A DOSE RANGING STUDY OF ATENOLOL IN HYPERTENSION: FALL IN BLOOD PRESSURE AND PLASMA RENIN ACTIVITY, BETA-BLOCKADE AND STEADY-STATE PHARMACOKINETICS

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- 1 The relationship between the oral dosage and plasma concentration of the long-acting cardioselective β -adrenoceptor blocker atenolol and the antihypertensive response to the degree of β -adrenoceptor blockade and change in plasma renin activity (PRA) was evaluated in patients with mild-to-moderate essential hypertension in a double-blind, randomized, between-patient, dose-ranging (25, 50 or 100 mg once daily for 4 weeks) study.
- 2 The optimum, or minimum, daily dose of atenolol to treat patients with mild-to-moderate hypertension was not clearly identified in this study. A between-treatment comparison did not demonstrate that all blood pressure falls were always less in the 25 mg group than in the other two groups. Calculation of β -error or the power for the negative results between doses suggested that a large sample size is required to draw a conclusion that no dose-antihypertensive relationship of atenolol exists in the treatment of mild-to-moderate hypertension.
- 3 A relatively flat plasma concentration-antihypertensive response relationship was observed.
- 4 Steady-state plasma concentrations of atenolol were dose-related and renal drug clearance was well correlated with individual creatinine clearance.
- 5 β -adrenoceptor blockade was better correlated with plasma atenolol concentration. Correlations which were less strong were between plasma drug concentration and change in various blood pressures and between blood pressure falls and β -adrenoceptor blockade.
- 6 There was no relationship between the fall in blood pressure and change in PRA. Atenolol appeared to suppress PRA in an all-or-none fashion.

Introduction

In controlled studies of patients with mild-to-moderate essential hypertension atenolol, a long-acting non-metabolized cardioselective β -adrenoceptor blocking drug, has been shown to control blood pressure after once-daily administration (Douglas-Jones & Cruickshank, 1976; Marshall *et al.*, 1977; Myers *et al.*, 1976; Wilcox, 1978). However, it is apparent from a review of the available literature (Douglas-Jones & Cruickshank, 1976; Jeffers *et al.*, 1977; Marshall *et al.*, 1977; Myers *et al.*, 1976; Petrie *et al.*, 1977) that the minimum threshold, or optimum, daily dose of atenolol for blood pressure control in hypertensive patients has not been precisely established yet. Marshall *et al.* (1979) studied the effects of 25, 50, 75 and 100 mg of atenolol given to patients with hypertension. In this paper, however, blood pressure measurements were made at 6–8 h after dosing when all doses looked similar. The present

paper extends these observations to measurements made 24 h after dosing, which is more applicable for routine use. Marshall *et al.* (1979) also found, incidentally, no relationship between blockade of the heart rate response to exercise and antihypertensive effect of atenolol.

We therefore set out (1) to study the antihypertensive effect of 25, 50 and 100 mg doses given once-daily; (2) to measure the steady-state plasma concentrations and investigate their relationships to the reduction in blood pressure and β -adrenoceptor blocking activity over 24 h after a 4 week treatment period; (3) to assess hyporeninaemic effects and renal drug clearance in relation to creatinine clearance.

A preliminary account of this study was presented at the International Symposium on β -adrenoceptor blockade in the 1980s: focus on atenolol held at Monte Carlo, Monaco, June 7–10, 1982.

Methods

Patients

Criteria for inclusion in the study were: (1) stable, uncomplicated hypertension of mild to moderate severity defined as supine and standing diastolic blood pressures between 95 and 114 mm Hg (WHO stage I or II); (2) age less than 65 years; (3) absence of congestive heart failure, obstructive airway disease, insulin-treated diabetes, heart block, bradycardia (heart rate less than 50 beats/min), cerebrovascular or peripheral vascular disease, renal or hepatic disease.

Information about compliance of the patients was obtained before the study commenced. Only patients characterized as compliant (on the basis of pill counts and clinical attendance) were included. Thus, 21 patients (13 men and eight women) aged 41–62 years, were selected for the study.

Informed consent was obtained from all patients. Fifteen patients were newly diagnosed essential hypertensives and the remaining six were receiving a thiazide diuretic. This was discontinued at least 7 days before study. All necessary diagnostic procedures were made to exclude secondary forms of hypertension as described earlier (Ishizaki *et al.*, 1978, 1980). Since standing diastolic blood pressure exceeded 115 mm Hg in one patient after the thiazide therapy was withdrawn during the control period, he was excluded from further study. The data constituting this report are derived from the remaining 20 patients.

Study design

The study design of the active treatment period was double-blind, randomized, between-patient. The patients were allocated to the active treatment at the end of a 4 week placebo period if their blood pressures met with the required criteria. The treatment comprised three randomly allocated, 4 week periods of either 25, 50 or 100 mg atenolol, taken once-daily. The patients remained on no dietary restrictions throughout this study although they were advised to avoid excess salt intake.

Patients were seen weekly. Blood pressure readings were taken after a full 24 h since their last dose had elapsed. On the final days of the placebo and active treatment periods, patients were asked to delay their final dose until after all the study procedures of their baseline measurements had been finished. The study procedures in order were to collect blood samples both for the determinations of plasma renin activity (PRA) (after the subject had been supine overnight) and of atenolol concentration at time 0 (i.e., just before the final dose), and then to measure supine and standing blood pressure and heart rate.

Blood samples for determining atenolol concentrations in plasma were collected at various times up to

24 h after the final dose. Blood pressure and heart rate at rest were also recorded every 2 h for 12 h and again at 24 h, after the final dose, but just before the blood collection. The exercise test was performed at 4, 6, 8 and 24 h after the final dose. The 24 h urinary collection after the final dose was done for determining the endogenous creatinine clearance and renal drug clearance in all subjects. Plasma and urine samples were frozen at -20°C until assayed.

Measurements

Blood pressure measurements were obtained with a standard calibrated mercury sphygmomanometer with the cuff always on the right arm. All measurements were made by the same experienced observer throughout. Each value was the mean of two to three consecutive readings but a single measurement of blood pressure was taken immediately after completion of the exercise test. Diastolic blood pressure was taken as the value at the disappearance of the Korotkoff sounds. Mean blood pressure was calculated as the diastolic pressure plus one third of pulse pressure.

An exercise test was done by using a bicycle ergometer and the details about the test after β -adrenoceptor blockade have been reported previously (Ishizaki & Tawara, 1978; Ishizaki *et al.*, 1980). Briefly, during the test the heart rate was continuously monitored by a telemetric cardi tachometer (Sanei Model 2140), triggering with a chest lead electrocardiogram and recorded by a recticorder (Sanei Model 142-8); exercise work load was individually assigned during the placebo period so as to obtain a plateau level of heart rate of 125 beats/min or greater (Carruthers *et al.*, 1976) for a given time of at least 3 min; the same work load was used for each subject during the tests during active treatment; the exercise-heart rate triggered by the cardi tachometer immediately after completion of the test was recorded; the β -adrenoceptor blocking activity of atenolol was assessed by drug-induced reduction of exercise heart rate expressed as a percent of the control exercise heart rate (McDevitt, 1977). The control exercise heart rates observed at each pre-drug period of 25-, 50-, and 100-mg groups ranged from 135 to 165 (mean $\pm$ s.e. mean, 140.6 ± 6.6) beats/min, from 128 to 175 (134.4 ± 8.0) beats/min, and from 135 to 167 (143.5 ± 9.3) beats/min, respectively.

Atenolol assay in biological fluids was undertaken with the gas-chromatographic method as described by Scales & Copsey (1975). PRA was measured by radioimmunoassay by a method similar to that of Haber *et al.* (1969), described in our previous study (Ishizaki *et al.*, 1978).

Pharmacokinetic and statistical calculations

The following pharmacokinetic parameters of atenolol at steady-state were estimated: the elimination

half-life ($t_{1/2}$) of the terminal log linear phases of the drug concentration in plasma was calculated from the best fitting value by means of the linear regression procedure; the area under the curve against time (AUC) for each patient at each oral dose was calculated by the trapezoidal rule. The mean steady-state atenolol plasma concentration (C_{ss}) was determined according to $C_{ss} = [AUC]_0^{24} / \tau$, where $[AUC]_0^{24}$ is the AUC value during the dosage interval of this study ($\tau = 24$ h); individual renal clearance of drug was calculated by dividing the urinary amount of atenolol excreted in the time interval 0 to 24 h after the final ingestion by the value of $[AUC]_0^{24}$. The steady-state maximum atenolol concentration (C_{max}) and time after the final dose to peak concentration (t_{max}) were read from the concentration-time data after the final dose; the plasma atenolol concentration observed at overnight after the last dose and 24 h after the final dose were considered the steady-state minimum or trough values (C_{min}).

Statistical comparison of blood pressure and heart rate was done by Student's *t*-test or an analysis of one-way variance where appropriate. Data are expressed as mean values ± 1 (s.e. mean). Regression line was calculated by the least squares analysis and tested for coefficient correlation. The minimum significance was considered $P < 0.05$.

Results

Clinical and laboratory characteristics of patients who had been allocated to each study group are given in Table 1. The baseline data of blood pressure, heart

rate and PRA obtained at the end of the placebo period are summarized in Table 2. There was no statistically significant difference of clinical and laboratory findings between the three study groups; nor was there a significant difference of the baseline haemodynamic data at the 24 h of the final placebo dosing among the three study groups. The distribution of hypertensive patients allocated to each treatment group was considered comparable in terms of the degree of high blood pressure and heart rate.

Blood pressure and heart rate at rest, supine and standing positions obtained after 2 and 4 weeks of each active treatment group are given in Table 2. Except for supine and standing heart rates and supine blood pressure in 25 mg treatment group, 4 weeks' active treatment significantly ($P < 0.05$ – 0.01) decreased blood pressure and heart rate. Blood pressure and heart rate observed after 2 weeks of each treatment showed a similar trend towards those observed at the 4 weeks (Table 2).

The data of a between-treatment comparison (variance analysis) after 4-weeks' treatment with atenolol 25, 50 and 100 mg are given in Table 3, which revealed no statistical difference between the effects of the three doses of atenolol on blood pressures and heart rates observed at 24 h after the final once-daily dosing, except for the following values reaching the minimum level of significant difference: supine systolic pressure in 25 mg vs 100 mg group; supine heart rate in 25 or 50 mg vs 100 mg group; standing heart rate in 25 mg vs 100 mg group. The effects of 50 and 100 mg once-daily differed little if at all. The changes in blood pressure observed after 2-weeks' treatment with atenolol 50 and 100 mg did not differ for these

Table 1 Some clinical and laboratory characteristics of the study group at the end of a 4-week placebo run-in period

	Once-daily dose of atenolol		
	25 mg group	50 mg group	100 mg group
Number	7	7	6
Age (years)	50.1 $\pm$ 2.2*	56.7 $\pm$ 2.7	51.7 $\pm$ 2.0
Weight (kg)	61.5 $\pm$ 1.9	63.1 $\pm$ 4.4	60.8 $\pm$ 2.0
LVH (+)	2	3	3
LVH (–)	5	4	3
Optic fundi (KWB)			
0	1	0	1
I	3	4	1
II	3	3	4
<i>Laboratory findings</i>			
Creatinine (mg/100 ml)	0.96 $\pm$ 0.07	1.12 $\pm$ 0.07	1.15 $\pm$ 0.11
BUN (mg/100 ml)	15.3 $\pm$ 0.15	16.4 $\pm$ 1.4	17.9 $\pm$ 1.7
Na (mEq/l)	142.0 $\pm$ 1.0	143.3 $\pm$ 1.0	140.8 $\pm$ 1.6
K (mEq/l)	3.99 $\pm$ 0.11	4.10 $\pm$ 0.14	3.98 $\pm$ 0.17
Cl (mEq/l)	105.7 $\pm$ 0.9	106.0 $\pm$ 1.0	104.0 $\pm$ 1.9

* Values shown are mean values $\pm$ s.e. mean.

(+) = present; (–) = absent; KWB = Keith-Wagener-Barker classification; BUN = blood urea nitrogen.

Table 2 Blood pressures (mm Hg), heart rates (beats min⁻¹) and PRA (ng ml⁻¹ h⁻¹) on the final day of placebo and 24 h after the 2- and 4-weeks' once-daily dosing of atenolol in each study group

	Atenolol 25 mg			Atenolol 50 mg			Atenolol 100 mg		
	Placebo	Active		Placebo	Active		Placebo	Active	
		2-week	4-week		2-week	4-week		2-week	4-week
Supine									
SBP	171 ± 6	162 ± 8	162 ± 6	174 ± 6	147 ± 6 ^a	160 ± 5 ^c	181 ± 8	150 ± 3 ^c	154 ± 6 ^a
DBP	107 ± 3	100 ± 4	100 ± 4	106 ± 2	86 ± 3 ^a	93 ± 3 ^a	108 ± 5	86 ± 4 ^b	89 ± 4 ^c
Heart rate	79 ± 5	62 ± 1 ^a	70 ± 3	71 ± 3	60 ± 2 ^a	63 ± 2 ^b	79 ± 5	60 ± 3 ^b	58 ± 3 ^a
Standing									
SBP	166 ± 6	156 ± 9	152 ± 7 ^a	174 ± 7	147 ± 8 ^a	157 ± 9 ^a	175 ± 6	146 ± 5 ^c	143 ± 7 ^b
DBP	108 ± 3	99 ± 4	94 ± 4 ^a	107 ± 2	90 ± 4 ^a	97 ± 4 ^c	110 ± 4	87 ± 3 ^a	91 ± 3 ^b
Heart rate	80 ± 4	66 ± 1 ^c	74 ± 3	77 ± 4	63 ± 2 ^a	65 ± 2 ^c	84 ± 6	62 ± 3 ^a	64 ± 2 ^b
PRA [‡]	1.84 ± 0.45	—	0.51 ± 0.30 ^c	1.13 ± 0.08	—	0.33 ± 0.08 ^a	1.12 ± 0.29	—	0.35 ± 0.16 ^c

Values shown are mean values ± s.e. mean.

Statistically significant differences between values in the placebo period and the atenolol period within each group are:

^a $P < 0.01$, ^b $P < 0.02$ and ^c $P < 0.05$.

SBP = systolic blood pressure; DBP = diastolic blood pressure; PRA = plasma renin activity (at supine rest).

[‡] Measured at overnight supine rest (24 h after the preceding dose of the final atenolol).

two treatments, while the changes in blood pressure in the 25 mg group were significantly ($P < 0.05$) less than those in 50 and 100 mg groups.

Figure 1 shows time course of rest and post-exercise haemodynamics during the final day of active treatment. The mean blood pressure in the standing position fell significantly (at least $P < 0.05$) from placebo values at 24 h after the final dose of atenolol 25, 50 and 100 mg, respectively (Figure 1a). The respective changes in mean blood pressure, however, did not reach statistical difference between treatment groups. There was a progressive reduction in the mean blood pressure and standing heart rate at 6 and 4 h, Figure 1a, b, respectively.

Post-exercise values for blood pressure and heart rate examined at all times after the final dose were significantly (at least $P < 0.05$) lowered as compared to the respective placebo values (Figure 1c, d). A between-treatment comparison of the changes in sys-

tolic, mean and diastolic blood pressures, however, reached no statistical difference, although the changes were somewhat greater at all times in 100 mg dose.

All patients dropped their PRA on the active treatment and the mean ± s.e. mean values before and after the 4 weeks' active treatment are given in Table 2. In contrast to the baseline haemodynamic data, however, the values for PRA were more variable, ranging from 0.18 to 3.53 (1.38 ± 0.21) ng ml⁻¹ h⁻¹ in all subjects. All active treatments suppressed PRA significantly ($P < 0.05$) as compared to the placebo values (Table 2). There was no significant difference of the mean changes in PRA between the three treatment groups (Table 3).

Figure 2 shows the changes in blood pressures in relation to the changes in PRA in each study group. The 25 mg dose was already effective in decreasing PRA without decreasing arterial pressure. However,

Table 3 Comparison of effects of atenolol dose on blood pressure, heart rate and plasma renin activity, 24 h after the final once-daily dosing of atenolol

	Supine changes			Standing changes		
	25 mg	50 mg	100 mg	25 mg	50 mg	100 mg
Blood pressure (mm Hg)						
Systolic	-9 ± 4	-14 ± 5	-27 ± 5*	-14 ± 4	-17 ± 4	-32 ± 9
Diastolic	-7 ± 3	-13 ± 2	-19 ± 8	-14 ± 3	-10 ± 3	-19 ± 5
Heart rate (beats/min)	-10 ± 4	-8 ± 2	-21 ± 4*†	-6 ± 3	-12 ± 4	-21 ± 6*
Plasma renin activity (ng ml ⁻¹ h ⁻¹)	-1.33 ± 0.50	-0.80 ± 0.21	-0.77 ± 0.26	—	—	—

Values are expressed as mean ± s.e. mean of differences between values in the placebo period and the atenolol period.

* Significant decrease ($P < 0.05$) as compared to the 25 mg group.

† Significant decrease ($P < 0.05$) as compared to the 50 mg group.

Figure 1 Time course of rest standing and post-exercise blood pressures (a and c) and heart rates (b and d) during 24 h after final dosing of atenolol 25 (○), 50 (▲) and 100 (●) mg administered once daily for 4 weeks. All values are shown as the mean $\pm$ s.e. mean. * $P < 0.05$ (variance analysis) compared to 25 mg group for rest standing and post-exercise haemodynamic data (b and d). No haemodynamic variables between 50 and 100 mg groups reached statistical difference. Except for resting standing heart rates 24 h after final dosing of atenolol 25 mg (Table 2), all values for resting standing and post-exercise haemodynamics were significantly (at least $P < 0.05$ by Student's *t*-test) lowered as compared with the respective placebo values.

Figure 2 Changes in blood pressure (systolic □, diastolic ■) in relation to changes in PRA in the three study groups. * $P < 0.05$ and ** $P < 0.01$ compared to its own placebo value.

the renin-suppressive effect was apparently the greatest obtainable, though not statistically significant, with the smallest dose of atenolol.

Table 4 summarizes pharmacokinetic data of atenolol at steady-state in each study group and the overall mean values are given where appropriate. The values for $t_{1/2}$, t_{max} and renal clearance of atenolol did not differ among the three treatment groups, while plasma concentrations at steady-state, except for the C_{max} value between 25 and 50 mg groups, showed dose-related differences. The interindividual difference in the C_{ss} value was small, ranging from 2.2- to 3.6-fold among the three different doses.

We analysed all probabilities of the correlations among the steady-state plasma atenolol concentrations, the changes in the various blood pressures, the change in exercise tachycardia, the change in PRA, the atenolol renal and creatinine clearances. The highest correlation coefficient value was achieved between pre-treatment PRA and change in PRA after atenolol ($r = 0.943$, $n = 20$, $P < 0.001$). There was no statistically significant correlation between the changes in blood pressures and the pretreatment PRA. The atenolol concentrations in plasma were associated with the clinical β_1 -adrenoceptor blockade ($r = 0.571$, $n = 80$, $P < 0.001$). The correlation coefficients were higher individually than in the group as a whole, ranging 0.392 to 0.998 with a mean r -value of 0.825 in 20 patients. The creatinine clearance ranged from 50 to 133 (mean $\pm$ s.e. mean, 74 ± 4) ml min⁻¹ 1.73 m⁻², whereas the atenolol renal clear-

Table 4 Atenolol pharmacokinetics at steady-state

	Once-daily dose of atenolol			
	25 mg (n = 7)	50 mg (n = 7)	100 mg (n = 6)	Overall (n = 20)
$t_{1/2}$ (h)	8.6 ± 1.3	10.4 ± 0.9	9.8 ± 1.7	9.6 ± 0.7
$t_{\max}$ (h)	4.0 ± 0.7	3.6 ± 0.2	3.5 ± 0.2	3.7 ± 0.3
Renal clearance (ml min ⁻¹ 1.73 m ⁻²)	82 ± 15	81 ± 12	77 ± 16	80 ± 3
$C_{\max}$ (ng/ml)	117 ± 23	219 ± 43	390 ± 34	—
C (ng/ml)	43 ± 8	99 ± 20	175 ± 18	—
$C_{\min}^*$ (ng/ml)	16 ± 2	40 ± 8	68 ± 11	—

Values shown are mean values ± s.e. mean.

n = number of patients; $t_{1/2}$ = elimination half-life; $t_{\max}$ = time after the final dose to peak concentration; $C_{\max}$ = maximum steady-state concentration observed; C = mean steady-state concentration calculated; $C_{\min}$ = minimum steady-state concentration observed at 24 h after the final dose.

* Overnight (zero time or just before the final dose) values in 25, 50 and 100 mg groups were 14 ± 3, 28 ± 5 ($P < 0.05$ from 25 mg) and 73 ± 14 ($P < 0.01$ from 50 mg), respectively, which did not significantly differ from those 24 h after the final dose within each group.

ance ranged from 24 to 143 ml min⁻¹ 1.73 m⁻² in all subjects. These values were correlated significantly ($r = 0.660$, $n = 20$, $P < 0.005$).

When we analysed the data of relationship between the logarithmic atenolol concentration intervals and fall in mean blood pressure as applied for propranolol (Esler *et al.*, 1977), a relatively flat concentration-response relationship was obtained (Figure 3). There was a weak correlation between atenolol concentrations in plasma and fall in mean blood pressure in the supine ($r = 0.369$, $P < 0.001$) and standing positions ($r = 0.219$, $P < 0.01$) in all observations ($n = 160$). The coefficient values achieved between plasma atenolol concentrations and reduction in other blood pressures ($r = 0.172$ – 0.386 , $n = 160$ each, $P < 0.05$ – 0.001), and between reduction in various blood pressures and degree of β -adrenoceptor blockade ($r = 0.289$ – 0.445 , $n = 80$ each, $P < 0.05$ – 0.001) were found no greater than the value found between drug concentrations and β -adrenoceptor blockade ($r = 0.571$, $n = 80$, $P < 0.001$).

Discussion

Some comments on our study design, which may be subject to certain criticisms, will be required. The protocol we employed was double-blind, randomized, between-patient but no cross-over design was used because a within-patient cross-over design involving three doses per patient (with mild-to-moderate hypertension) was not possible in view of the greater inconvenience to each individual, since the steady-state pharmacokinetics study together with pharma-

codynamic assessment undertaken mostly on an inpatient basis requires multiple blood samplings, frequent exercise testing and hospital admission. Since the clinical characteristics were essentially similar (Table 1) and the baseline data were not significantly different between the three treatment groups (Table 2), it is unlikely that our results could be entirely explained by the chance observation, allocation methodology or between-treatment comparison.

The present study confirms previous studies demonstrating, in general, no clear-cut dose-anti-

Figure 3 Relation of fall in mean blood pressure (standing and supine) to plasma atenolol concentration. Mean ± s.e. mean values are plotted for the logarithmic plasma atenolol intervals 5 to 10, 11 to 20, . . . 32 to 640 ng/ml. The number of observations (n) at each point is indicated.

hypertensive response relationship of β -adrenoceptor blockers in patients with mild-to-moderate hypertension (Douglas-Jones & Cruickshank, 1976; Douglas-Jones *et al.*, 1978; Marshall *et al.*, 1977, 1979; Myers *et al.*, 1976; Myers & Thiessen, 1980; Serlin *et al.*, 1980) and extends these observations by documenting that the plasma concentration of a β -adrenoceptor blocker such as atenolol is not a reliable predictor of the hypotensive effect. This seems to be consistent with previous studies where even if a significant correlation between plasma levels of several β -adrenoceptor blockers and fall in some of blood pressures was found, it was of a weak order or equivocal (Anavekar *et al.*, 1975; Collste *et al.*, 1976). Others did not find any correlation between antihypertensive response and plasma concentration of propranolol (Kredit *et al.*, 1980; Lehtonen *et al.*, 1977) or metoprolol (Bengtsson *et al.*, 1975; von Bahr *et al.*, 1976).

One objective of the study was that we could determine the optimum or minimum dose for once-daily administration of atenolol to treat patients with mild-to-moderate hypertension. However, the minimum daily dose of atenolol to treat those hypertensives was not clearly identified in this study. For instance, a once-daily dose of 25 mg of atenolol appears not to be an unequivocally clear-cut minimum dose for the hypotensive effect in patients with mild or moderate hypertension as compared to the 50 mg and 100 mg doses: (1) when a satisfactory response was defined as a final supine diastolic blood pressure of 90 mm Hg or less on once-daily dosing with atenolol in patients with mild or moderate hypertension (Douglas-Jones & Cruickshank, 1976), two (29%) on 25 mg, four (57%) on 50 mg, and four (67%) on 100 mg achieved this response among our limited number of study subjects; and (2) the number of patients who dropped their final supine diastolic blood pressure by 10 mm Hg or more was four each in the three study groups. Although a once-daily 50 mg or 100 mg regimen of atenolol lowered significantly all blood pressures throughout 24 h and by the certain periods of time (2 to 4 weeks) (Table 2) and the majority of haemodynamic variables examined did not differ between the 50 and 100 mg groups but some did differ between the 25 and 100 mg groups (Figure 1, Table 3), we are tempted to state that whether a once-daily 50 mg of this β -adrenoceptor blocker may be a minimum dose in the treatment of mild-to-moderate hypertension remains unanswered from this study when the results are viewed overall. The reason for this may reside in the small number of patients used in each dose group.

Although the variance analysis of our results (Table 3) shows that the majority of the mean changes in blood pressure did not reach statistically significant difference between the 25 and 50 mg groups or 50 and 100 mg groups, the quest for validity would require protection from a false conclusion of difference when none exists (type I error, α). There

would be the risk of mistake, such that the false conclusion is drawn that no difference exists, when in fact it does (type II error, β) (Feinstein, 1975; Freiman *et al.*, 1978). Unfortunately, many studies in which the relationship between dose and antihypertensive effect of β -adrenoceptor blocking drugs including atenolol was examined and negative (no significant differences between dose) conclusions were drawn (Douglas-Jones & Cruickshank, 1976; Douglas-Jones *et al.*, 1978; Jeffers *et al.*, 1977; Marshall *et al.*, 1979; Myers *et al.*, 1976; Myers & Thiessen, 1980; Petrie *et al.*, 1977; Serlin *et al.*, 1980) have not shown β -error or the power. This may be largely due to the fact that most studies included too few patients to provide reasonable assurance that a meaningful difference would not be missed.

Our study is no exception. With this limitation in mind, we estimated the power. The value of β for the comparison of blood pressure fall between the 25 and 50 mg groups ranged from 0.962 to 0.894 (power, 3.8 to 10.6%), while the value for the comparison between the 50 and 100 mg groups ranged from 0.972 to 0.860 (2.8 to 14.0%). On the basis of the statistical data of β -error or the power, we can neither reject nor accept the null hypothesis, H_0 (Feinstein, 1975). Clearly, a large sample size is required to draw a conclusion for more unquestionably proving the proposed research aim that a no dose-antihypertensive response relationship of atenolol exists. This certainly requires further study under a large-scale trial protocol.

The observation that the higher the predrug PRA the greater the postdrug change, may imply that the renin-suppressing activity by a β -adrenoceptor blocker is likely to be an all-or-none phenomenon, since each dose lowered PRA significantly (Table 2) with the magnitude of renin suppression not differing between the three groups (Table 3, Figure 2). Our result is considered consistent with observations indicating (1) that the renin responsiveness to atenolol tends to increase as the pretreatment renin value increases (Amery *et al.*, 1977) and the renin-suppressing effect of propranolol occurs at doses of the drug lower than that usually needed to lower blood pressure (Esler *et al.*, 1977; Morgan *et al.*, 1975), and (2) that several β_1 -adrenergic receptor blockers including atenolol can induce reduction in PRA at rest (Amery *et al.*, 1977; Bühler *et al.*, 1975; Distler *et al.*, 1978).

Some investigators have reported that cardiac β -adrenoceptor blockade, rather than suppression of PRA, may be one of the mechanisms for the hypotensive effects observed with propranolol (Esler *et al.*, 1977) and atenolol (Distler *et al.*, 1978). However, Marshall *et al.* (1979) found no relationship between β -adrenoceptor blockade and antihypertensive effect of atenolol. In the present study, correlation coefficient values calculated between β -adrenoceptor blockade and reduction of various blood pressures,

although of a low order ($r = 0.289-0.445$, $n = 80$), reached a significant level ($P < 0.05-0.001$). One may assume the likelihood that a minor part of the blood pressure reduction can be explained by β_1 -adrenoceptor blockade, even though the time-course of the decrease in blood pressure after the final dose of atenolol was not necessarily matched by identical effects on heart rates at rest or upon exercise (Figure 1). However, the coefficient values were not more than the value between plasma atenolol concentration and β_1 -adrenoceptor blockade ($r = 0.571$, $n = 80$, $P < 0.001$). When considered overall, whether our results are compatible with those observed by the previous investigators (Esler *et al.*, 1977; Distler *et al.*, 1979) awaits further study.

Esler *et al.* (1977) found that, when the fall in mean blood pressure and the plasma propranolol concentration interval were compared overall, a biphasic concentration-response relationship was noted, and that patients with high PRA had substantial falls in pressure at propranolol levels of 3 to 30 ng/ml. Hollifield *et al.* (1976) reported that an antihypertensive effect occurs in both high renin and low renin hypertension during large dose (320 to 960 mg/day) propranolol therapy, independent of changes in PRA. Whether our findings are in general agreement with the concept of a biphasic dose- or concentration-response relationship for the antihypertensive effect of propranolol (Esler *et al.*, 1977; Hollifield *et al.*, 1976) cannot be answered with certainty from our study because mono- and biphasic components are not clearly discernible in the concentration-response curve (Figure 3) and atenolol doses greater than 100 mg were not examined.

With the above limitation on one hand, however, we are tempted to speculate that the difference of β -adrenoceptor blockers' physicochemical properties may be related to a dissimilarity in the concentration-response curve. Of particular note in both animal (van Zwieten & Timmermans, 1979) and human (Cruickshank, 1980; Cruickshank *et al.*, 1980; Neil-Dwyer *et al.*, 1981) studies was that a hydrophilic β -adrenoceptor blocker, atenolol, has little access to the central nervous system (CNS), which is in contrast with the lipophilic drug propranolol (Cruickshank, 1980; Cruickshank *et al.*, 1980; Myers *et al.*, 1975; Neil-Dwyer *et al.*, 1981). Such physicochemical-related differences between atenolol and propranolol may be related to a dual mechanism through which propranolol's antihypertensive action is mediated—a low-to-moderate dose, renin-associated mechanism, and a high dose, renin-independent mechanism, which is possibly CNS-related (Hollifield *et al.*, 1976). Atenolol's action on the other hand may be via a one-compartment mechanism leading to a low dose, dose-independent effect, unrelated to renin plus CNS effect(s) as suggested by the results of this study. However, this explanation remains highly speculative and clearly awaits further study.

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