Br. J. Pharmac. (1976), **58**, 43–46

CIRCULATORY EFFECTS OF ORAL AND SUBCUTANEOUS ADMINISTRATION IN NORMAL SUBJECTS OF A NEW BRONCHODILATOR, IBUTEROL, A PRO-DRUG TO TERBUTALINE

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1 The di-isobutyryl ester of terbutaline, ibuterol, was given subcutaneously and orally to healthy volunteers and its effects on heart rate, arterial blood pressure, and ECG were compared with those of terbutaline itself. The effects of the two substances were qualitatively identical, but quantitatively different.

2 By mouth, ibuterol acted more rapidly, and was 2–3 times more active. After intramuscular injection, ibuterol caused less increase in local blood flow than terbutaline.

3 Ibuterol can be regarded as a pro-drug, which in itself has little activity, but which can be made active in the body.

Introduction

Modern sympathomimetic bronchodilators are active by mouth and cause fewer cardiac side effects in relation to their bronchodilator effects. The best known of these drugs are terbutaline and salbutamol (Carlström, 1970; Lewis, 1971). Terbutaline has to be given in much larger doses by mouth to produce the same effects as a subcutaneous injection (Arner, Bertler, Karlefors & Westling, 1970). The di-isobutyryl ester of terbutaline (ibuterol) is hydrolyzed in the body of experimental animals to the active drug terbutaline (Olsson, Persson, Persson & Sörenby, 1974).

Methods

Drugs

Terbutaline was used as the sulphate, molecular weight 549 (equivalent weight 274) and ibuterol as the hydrochloride, molecular weight 402. The ratio between equivalent doses of ibuterol hydrochloride and terbutaline sulphate is 1.47. Both drugs were given in 50 ml water by the mouth, and in 0.5 ml sterile 0.9% w/v NaCl solution subcutaneously. Ibuterol and terbutaline (Bricanyl) were supplied by AB Draco, Sweden (a subsidiary of AB Astra, Sweden).

Subjects

Eight healthy male volunteers were informed of the nature of the study and received payment. Four of the subjects were used in experiments on the effects of drugs on heart rate, blood pressure, and ECG. In the remaining four subjects muscle blood flow was measured.

Procedures

Measurements of heart rate, blood pressure, and ECG. The subjects were fasting, and smoking was not allowed before the test. They sat in a reclining chair. Heart rate was measured from a continuous ECG (CR chest leads); T wave amplitude was measured in lead CR5. Arterial arm blood pressure was measured by the auscultatory method. Baseline values were obtained at the end of a 60 min resting period. Observations were made at 5 or 15 min intervals for 240 min after the drug (or placebo). A light meal (bread, butter, milk) was given 180 min after the drug. Subjective symptoms were recorded. Average basal values for heart rate were 48–61 beats/minute. There were no significant differences between basal values on different days in each individual.

Each of the four subjects was first given 4 drug treatments by mouth at one week intervals, 5 and 10 mg of terbutaline sulphate and of ibuterol hydrochloride (Latin square design). Thereafter the effects of subcutaneous administration of 0.5 and 1.0 mg terbutaline sulphate and 1.25 and 2.5 mg ibuterol hydrochloride were studied in the same way.

Measurement of muscle blood flow. Blood flow in the anterior tibial muscle was measured by the

^{133}xenon wash-out technique (Lindbjerg, 1965; Arner *et al.*, 1970). In each of the four subjects muscle blood flow was studied four times in both legs, and each subject received two doses of terbutaline sulphate and two doses of ibuterol hydrochloride, so that eight observations were made on each drug dose.

Statistical analysis

Analysis of variance, and '4 point assay' for determination of relative potency were used. The total effect on the heart rate was calculated as the area of increased heart rate over 3 and 4 hours.

Results

Qualitative effects of ibuterol

Tachycardia, increase in systolic blood pressure and pulse pressure, and decrease in T wave amplitude were regularly seen. The systolic blood pressure returned more rapidly towards the baseline than the heart rate (Figures 1 and 2). The patients often reported palpitations and tremor, particularly after the higher doses of the drugs. The circulatory effects of the meal were similar to those of the smaller drug doses (Figure 1).

Activity of ibuterol in relation to terbutaline; subcutaneous injection

Both drugs acted within 5 min and gave peak heart rates at 30–60 min (Figure 2). Thereafter, the effects of terbutaline declined more rapidly, but even after 180 min the heart rate was still increased. The effects of ibuterol lasted slightly longer. On a molar basis ibuterol was less active than terbutaline; the equiactive doses being related approximately 1.5 : 1 (Table 1).

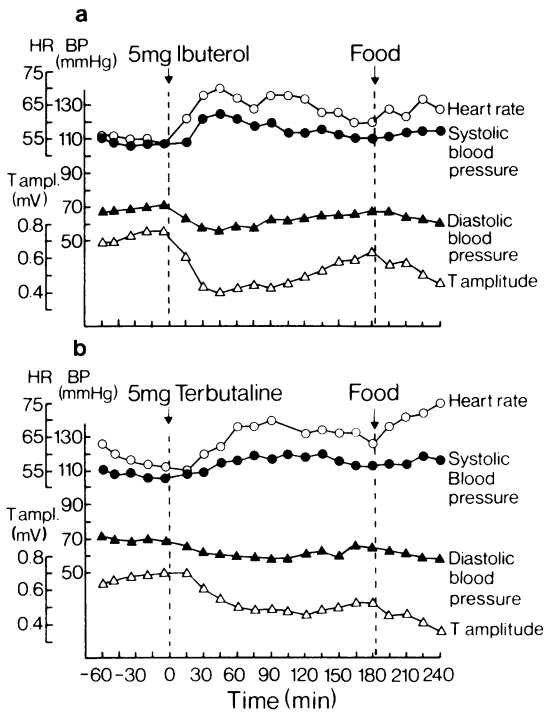

Figure 1 Mean values for heart rate (beats/min), arterial blood pressure (1 mmHg ≈133 Pa) and T wave amplitude after oral administration of (a) 5 mg ibuterol, (b) 5 mg terbutaline. Drugs were given at 0 min and a light meal just after the observation at 180 minutes.

Activity of ibuterol in relation to terbutaline; oral administration

Ibuterol acted more rapidly and caused significant increase in heart rate in less than 15 min whereas

Table 1 Ratio between equiactive doses of ibuterol and terbutaline

Ratio	*Maximal increase in heart rate*	*Total increase in heart rate*	
Equiactive doses		*over 3 h*	*over 4 h*
Ibuterol s.c. / Terbutaline s.c.	1.5 (1.27–1.92)	1.4 (1.15–1.67)	1.4 (1.12–1.68)
Terbutaline orally / Terbutaline s.c.	15 (11.6–18.5)	13 (10.5–1.67)	11 (9.2 –14.1)
Ibuterol orally / Ibuterol s.c.	5.2 (4.1–6.5)	5.0 (4.0–6.3)	4.9 (3.9–6.0)

The ratios are calculated on a molar basis and based on changes in heart rate expressed in three different ways. Mean values (and 95% confidence limits) are given.

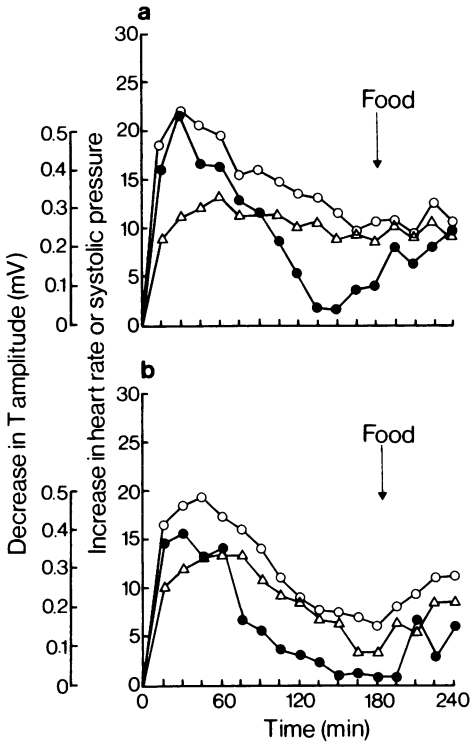

Figure 2 Mean changes in heart rate (O, beats/min), systolic blood pressure (●, mmHg; 1 mmHg ≈ 133 Pa) and T wave amplitude (△) after subcutaneous administration of (a) 1.25 mg ibuterol, (b) 0.5 mg terbutaline. Drugs were given at 0 min and a light meal just after the observation at 180 minutes.

terbutaline acted only after a delay of 15–30 min (Figure 1). In addition the maximal effects of terbutaline occurred later. There were similar differences for arterial blood pressure and T wave amplitude.

Table 1 shows the relative potency of the two drugs. The effectiveness by mouth, as compared to that after subcutaneous administration, was greater for ibuterol than for terbutaline.

Direct effects of ibuterol and terbutaline on muscle blood flow

Resting blood flow without drugs under the present experimental conditions was 1 to 4 ml blood min^{-1} 100 ml $tissue^{-1}$. Table 2 shows that 0–2 min after injection, a 60 times greater concentration of ibuterol than of terbutaline was required to produce the same blood flow. Clearly, ibuterol was a less potent vasodilator than terbutaline. Physostigmine (to a final concentration of 10 μg/ml) did not change the responses to ibuterol or terbutaline appreciably. This suggests absence of local hydrolysis of ibuterol (cf. Olsson *et al.*, 1974).

Discussion

With both ibuterol and terbutaline the pressor effect waned earlier than the tachycardia. The phenomenon may indicate differences in adaptation between receptors (or mechanism) responsible for the cardiovascular actions of the drugs (cf. Conolly, Davies, Dollery & George, 1971).

Ibuterol is slightly less active than terbutaline after subcutaneous injection. A similar difference was observed in animal experiments (Olsson *et al.*, 1974) and may be due to incomplete hydrolysis of ibuterol.

By mouth ibuterol was more effective, and also acted faster than terbutaline. These differences may be related to the different physicochemical properties of the two drugs which could influence the site or mode of absorption. Ibuterol is lipophilic and terbutaline is hydrophilic.

Ibuterol can be regarded as a pro-drug to terbutaline (Review notice, 1974). The greater oral efficiency of ibuterol may give more rapid and predictable therapeutic effects (Arner & Magnusson, 1976).

Table 2 Muscular blood flow in response to ibuterol and terbutaline added locally

Drug	*Concentration (μg/ml)*	*Blood flow (ml min^{-1} 100 ml^{-1})*	
		0–2 min	*3–5 min*
Ibuterol hydrochloride	12.5	14.0 ± 2.5	14.0 ± 1.2
Ibuterol hydrochloride	200	20.4 ± 1.7	23.1 ± 2.3
Terbutaline sulphate	3.125	20.0 ± 2.5	18.6 ± 2.2
Terbutaline sulphate	50	30.0 ± 4.6	29.8 ± 2.5

Average values ± s.e. mean are given for eight observations immediately (0–2 min) and 3–5 min after injection. Note that the injected volume was 0.2 ml and consequently the doses of drugs varied from 0.625 to 40 μg.

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(Received October 9, 1975.
Revised March 1, 1976.)