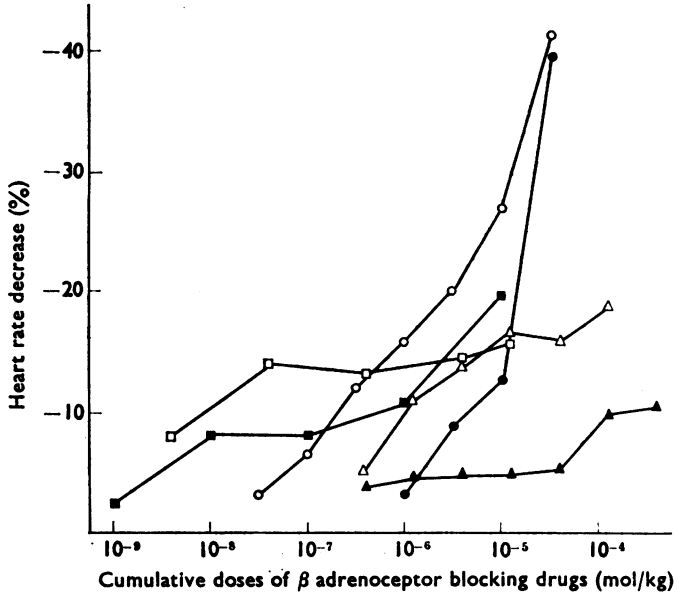

FIG. 3. Variations in heart rate induced in guinea-pigs by (±)-propranolol (○), (+)-propranolol (●), (±)-sotalol (△), (±)-practolol (▲), (±)-pindolol (□) and (±)-procinolol (■).

TABLE 3. *Snedecor's* F *and correlation coefficient* (r) *values for the effects of the six β-adrenoceptor blocking agents on heart rate and airway resistance in guinea-pigs*

	Number of pairs of experimental values	Snedecor's *F* values	Correlation coefficient values (*r*)
(±)-Propranolol	63	39·7†	0·48*
(+)-Propranolol	49	17·7†	0·50*
Sotalol	56	16·3†	0·44*
Pindolol	56	24·1†	0·53*
Procinolol	49	27·1†	0·53*
Practolol	63	2·9	0·17

* $P<0{\cdot}01$. † $P<0{\cdot}001$.

no cardiac depressant effects (Boissier *et al.*, 1971b). Thus, with these two drugs, the plateau decrease in heart rate observed in guinea-pigs and also the plateau increase in airway resistance can probably be accounted for by the suppression of sympathetic tone at both levels. This is also probably the case with pindolol, though the partial β-adrenoceptor agonist effects of the drug (Barrett & Carter, 1970) and its slight cardiac depressant effects (Lubawski & Wale, 1969; Giudicelli, Schmitt & Boissier, 1969; Singh & Vaughan-Williams, 1970) may also be partially involved, especially at the heart level. It could be stated that these effects balance each other, but this is unlikely since the former occur with lower doses than the latter.

The second type of dose-response curve is given by (±)-propranolol and (+)-propranolol, which induce dose-related changes in airway resistance and heart rate. The bradycardia produced by propranolol is not only due to sympathetic tone suppression, but also to the superimposed myocardial depressant effects, which appear with doses ranging from 0·25 to 1·25 mg/kg (Nakano & Kusahari, 1966; Hahn, Pendleton & Wardell, 1968; Aberg, Dzedin, Lundholm, Olsson & Svedmyr, 1969). Therefore, it is interesting to observe that the dose-response curve to (±)-propranolol on heart rate crosses the zone of maximal bradycardia (8 to 16%) induced by sotalol, pindolol and procinolol precisely in a dosage of 0·26 mg/kg (1×10^{-6} mol/kg). Thus, it appears that (±)-propranolol reduces heart rate mainly by sympathetic tone suppression in doses up to 0·26 mg/kg and probably by superimposed direct myocardial depressant effects at higher doses. The same phenomenon is observed with (+)-propranolol, but since this drug has 1/10 to 1/100 of the β-adrenoceptor blocking activity of (±)-propranolol (Howe & Shanks, 1966; Kaumann & Blinks, 1967; Levy, 1968), the dose-response curve to (+)-propranolol is shifted to the right when compared to that of (±)-propranolol and crosses the 8 to 16% bradycardia zone in a dosage of 2·6 mg/kg (1×10^{-5} mol/kg). The myocardial depressant effects of (+)-propranolol (Parmley & Braunwald, 1967; Barrett & Cullum, 1968) probably explain the additional slowing effects of the drug in doses above 2·6 mg/kg.

Similar changes are observed at the bronchopulmonary level. The increases in airway resistance with (±)-propranolol with doses up to 0·26 mg/kg, and with (+)-propranolol at the dose of 2·6 mg/kg, reach values of 10 and 16% and are probably mainly the result of sympathetic tone suppression. Above these doses, the additional increases in airway resistance observed can probably be accounted for by a direct and non-specific effect of both drugs on the bronchial smooth muscle. Recently, Guirgis (1969) and Moore & O'Donnell (1970) demonstrated that (±)-propranolol induces increases in tone in guinea-pig isolated tracheal chains, and Drimal, Aviado & Cho (1971) have shown that after oxprenolol-induced β-adrenoceptor blockade, (±)-propranolol was still able to increase airway resistance greatly.

Practolol-induced variations in heart rate and airway resistance remain very moderate in a wide range of doses. On heart rate a significant bradycardia was observed only with the high dose of 100 mg/kg ($4{\cdot}1 \times 10^{-4}$ mol/kg). Since practolol has *in vivo* 1/3 to 1/7 of the β-adrenoceptor blocking activity of (±)-propranolol on the heart (Dunlop & Shanks, 1968; Wale, Pun & Rand, 1969; Barrett & Carter, 1970; Boissier, Advenier, Giudicelli & Viars, 1971a), these data can only be explained by the strong partial β-adrenoceptor agonist properties of

the drug (Dunlop & Shanks, 1968; Wale *et al.*, 1969; Barrett & Carter, 1970). Similarly, at the bronchopulmonary level, increases in airway resistance were only observed with doses of 10 and 30 mg/kg ($4{\cdot}1 \times 10^{-5}$ and $1{\cdot}2 \times 10^{-4}$ mol/kg). In spite of its β_1-adrenoceptor selectivity, practolol has, *in vivo*, 1/15 to 1/17 of the β-adrenoceptor blocking activity of (±)-propranolol in the bronchopulmonary system (Wale *et al.*, 1969; Boissier *et al.*, 1971a). Thus, the moderate increase in airway resistance induced by practolol in guinea-pigs can also probably be explained by the β-adrenoceptor agonist effects of the drug at this level (Wale *et al.*, 1969). These results confirm that practolol has only weak bronchoconstrictor effects (Macdonald & McNeill, 1968; Beumer, 1969; Areskrog & Adolfsson, 1969).

A linear regression and a significant correlation between increases in airway resistance and decreases in heart rate have been found with (±)-propranolol, (+)-propranolol, sotalol, pindolol and procinolol. Since there is apparently no physiological link between the two phenomena, the probable explanation is that both are induced, at least in a wide range of doses, by β-adrenoceptor blockade. The five above mentioned drugs are non-selective β-adrenoceptor blocking agents and their affinity for cardiac and bronchopulmonary β-adrenoceptors is approximately identical. Furthermore, in the case of (±)-propranolol and (+)-propranolol, a local direct effect on cardiac and bronchial smooth muscles probably develops simultaneously at both levels when high doses are used. In the case of practolol, the lack of correlation between increase in airway resistance and decrease in heart rate could simply be explained by the fact that practolol is a selective β_1-adrenoceptor blocking agent and that it has therefore a greater affinity for cardiac than for bronchopulmonary adrenoceptors. However, if this was the only explanation, the bradycardia should be more pronounced than the increase in airway resistance. This is not the case and the discrepancy remains unexplained, probably because many other factors are involved.

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