Br. J. clin. Pharmac. (1976), 3, 267-272.

HUMAN PHARMACOKINETIC AND PHARMACODYNAMIC STUDIES ON ATENOLOL (ICI 66,082), A NEW CARDIOSELECTIVE β-ADRENOCEPTOR BLOCKING DRUG

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1 The β-adrenoceptor blocking effects of orally administered atenolol on tachycardia induced by intravenous isoprenaline or by exercise have been studied in normal volunteers, and compared with the effects of similar doses of propranolol.

2 The blood levels of atenolol at various times after oral administration were determined by g.l.c. and correlated with the degree of inhibition of tachycardia.

3 Atenolol was shown to be a β-adrenoceptor blocker in man, as in animals, in that it antagonized the chronotropic effects of isoprenaline and of exercise.

4 The inhibitory effect of atenolol on exercise-induced tachycardia was evident at a concentration in blood of 0.2 μg/ml and virtually complete at 0.5 μg/ml. Higher concentrations than this did not produce significantly greater blockade.

5 The effects of atenolol on exercise-induced tachycardia were similar to those of propranolol but it was less effective in blocking the rise in heart rate and fall in diastolic blood-pressure induced by intravenous infusion of isoprenaline. This separation of effects is considered characteristic of drugs causing preferential blockade of cardiac β-adrenoreceptors.

6 The half-life of atenolol in blood was calculated to be about 9 hours.

Introduction

Atenolol (ICI 66,082, Tenormin*) is an example of the *p*-substituted phenoxy propanolamine series of β-adrenoceptor blocking agents and its structure is shown in Figure 1.

Its pharmacological properties have been compared in animal studies with those of propranolol and practolol (Barrett, Carter, Fitzgerald, Hall & Le Count, 1973; Hainsworth, Karim & Stoker, 1973, 1974; Harry, Knapp &

*Tenormin is a Trade Mark, the property of Imperial Chemical Industries Ltd.

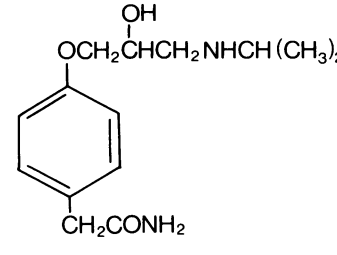

Figure 1 The structural formula of atenolol.

Linden 1973, 1974) and may be summarized thus:
1 Atenolol resembles propranolol and practolol in being an inhibitor of cardiac β-adrenoceptors; its potency resembles that of propranolol and is greater than that of practolol.
2 It resembles practolol in that doses of atenolol which block cardiac β-adrenoceptors do not block peripheral vascular receptors.
3 It differs from propranolol but resembles practolol in not possessing membrane-stabilizing (local anaesthetic and quinidine-like) properties.
4 It resembles propranolol, but differs from practolol, in not possessing intrinsic sympathomimetic (partial agonist) activity.

This combination of properties is different from that offered by available β-adrenoceptor blocking drugs, and experiments were therefore undertaken to evaluate the compound as a β-adrenoceptor blocking agent in man, to estimate its potency as compared with propranolol, and to calculate its half-life.

Methods

The volunteers who took part in these experiments were men between the ages of 21 and 52 years. All were able to understand the nature of the drugs and procedures to which they were exposed, and these were carefully explained to them. Preliminary medical and laboratory examinations were carried out in each instance to ensure that their cardiovascular, renal, hepatic, and haematological status lay within normal limits. All experiments were carried out after a light standard breakfast of one cup of tea or coffee and one slice of lightly buttered toast.

All doses of drugs are stated as base unless otherwise specified.

Design of study

The effect on the tachycardia induced by isoprenaline or by exercise was used to estimate β-adrenergic receptor blockade. To avoid the influence of variability in absorption of drug or in timing of the tests, the effect of atenolol was, where possible, related to its concentration in the blood rather than to the dose administered.

The study was carried out in five phases:
1 an experiment to measure the effect of atenolol at different doses on the tachycardia induced by maximal exercise and by intravenous bolus injections of isoprenaline; 2 a comparison of the effects of atenolol and propranolol on the tachycardia and changes in blood-pressure induced by continuous intravenous infusion of isoprenaline; 3 a comparison of the effects of atenolol and propranolol on tachycardia induced by maximal exercise; 4 a study of the relationship between the effect of atenolol on maximal exercise tachycardia and its concentration in the blood; 5 a pharmacokinetic experiment to establish the blood level and half-life after a single oral dose.

Phase 1 Effect on tachycardia induced by bolus injections of isoprenaline or by exercise

Subjects and procedures Four subjects aged from 34 to 52 years took part. Three dosage levels of atenolol (25, 75 and 150 mg), were used to provide a wide range of blood levels.

Four tests were performed on each subject. A control procedure was first carried out without drug, and then repeated on the same day 90 min after atenolol (25 mg orally). On a subsequent day, the procedure was carried out after a dose of 75 mg and then repeated after a further dose of 75 mg, i.e. after a total of 150 mg. The procedure followed for each test is outlined below:
1 Blood samples were collected for blood level of drug.
2 Increasing injections of isoprenaline were given intravenously at 5 min intervals until increases in heart rate of approximately 25 beats above control were obtained.
3 Maximal exercise was performed 15 min after the completion of the isoprenaline injections.
4 Heart rates were recorded continuously by ECG through self-adhesive electrodes over the sternum.

The exercise test was performed on a treadmill with a 1/10 incline. The speed was adjusted for each subject at a convenient submaximal level which had been determined in a preliminary test. This was held for 2 min and then a maximal level was imposed for 1 minute. The electrocardiogram was monitored throughout the test. After exercise, blood was again collected for measurement of the blood level of the compound.

Phase 2 Effects of atenolol and propranolol on tachycardia induced by infused isoprenaline or by exercise

Subjects and procedures Four subjects aged 21 to 30 years took part.

The degree of β-adrenoceptor blockade produced by equal doses of atenolol and propranolol was measured by (1) inhibition of the cardiovascular response to infused isoprenaline and (2) by the effect on heart rate during exercise. The dose of each drug was 25 mg administered orally as an aqueous solution, the solutions being so labelled that the investigators carrying out the

measurements did not know which drug had been given.

Three tests were performed on each subject.

1 On the first occasion the infusion rate of isoprenaline necessary to raise the heart rate about 50 beats above its normal resting value was determined. The infusion was started at a rate of 1 μg/min and this was doubled at intervals of 6 min to allow a steady state to become established. The resting blood pressure was recorded by auscultation before the infusion, and at 2 min intervals during and after the infusion until the heart rate returned to normal. Blood-pressure measurements were made with an ordinary mercury sphygmomanometer by the same experienced observer throughout. Phase 4 (muffling) of the Korotkoff sounds was taken as the diastolic end-point. One to one and a half hours after the infusion the subjects undertook a maximal exercise test similar to that described in the previous experiment.

2 On the second occasion resting heart rate and blood-pressure were measured as before. Blood was drawn as a blank for blood levels of drug. One of the drugs was then swallowed (25 mg in a 50 ml 0.05 solution) and washed down with water (150 ml). Ninety minutes after ingestion of the drug blood was drawn for estimation of drug levels, and an isoprenaline infusion was then started. The dosage rate needed to increase the heart rate above its resting value by an extent similar to that achieved in the control test was established. An arbitrary upper limit was applied to the dose rate of isoprenaline; doses in excess of twenty times the maximum used in the control experiment were not given. Blood pressure was measured as in 1 and for 30 min after the infusion was stopped. A maximal exercise test was subsequently performed as in 1.

3 The procedure as in 1 was repeated using the other test drug.

Phase 3 Effects of atenolol and propranolol on maximal exercise tachycardia

Subjects and procedures The comparative blocking effects of atenolol and propranolol on maximal exercise tachycardia were studied in nine male subjects aged between 22 and 45. Both drugs were given orally as aqueous solution in doses of 25 mg and 75 mg; maximal exercise tachycardia was induced and measured as already described.

Phase 4 Correlation of blood levels of atenolol and effect on maximal exercise tachycardia

Subjects and procedures In order to correlate blood levels of atenolol with the effect on maximal exercise tachycardia, further exercise tests were performed in a total of ten male subjects aged from 21 to 52 years. Atenolol was given orally in doses from 25 mg to 150 mg to produce blood levels of drug ranging from 0.15 μg/ml to 1.35 μg/ml. Procedures and precautions were as already described; blood levels were calculated as the mean values of samples taken just before and just after the exercise tests.

Phase 5 Pharmacokinetic study

Subjects and procedures Five subjects whose mean weight was 69 kg (range 64-73) and mean age 38 years (range 34-45) took part. Atenolol (100 mg) was administered orally at 09.00 h as a solution in 100 ml of water and washed down with a further 100 ml. Blood samples were taken before and 0.5,1,2,3,5,7.5,10 and 24 h after the dose. Blood levels were assayed by g.l.c. using an electron capture technique as described by Scales (1975). Collections of urine were made at 2-hourly intervals for 12 h after dosing and at 24 and 48 h and similarly estimated.

Results

The effect of atenolol at various blood levels on the increase in heart rate produced by bolus i.v. injections of isoprenaline is shown in Figure 2. There is a shift of the dose response curve to the right with increasing plasma concentrations of the drug, demonstrating antagonism of the chronotropic effect of isoprenaline. It is not possible in man to perform a full dose response curve to isoprenaline, but after a dose of atenolol (75 mg) and at a blood level of 0.36 μg/ml an isoprenaline dose ratio of 6 was achieved.

The effects of atenolol and of propranolol each in an oral dose of 25 mg on the heart-rate dose-response to i.v. infused isoprenaline are shown in Figure 3. Propranolol produced a clear shift to the right but this was much less marked with atenolol, despite a tenfold higher blood level. The effects observed on the diastolic blood pressure of these subjects are shown in Figure 4. Although definition of a diastolic end-point by auscultation becomes difficult in the presence of marked vasodilatation, atenolol is clearly less efficient than is propranolol in blocking the fall in diastolic blood pressure produced by intravenous infusion of isoprenaline.

The effects of propranolol and of atenolol in doses of 25 mg and 75 mg on maximum exercise tachycardia are given in Table 1. At these doses, both drugs reduced the tachycardia of maximal exercise. The effects were almost identical at the

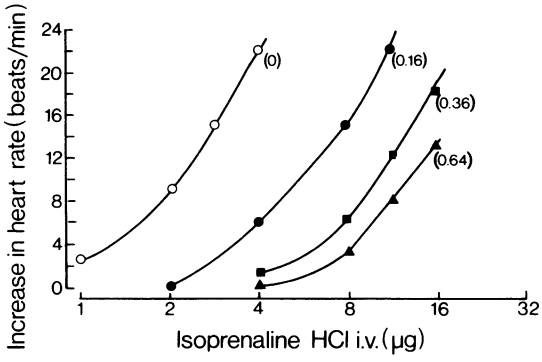

Figure 2 Mean (n = 4) dose response of heart rate to isoprenaline before (○) and after the oral administration of atenolol (25 mg ●; 75 mg ■; 150 mg ▲). The numbers in brackets are the plasma concentrations of atenolol in μg/ml.

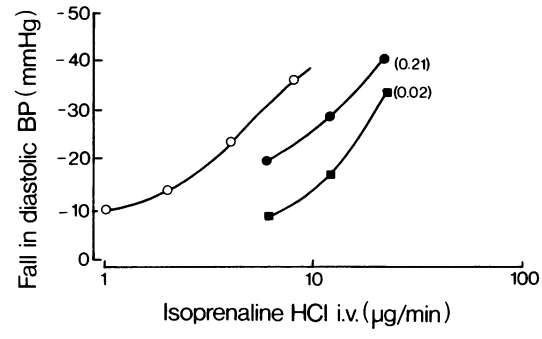

Figure 4 Mean (n = 4) dose response curves to isoprenaline on diastolic blood pressure before (○) and after the oral administration of atenolol (25 mg ●) and propranolol (25 mg ■). The numbers in brackets are the plasma concentrations of the drugs in μg/ml.

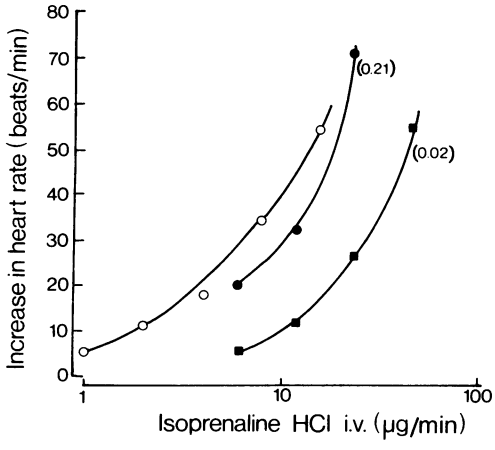

Figure 3 Mean (n = 4) dose response curves to isoprenaline on heart rate before (○) and after the oral administration of atenolol (25 mg ●) and propranolol (25 mg ■). The numbers in brackets are the plasma concentrations of the drugs in μg/ml.

lower dose; propranolol (75 mg) produced a greater depression in heart rate than did atenolol (75 mg) but the difference was not significant ($P > 0.2$).

Figure 5 shows the relationship between blood levels of atenolol and heart rate during maximal exercise in ten subjects. The tachycardia induced by maximal exercise without medication ranged from 172-204 beats/minute. Repeat exercise tests were performed after doses of atenolol (25-150 mg) and at varying times to produce blood levels of drug which ranged from 0.2 to 1.35 μg/ml. Although there was considerable scatter in the responses it can be seen that a near maximum reduction in heart rate, to 160-108 beats/min, was achieved at a blood level of approximately 0.5 μg/ml. In only three subjects did a higher level, of between 0.8 μg/ml and 1.0 μg/ml, produce a further reduction. These tests were performed at different times after dosing to fit in with other studies and to produce a suitable range of blood levels, but a blood level of 0.5 μg/ml or more would be expected to occur within 90 min of the oral administration of a 100 mg dose of atenolol (Figure 6).

The concentrations of atenolol present in blood at various intervals after administration of 100 mg by mouth are shown in Figure 6. The mean peak concentration was 0.9 μg/ml and occurred about 2 h after ingestion; the blood half-life was of the order of 9 hours. The cumulative urinary excretion of atenolol by the same subjects is shown in

Table 1 Comparative effects of atenolol and propranolol on maximal exercise tachycardia in nine subjects

	Heart rate (beats/min)			
Control	*Atenolol (25 mg)*	*Propranolol (25 mg)*	*Atenolol (75 mg)*	*Propranolol (75 mg)*
Mean 185	167	169	158	147
s.e. mean 3.0	4.3	5.2	5.4	5.1

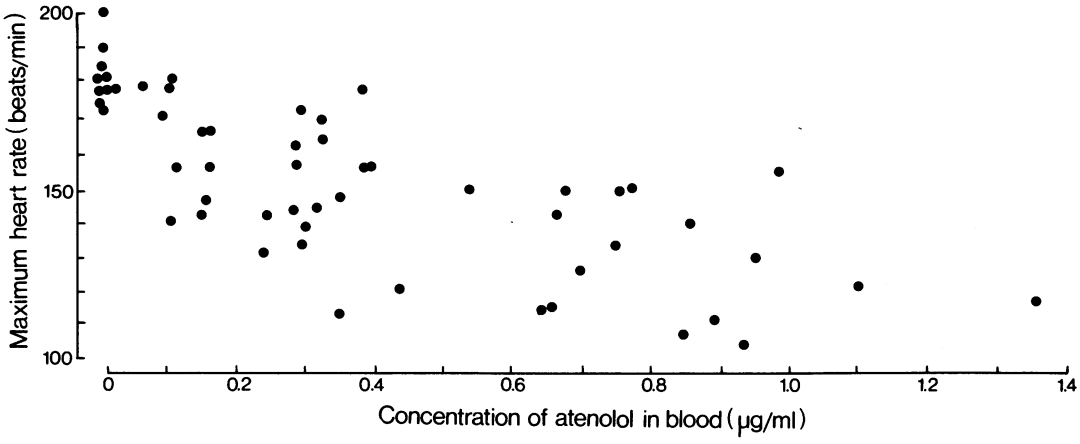

Figure 5 The relationship between blood levels of atenolol and heart rate during maximal exercise in ten subjects.

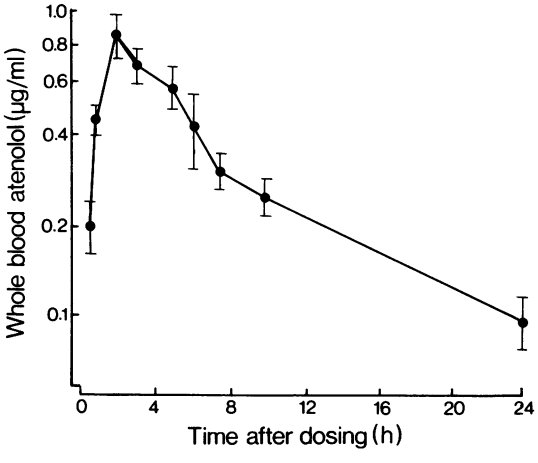

Figure 6 Mean ± s.e. mean concentrations of atenolol in volunteers (n = 5) after a single oral 100 mg dose. The half-life for atenolol was 9 hours.

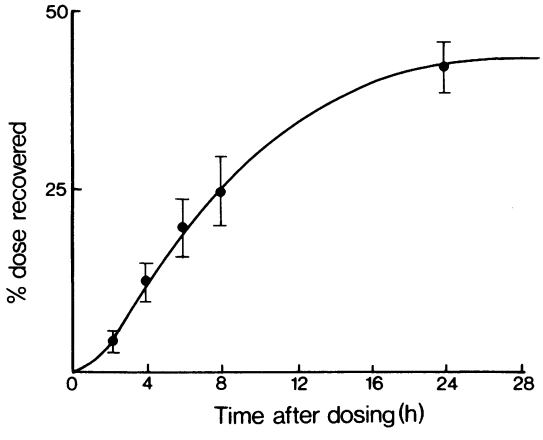

Figure 7 Mean ± s.e. mean cumulative urinary recovery of atenolol in volunteers (n = 5) after a single oral 100 mg dose.

Figure 7. Approximately 45% of the orally administered dose appeared in the urine during the 48 h after administration, by which time urinary excretion had become negligible.

Adverse reactions

At the doses used in these studies, both atenolol and propranolol were well tolerated and no adverse reactions occurred that could be attributed to either drug. Some subjects found the exercise tests more laborious after having taken the higher doses of one or other drug, but this effect was not consistent.

Discussion

These experiments establish that atenolol is an effective β-adrenoceptor blocker in man, since it produced a rightward parallel shift in the heart-rate dose-response curve to isoprenaline, and partially inhibited the tachycardia induced by maximal exercise.

Comparisons with propranolol indicate that in doses of 25 mg both drugs reduce exercise-induced tachycardia to approximately the same extent, but that their effects on the response to isoprenaline infusion are clearly different. A similar difference between selective and non-selective β-adrenoceptor

blockers has been demonstrated also by Taylor *et al.* (1974).

The difference presumably lies in the lack of peripheral blockade with atenolol, permitting peripheral vasodilatation to occur with some reflex tachycardia. If this is indeed the explanation it would indicate that part, at least, of the tachycardia produced during isoprenaline infusion is mediated by withdrawal of vagal inhibition. The use of 'bolus' injections of isoprenaline may more accurately reflect the cardiac blocking actions of atenolol since the concentration of agonist reaching the heart is proportionately much greater than that reaching the periphery and the maximal effect may emerge before it is complicated by reflex activity. The heart-rate response to infused isoprenaline may underestimate the action of selective β-adrenoceptor antagonists on the heart and thus be of doubtful value in their assessment.

When the inhibition of maximal exercise tachycardia produced by atenolol is related to the concentration of drug in the blood (Figure 5), it appears that an effect becomes evident at 0.2 μg/ml and is marked at 0.5 μg/ml. Higher concentrations than this do not produce significantly greater blockade.

Reference to the pharmacokinetic data in Figure 6 indicates that a dose of 100 mg given twice daily should produce a therapeutically adequate degree of β-adrenoceptor blockade. The small standard error of the concentration in blood suggests that the action of atenolol is likely to be fairly uniform between individuals.

The fact that only 45% of an orally administered dose appears in the urine suggests that absorption is fairly consistently incomplete, that substantial metabolism takes place, that excretion occurs also via the bile and faeces, or that a combination of these factors operates. The shape of the curve in Figure 6, with a 'shoulder' at about 5 h, suggests the possibility of enterohepatic recirculation. Further investigations to elucidate these problems are in progress.

Our thanks are due to Mrs M.A. Austin for technical assistance, and to the volunteers for their willing cooperation.

Reprint requests should be addressed to W.T.S.

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(Received March 21, 1975)