BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 7, 223–231 (1986)

BIOAVAILABILITY IN MAN OF ATENOLOL AND CHLORTHALIDONE FROM A COMBINATION FORMULATION

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ABSTRACT

In this comparative bioavailability study in 12 healthy volunteers the blood level profiles and urinary recoveries of both atenolol and chlorthalidone were studied following the administration of the drugs as a fixed combination ('Tenoret 50'), as a free combination, and individually, at doses of 50 mg atenolol and 12·5 mg chlorthalidone.

There were no statistically or clinically significant differences between the three treatments of atenolol in terms of individual blood levels, areas under the curve, and urinary excretion. The mean half-lives were between 5 and 7 h, in agreement with other published data. The variation in peak systemic levels is less than that observed for a number of other β-blocking drugs and is of the same order as seen in other investigations involving atenolol. Thus the bioavailability of atenolol from the fixed combination is equivalent to that from the free combination and from the atenolol tablet.

The mean peak blood concentrations of chlorthalidone were 0·94, 1·00, and 0·99 μg ml^{-1} for the fixed and free combinations and the chlorthalidone tablet, respectively. The mean areas under the curve were also similar as were the mean half-lives and urinary recovery. There were no statistically or clinically significant differences between the three treatments. Thus the bioavailability of chlorthalidone from the fixed combination is equivalent to that from the free combination and from the chlorthalidone tablet.

It is concluded that combining chlorthalidone and atenolol in a single tablet does not affect the systemic bioavailability of either component.

KEY WORDS Atenolol Chlorthalidone Comparative bioavailability Pharmacokinetics Human 'Tenoret 50'

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0142–2782/86/030223–09$05.00

Received 14 July 1984
Revised 11 December 1984

INTRODUCTION

Atenolol ('Tenormin')* is a β adrenoceptor blocking agent developed by the Pharmaceuticals Division of Imperial Chemical Industries plc in the United Kingdom. In animal studies atenolol has been shown to be cardioselective and devoid of intrinsic sympathomimetic and membrane-stabilizing activities.[1–3]

Atenolol is a hydrophilic drug and, in accord with other hydrophilic drugs, it has difficulty in crossing cellular membranes such that in man only about 50 per cent of an oral dose is absorbed.[4] However, for a given dose the blood levels of atenolol are relatively constant and predictable varying only three- to four-fold between patients.[5–7] The half-life of atenolol after a single dose is 6 to 9 h[8] and does not change after chronic administration[9] but does alter in renal insufficiency;[10,11] it is poorly protein bound at about 3 per cent[12] and, in spite of this, and because of its high degree of hydrophilicity it has a low volume of distribution at 0·71 kg^{-1} [5] which closely approximates to human body water. There is a very low concentration of atenolol in the central nervous system in contrast to lipid soluble drugs such as propranolol.[13] Atenolol is metabolized to a very small extent following both intravenous and oral dosing[14] and it has been shown to cross the placental barrier.[15] Atenolol blood levels have been shown not to correlate with its antihypertensive effect.[16]

Beta-blocking drugs and diuretics are frequently co-prescribed in the treatment of hypertension. Chlorthalidone is a widely used effective diuretic which has been administered with atenolol without clinical problems. Since both drugs are administered once daily a fixed combination of atenolol and chlorthalidone for once daily administration in hypertension seemed a logical progression. To this end a fixed combination of atenolol (100 mg) and chlorthalidone (25 mg) was developed which is now available ('Tenoretic')* for the treatment of hypertension. The bioavailability of both drugs from this combination product has been studied.[17,18] However, for some groups of patients, experience suggests that a half-strength 'Tenoretic' comprising 50 mg atenolol and 12·5 mg chlorthalidone ('Tenoret 50')* should be made available and the present study is to determine the bioavailability of such a preparation in comparison with its constituents administered separately and together.

MATERIALS AND METHODS

Volunteer selection

The study was carried out under medical supervision in the Clinical

*'Tenormin', 'Tenoretic', and 'Tenoret 50' are trade marks, the property of Imperial Chemical Industries plc.

Pharmacology Unit of Imperial Chemical Industries plc, Pharmaceuticals Division, and was approved by the ethical committee of the Division.

Twelve healthy adult males were selected from those who responded to a request for volunteers. The volunteers were employees of the Division. Selection was based on the subject's willingness to participate, his availability for the study dates, and the absence of any significant abnormality on a pre-study examination which included a clinical history, complete physical examination, 12-lead electrocardiogram (ECG), and laboratory tests (haematology, urine analysis, and blood chemistry).

Volunteers were excluded if the pre-study examination indicated a history or evidence of: anaemia, asthma, hay fever, allergy, eczema, peptic ulcer, jaundice, or heart, respiratory, gastrointestinal, genitourinary, central nervous, locomotor, skin or psychiatric disease. No subject was receiving or had recently received any form of continuous drug therapy. Each subject agreed not to take concomitant medication, ingest alcohol or take excessive fluids for the duration of the study.

The twelve male subjects ranged in age from 27 to 44 years (mean 34 years) and in weight from 61 to 89 kg (mean 76 kg).

Drug presentation and doses

The four dosage regimens for oral administration were supplied as follows:

Regimen A. (1) 'Tenoret 50', white, film-coated sales tablet containing 50 mg atenolol and 12·5 mg chlorthalidone. (2) A placebo tablet.
Regimen B. (1) 50 mg atenolol white, film-coated calcium phosphate clinical trials tablet and (2) 12·5 mg chlorthalidone white, film-coated tablet.
Regimen C. (1) 50 mg atenolol white, film-coated calcium phosphate clinical trials tablet. (2) A placebo tablet.
Regimen D. (1) 12·5 mg chlorthalidone white, film-coated tablet. (2) A placebo tablet.

Procedures

Each volunteer was given a complete explanation of the details of the study and gave his consent in writing prior to participation. The 12 subjects then received single doses of the four oral regimens in a randomized double-blind crossover manner, with at least 2 weeks between doses for the chlorthalidone regimens. Each dose was administered with 100 ml water at 9.00 am after a light breakfast (tea or coffee and toast). Normal meals were allowed during the 48 hour evaluation period. The subjects were ambulatory in and around the Clinical Pharmacology Unit for the first 3 hours and then allowed to resume their normal working duties. The 12 hour blood samples were taken by the medical staff visiting the subjects in their homes.

Blood samples for measurement of whole blood concentrations of atenolol and chlorthalidone were taken from an antecubital vein just before and at 1,

3, 5, 7, 12, 24, 48, and 72 hours after drug administration. The samples were collected in tubes containing a suitable anticoagulant. Approximately 20 ml was taken before dosing and aliquots were removed for drug analysis; the remaining aliquots were then pooled for generating calibration curves. The samples taken after dosing were approximately 10 ml. Samples were stored at −20° prior to analysis.

Urine samples were collected before drug administration and the time periods 0–24 h, 24–48 h, and 48–72 h after drug administration. The total volume was measured and recorded. The urine was stored at −20° prior to analysis.

Drug analysis

The analyses of atenolol in the blood and urine were performed by a modification of the gas-liquid chromatography method of Scales and Copsey[19] and a fluorescence method.[20] The analyses of chlorthalidone were done by high pressure liquid chromatography using the method of McAinsh *et al.*[18]

Physiological measurements

On each occasion a blood sample was taken, and the subject's resting pulse (by palpation) and blood pressure were recorded using a standard mercury sphygmomanometer and cuff. The diastolic pressure was determined using Korotkoff sound 4 or 5.

MATHEMATICAL CONSIDERATIONS

Determination of pharmacokinetic parameters

Elimination rate constants (β) were estimated by linear regression from the slope of the terminal linear segment of the curve of the logarithm of the blood concentration ($c(t)$) versus time (t). The half-life was calculated by the expression:

$$t_{1/2} = \frac{0{\cdot}693}{\beta}$$

and the area under the blood level curve to infinity (AUC_∞) by the expression:

$$AUC_\infty = [AUC_{(0-t)}]\,\text{trapezoidal} + \frac{c(t)^{\text{theoretical}}}{\beta}$$

where (t) is the time of the last experimental point and $c(t)^{\text{theoretical}}$ is the predicted concentration at that time from the linear regression analysis.

The mean peak blood levels were calculated by taking the mean of the individual maximum concentrations for each treatment.

Statistics

An analysis of variance allowing for patients, treatments, and visits was carried out on the concentrations of each drug in the blood at each time point and on the half-lives, areas under the blood level curve, total urinary excretion, blood pressures, and pulse rates. The means of the data were adjusted to allow for missing values where necessary. Overall F-tests for treatments comparing the treatment sums of squares with the residual sum of squares from each analysis of variance were made. In addition pairs of treatments were compared using Student's t-test. More weight should be given to results from the t-tests where the overall F-test was significant to safeguard against spuriously significant t-tests.

RESULTS

No untoward effects occurred during this investigation and each volunteer completed each section of the study.

Levels in blood

Atenolol. The mean concentrations of atenolol in the blood are illustrated in Figure 1. Atenolol was not detected in the predose aliquots or in the samples taken after administration of regimen D (chlorthalidone only).

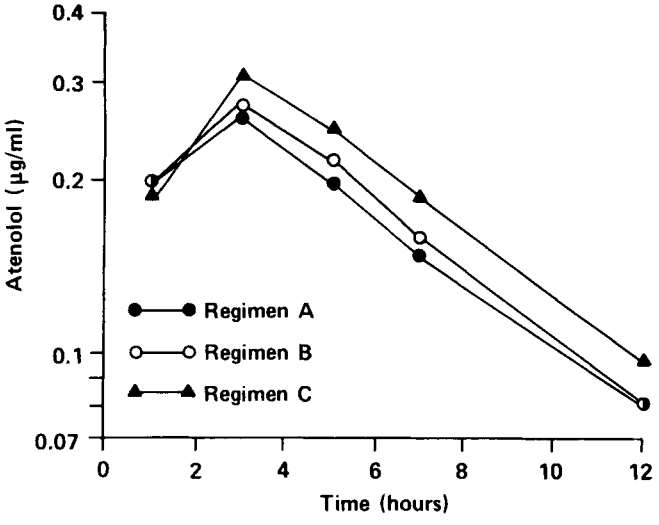

Figure 1. Mean levels of atenolol (µg ml^{-1}) in whole blood of 12 volunteers

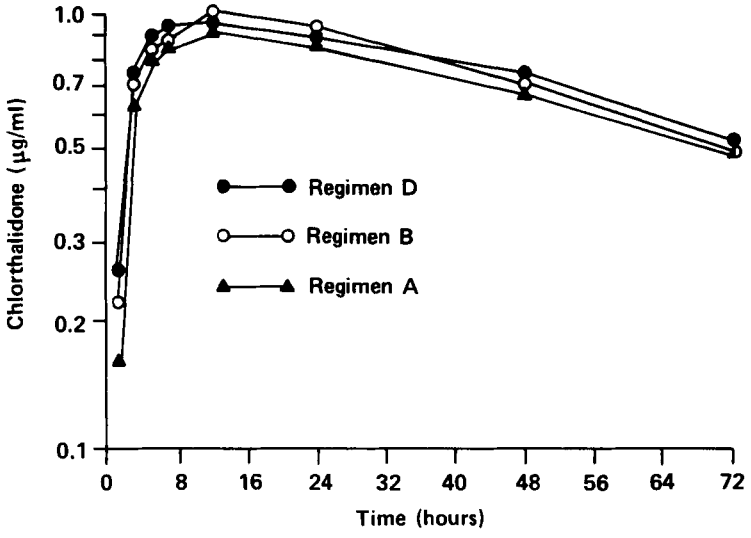

Figure 2. Mean levels of chlorthalidone (μg ml^{-1}) in whole blood of 12 volunteers

The mean peak concentrations of atenolol (± S.E.) in the blood occurring 3 h after administration were 0·28 ± 0·03, 0·29 ± 0·03, and 0·33 ± 0·03 μg ml^{-1} for the fixed and free combinations and the atenolol dose, respectively. The final elimination phase was associated with a mean half-life of 5–7 h for all regimens. The mean areas under the blood level curve to infinity for regimens A, B, and C were 2·56 ± 0·30 (S.E.), 2·63 ± 0·20, and 3·25 ± 0·30 μg ml^{-1} h, respectively. The only statistically significant differences between the three atenolol regimens A, B, and C in terms of blood level, half-life, area under the curve or urinary excretion of atenolol occurred for the blood levels between regimens A and C at 5 and 7 h and in the half-life between regimens A and B and between treatments B and C. These differences are small and unlikely to be of any clinical significance. This is further emphasized by the observation that there was no statistically significant difference in half-life between regimens A and C.

Chlorthalidone. The mean concentrations of chlorthalidone are illustrated in Figure 2. Chlorthalidone was not detected in the predose aliquots or in the samples taken after the administration of regimen C (atenolol only).

The mean peak concentrations of chlorthalidone in blood occurring 12 h after administration were 0·94 ± 0·04 (S.E.), 1·00 ± 0·02, and 0·99 ± 0·03 μg ml^{-1} for the fixed and free combinations and the chlorthalidone tablet, respectively. The mean half-life was 58 ± 4 (S.E.), 53 ± 3, and 60 ± 4 h for the fixed and free combination and the chlorthalidone dose, respectively. The mean areas under the blood level curve to infinity for these regimens were 96 ± 8, 94 ± 5, and 101 ± 6 μg ml^{-1} h, respectively.

Table 1. Mean urinary recovery of atenolol (mg)

Regimen	Parameter	Time period (h) 0–24	24–48	48–72	Total (mg)	% of Dose
A	Mean	14·24	1·42	0·31	15·96	32
	S.E.	1·90	0·22	0·12	2·03	4
B	Mean	14·56	1·39	0·52	16·47	33
	S.E.	2·03	0·20	0·20	2·17	4
C	Mean	17·39	1·32	0·24	18·96	38
	S.E.	1·74	0·28	0·11	1·97	4
D	Mean	ND	ND	ND	ND	ND
	S.E.	ND	ND	ND	ND	ND

ND: Non-detectable, limit of detection 0·58 ± 0·18 μg ml^{-1}.
A: 'Tenoret 50' white, film-coated tablet containing 50 mg atenolol and 12·5 mg chlorthalidone.
B: (1) 50 mg atenolol white, film-coated tablet, (2) 12·5 mg chlorthalidone white, film coated tablet.
C: 50 mg atenolol white, film-coated tablet.
D: 12·5 mg chlorthalidone white, film-coated tablet.

The statistical analysis of the data shows that the only significant difference occurred between the blood levels of chlorthalidone 1, 3, and 5 h after dosing between regimens A and D. At all other time points there were no statistically significant differences in the systemic levels of chlorthalidone or the areas under the curve.

Table 2. Mean urinary recovery of chlorthalidone (mg)

Regimen	Parameter	Time period (h) 0–24	24–48	48–72	Total (mg)	% of Dose
A	Mean	2·51	1·43	1·14	5·07	41
	S.E.	0·15	0·10	0·15	0·29	2
B	Mean	2·62	1·34	1·08	5·04	40
	S.E.	0·21	0·07	0·07	0·29	2
C	Mean	ND	ND	ND	ND	ND
	S.E.	ND	ND	ND	ND	ND
D	Mean	2·29	1·48	1·09	5·49	44
	S.E.	0·15	0·09	0·07	0·30	2

ND: Non-detectable, limit of detection 0·07 ± 0·01 μg ml^{-1}.
A: (1) 'Tenoret 50' white, film-coated tablet containing 50 mg atenolol and 12·5 mg chlorthalidone, (2) a placebo tablet.
B: (1) 50 mg atenolol white, film-coated tablet, (2) 12·5 mg chlorthalidone white, film-coated tablet.
C: (1) 50 mg atenolol white, film-coated tablet, (2) a placebo tablet.
D: (1) 12·5 mg chlorthalidone white, film-coated tablet, (2) a placebo tablet.

Recovery

Atenolol. The mean urinary recoveries of unchanged atenolol for the 72 h period after drug administration were 16·0 ± 2·0 (S.E.), 16·5 ± 2·2 and 19·0 ± 2·0 mg i.e. 32, 33, and 38 per cent of the dose, for the fixed and free combinations and the atenolol tablet, respectively (Table 1). There were no statistically significant differences between regimens in these results and the majority of the urinary elimination of atenolol occurred within 24 hour of dosing.

Chlorthalidone. The mean urinary recoveries of unchanged chlorthalidone for the 72 h period after drug administration were 5·07 ± 0·29 (S.E.), 5·04 ± 0·29, and 5·49 ± 0·30 mg, i.e. 41, 40, and 44 per cent of the dose, for the fixed and free combinations and the chlorthalidone tablet, respectively (Table 2). It was noted, however, that urinary elimination of chlorthalidone was still occurring between 48 and 72 h after dosing, and may continue beyond this time, thus increasing the reported urinary recoveries. As expected no urine levels of chlorthalidone were observed after dosing with regimen C (atenolol only). There were no statistically significant differences between regimens in these results.

Adverse reactions

No adverse reactions were observed or reported during the course of the study.

DISCUSSION

The results of this investigation show that there were no statistically significant differences of clinical importance between the blood levels, areas-under-the-curve, and urine excretion of atenolol in the three regimens in which it was present. Furthermore there was no difference in half-life between regimens A and C but the half-life for regimen B was lower than that for A and C. Individual peak values ranged from 0·11 to 0·49 μg ml^{-1}, a three-fold variation. The variation in peak systemic levels is less than that observed for a number of other β-blocking drugs and is of the same order as that seen in other investigations involving atenolol. Moreover the half-life measurements, area under the curve, and urinary elimination results are in good agreement with previously published data taking into account the difference in dose.[18] Thus the bioavailability of atenolol from the fixed combination is equivalent to that from the free combination and that from the tablet containing atenolol alone. Therefore it is concluded that co-administration of chlorthalidone does not affect the absorption and elimination of atenolol in volunteers.

The mean peak blood concentrations of chlorthalidone were 0·94, 1·00, and 0·99 μg ml^{-1} for the fixed and free combinations and the chlorthalidone tablet, respectively. The mean areas under the curve were very similar being

96, 94, and 101 μg ml^{-1} h, respectively. The mean half-lives and the urinary excretion results were also similar. There were no statistically or clinically significant differences between regimens for these pharmacokinetic parameters. Thus the bioavailability of chlorthalidone from the fixed combination is equivalent to that from the free combination and that from the tablet containing chlorthalidone alone. It is concluded therefore that coadministration of atenolol does not affect the absorption and elimination of chlorthalidone in volunteers.

Finally it is concluded that combining chlorthalidone (12·5 mg) and atenolol (50 mg) in the 'Tenoret 50' tablet does not affect the systemic bioavailability of either component.

ACKNOWLEDGEMENTS

The authors wish to thank Mrs Y. Barker for the determination of blood levels and Mr B. J. Middleton for statistical calculations.

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