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The response to the first dose of an angiotensin converting enzyme inhibitor in uncomplicated hypertension — A placebo controlled study utilising ambulatory blood pressure recording

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1 The importance of total dose to the initial hypotensive response with an angiotensin converting enzyme inhibitor (quinapril) was assessed using a suggested 'maintenance' dose (20 mg) or matched placebo in a randomised double-blind study in patients with uncomplicated hypertension.

2 Thirty-two patients were recruited who were not on therapy or had not received diuretic therapy in their existing drug treatment in the preceding 4 weeks. Secondary causes of hypertension had previously been excluded and sustained clinic blood pressures of SBP > 160 mmHg and/or DBP > 90 mmHg were taken as indications for a trial of adjuvant or monotherapy with an ACE inhibitor.

3 After uneventful supervised therapy with quinapril in an open pilot study (n = 5) 27 patients entered a double-blind, randomised, crossover study of quinapril or placebo using ambulatory monitoring to assess BP response.

4 All patients remained asymptomatic and both therapy and monitoring were well tolerated. A smooth onset of antihypertensive effect was noted with an overall 24 h placebo corrected fall in systolic BP of 9.9 mmHg (7.2—12.6 95% CI) and diastolic BP of 6.4 mmHg (4.2–8.8) with no significant effect on heart rate. Individual placebo corrected maximal responses during the first 8 h following quinapril showed a wide range for both systolic (+1.56 to 44.0 mmHg) and diastolic (+2.3 to −35.6 mmHg) pressure. Larger falls tended to be associated with higher baseline pretreatment pressures but in no case did absolute systolic pressure fall below 100 mmHg during the first 8 h following administration of placebo or quinapril. In this relatively small study blood pressure responses were not correlated either to pretreatment plasma renin or starting blood pressure.

5 This study suggests that in uncomplicated hypertension, in the absence of sodium or volume depletion or other predisposing conditions such as cardiac failure, an excessive fall in blood pressure is unlikely to occur and therefore dosage reduction is probably unnecessary.

Keywords first dose hypotension ACE inhibition quinapril essential hypertension ambulatory blood pressure recording

Introduction

Inhibitors of angiotensin converting enzyme (ACE) are increasingly recognised as effective antihypertensive drugs regardless of age, sex or plasma renin activity (Williams, 1988). Early studies with these drugs used high doses and this was associated with a spectrum of dose related side effects (Di Bianco, 1986). The use of ACE inhibitors in severe hypertension associated with renal diseases (Johnston, 1988) and in chronic cardiac failure was reported to be associated with marked first dose hypotension with concomitant organ hypo-

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perfusion damage (Cleland *et al.*, 1985; LaBarre *et al.*, 1982; Lantz *et al.*, 1984; Mujais *et al.*, 1984). Although attempts have been made to define factors predicting such responses (Hodsman *et al.*, 1983) there is no good discriminant of predisposition to a marked hypotensive response.

Despite the lack of a definable dose to effect relationship it is generally recommended that low doses of short acting ACE inhibitors should be employed initially, with a period of diuretic withdrawal if these agents have been previously employed. These guidelines remain reasonable for patients with cardiac failure, advanced renal disease or suspected renovascular hypertension. The relevance of these guidelines to the larger population of patients with uncomplicated essential hypertension is unclear.

In the present study we have examined the response to the first dose of an ACE inhibitor in patients with essential hypertension in whom the introduction of this class of agents was deemed clinically appropriate from clinic blood pressures. We have employed accepted clinical criteria to exclude those patients who might exhibit a marked response. In order to assess the response to drug therapy in the community we have employed ambulatory recording techniques. We describe below our findings using the relatively high dose of 20 mg orally of the recently introduced prodrug ACE inhibitor, quinapril (Sedman & Posvar, 1989).

Methods

Thirty-two patients with SBP > 160 and/or DBP < 90 mmHg whose history and presentation would merit the introduction of ACE inhibitor therapy were recruited from our Blood Pressure Clinic, which has been described previously (Rubin *et al.*, 1984). No patient had received diuretics in the previous 4 weeks and patients with a history of peripheral vascular disease, previous myocardial infarction, stroke or cardiac failure or with a serum creatinine greater than 140 μmol l^{-1} at last annual review were excluded. Where relevant the dose of existing antihypertensive therapy had been maintained for 4 weeks and poor compliance was excluded by direct questioning. Details of the patient population are given in Table 1. The study protocol was approved by our local Research and Ethics Committee and written informed consent was obtained in each case.

All patients were recruited consecutively on the basis of clinical decisions to institute ACE inhibitor therapy based on clinic blood pressure readings recorded in triplicate supine and erect with a Sentron semi-

Table 1 Patient demography, concurrent therapy, biochemistry and clinic blood pressure

Study phase	*Patient*	*Sex*	*Weight (kg)*	*Age (years)*	*Clinic blood pressure*		*Therapy (mg)*	*Sodium (mmol l^{-1})*	*Urea (mmol l^{-1})*	*Creatinine (mol l^{-1})*
					Supine	*Erect*				
O	1	M	84.4	52	153/103	174/107	DIL 120 three times daily	144	6.6	86
O	2	M	80.2	45	143/95	140/95	—	144	4.7	97
O	3	M	63	61	192/104	205/100	ATEN 100 daily	144	6.7	136
O	4	F	64.2	54	186/93	181/96	ATEN 100 daily	143	6.4	67
O	5	M	73.6	63	160/104	174/110	CIM 400 t	138	4.9	80
DB	6	M	66.6	45	165/94	150/97	— night	141	4.8	95
DB	7	M	60	77	174/104	186/95	—	144	9.3	106
DB	8	F	66.8	47	163/94	156/91	DIL 120 three times daily	131	4.2	81
DB	9	M	95.8	39	146/101	151/92	—	142	8.2	78
DB	10	M	84	65	169/98	159/91	ATEN 100 daily NIFR 20 twice daily	139	7.2	99
DB	11	M	77.7	61	133/90	150/95	DIL 60 twice daily	147	6.3	96
DB	12	M	75	51	165/104	149/102	DOX 4 twice daily	142	6.4	90
DB	13	M	78.6	34	141/97	135/93	PROP 80 twice daily	142	5.4	93
DB	14	M	77.2	68	191/104	191/106	—	138	7.8	81
DB	15	F	67	54	181/94	186/102	HRT	141	5.8	84
DB	16	M	112.4	40	156/96	151/105	ASP 75 daily	141	6.7	115
DB	17	F	57	46	148/92	141/93	—	141	7.2	90
DB	18	M	102	47	157/101	146/104	ALLOP 300 daily	139	5.6	95
DB	19	F	63.2	62	158/104	176/103	ASP 75 daily	141	5.5	76
DB	20	F	42	24	151/93	150/104	—	140	3.5	54
DB	21	M	73	44	161/94	148/99	—	137	3.6	74
DB	22	M	76	57	185/92	200/108	ATEN 100 twice daily	140	5.2	114
DB	23	F	65.8	48	162/110	171/111	DOX 4 twice daily	140	5.6	78
DB	24	F	54.1	29	139/93	138/94	ATEN 50 daily	142	4.7	76
DB	25	M	90.5	34	164/95	179/100	—	143	5.8	97
DB	26	F	68	46	163/100	158/95	DOX 2 daily	140	5.1	64
DB	27	F	87.4	53	162/110	166/104	ATEN 100 daily	139	5.8	78
DB	28	F	57.5	49	136/90	133/97	ATEN 100 daily	139	5.3	76
DB	29	F	58.2	43	143/89	149/103	ATEN 100 daily	143	5.0	93

O = Open study DB = Double-blind randomised

Concomitant therapy:
ATEN = atenolol, DIL = ditiazem, NIFR = nifedipine retard, DOX = doxazosin, ASP = aspirin, PROP = propranolol, CIM = cimetidine, HRT = hormone replacement therapy, ALLOP = allopurinol

automated sphygmomanometer (Bard International, Sunderland, U.K.). Patients with clinic diastolic blood pressure readings > 90 mmHg or systolic blood pressure > 160 mmHg on two consecutive visits at least 1 month apart were considered suitable for inclusion.

Patients were asked to attend for two periods of single dose administration of either oral quinapril (20 mg) or a matching placebo given in random order in a double-blind, crossover design. Treatment days were arranged at least 10 days apart and doses were given between 09.00 and 12.00 h each day. During both phases full 24 h ambulatory recordings were obtained using Spacelabs 90207 monitors (Spacelabs. Inc. Redmond, Washington). These monitors have previously been validated against conventional static and ambulatory monitors and have been shown to be both reliable and accurate (O'Brien *et al.*, 1991). The monitors were set to record at 20 min intervals between 07.00 and 22.00 h and hourly between 22.00 and 07.00 h. A greater than 80% successful recording was required for acceptance and this was achieved on all records with the exception of one study due to instrument failure. This study was repeated successfully under double-blind conditions. Times of concomitant medication, where relevant, were recorded by each patient.

On each treatment day patients rested supine for 20–30 min. Blood was drawn for the determination of circulating plasma renin activity and angiotensin converting enzyme activity determined by established assay procedures (Cushman & Cheung, 1971; Derkx *et al.*, 1979). For safety reasons the first five patients were studied in an open setting monitored in the Clinical Pharmacology Research Unit for 5 h after oral dosing with active quinapril. The remaining 27 patients participated in the double-blind study. They were given their randomly assigned treatment and asked to conduct their usual daily activities during the following 24 h. The following morning they returned the monitor and after a further period of 20–30 min of supine rest a further venous blood sample was drawn for plasma renin and ACE activities.

The ambulatory blood pressure and heart rate recordings were used to generate hourly average systolic and diastolic pressures and heart rate profiles for each of the two study days. Individual hourly average data although comprising three readings during 07.00 h–22.00 h contained occasional records which derived from spurious or failed individual recordings. Only three recordings could be readily identified as inconsistent and therefore removed from the record. Two occurred in separate individuals during the placebo phase (36/24 and 29/16) and one in a further individual during the quinapril phase (27/22). In order to address the remaining variability without deleting data we chose to re-analyse the observed patterns by producing smoothed curves derived by the running median technique described by Velleman (1980). Such manipulation has been accepted as an important adjunct to interpretation of ambulatory blood pressure data (Streitberg *et al.*, 1989). The magnitude of the response to quinapril was further summarised for each individual as the placebo corrected hourly average systolic blood pressure fall. This profile represented the area under the 24 h time plot of placebo SBP values minus quinapril values and was derived by the trapezoidal rule. The 24 h profiles adjusted to the time of treatment were compared using repeated measures analysis of variance followed by multiple *t*-testing with Bonferroni correction. A probability value of less than 5% was taken to be significant.

Results

The first five patients studied in a single-blind open assessment showed no marked falls in blood pressure after oral quinapril when compared with placebo in the same subject. These open pilot data are not presented in detail here. Twenty-seven further patients were studied double-blind and of these three patients failed to complete the study. Two failed to attend for the second day and defaulted from the clinic unrelated to the medication or study. One patient attended for ambulatory monitoring but refused to take the second treatment, having previously received placebo. The refusal was due to dissatisfaction with the ABP instrument and unrelated to the previous or concurrent medication. All other patients undergoing the double-blind study tolerated treatment and monitoring without complaint and were asymptomatic throughout.

The 24 h profiles (hourly average values) of the patients completing both phases of the double-blind study (n = 24) are shown for systolic and diastolic pressure in Figure 1. The mean placebo corrected fall in systolic and diastolic pressures over the whole 24 h of observation were 9.9 (7.2–12.6, 95% CI) mmHg and 6.4 (4.2–8.8) mmHg respectively. The mean arterial pressure fell by 7.7 (5.4–10.0) mmHg. The 24 h average blood pressure in these patients was reduced from 143.5/89.3 mmHg on placebo to 133.5/82.9 mmHg on quinapril. There was no significant effect of quinapril on heart rate. The absolute values for all recorded systolic pressures over 24 h are given as an interval histogram (Figure 2). This figure represents 1069 values during the quinapril phase and 1095 values during the placebo phase for the 24 patients completing both phases. Only the three recordings detailed above have been excluded. There is no marked increase in the number of SBP recordings less than 100 mmHg

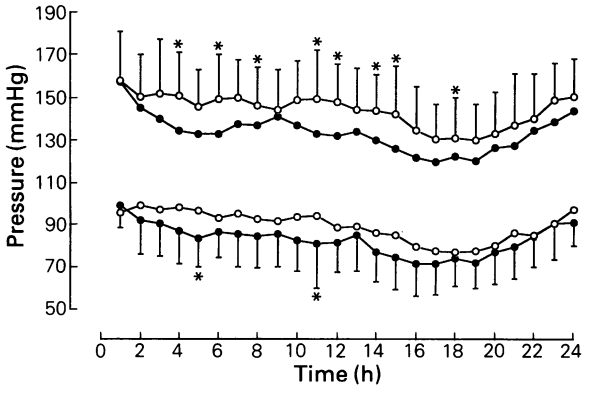

Figure 1 Hourly mean profiles (mean ± 1s.d.) of SBP and DBP in double-blind study (n = 24) (○ placebo; ● quinapril 20 mg orally). * $P < 0.01$.

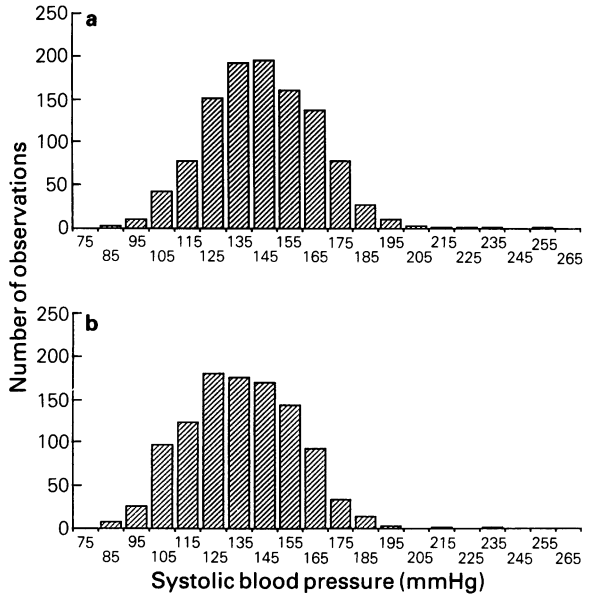

Figure 2 Frequency histogram of absolute recorded systolic blood pressures during 24 h monitoring after placebo (a) (n = 1095) or quinapril 20 mg (b) (n = 1069).

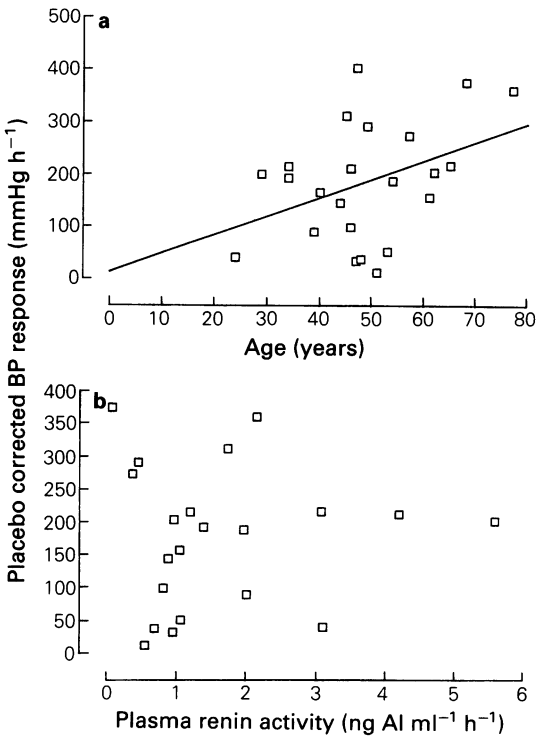

Figure 3 Relationship between response to quinapril, expressed as the AUC of the placebo corrected systolic blood pressure profile over 24 h and (a) patient age (r = 0.46, P = 0.03) and (b) pretreatment plasma renin activity (r = 0.30, NS).

(placebo, 14; quinapril, 33). None of these values occurred during the first 8 h following dosing during either phase.

Individual smoothing of the hourly averaged haemodynamic data re-affirmed the observed patterns of response showing significant placebo corrected falls in smoothed hourly mean systolic BP of 9.8 (7.1–12.6) mmHg, diastolic BP of 6.8 (4.6–9.0) mmHg and MAP of 8.0 (5.7–10.4) mmHg; the differences between treatments were significant between 3 and 16 h after dosing and again there was no consistent effect on heart rate. Using smoothed data curves the overall 24 h mean blood pressure response to quinapril was essentially unaltered from that observed using the raw data (143.2/89.1 after placebo *vs* 133.4/82.3 after quinapril).

The placebo corrected area under the 24 h profile of systolic BP, as an index of overall response, was positively correlated to patient age (r = 0.46 P = 0.03, Figure 3a) but not to the starting (pretreatment) systolic blood pressure (determined using the monitors after supine rest and using the average of the two treatment phases) (r = 0.33, NS).

As would be expected with a long acting prodrug ACEI such as quinapril, there was a significant fall in the plasma ACE activity after active treatment even at 24 h (22.5 ± 4.8 EU ml^{-1} *vs* 8.8 ± 4.1 EU ml^{-1}). The group as a whole was a representative sample of uncomplicated essential hypertension and neither 'high' nor 'low renin' patients were over represented. Those patients who were receiving β-adrenoceptor blocking drugs did not have particularly low levels of circulating PRA. Plasma renin activity (PRA) was not significantly different at 24 h after dosing with either placebo (1.69 ± 1.25 ngAI ml^{-1} h^{-1}) or quinapril (2.10 ± 1.55 ngAI ml^{-1} h^{-1}). Baseline plasma renin activity did not correlate with the observed blood pressure response to quinapril as summarised by the 24 h placebo corrected AUC for systolic blood pressure (r = 0.03, NS, Figure 3b).

Discussion

The reported first dose hypotensive reactions to ACE inhibitors have been identified in several case reports. There remains controversy about the frequency and origin of this phenomenon. Although attempts have been made to define predictive factors (Hodsman *et al.*, 1983) the exact nature is still unclear with only a few indicators of predisposition such as heart failure or severe salt or volume depletion. The fall in blood pressure may be dose related or it may reflect a wide individual range of responsiveness, as has been noted with other antihypertensive agents (Donnelly *et al.*, 1989). It may be a consequence of idiosyncratic vagal activation (Mark, 1983; Semple *et al.*, 1988). Its relevance to the use of ACE inhibitors in uncomplicated essential hypertension is unclear. We have attempted to address this question in a group of patients with essential hypertension and found no evidence of a marked initial response after quinapril 20 mg orally. This is not to suggest that subsequent antihypertensive effect would be modest as the maximal response to ACE inhibitor drugs may develop over periods of weeks or months (Belz *et al.*, 1988). Equally, although our patients recorded no symptomatic episodes of hypotension clearly transient falls in blood pressure could have occurred between the 20 min sampling intervals. From the frequency histogram of all recorded values (Figure 2) isolated low readings occur roughly as frequently after placebo as active drug and in most instances these are nocturnal. This reinforces the need to incorporate an adequate placebo assessment into 24 h

ambulatory profiles of drug effect. The pattern of response which we observed also illustrates the definition of blood pressure response using limited data smoothing techniques which do not fundamentally alter the results of conclusions. Given the pattern of response which we have observed we would suggest that at least in the case of quinapril, this drug can be given to patients with essential hypertension without substantial acute adverse haemodynamic consequences. There was no evidence from baseline plasma renin activity to suggest that we had selected a 'low renin' population which some authors claim may attenuate or negate the response to ACE inhibitor drugs (Buhler, 1988; Laragh, 1989). Furthermore although a number of our patients were receiving β-adrenoceptor antagonists there was no consistent reduction of plasma renin activity in this group nor was there a lack of response associated with low plasma renin. It has been suggested that the circulating level of renin may not define intra renal changes of the hormone in sufficient detail to predict initial response to ACE inhibitors (Laragh, 1989). We chose to examine the effect of retaining a maintenance dose to initiate treatment. Whether or not smaller doses of the same agent would give similar falls in blood pressure on single dose administration remain open to question as does the question of the development of a greater response with long term therapy.

Early experience with high doses of captopril ($\geqslant$ 200 mg day^{-1}) resulted in a high incidence of side effects (Di Bianco, 1986). In the present study we used a relatively high dose of the prodrug ACE inhibitor quinapril (Maclean, 1989). The recommended starting dose of quinapril is 5 mg (2.5 mg in the elderly or those with cardiac failure, British National Formulary No. 19, 1990). The proposed maintenance dose is 20 to 40 mg as a single or two divided doses. For the purposes of our study we employed 20 mg which is the usual maximal single dose as the starting dose. It is possible, but we believe unlikely, that our observations are specific for or limited to quinapril or would be altered by even high doses. It has been our clinical experience over several years that a pronounced fall in blood pressure after the first dose of an ACE inhibitor in uncomplicated essential hypertension is unusual.

In this study we have employed ambulatory blood pressure monitoring which has been proposed to increase the statistical power of definition of antihypertensive effect (Coats *et al.*, 1989). It is also of value in reducing the over-diagnosis of hypertension and its concomitant over-treatment (O'Brien & O'Malley, 1988; Weber *et al.*, 1987; White & Morganroth, 1989). In addition, ambulatory monitoring may provide a better index of prospective end organ damage and can delineate those agents which provide a profile of antihypertensive effect which mimics the normal diurnal pattern and does not compromise organ perfusion during sleep (O'Brien *et al.*, 1989). Ambulatory studies with ACE inhibitors are relatively uncommon (Graetlinger *et al.*, 1989; Lacourciere & Provencher, 1989; van den Meiracker *et al.*, 1989; Verdecchia *et al.*, 1988) but suggest that in patients on long term therapy a diurnal blood pressure reduction is achieved while maintaining the normal circadian variation (Cheung *et al.*, 1989). Such a pattern has not been seen with some alternative classes of anti-hypertensive drugs (Rion *et al.*, 1985). In our study we found no evidence of a selective or greater effect on systolic blood pressure as has been suggested by some workers with other ACE inhibitors (Asmar *et al.*, 1988). Although some of our patients were on a range of concomitant drug therapy it is unlikely that any of these would have masked a first dose hypotensive effect and indeed some cases, e.g. combinations with calcium antagonists, might produce an additive or synergistic response.

In conclusion, in patients with essential hypertension, our study employing ambulatory monitoring has revealed no evidence of marked first dose hypotension to a relatively high dose of the ACE inhibitor quinapril. We believe that this study supports the view that ACE inhibitors can be safely commenced in the vast majority of patients with essential hypertension in the community if patients on diuretics and those with other causes for salt or fluid depletion are avoided.

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