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Preliminary investigations of a new beta-adrenoceptive receptor blocking drug, LB46, in man

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1. Preliminary studies in man of a new beta-adrenoceptive receptor blocking drug, DL-4-(2-hydroxy-3-isopropylaminopropoxy)-indole (LB46), are described.

2. LB46, 0·5 mg by oral administration, appeared to be of similar potency to propranolol 20 mg in inhibiting isoprenaline-induced and exercise-induced tachycardia.

3. In comparable beta-receptor blocking doses LB46 did not show the negative chronotropic property possessed by propranolol.

A new compound, DL-4-(2-hydroxy-3-isopropylaminopropoxy)-indole (LB46 ; Sandoz Products Ltd. ; Fig. 1) has been shown to possess potent and specific beta-receptor blocking properties (Saameli, 1967). Tablets of LB46 have now been made available for testing in man and it was decided to compare it with a beta-receptor blocking drug of known therapeutic value (propranolol hydrochloride, I.C.I. Pharmaceuticals) in a series of experimental situations that have been described in an earlier paper (Hill & Turner, 1967).

Methods

Resting pulse rate

Eight healthy male volunteers aged 22–26 yr sat quietly for 10 min before their heart rate was determined using a Cambridge direct writing electrocardiograph. They were then given by oral administration one of the preparations under investigation and their resting heart rate redetermined by the same procedure 2 hr later.

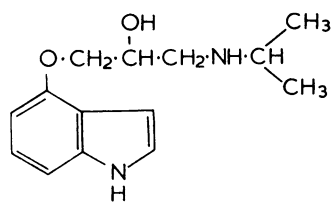

FIG. 1. Structure of LB46.

Isoprenaline-induced tachycardia

Eight healthy male volunteers aged 22–26 yr were investigated using the technique described by Hill & Turner (1967). The subjects were first rested for 10 min in a seated position, after which their heart rate was recorded using a Cambridge electrocardiograph. They were then given standardized inhalations of 2% isoprenaline administered at 8 l./min by a Wright nebulizer until the number of breaths required to cause a consistent rise in heart rate of between 30–40 beats/min had been determined. On each occasion this was preceded by the same number of breaths of water vapour in an attempt to eliminate errors due to the increase in heart rate as a result of deep breathing. The heart rate was recorded every 15 sec for 2 min after cessation of both the air and the isoprenaline inhalations and the maximum increase in rate, obtained after isoprenaline, was calculated by subtraction. The procedure was then repeated on 4 different days, 2 hr after oral administration of the preparations under investigation.

Exercise-induced tachycardia

Nine healthy male volunteers aged 22–26 yr were investigated using the method based on that of Hill & Turner (1967). The subjects were seated at rest for 10 min and a resting pulse rate obtained. Two hours after oral administration of the preparations the subjects lay at rest for 10 min before records were taken. Measurements of heart rate were then made at the following times: lying at rest, 30 sec after sitting up, 30 sec after standing up, during the last 10 sec of each of six 2-min periods of exercise, taken consecutively and without a break for rest, on a motor-driven treadmill at the following speeds and inclines: 1, 2, 3 miles/hr on the flat, and 3 miles/hr on a 3°, 6° and 9° incline.

All three studies were conducted under double-blind conditions and the order of administration of treatments randomized in latin square sequences. The preparations studied in each subject in the first two tests were LB46 (0·5 and 2 mg), propranolol (20 mg) and placebo. In the exercise-induced tachycardia test, LB46 (0·5 mg) was compared with propranolol (20 mg) and placebo.

Results

Table 1 shows the differences in the fall in resting heart rate (±S.E.), with the corresponding *P* values, that occurred after the three treatments when compared with the placebo. It was found that propranolol (20 mg) produced a significant fall compared with the control ($P<0·05$), whereas both doses of LB46 had no such effect.

TABLE 1. *Mean difference in fall in resting heart rate (beats/min±S.E.) between placebo and LB46 (0·5 and 2·0 mg) and propranolol (20 mg) 2 hr after oral administration (n=8)*

Treatment	Difference in fall in heart rate	Standard error	*P* value
LB46 (0·5 mg)	7·0	±3·61	NS
LB46 (2 mg)	6·75	±4·70	NS
Propranolol (20 mg)	9·00	±3·55	<0·05

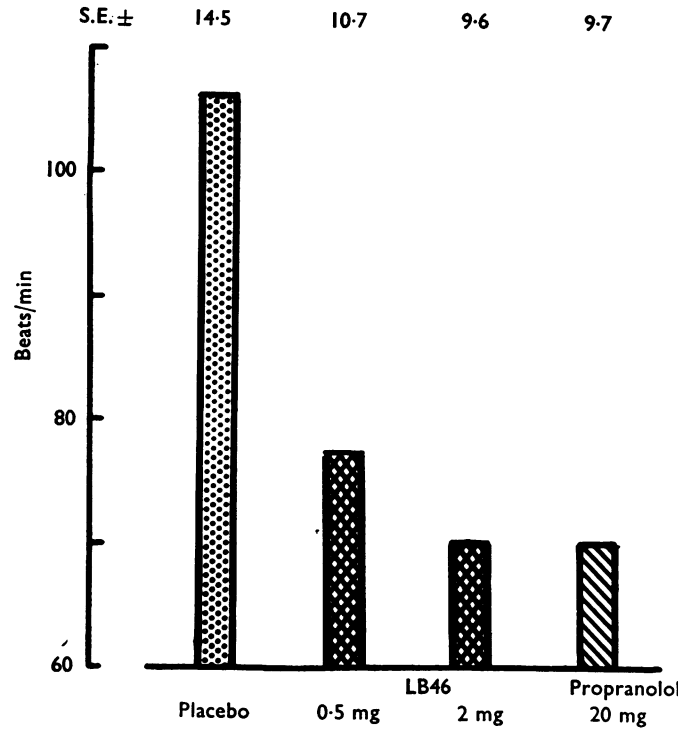

FIG. 2. Mean maximum heart rate in eight subjects (beats/min) following a standard inhalation of isoprenaline 2% 2 hr after oral administration of placebo, LB46 (0·5, 2·0 mg) and propranolol (20 mg).

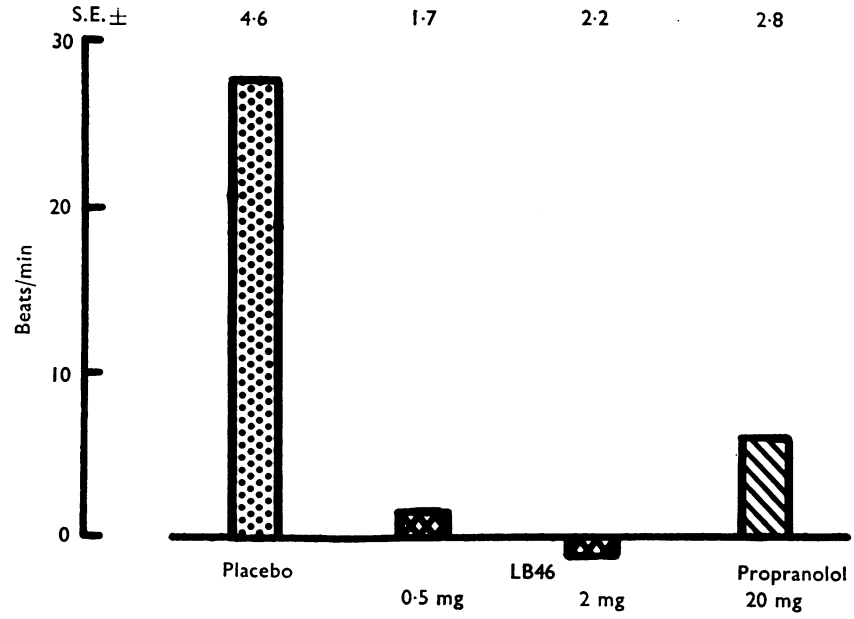

FIG. 3. Mean increase in heart rate in eight subjects (beats/min) due to isoprenaline inhalation when compared with inhalation of water vapour, 2 hr after oral administration of placebo, LB46 (0·5, 2·0 mg) and propranolol (20 mg).

Figure 2 shows the maximum pulse rate in beats/min (±S.E.) following inhalation of 2% isoprenaline aerosol 2 hr after oral administration of LB46 (0·5 and 2 mg), propranolol (20 mg) and placebo. A graded response was obtained, the propranolol (20 mg) being equipotent with LB46 (2 mg). When, however, the rise in heart rate following inhalation of water vapour was taken into account, and the increase in pulse rate in beats/min (±S.E.) due to isoprenaline inhalation alone was plotted (Fig. 3), it was observed that all three "active" treatments caused a significant reduction in isoprenaline-induced tachycardia ($P<0·01$) and that both doses of LB46 were significantly more effective than the propranolol ($P<0·05$).

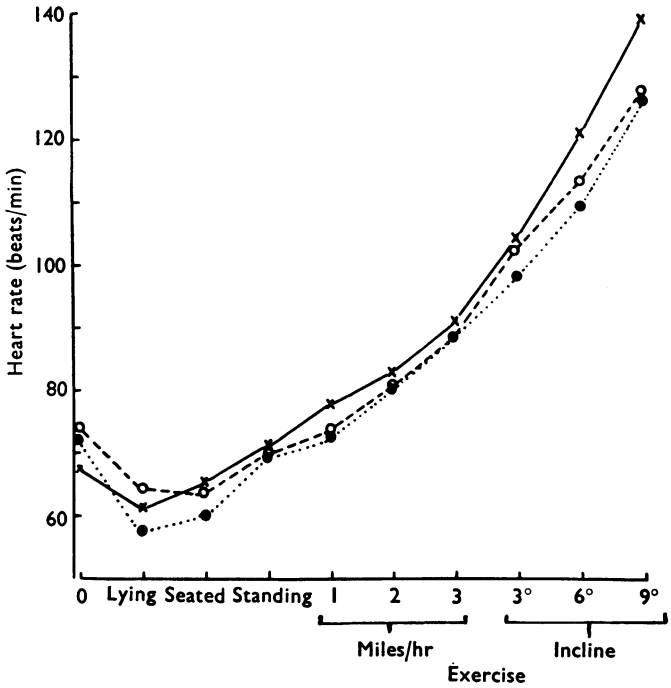

FIG. 4. Mean heart rate in nine subjects (beats/min) at rest, standing and at the end of six consecutive 2 min periods of exercise 2 hr after oral administration of placebo (×——×) LB46 0·5 mg (○- - -○) and propranolol 20 mg (●- - -●).

TABLE 2. *Mean differences in resting heart rate (beats/min±S.E.) between placebo and LB46 (0·5 mg) and propranolol (20 mg) during the first 2 hr after administration of these compounds, and after strenuous exercise (n=9).*

Treatment	Value	0–2 hr	6°	9°
LB46	$\bar{x}$	−3·22	−8	−11·3
(0·5 mg)	S.E.	±4·41	±5·6	± 3·9
	P	NS	NS	<0·02
Propranolol	$\bar{x}$	−9·6	−12·8	−12·6
(20 mg)	S.E.	±2·65	±4·78	±3·8
	P	<0·01	<0·05	<0·01

For details of exercise schedules see text.

Figure 4 shows the mean pulse rates in beats/min at 0 hr, 2 hr, and at the various exercise levels after oral administration of LB46 (0·5 mg), propranolol (20 mg) and placebo. It was found (Table 2) that propranolol (20 mg) produced a significant fall in resting heart rate compared with LB46 (0·5 mg) and placebo in the first 2 hr. Both LB46 (0·5 mg) and propranolol (20 mg) had no significant effect in exercise-induced tachycardia except at the most extreme levels (Table 2), where both drugs produced a significant reduction in heart rate compared with the placebo, but there was no significant difference between the drugs.

Discussion

These results confirm observations in laboratory animals and isolated tissues (Saameli, 1967) that LB46 is a beta-receptor blocking drug with a potency 20–40 times that of propranolol. A significant difference between the compounds was demonstrated, however, in that a dose of LB46 which inhibited isoprenaline-induced tachycardia to an extent comparable with that of propranolol failed to produce the negative chronotropic effect on resting heart rate seen with propranolol. This may reflect some intrinsic sympathomimetic activity of LB46, which was suggested in studies on preparations of isolated guinea-pig atria (Saameli, 1967). Another, less likely, explanation may be that the negative chronotropic action of propranolol is related to its direct myocardial depressant activity, which may not be possessed by LB46.

This compound appears, therefore, to possess considerable beta-receptor blocking activity both in laboratory animals and man, and further studies of its pharmacological and therapeutic activity are indicated.

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REFERENCES

HILL, R. C. & TURNER P. (1967). The effects of a new beta-adrenoceptive receptor blocking drug on heart rate in man. *Br. J. Pharmac. Chemother.*, **32**, 663–670.

SAAMELI, K. (1967). Comparative studies with β-receptor blocking agents and quinidine. *Helv. physiol. Acta*, **25**, *CR* 432–*CR* 433.

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