The effects of age on the pharmacokinetics, antihypertensive efficacy and general tolerability of diltiazem

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- 1 This study investigated the influence of age on the pharmacokinetics, pharmacodynamics, general tolerability and concentration-effect relationships in 18 patients with essential hypertension (age range 23–73 years) during treatment with diltiazem, a non selective β -adrenoceptor antagonist with vasodilator properties.
- 2 There were no significant age-related changes in pharmacokinetics for either acute or chronic treatment with diltiazem, although there were significant changes in elimination half-life from 7.8 to 11.7 h ($P < 0.05$) and in AUC from 261 to 352 ng ml⁻¹ h ($P < 0.005$) following translation from acute to chronic dosing.
- 3 In absolute terms, diltiazem treatment (as compared with placebo) produced numerically larger falls in average blood pressure in the six oldest as compared with the six youngest patients: for example, supine blood pressure fell by, respectively, 29/15 and 10/7 mm Hg during chronic treatment.
- 4 Using an integrated kinetic-dynamic model, blood pressure responsiveness was characterised by relating the fall in blood pressure (mmHg) to the plasma drug concentrations in each individual patient. No independent age-related effect was demonstrated. There was a significant relationship between response and the height of initial blood pressure which tended to be higher in the elderly patients.
- 5 Patient tolerability was generally satisfactory and there was no differential age-related effect.
- 6 This study has shown that the antihypertensive efficacy of diltiazem is not attenuated in the elderly and that there are no significant age-related differences in pharmacokinetics or pharmacodynamics.

Keywords diltiazem pharmacokinetics concentration effect analysis elderly hypertension

Introduction

Diltiazem, which is the RR diastereoisomer component of labetalol, is a non selective β -adrenoceptor antagonist with partial β_2 -adrenoceptor agonism and negligible α_1 -adrenoceptor blocking activity in man (Chrisp & Goa, 1990). Peripheral vasodilatation, related to the β_2 -adrenoceptor agonist properties, is thought to contribute significantly to the antihypertensive efficacy (Grossman *et al.*, 1989; Lund-Johansen, 1988).

It has been argued that conventional β -adrenoceptor antagonist drugs are less effective in elderly hypertensive patients (Buhler, 1983; Buhler *et al.*, 1975) and this has been attributed to age-related changes in β -adrenoceptor mediated responses (Dillon *et al.*, 1980; Vestal *et al.*, 1979). However, the ageing process is associated with reductions in hepatic metabolic capacity (Woodhouse &

Wynne, 1988) and in renal function (Rowe *et al.*, 1976) and an alternative or additional explanation is that plasma drug concentrations and pharmacokinetics are perturbed in the elderly (Castleden & George, 1979; Kendall *et al.*, 1977) leading to an alteration in the magnitude of the elderly patient's response (Conway, 1970).

Accordingly an investigation into the effect of age on the responsiveness to an antihypertensive drug requires examination not only of the measured blood pressure reduction but also of the associated plasma drug concentration.

The principal aims of this study, therefore, were to evaluate the effect of age on the pharmacokinetics and pharmacodynamics of diltiazem in patients with essential hypertension and, using concentration-effect analysis,

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to identify whether or not age had any effect on the relationship between plasma dilevalol concentrations and hypotensive response.

Methods

Outline of study

Eighteen patients with mild to moderate essential hypertension (150/90–210/120 mmHg) consented to participate in this study which received prior approval from the hospital Research and Ethics Committee. Patients were either on no treatment or had unsatisfactory therapy withdrawn for not less than 4 weeks prior to study. Only one patient was a cigarette smoker. No patient had any clinically significant abnormality on routine clinical and laboratory investigation. For the purpose of recruitment, patients were allocated into three age groups: a young group – less than 50 years, a middle group – 50–65 years and an elderly group – over 65 years. Mean age and s.d. in the groups were 38 ± 9 years (four male, two female), 57 ± 3 years (three male, three female) and 69 ± 5 years (three male, three female), respectively.

Following entry into the study, patients received placebo for 3 weeks. At the end of weeks 2 and 3 they attended for 2 separate acute single dose study days in which either oral dilevalol 200 mg or matched placebo were administered according to a randomised balanced double-blind crossover design. After the second study day all patients commenced a 4 week treatment period with dilevalol 200 mg daily and returned for a final study day at the end of this chronic dosing period. On each of the 3 days patients attended for a 10 h study day at the Clinical Pharmacology Research Unit (CPRU) following an overnight fast and abstention from caffeine, nicotine and alcohol from 22.00 h the previous evening. After insertion of an indwelling intravenous catheter into a forearm vein and a period of at least 20 min recumbent rest dilevalol, or placebo, was ingested with 150 ml water. Thereafter measurements were made in duplicate of supine and erect blood pressure and heart rate using a semi-automated sphygmomanometer (Sentron, Bard Medical) at frequent intervals and 24 h after dosing. (The sphygmomanometer is routinely serviced on a monthly basis and calibrated against a mercury column by the hospital Medical Physics Department). At corresponding times but additionally at 33 and 48 h after dosing, venous blood was withdrawn for the measurement of plasma dilevalol concentrations. A standard light lunch was provided after 4 h on each study day.

Side effects during each treatment period preceding each study day were monitored by spontaneous reporting and by a 15 point questionnaire including known adverse effects of β -adrenoceptor antagonists and 'dummy' symptoms. In addition patients were requested to complete on each study day 10 cm continuous visual analogue scales with labels of semantic opposites for sedation (wide awake – nearly asleep) tenseness (tense – relaxed) happiness (happy – sad) and clearheadedness (muzzy – clearheaded).

Pulmonary function tests were performed in the routine clinical lung laboratory at a standardised time for each

patient approximately 3 or 5 h after dosing on each study day.

Plasma concentrations of dilevalol were measured by h.p.l.c. (Alton *et al.*, 1988). The inter- and intra-assay coefficients of variation for the drug assay were 7.4% and 4.6% respectively, over the assay range 2–400 ng ml⁻¹.

Pharmacokinetic and concentration-effect analysis

A hierarchy of pharmacokinetic models was fitted to the plasma dilevalol concentration data using a non-linear least squares fitting procedure. In all instances with both acute and steady state therapy as adjudged by a number of criteria of goodness of fit (general linear test, z value for runs in the residuals and Akaike Information Criterion values), a two-compartment model with first order input was the most appropriate model. Measurements derived on each study day were the elimination half-life, area under the curve (AUC), $C_{\max}$ and $t_{\max}$.

For the concentration-effect analysis the two-compartment model was augmented by an 'effect' compartment as described by Holford & Sheiner (1981) and applied to antihypertensive therapy by Donnelly *et al.* (1988). The antihypertensive response (systolic and diastolic blood pressure) for each patient was calculated during acute and chronic dosing by relating the placebo corrected change in blood pressure (mmHg) to the plasma drug concentration-time profile and in all cases the concentration-effect relationship was most appropriately described by a Langmuir ($E_{\max}$) model.

Statistical analysis

The blood pressure and heart rate data were evaluated by repeated measures analysis of variance. ANOVA was also used for the assessment of the pulmonary function tests and visual analogue scores. For illustrative purposes the data are presented for three different age groups but possible differences related to age were excluded on the basis of analysis of co-variance (ANCOVA) with age as the co-variate. ANCOVA was also used to test for differences related to starting blood pressure using starting BP as the co-variate. The pharmacokinetic parameters on the acute and chronic therapy were compared by paired *t*-test. Results throughout are presented as mean $\pm$ s.d.

Results

Blood pressure

Both acute and chronic dilevalol treatment produced significant reductions in supine and erect blood pressure, with the lowest blood pressure recorded at 6–7 h after dosing (Figure 1). For example supine blood pressure fell from a baseline of $164/98 \pm 18/8$ to $130/76 \pm 18/11$ mmHg at 6 h following acute dilevalol compared with a change from $170/100 \pm 18/4$ to $152/88 \pm 21/12$ at 6 h after placebo. The corresponding changes for erect blood pressure were from a baseline of $163/100 \pm 18/7$ to $127/79 \pm 18/11$ mmHg compared with $167/101 \pm 18/8$ to $153/93 \pm 24/10$ mmHg at 6 h after placebo.

Figure 1 Mean profiles of supine systolic and diastolic blood pressure and heart rate in 18 patients following treatment with placebo (○), acute (□) and chronic (■) diltiazem.

Starting values (24 h after the previous day's dose) were significantly lower on the chronic diltiazem treatment day at $154/92 \pm 19/9$ mmHg compared with $164/98 \pm 18/9$ mmHg before the first dose but across the whole study day there were no significant differences between the profiles of single dose as compared to multiple dose diltiazem (Figure 1).

The falls in blood pressure achieved during acute and chronic treatment (adjusted for placebo) expressed as an average over the study day for the young and elderly group are shown in Table 1. In absolute terms the elderly showed a greater fall in blood pressure compared with

the young group. When allowance is made for the difference in starting blood pressure ($176/100 \pm 9/10$ supine and $179/104 \pm 12/9$ mmHg erect in the elderly and correspondingly $159/99 \pm 14/10$ and $154/100 \pm 15/8$ mmHg in the young) and linear regression analysis is applied across the whole age range, no significant age-related differences were demonstrated. Neither group showed evidence of a significant postural component to the hypotensive effect. For example, in the elderly group during chronic treatment the supine reduction in blood pressure was $24/12$ mmHg and erect reduction was $24/13$ mmHg (Table 1).

Heart rate

Both acute and chronic diltiazem treatment produced significant reductions in supine and erect heart rates with no significant differences apart from the baseline values on the final study day when, for example, supine heart rate was 70 ± 11 beats min^{-1} during chronic diltiazem treatment compared with 78 ± 19 beats min^{-1} before the first dose (Figure 1). No age-related differences were detected. The peak effect on heart rate reduction occurred by 2–4 h (Figure 1) in contrast to time of maximum blood pressure reduction at 6 h.

Pharmacokinetics

The plasma drug concentration-time profiles for representative young and elderly subjects after a single dose and at steady state are shown in Figure 2. Peak plasma drug concentration occurred around 1 h in all age groups and diltiazem was detectable in all patients at 24 h after dosing.

The mean derived pharmacokinetic parameters for the three age groups are shown in Table 2. No age-related differences for any value was demonstrable either by comparison of the different groups or by application of linear regression analysis.

Table 1 Summary of placebo-corrected responses for blood pressure and heart rate: calculated as the average from all measurements obtained across the 12 h of each study day

	<i>Acute dilevalol</i>		<i>Chronic dilevalol</i>		
<i>Young</i>					
Supine	-7/3 -7	(± 7/10) (± 7)	-10/7 -5	(± 9/6) (± 8)	mmHg beats min ⁻¹
Erect	-5/3 -14	(± 10/9) (± 10)	-10/7 -10	(± 4/5) (± 10)	mmHg beats min ⁻¹
<i>Middle</i>					
Supine	-11/7 -6	(± 11/4) (± 5)	-7/10 -7	(± 6/4) (± 4)	mmHg beats min ⁻¹
Erect	-19/9 -8	(± 12/3) (± 5)	-11/11 -11	(± 10/6) (± 5)	mmHg beats min ⁻¹
<i>Elderly</i>					
Supine	-22/11 -8	(± 13/8) (± 4)	-29/15 -9	(± 10/8) (± 6)	mmHg beats min ⁻¹
Erect	-18/9 -12	(± 15/10) (± 6)	-28/15 -13	(± 11/12) (± 6)	mmHg beats min ⁻¹

Figure 2 Plasma drug concentration-time profiles following acute (□) and chronic (●) dosing with dilevalol in a representative young subject (left panel) and a representative elderly subject (right panel).

Table 2 Mean derived pharmacokinetic parameters in young ($n = 6$), middle aged ($n = 6$) and elderly ($n = 6$) groups following acute and chronic treatment with oral dilevalol 200 mg daily

	$AUC (ng\ ml^{-1}\ h)$		$t_{1/2} (h)$		$C_{max} (ng\ ml^{-1})$		$t_{max} (h)$	
	Acute	Chronic	Acute	Chronic	Acute	Chronic	Acute	Chronic
Young	$270 \pm 139^*$	379 ± 220	$7.2 \pm 2.1^*$	11.4 ± 3.9	108 ± 40	131 ± 98	0.8 ± 0.4	0.6 ± 0.1
Middle	243 ± 64	303 ± 106	$7.8 \pm 2.5^*$	11.6 ± 1.0	80 ± 38	108 ± 63	0.9 ± 0.4	0.7 ± 0.2
Elderly	269 ± 103	373 ± 121	$8.4 \pm 3.2^*$	12.2 ± 2.6	75 ± 54	93 ± 32	0.7 ± 0.4	1.0 ± 0.3
All ($n = 18$)	$261 \pm 102.6^{**}$	352 ± 152	$7.8 \pm 2.6^*$	11.7 ± 2.5	93.8 ± 41	115 ± 69	0.8 ± 0.4	0.7 ± 0.3

* $P < 0.05$, ** $P < 0.005$, acute vs chronic.

There was a significant change in terminal elimination half-life between acute and chronic dosing with overall mean values of 7.8 ± 2.6 h after a single dose compared to 11.7 ± 2.5 h at steady state. This was paralleled by a significant increase in AUC from 261 ± 101 to 352 ± 152 $ng\ ml^{-1}\ h$. These changes were observed throughout the age range. C_{max} and t_{max} remained unchanged between acute and chronic treatment.

Concentration-effect relationships

From the concentration-effect analysis the following parameters were derived: E_{max} , which is the potential maximum blood pressure reduction in each patient; Ce_{50} , which is the concentration in the effect compartment required to achieve 50% of the maximum response; and K_{eg} , which is the rate constant characterising the temporal discrepancy between the peak plasma drug concentrations and the peak antihypertensive response. These values are shown for erect systolic and diastolic pressure respectively in Tables 3 and 4.

No significant age-related effects were observed by

comparison of the three groups for both systolic and diastolic blood pressure. Over the whole group, however, the translation from acute to steady state therapy was associated with a significant increase in the Ce_{50} value for systolic blood pressure and a similar but non significant trend for diastolic blood pressure. From this integrated assessment of antihypertensive responsiveness further analysis was undertaken across the age range with correlations between responsiveness (E_{max}) and age and between E_{max} (systolic) and starting blood pressure. There was a significant relationship (Figure 3) between responsiveness and starting blood pressure after both acute ($r = 0.80$; $P < 0.05$) and chronic dosing ($r = 0.76$; $P < 0.05$) but not between responsiveness and age (Figure 3). Comparable correlations between E_{max} and starting blood pressure were observed for diastolic values.

Side effects and visual analogue scores

Dilevalol was generally well tolerated by all patients and there were no withdrawals. Adverse events recorded during chronic therapy were generally mild. There were

Table 3 Concentration-effect parameters in the three groups of six patients for changes in erect systolic blood pressure after acute and chronic treatment with dilevalol 200 mg. Patients 1–6 = young group, patients 7–12 = middle group, patients 13–18 = elderly group

Patient	$E_{\max}$ (mmHg)		Ce_{50} (ng ml ⁻¹)		K_{eg} (l h ⁻¹)	
	Acute	Steady state	Acute	Steady state	Acute	Steady state
<i>Patients 1–6</i>						
Group mean $\pm$ s.d.	28.2 $\pm$ 4.7	28.8 $\pm$ 6.3	21.1 $\pm$ 16.4	24.4 $\pm$ 11.5	0.18 $\pm$ 0.11	0.15 $\pm$ 0.09
<i>Patients 7–12</i>						
Group mean $\pm$ s.d.	41.2 $\pm$ 15.9	42.0 $\pm$ 18.9	11.6 $\pm$ 7.0	19.6 $\pm$ 5.0	0.18 $\pm$ 0.20	0.13 $\pm$ 0.10
<i>Patients 13–18</i>						
Group mean $\pm$ s.d.	40.6 $\pm$ 5.9	38.4 $\pm$ 9.1	13.5 $\pm$ 4.8	18.1 $\pm$ 3.9	0.22 $\pm$ 0.12	0.33 $\pm$ 0.16
<i>All patients</i>						
Overall mean $\pm$ s.d.	36.7 $\pm$ 11.3	36.4 $\pm$ 13.2	15.4 $\pm$ 10.8	21.3 $\pm$ 7.3	0.19 $\pm$ 0.14	0.20 $\pm$ 0.15

Table 4 Concentration-effect parameters in the three groups of six patients for changes in erect diastolic blood pressure after acute and chronic treatment with dilevalol 200 mg. Patients 1–6 = young group, patients 7–12 = middle group, patients 13–18 = elderly group

Patient	$E_{\max}$ (mmHg)		Ce_{50} (ng ml ⁻¹)		K_{eg} (l h ⁻¹)	
	Acute	Steady state	Acute	Steady state	Acute	Steady state
<i>Patients 1–6</i>						
Group mean $\pm$ s.d.	22.7 $\pm$ 9.8	24.3 $\pm$ 9.2	18.1 $\pm$ 8.6	22.2 $\pm$ 10.3	0.23 $\pm$ 0.11	0.19 $\pm$ 0.10
<i>Patients 7–12</i>						
Group mean $\pm$ s.d.	29.5 $\pm$ 12.3	30.5 $\pm$ 13.5	14.6 $\pm$ 6.6	19.5 $\pm$ 9.9	0.22 $\pm$ 0.16	0.14 $\pm$ 0.10
<i>Patients 13–18</i>						
Group mean $\pm$ s.d.	28.4 $\pm$ 15.6	25.2 $\pm$ 14.3	16.2 $\pm$ 13.9	20.3 $\pm$ 13.0	0.42 $\pm$ 0.33	0.41 $\pm$ 0.33
<i>All patients</i>						
Overall mean $\pm$ s.d.	26.8 $\pm$ 12.4	26.7 $\pm$ 12.1	17.3 $\pm$ 10.6	20.7 $\pm$ 10.6	0.29 $\pm$ 0.23	0.25 $\pm$ 0.23

Figure 3 a) Relationship between initial erect systolic blood pressure and $E_{\max}$ response following chronic dosing with dilevalol. b) Relationship between age and $E_{\max}$ response following chronic dosing with dilevalol in 18 patients with essential hypertension.

no significant changes in visual analogue scale reporting over the course of the study (Table 5). There were no significant differential age-related effects observed in any adverse event measurement. Similarly, there were no significant treatment-related effects on pulmonary function, with a mean decrease of less than 4% FEV₁ after 4 weeks treatment with dilevalol, as compared with placebo.

Discussion

The pharmacokinetic parameters determined for dilevalol in this study are broadly similar to previous measurements in healthy subjects and hypertensive patients (Fujimura *et al.*, 1989; Kramer *et al.*, 1988, 1989; Tenero *et al.*, 1989).

There were no significant age-related pharmacokinetic differences but there were significant changes (in all age groups) in the translation from acute to chronic therapy with a significant increase in terminal elimination half life from 7.8 to 11.7 h and an associated increase of 35% in AUC. This is consistent with a previous report which described a significant 42% increase in AUC after 8 days dosing to healthy subjects (Fujimura *et al.*, 1989). In addition, reported elimination half-lives following single oral or intravenous doses lie between 8 and 12 h (Auer *et al.*, 1988; Kramer *et al.*, 1988), whereas during chronic dosing values of 13.4, 16.6 and 17.1 h have been observed

Table 5 Side effects and pulmonary function tests

	Placebo	Acute	Chronic
a) Visual analogue scale for symptom reporting*			
Sedation	27.6 ± 20	30.0 ± 27	49.7 ± 31
Tenseness	74.2 ± 24	61.2 ± 34	49.7 ± 31
Happiness	24.2 ± 18	22.6 ± 18	25.7 ± 17
Clearheadedness	69.9 ± 27	70.2 ± 27	68.3 ± 23
b) Pulmonary function tests			
FEV ₁ (l)	2.07 ± 0.52	2.12 ± 0.56	2.00 ± 0.69
FVC (l)	2.81 ± 0.74	2.84 ± 0.81	2.61 ± 0.90
FEV ₁ /FVC%	78.3 ± 8.1	75.7 ± 6.9	76.7 ± 8.9

*Increasing values represent increasing sedation, decreasing tenseness, decreasing happiness and increasing clearheadedness.

(Kramer *et al.*, 1989). A decrease in drug clearance is the likely explanation for these changes, perhaps reflecting auto-inhibition of hepatic drug metabolising capacity. Analogous inhibitory effects have been reported for propranolol (McDevitt, 1988) and for cimetidine which has been shown to inhibit the metabolism of both labetalol (Daneshmend & Roberts, 1984) and also dilevalol, albeit to a lesser extent (Tenero *et al.*, 1989).

This study indicates that there is no independent age-related difference in the antihypertensive response to dilevalol. In fact, the elderly group had an apparently greater hypotensive response, although this was related directly to their higher starting blood pressure values. It is now well recognised that, irrespective of the therapeutic class of agent used, the higher the initial blood pressure value the greater the magnitude of the response to treatment (Sumner *et al.*, 1988). The relative efficacy of β -adrenoceptor blocking agents in the elderly is still contentious. Some reports have proposed that response is attenuated with advancing age (Buhler, 1983; Buhler *et al.*, 1975) and, despite apparently contradictory clinical trials (Andersen, 1985; Wikstrand *et al.*, 1986), this

appears the majority view according to a survey of reviewers' opinions (Fitzgerald, 1988). The latter author has highlighted the lack of appropriate controlled data and the confounding aspect of concurrent therapy. Thus, despite the preconceptions of a possible reduction in efficacy in the elderly, dilevalol was effective for 24 h after once daily dosing across the age range and the blood pressure and heart rate profiles appeared broadly congruent following acute and chronic treatment.

Relationships between plasma concentrations of β -adrenoceptor blocking drugs and chronic hypotensive response have often proved elusive. Since inter-subject differences in drug disposition, particularly for a drug with high first pass extraction, may lead to changes in plasma drug concentration sufficient to modify the magnitude of the hypotensive response, concentration-effect relationships were characterised on an individual basis in this study. This individualised approach is particularly pertinent in age-related studies since the ageing process has the potential to perturb both pharmacokinetics and pharmacodynamic responses (Meredith *et al.*, 1987). Similar concentration-effect relationships have been described using this method for other drugs with mixed β -adrenoceptor blocker and α -adrenoceptor blocker/vasodilator activity (Elliott *et al.*, 1984).

In summary, there was no evidence from this study that age had a significant influence on the pharmacokinetics or antihypertensive response to dilevalol. It is apparent from the individually-derived concentration-effect relationships that there was a significant correlation between the magnitude of the blood pressure reduction and the height of the initial blood pressure, which tended to be higher in the elderly patients, but there was no suggestion that age was an independent contributory factor. Thus despite concerns that a drug with β -adrenoceptor blocking activity might have reduced efficacy in the elderly, this did not appear to apply to dilevalol.

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