A PHARMACOLOGICAL EVALUATION OF THE POTENTIAL OF A BRONCHODILATOR TRIMETOQUINOL TO PRODUCE TACHYCARDIA AND SKELETAL MUSCLE TREMOR

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SYNOPSIS

(−)Trimetoquinol, a potent β-adreno receptor agonist, was pharmacologically evaluated for its potential to produce tachycardia and skeletal muscle tremor. (−)Trimetoquinol was found to be slightly less potent than (−)isoprenaline in depressing incomplete tetanic contractions of the soleus muscle and in producing its positive chronotropic and vasodepressor effects in anaesthetised cats. The results strongly suggest that (−)trimetoquinol, when used as a bronchodilator in asthmatic patients, is as likely as (−)isoprenaline to cause tachycardia and muscle tremor as side effects.

INTRODUCTION

Trimetoquinol possesses β-receptor stimulant activity and it belongs to a series of related 1-substituted 6, 7-dihydroxy-1,2,3, 4-tetrahydroisoquinoline (1, 2). Trimetoquinol is the most potent member of the group and was first described in 1966 (3). Chemically trimetoquinol is 1-(3', 4', 5'-trimethoxybenzyl)-6, 7-dihydroxy-1,2,3, 4-tetrahydroisoquinoline (fig. 1) and it was developed by Tanabe Seiyaku Co., Japan (4).

Sympathomimetic bronchodilators may produce in man side effects such as tachycardia and a disturbing skeletal muscle tremor. Since trimetoquinol, a potent β-receptor agonist, is used as a bronchodilator in the treatment of asthmatic patients it would be useful to determine the potential of trimetoquinol to produce such side effects.

In the present study the potential of trimetoquinol (laevo-siomer) to produce tachycardia and skeletal muscle tremor was pharmacologically evaluated by comparing the quantitative effects of (−)trimetoquinol with that of (−)isoprenaline on the heart rate and incomplete tetanic contractions of the soleus muscle of anaesthetized cats. The cat was chosen as the animal model for this study because it most closely resembles man in the pattern of its responses to sympathomimetic bronchodilators (5).

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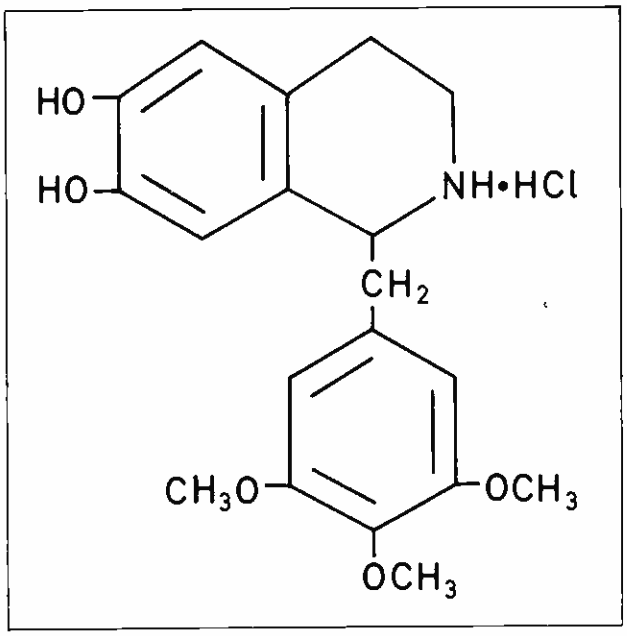

Fig. 1 Structure of trimetoquinol: (ℓ -1-(3' , 4' , 5'-trimethoxybenzyl)-6, 7-dihydroxy-1, 2, 3, 4-tetrahydroisoquinoline).

METHODS

Adult cats of either sex were anaesthetized by intraperitoneal injection of a mixture of α-chloralose (80mg/kg) and sodium pentobarbitone (6mg/kg). The trachea was cannulated and animals were allowed to breathe spontaneously.

The soleus muscle was prepared for recording of incomplete tetanic contractions as described (6). The muscle nerve was stimulated once every 10s at a frequency of 5Hz for 1 second (Devices Isolated Stimulator MK IV with digitimer). Isometric muscle tension was recorded with a Grass force-displacement transducer (Model FT 03C). A resting tension of between 60 and 100g was applied to the muscle and maintained at a constant level throughout each experiment.

General arterial blood pressure was monitored from a common carotid artery with a Statham (Model P23AC) pressure transducer. The heart rate was recorded with a Grass (Model 7P4 DF) tachograph triggered by the arterial pulse.

Drugs were administered cumulatively through a cannulated brachial vein (7). In each animal 2 to 3 dose-response curves for (−)isoprenaline were established before constructing 1 or 2 for (−)trimetoquinol; where 2 curves for trimetoquinol were done this was alternated with a curve for (−)isoprenaline. In all experiments heart rate, arterial blood pressure and incomplete tetanic contractions of the soleus muscle were recorded simultaneously on a Grass 6-Channel curvilinear polygraph (Model 7C).

Drugs used: (−)isoprenaline sulphate (Burroughs Wellcome); (−)trimetoquinol (trimetoquinol hydrochloride injection 0.1mg/ml; Tanabe Seiyaku Co., Inolin injection); dl-propranolol hydrochloride (I.C.I. Ltd.). All drugs solutions were prepared in 0.9% w/v sodium chloride just prior to use and kept at 4°C throughout each experiment. The doses of drugs used refer to the salts.

Expression of results: results are given as the mean ± standard error of mean of 11 determinations except where indicated otherwise.

RESULTS

A typical record of the effects of trimetoquinol on contractions of the cat soleus muscle during cumulative dose administration of the drug is given in fig. 2. Trimetoquinol, like adrenaline and isoprenaline (8)

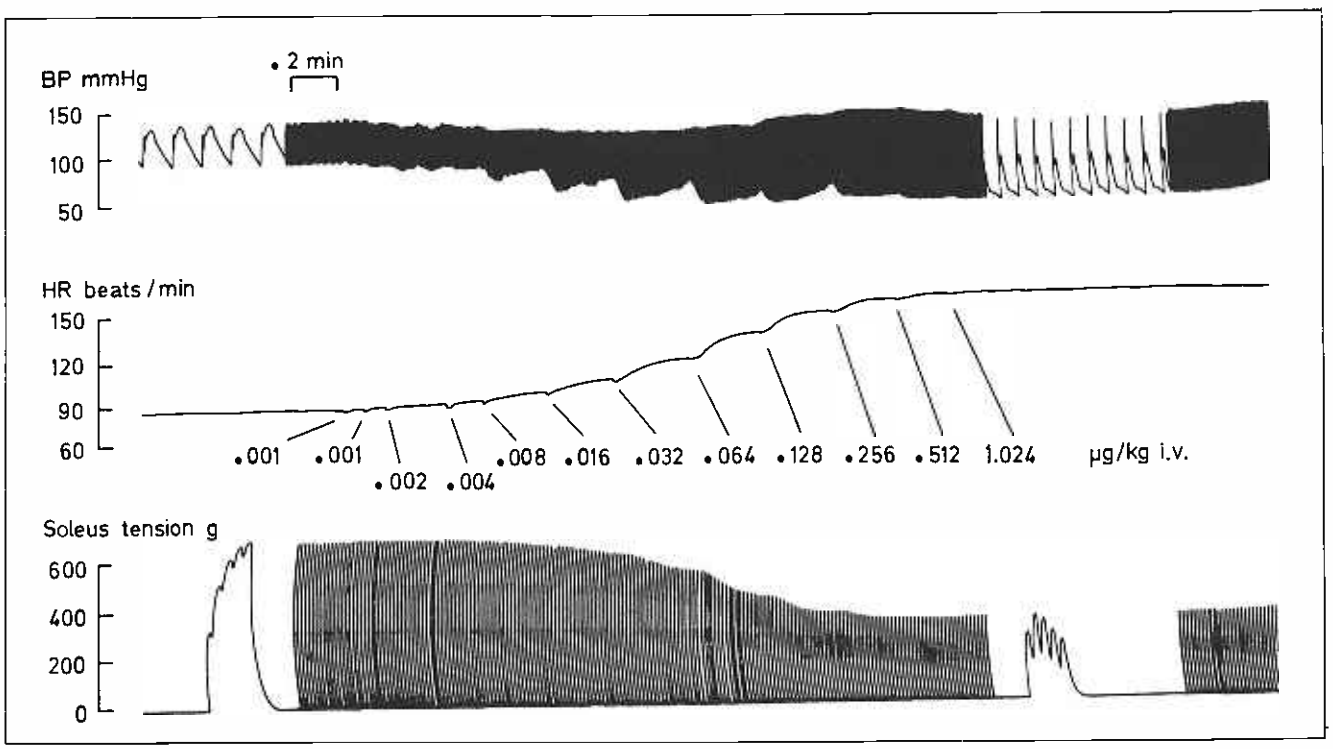

Fig. 2 A typical record showing the effects of cumulative doses of trimetoquinol on the blood pressure (BP), heart rate (HR) and soleus tension of the anaesthetized cat.

produced a decrease in the tension and duration of the maximal twitch, and a pronounced decrease in the fusion of incomplete tetanic contractions of the soleus muscle; the degree of response was graded according to the cumulative dose of drug administered.

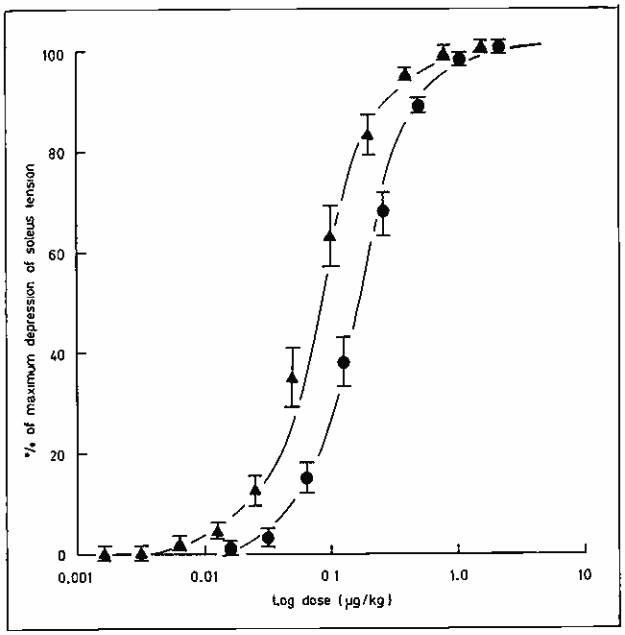

Fig. 3 Cumulative dose-response curves for (−)isoprenaline (▲) and trimetoquinol (●) on incomplete tetanic contractions of the soleus muscle. The responses are expressed as the percentage of the maximal depression of contraction. Each point is the mean ± s.e.m. of 11 determinations.

Fig. 3 shows the cumulative dose-response curves for (−)isoprenaline and (−)trimetoquinol on the soleus muscle. Within the 20-80% range of responses the curves are straight and about parallel to one another. The closeness of the curves indicates that there is little difference in potency between (−)isoprenaline and (−)trimetoquinol; the dose (μg/kg) required to produce 50% of maximal response (ED_{50}) was 0.08 for (−)isoprenaline and 0.18 for (−)trimetoquinol. Thus the ED_{50} ratio (isoprenaline : trimetoquinol) is 0.44.

There is a small difference in the maximal depression of developed muscle tension produced by (−)isoprenaline (51 ± 1.6%) and (−)trimetoquinol (48 ± 1.8%); however, the difference is not significant statistically ($0.2 < p < 0.3$). The time to half return from the maximal response for (−)trimetoquinol (25 to >120 min) was much greater than for (−)isoprenaline (6 to 14 min).

The results from a typical experiment showing the effects of trimetoquinol on heart rate and blood pressure during cumulative dose administration of the drug are also given in fig. 2. Each dose was injected at the peak of the rise in heart rate produced by the previous dose. (−)Trimetoquinol, like (−)isoprenaline, produced positive chronotropic and vasodepressor responses in the anaesthetized cat; the degree of response varied according to the dose of drug administered. With each dose of (−)isoprenaline in the series, the maximal increase in heart rate occurred within less than 1 minute, whereas with (−)trimetoquinol peak response was reached in 2-4 minutes.

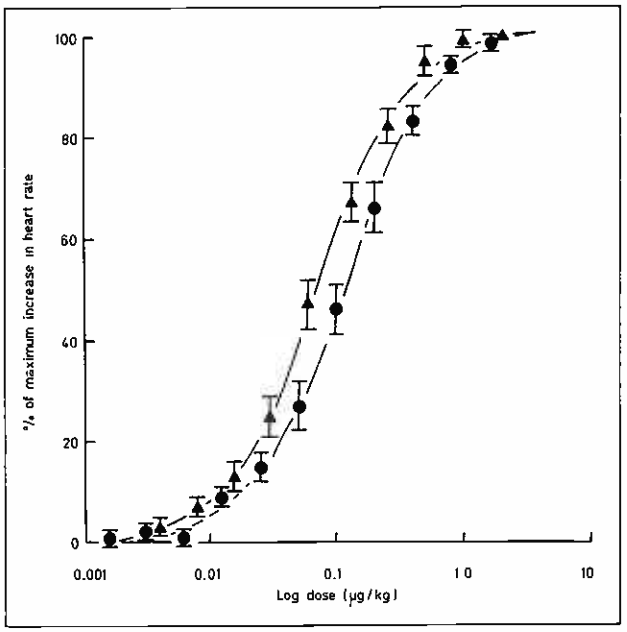

Fig. 4 Cumulative dose-response curves for (−)isoprenaline (▲) and trimetoquinol (●) on heart rate. The responses are expressed as the percentage of the maximal increase in heart rate. Each point is the mean ± s.e.m. of 11 determinations.

The cumulative dose-response curves for (−)isoprenaline and (−)trimetoquinol on the heart rate are shown in fig. 4. The curves are straight and about parallel within the 30-80% range of responses. The difference in chronotropic activity of the two drugs is small considering the closeness of the two curves; the ED_{50} value was 0.07 for (−)isoprenaline and 0.12 for (−)trimetoquinol. The ED_{50} ratio for the two drugs is therefore 0.58.

Similar maximal heart rate (beats/min) responses were produced by (−)isoprenaline and (−)trimetoquinol from resting levels of about 90 beats/min; the nett increase in heart rate was 77 ± 4.7 for (−)isoprenaline and 70 ± 5.1 for (−)trimetoquinol; the difference is not significant statistically ($0.3 < p < 0.4$). In all experiments the time to half-return from maximal response was much longer for (−)trimetoquinol (25 to 60 min) than for (−)isoprenaline (3.5 to 7.5 min).

Vasodepressor responses, gradually increasing in magnitude, were also obtained during the cumulative administration of (−)isoprenaline and (−)trimetoquinol (see fig. 2). For both drugs, the duration of vasodepression was approximately half that of the rises in heart rate. However, the depressor responses to (−)trimetoquinol and (−)isoprenaline were of similar magnitude (33 to 67%). In all the experiments, the minimum dose (about 1 to 1.6mg/kg) required to produce the maximal response was similar for both drugs.

The intravenous injection of the β-receptor antagonist propranolol (0.5mg/kg) completely antagonised the effects of (−)trimetoquinol on heart rate, blood pressure and on soleus muscle contractions.

DISCUSSION

The results show that, in the anaesthetized cat,

(−)trimetoquinol has similar potency to (−)isoprenaline with respect to its positive chronotropic activity and its effect in causing a decrease in the incomplete tetanic contractions of the soleus muscle; the ED_{50} ratios (isoprenaline : trimetoquinol) obtained were 0.58 for chronotropic activity and 0.44 for depression of soleus muscle contraction.

The stimulant effects on the heart are believed to be subserved by β_1-receptors whereas effects on skeletal (soleus) muscle are attributable to stimulation of β_2-receptors (6, 9, 10). The ED_{50} ratios indicate that (−)isoprenaline was slightly more potent than (−)trimetoquinol on the heart and soleus muscle; thus trimetoquinol practically has no selective action on either β_1- or β_2-receptors. Similar comparisons made for salbutamol and isoetharine (11) and for MJ-9184-1 (12) have shown that these β-agonists are much less potent than (−)isoprenaline on the heart and soleus muscle; moreover, the drugs were found to be more selective in action for β_2- than for β_1-receptors.

The time to half-return from maximal response was greater for (−)trimetoquinol (25 to > 120min for depression of muscle tension and 25 to 60 min for heart rate) than for isoprenaline (6 to 14 min and 3.5 to 7.1 min, respectively). (−)Trimetoquinol therefore has a longer duration of action than (−)isoprenaline on the heart as well as on the soleus muscle. For both drugs, however, the effects on the soleus muscle were generally of a longer duration than those on the heart. The vasodepressor responses to (−)trimetoquinol and (−)isoprenaline were of similar magnitude; there was only a slight difference in the minimal dose of each drug required to produce the maximal fall in diastolic blood pressure. This provides further evidence that (−)trimetoquinol and (−)isoprenaline are almost equipotent at β_2-receptor sites.

Sympathomimetic bronchodilators may produce in man side effects such as tachycardia and a disturbing skeletal muscle tremor. The occurrence of tachycardia can be attributed to β_1-receptor stimulation (13, 14) whereas muscle tremor, like the bronchodilator effect, has been attributed to β_2-receptor stimulation (2, 6). The results obtained have shown that (−)trimetoquinol lacks selectivity in its action on β-receptor sites.

Thus, when used as a bronchodilator, (−)trimetoquinol is as likely as (−)isoprenaline to give rise to the side effects of tachycardia and skeletal muscle tremor. These side effects can be expected to be more persistent with trimetoquinol since it has a longer duration of action on the heart as well as on the soleus muscle. Observations of such side effects occurring in asthmatic patients treated with (−)trimetoquinol have already been reported (15, 16).

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