BIOPHARMACEUTICS & DRUG DISPOSITION, VOL. 1, 323–332 (1980)

BIOAVAILABILITY OF ATENOLOL FORMULATIONS

JAMES MCAINSH*, WILFRED T. SIMPSON, BRIAN F. HOLMES, JEAN YOUNG AND STUART H. ELLIS

Imperial Chemical Industries Limited, Pharmaceuticals Division, Mereside, Alderley Edge, Cheshire, U.K.

SUMMARY

In this comparative bioavailability study two tablet formulations of atenolol (sales and clinical trial) were compared with an oral solution. Twelve healthy adult male volunteers received, on a cross-over basis, on three separate occasions, 100 mg oral dose of the three formulations of atenolol. Bioavailability was based on concentrations of atenolol in whole blood and urine. The atenolol blood levels peaked at approximately 3 h after dosing, with individual values ranging from 0·21 to 0·92 μg ml^{-1} (a four-fold difference), with all three formulations. Three-fold variations among subjects occurred in the areas under the curve (AUC) and urinary recoveries. The average elimination half-life of atenolol was between 6 and 7 h for all three formulations. Some statistically significant differences were observed between the tablets and the aqueous solution: the AUC (∞) and mean peak blood concentrations were significantly greater with the U.K. sales tablet than the solution, and the mean concentrations in the blood at certain specified times after administration were significantly greater with the two tablet formulations than the solution. The profiles of absorption and excretion of the two tablet formulations were similar.

No adverse reactions were encountered in this study and all subjects completed the study without incident.

KEY WORDS Comparative bioavailability Atenolol Pharmacokinetics Human

INTRODUCTION

Atenolol (Tenormin^{R})† is a β-adrenoreceptor blocking agent developed by the Pharmaceuticals Division of Imperial Chemical Industries Limited in the United Kingdom. In animal studies atenolol has been shown to be cardioselective and devoid of intrinsic sympathomimetic and membrane-stabilizing activity.[1–3]

Atenolol is completely absorbed in dogs and incompletely absorbed in rats, mice, and rabbits, after oral administration. Studies with ^{14}C-atenolol have shown that metabolism in the dog and rat is small, most of the drug being excreted in the urine unchanged. Biliary excretion is minimal.[4]

* *Requests for reprints to* Dr. J. McAinsh, Safety of Medicines Department.

† Tenormin^{R} is a trade mark, the property of Imperial Chemical Industries Limited.

0142–2782/80/0001–0601–0323$01.00 *Received 8 October 1979*

 Revised 16 November 1979

Atenolol is an effective antihypertensive agent in man. The drug is now marketed in the United Kingdom and other countries, with approximately 750 000 patient years' exposure. Further details of the drug's pharmacological profile and clinical usefulness are given in the proceedings of an atenolol symposium held in October 1976.[5]

The purpose of this study was to determine, from whole blood and urine concentrations of atenolol in normal subjects, the comparative bioavailability of 100 mg doses given as the proposed and now established U.K. sales tablet, a U.K. clinical trial tablet, and oral solution of atenolol.

MATERIALS AND METHODS

Procedure

The study was carried out under medical supervision in the Clinical Pharmacology Unit of Imperial Chemical Industries Limited, 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. The pre-study examination included a screening history, complete physical examination, 12-lead electrocardiogram (ECG), and laboratory tests (haematology, urinalysis and blood chemistry).

Volunteers were generally excluded if the pre-study examination indicated a history or evidence of: 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. One subject had a history of hay fever and one an allergy to wool, neither of which was considered clinically significant. In addition, although there were minor deviations from normality in the clinical laboratory and ECG examinations, none of these was considered clinically significant by the medical adviser. Each subject agreed not to take concomitant medication or ingest alcohol during the study.

The 12 male subjects ranged in age from 23 to 51 years (mean, 32 years) and in weight from 61 to 90 kg (mean, 76 kg).

The three formulations of atenolol for oral administration were supplied as follows:

Formulation A—100 mg orange film-coated tablet; proposed U.K. sales formulation based on an aqueous granulation process.

Formulation B—100 mg white film-coated tablet; U.K. clinical trial formulation based on a solvent granulation process.

Formulation C— 100 ml aqueous solution of atenolol (1 mg ml^{-1}), buffered with an equimolar amount of citric acid.

The tablets and solution were made in conformity with the physical and chemical specifications and the standards of purity, stability and assay potency in operation at ICI at the time of this study.

Each volunteer was given a complete explanation of the details of the study and gave his consent in writing prior to participation. The twelve subjects then received single 100 mg doses of three oral formulations of atenolol in a randomized manner (see Table 1), with at least 7 days between doses. The subjects were aware of the formulation received each time. Each dose of atenolol was administered with 100 ml water at 9.00 a.m. after a light breakfast (tea or coffee and toast). Normal meals were allowed during the 48 h evaluation period. The subjects were ambulatory in and around the clinical pharmacology unit for the first 8 h and then were allowed to go home. After 24 h the subjects resumed their normal working duties.

Table 1. Randomization schedule

	Subject											
Period	RC	CT	AS	CR	GS	HA	JM	ME	AW	PM	DL	DT
1	C	A	B	A	B	C	B	C	A	B	A	C
2	B	C	A	B	C	A	A	B	C	C	B	A
3	A	B	C	C	A	B	C	A	B	A	C	B

A = 100 mg tablet, U.K. sales formulation.
B = 100 mg tablet, U.K. clinical trial formulation.
C = 100 ml aqueous solution (1 mg ml^{-1}).

Blood samples for measurement of whole blood concentrations of atenolol were taken from an antecubital vein just before and at 1, 3, 5, 7, 12, and 24 h 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 atenolol analysis; the remaining aliquots were then pooled for generating calibration curves. The samples taken after dosing were approximately 4 ml. Samples were refrigerated at 0 to 4° and promptly analysed.

Urine samples were collected before drug administration and for the time periods 0 to 24 h and 24 to 48 h after drug administration. The total volume was measured and recorded. The urine was refrigerated in plastic bottles at 0 to 4° and promptly analysed.

The analyses of atenolol in the blood and urine were done by the gas–liquid chromatography method of Scales and Copsey,[6] except for the 0- to 24-h urine samples, which were analysed by the fluorescence method.[7]

Pulse and blood pressure were monitored only for the emergence of adverse reactions. No physiological measurements were used as pharmacological end-points.

Pharmacokinetics

Elimination half-lives were estimated by linear regression from the slope (β) of the terminal (7- to 24-h) linear segment of the curve of the logarithm of the blood concentration *versus* time. The areas under the blood level curve to infinity were calculated by the expression:

$$\text{AUC}(\infty) = [\text{AUC}(0\text{–}24)]\,\text{trapezoidal} + [C(24)/\beta]$$

Statistics

Paired *t*-tests were carried out with standard methodology on the concentrations of atenolol in the blood at each time point and on the half-lives, areas under the blood level curve, and total urinary excretion. These parameters were also analysed by a confidence limit approach based on percentage difference.

RESULTS

Blood data

The mean concentrations of atenolol in the blood are given in Table 2 for the three formulations, also shown are the final phase half-lives, areas under the curves to infinity, and their means and standard errors. Individual and mean peaks and times to peak are shown, along with the results of paired *t*-tests of the means, in Table 3. The mean concentrations are illustrated in Figure 1. Atenolol was not detected in the pre-dose aliquots.

The mean peak concentrations of atenolol in the blood were $0{\cdot}65 \pm 0{\cdot}06$ (S.E.), $0{\cdot}61 \pm 0{\cdot}05$, and $0{\cdot}51 \pm 0{\cdot}05$ $\mu g\ ml^{-1}$ for the U.K. sales, clinical trial tablets, and aqueous solution, respectively; the mean time to peak was 2·8 h for all formulations. The final elimination phase began approximately 7 h after dosing and was associated with a mean half-life of 6 to 7 h for all formulations. The mean areas under the blood level curve to infinity for the three formulations were $6{\cdot}10 \pm 0{\cdot}29$ (S.E.), $5{\cdot}72 \pm 0{\cdot}38$, and $4{\cdot}96 \pm 0{\cdot}22$ $\mu g\ ml^{-1} \times h$, respectively.

Statistically significant differences between formulations, according to paired *t*-test analysis, were as follows. The mean concentrations of atenolol in the blood were significantly greater with the U.K. sales tablet than the aqueous solution at 3, 5, 7, and 12 h ($p < 0{\cdot}05$–$0{\cdot}001$), and significantly greater with the U.K. trial tablet than the solution at 7 h ($p < 0{\cdot}03$). The mean peak concentration in the blood and in the AUC(∞) of the U.K. sales tablet were significantly greater than with the solution ($p < 0{\cdot}03$ and $0{\cdot}01$ respectively—Tables 3 and 5).

Urine data

The mean urinary recoveries of unchanged atenolol for the 48 h period after drug administration were $47{\cdot}0 \pm 2{\cdot}9$ (S.E.), $43{\cdot}0 \pm 3{\cdot}3$, and $41{\cdot}5 \pm 2{\cdot}9$ mg, i.e. 47, 43, and 42 per cent of the dose, for the U.K. sales, clinical trial tablets, and aqueous solution, respectively (see Table 4). There was no statistically significant difference between formulations in these results (Table 5).

Table 2. Mean concentration of atenolol in whole blood

Formulation	Parameter	Concentration of atenolol (μg ml^{-1}) Hours after dosing 1	3	5	7	12	24	$t_{\frac{1}{2}}(\beta)$ (h)	AUC(∞) (μg ml^{-1} h)
A	Mean	0·388	*0·608*	0·510	0·326	0·163	0·048	6·54	6·10
	S.E.	0·076	0·058	0·041	0·021	0·011	0·002	0·42	0·29
B	Mean	0·310	*0·565*	0·471	0·311	0·157	0·047	6·69	5·72
	S.E.	0·095	0·051	0·042	0·027	0·014	0·004	0·52	0·38
C	Mean	0·378	*0·493*	0·405	0·248	0·137	0·040	6·78	4·96
	S.E.	0·031	0·051	0·029	0·016	0·008	0·004	0·51	0·22

A = 100 mg tablet, U.K. sales formulation.
B = 100 mg tablet, U.K. clinical trial formulation.
C = 100 ml aqueous solution (1 mg ml^{-1}).
Peak concentrations are set in italics.
S.E. = Standard error.

Table 3. Peak and time to peak concentrations of atenolol in whole blood

Subject	Formulation A Peak ($\mu g\ ml^{-1}$)	A Time to peak (h)	B Peak ($\mu g\ ml^{-1}$)	B Time to peak (h)	C Peak ($\mu g\ ml^{-1}$)	C Time to peak (h)
HA	0·59	5	0·58	5	0·47	3
RG	0·72	3	0·55	5	0·92	3
ME	0·26	3	0·21	3	0·35	3
DL	0·87	1	0·81	3	0·55	3
JM	0·40	3	0·53	1	0·27	3
PM	0·42	1	0·53	3	0·44	3
CR	0·47	3	0·62	3	0·41	3
AS	0·79	5	0·70	3	0·37	5
CT	0·84	1	0·78	1	0·49	1
DT	0·72	3	0·76	3	0·51	3
GS	0·88	3	0·87	1	0·72	3
AW	0·83	3	0·41	3	0·59	1
Mean	0·65	2·83	0·61	2·83	0·51	2·83
S.E.	0·06	0·39	0·05	0·39	0·05	0·30

Paired *t*-test

	Difference between mean peaks	Difference between times to peak
A–C	0·14 ($p<0·03$)*	0
B–C	0·10 ($p<0·12$)	0
A–B	0.04 ($p<0·40$)	0

A = U.K. sales tablet formulation.
B = U.K. clinical trial tablet formulation.
C = Aqueous solution.
* Significant at the 95 per cent confidence level.
S.E. = Standard error.

Physiological measurements

Pulse rate and systolic and diastolic blood pressure were monitored during the first 12 h after drug administration. No abnormalities occurred.

Clinical laboratory measurements

Although minor abnormalities were seen in the clinical chemistry results and electrocardiographic tracings, none was considered clinically significant by the Principal Investigator.

Adverse reactions

No adverse reactions were encountered in this study and all subjects completed the study without incident.

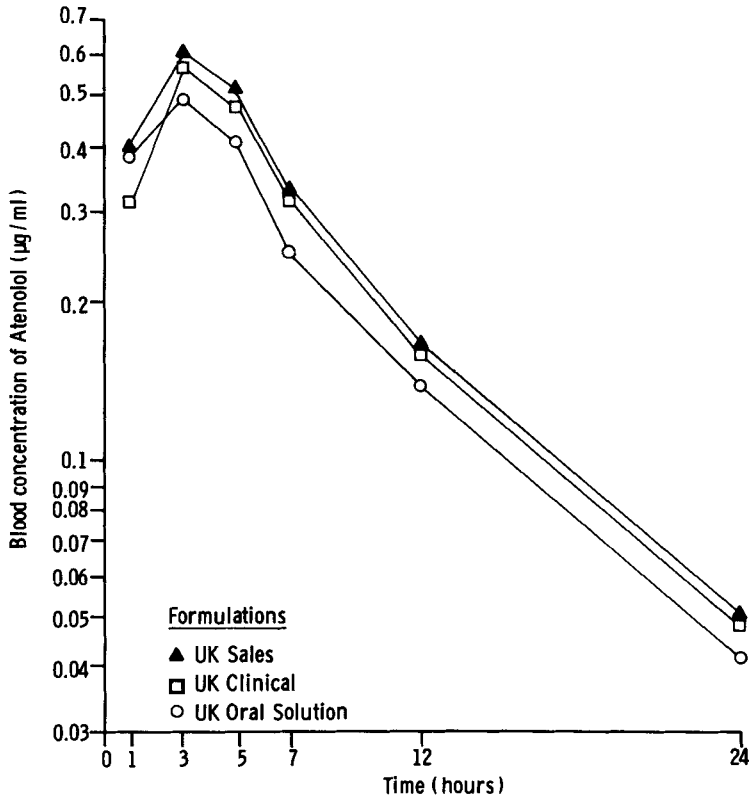

Figure 1. Blood level comparison

Table 4. Mean urinary recovery of atenolol

Formulation	Parameter	Urinary recovery (mg) 0–24 h*	24–48 h†	Total excreted in 48 h period (mg)	% of dose
A	Mean	42·6	4·4	47·0	47
	S.E.	2·9	0·4	2·9	3
B	Mean	38·9	4·1	43·0	43
	S.E.	3·4	0·3	3·3	3
C	Mean	36·4	5·1	41·5	42
	S.E.	2·8	0·4	2·9	3

A = U.K. sales tablet formulation.
B = U.K. clinical trial tablet formulation.
C = Aqueous solution.
* Fluorescence method.
† Gas–liquid chromatographic method.

Table 5. Paired *t*-test analysis of blood and urine data

Parameter	Formulation	Atenolol blood levels (μg ml^{-1})[7] Time after dose (h) 1	3	5	7	12	24	$t_{\frac{1}{2}}(\beta)$ (h)	AUC (∞) (μg ml^{-1} h)	Urinary excretion (0–48 h) (mg)
Mean	A	0·388	0·608	0·510	0·326	0·163	0·048	6·54	6·10	47·0
	B	0·310	0·565	0·471	0·311	0·157	0·047	6·69	5·72	43·0
	C	0·378	0·493	0·405	0·248	0·137	0·040	6·78	4·96	41·5
Mean difference	A − C	0·010	0·115*	0·105*	0·078†	0·026*	0·008	−0·24	1·14†	5·5
	B − C	−0·068	0·072	0·066	0·063*	0·020	0·007	−0·09	0·76	1·5
	A − B	0·078	0·043	0·039	0·015	0·006	0·001	−0·15	0·38	4·0
95% confidence limits for percentage difference‡	[(A − C)/C] × 100	3 ± 40	23 ± 23	26 ± 20	31 ± 23	20 ± 18	20 ± 20	−3 ± 20	23 ± 11	13 ± 18
	[(B − C)/C] × 100	−18 ± 51	15 ± 27	16 ± 21	25 ± 21	15 ± 19	16 ± 17	−1 ± 20	15 ± 13	4 ± 16
	[(A − B)/B] × 100	25 ± 38	7 ± 20	8 ± 22	5 ± 18	4 ± 19	3 ± 20	−2 ± 19	7 ± 11	9 ± 15

A = U.K. sales tablet formulation.
B = U.K. clinical trial tablet formulation.
C = Aqueous solution.
* $p < 0{\cdot}05$.
† $p < 0{\cdot}01$.
‡ = Percentage difference $\pm t_{11}$. S.E.—d%.

DISCUSSION

The mean peak blood concentrations of atenolol were 0·65, 0·61, and 0·51 μg ml^{-1} for the U.K. sales, U.K. clinical trial tablets, and aqueous solution, respectively. The difference between the sales tablet and the solution was statistically significant ($p<0·03$). Individual peaks ranged from 0·21 to 0·92 μg ml^{-1}, a four-fold variation. The mean time to peak was 2·8 h for all three formulations. The concentrations then decayed with a mean half-life of 6 to 7 h, with 24 h values ranging from 0·012 to 0·070 μg ml^{-1}, a six-fold variation. The significance of a 24 h duration of effect in the context of a shorter half-life has been discussed elsewhere.[8]

The four-fold variation in peak systemic blood levels is less than that observed with a number of other beta-adrenoceptor blocking drugs. For example, propranolol has shown a seven- to twenty-fold, [9,10] alprenolol a twenty-five-fold,[11,12] and metoprolol a sixteen-fold variability.[13]

The mean AUC(∞) was similar for the two tablet formulations (6·10 and 5·72 μg ml^{-1} h for the U.K. sales and clinical trial formulations, respectively), indicating comparable systemic bioavailability. The only significant difference in mean AUC(∞) was in the 23 per cent increase of the sales tablet over the solution ($p<0·01$).

There was no significant difference among the formulations in the 48 h urinary recovery of atenolol: the mean recovery ranged from 42 to 47 per cent for the three formulations, with individual values between 23 and 63 per cent, a three-fold variation.

In paired comparisons of blood levels of atenolol, 7 per cent more drug reached the systemic circulation from the proposed (and now established) U.K. sales formulation than the U.K. clinical trial formulation. This difference was not statistically significant, and the confidence limits ranged only from −4 to +18 per cent. This small difference between the two formulations was also observed in the urine data: 47 and 43 per cent excretion, respectively. As determined by the areas under the blood level curves more atenolol reached the systemic circulation with the two tablet formulations than with the aqueous solutions: 23 per cent more with the U.K. sales tablet (confidence limits from +12 to +34 per cent; statistically significant) and 15 per cent more with the U.K. trial tablet (not significant). Again the urinary data revealed similar differences, although only 13 and 4 per cent more atenolol was excreted into the urine with the U.K. sales and clinical trial formulations, respectively, than the solution (not significant).

Thus the profiles of absorption and excretion of the two tablet formulations were similar, both of which were marginally superior to the aqueous solution. This shows that the systemic bioavailability of atenolol is unaffected by the change from a solvent granulation process (as used for the clinical trial tablet) to the aqueous granulation process (as used for the sales tablet) and that the sales and clinical trial tablets are bioequivalent. This finding is in accord with the formulation's *in vitro* dissolution characteristics.

REFERENCES

1. A. M. Barrett, J. Carter, J. D. Fitzgerald, R. Hull and D. LeCount, *Br. J. Pharmacol.*, **48**, 340P (1973).
2. R. Hainsworth, F. Karim and J. B. Stoker, *Br. J. Pharmacol.*, **51**, 161 (1974).
3. J. D. Harry, M. J. Knapp and R. J. Linden, *Br. J. Pharmacol.*, **51**, 169 (1974).
4. P. R. Reeves, D. J. Barnfield, S. Longshaw, D. A. D. McIntosh and M. J. Winrow, *Xenobiotica*, **8**, 305 (1978).
5. B. J. Hoffbrand (Ed), *Postgrad. Med. J.*, **53**, Suppl. 3 (1977).
6. B. Scales and P. B. Copsey, *J. Pharm. Pharmacol.*, **27**, 430 (1975).
7. C. M. Kaye, *Br. J. Pharmacol*, **1**, 84 (1974).
8. J. McAinsh, *Postgrad. Med. J.*, **53**, Suppl. 3, 74 (1977).
9. D. G. Shand, E. M. Nuckolls and J. A. Oates, *Clin Pharmacol. Therap.*, **11**, 112 (1970).
10. D. G. Shand, *Drugs*, **7**, 39 (1974).
11. M. D. Rawlins, P. Collste, M. Frisk-Holmberg, M. Lind, J. Ostman and F. Sjoqvist, *Eur. J. Clin. Pharmacol.*, **7**, 353 (1974).
12. B. Ablad, M. Ervik, J. Hallgren, G. Johnsson and L. Solvell, *Eur. J. Clin. Pharmacol.*, **5**, 44 (1972).
13. C. Von Bahr, P. Collste, M. Frisk-Holmberg, K. Haglund, L. Jorfelt, J. Ostman and F. Sjoqvist, *Clin. Pharmacol. Therap.*, **20**, 130 (1976).