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Studies with abanoquil (UK-52,046) a novel quinoline α_1-adrenoceptor antagonist: II. Duration of action, pharmacokinetics and concentration-effect relationships in normotensive subjects

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1 This study further examines the quinoline-derivative abanoquil with particular respect to the duration of its α_1-adrenoceptor antagonist activity and its concentration-effect relationship following a single intravenous bolus dose of 0.5 $\mu g\ kg^{-1}$ in young, normotensive males.

2 α_1-adrenoceptor antagonism (as assessed by phenylephrine pressor responses) was detectable for up to 12 h post dosing: at 12 h there was a significant 1.5–fold rightward shift (95% CI: 2.2 to 1.1) of the pressor dose-response curve for diastolic blood pressure.

3 Despite evidence of substantial α_1-adrenoceptor antagonism abanoquil had no significant effect on blood pressure, supine and erect, but there were small and statistically significant increments in heart rate.

4 The degree of α_1-adrenoceptor antagonism was related to whole blood concentrations abanoquil: the PD-ratios of phenylephrine pressor responses performed at 1, 6, and 12 h post dosing were significantly correlated with log drug concentrations ($r = 0.57$ for systolic ($P < 0.05$) and $r = 0.78$ for diastolic blood pressure ($P < 0.005$).

5 In conclusion, abanoquil produced significant α_1-adrenoceptor antagonism which was related to circulating drug concentrations. The absence of other significant cardiovascular effects suggests that abanoquil warrants further clinical study as an antiarrhythmic agent.

Keywords abanoquil UK-52,046 α_1-adrenoceptor antagonist pharmacokinetics

Introduction

The results of preliminary studies in man have been consistent with those of animal studies in suggesting that abanoquil (UK-52,046) (4-amino-6-7-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinol-2-yl) quinoline methanesulphonate) may have a relative selectivity for cardiac rather than peripheral vascular α_1-adrenoceptors (Aubry *et al.*, 1988; Schafers *et al.*, 1991; Uprichard *et al.*, 1988). Thus, although 'conventional' α_1-adrenoceptor antagonist drugs (e.g. prazosin and doxazosin) produce measurable falls in blood pressure which can be used to monitor duration of action and to characterise concentration-effect relationships (Elliott *et al.*, 1988), there is no significant hypotensive response to abanoquil and an alternative pharmacodynamic index is required. α_1-adrenoceptor antagonist activity (as assessed by the pressor response to the α_1-adrenoceptor agonist, phenylephrine) has been used as an alternative index of drug effect in studies with both prazosin and doxazosin (Elliott *et al.*, 1988; Vincent *et al.*, 1983) and, additionally, the extent of the α_1-adrenoceptor antagonism has been correlated with drug concentrations as a preliminary guide to concentration-effect relationships (Vincent *et al.*, 1983).

The primary aims of this study were to examine the duration of α_1-adrenoceptor antagonist activity and the effects on blood pressure and heart rate. The secondary aims were to describe the pharmacokinetic profile and to investigate the concentration-effect relationship.

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Methods

Subjects

Six young, healthy, normotensive, male volunteers (age 23 ± 6 years, weight 76 ± 9 kg, height 181 ± 5 cm) who had no clinical, electrocardiographical, haematological or biochemical evidence of disease at pre-study evaluation were investigated. Biochemical and haematological screening was repeated prior to and 24 h after each study day as well as 2–4 weeks after cessation of the studies. All subjects gave written, informed consent and the protocol was approved by the institutional Research and Ethics Committee.

Study design

The study followed a single-blind, random-order, cross-over design in which each subject received on each of 2 study days separated by a minimum of 6 days, an intravenous (i.v.) bolus injection of either 0.5 $\mu g\ kg^{-1}$ abanoquil or placebo.

Phenylephrine pressor responses

As an index of α_1-adrenoceptor antagonist activity pressor dose-response studies with phenylephrine were carried out at 1, 6, 12 and 25 h after dosing. Phenylephrine, a selective α_1-adrenoceptor agonist, was administered as an intravenous infusion with at least three incremental dose steps over a dose range of 0.5 to 10 $\mu g\ kg^{-1}\ min^{-1}$ to produce a controlled increase in blood pressure of about 30 mm Hg. For each individual subject a dose-response curve was characterised by fitting a quadratic model to the data points representing the rise in blood pressure above baseline at each dose level. Pressor responsiveness was described in terms of PD_{20}-(systolic) and PD_{15}-values (diastolic) (i.e. the dose of phenylephrine required to elevate blood pressure by 20 or 15 mm Hg respectively). PD-ratios were also calculated for each individual subject (i.e. the ratio of PD-values obtained in the presence and absence of the antagonist abanoquil).

To test if any shift of the dose-response curve (to the right) produced by abanoquil was consistent with competitive antagonism, the pressor responses at 1 h post dosing in the presence and absence of the antagonist were also fitted simultaneously by a reduced quadratic model which describes the two dose-response curves as a set of parallel curves. This method has been described in detail previously (Sumner *et al.*, 1982; Sumner & Elliott, 1987).

Blood pressure and heart rate

Supine and erect blood pressures and heart rates were measured in duplicate using a semiautomated recorder (Datascope Accutorr 2 and 2A). Erect recordings were carried out after the subject had been standing for 2 min.

Whole blood concentrations, pharmacokinetics and the concentration-effect relationship

Venous blood samples were withdrawn from an indwelling intravenous cannula (in the opposite arm to the injection site) for the measurement of abanoquil. The concentrations of abanoquil in whole blood were measured with a newly developed, high performance liquid chromatography (h.p.l.c.) assay. Extraction of drug from 2 ml whole blood was achieved by addition of alkaline ether and back extraction into sulphuric acid (0.05 M). The h.p.l.c. assay utilised fluorescence detection (excitation 255 nm, emission 360 nm) with separation of drug and internal standard on a rigid macroporous copolymer column (Hamilton 5 micron PRP-1). With this column it is possible to use a basic (pH = 12) mobile phase which enhances both resolution and sensitivity. The limit of detection of this assay, defined as three times baseline noise is 20 $pg\ ml^{-1}$, the assay being linear in the range of 20–500 $pg\ ml^{-1}$. Inter- and intra-assay variability assessed across a concentration range was less than 10% (Table 1).

The pharmacokinetics of abanoquil were evaluated using a model-dependent least squares fitting procedure. A hierarchy of models was fitted to the whole blood concentration-time profile. Inter model comparisons by *F*-testing confirmed that the pharmacokinetic profile of abanoquil was most appropriately described by a two-compartment open model. The concentration-effect relationship was described by direct linear regression analysis, plotting the log transformed drug concentrations at 1, 6 and 12 h post-dose against the phenylephrine PD-ratios derived from the pressor infusions at 1, 6 and 12 h post-dosing.

Baroreflex sensitivity and electrocardiographic intervals

The heart rate *vs* blood pressure changes during phenylephrine infusion were further analysed to derive an index of 'baroreflex sensitivity' by linear regression analysis of the fall in heart rate per unit increase in blood pressure. The slope, 'm', calculated from this analysis was used as an index of baroreflex sensitivity (Morley *et al.*, 1984).

Electrocardiographic intervals were measured at 45 min post dosing (i.e. at the time of maximum antagonism of the phenylephrine pressor response) from a standard surface electrocardiogram recording. Two consecutive complexes were measured with a standard ECG ruler at a paper speed of 50 $mm\ s^{-1}$.

Statistical methods

Analysis of variance was used for the repeated measurements of supine and erect blood pressure and heart rate and for the PD values derived from the pressor dose

Table 1 Abanoquil concentration measurement by h.p.l.c.: assay precision

Concentration added ($pg\ ml^{-1}$)	*Concentration detected* ($pg\ ml^{-1}$)	*CV* (%)
50	58.0 ± 6.1	10.5
100	100.6 ± 6.5	6.5
200	193.7 ± 9.8	5.1
300	297.3 ± 10.2	3.4
400	409.3 ± 5.3	1.3

responses. PD-values were log-transformed for statistical analysis in order to achieve normal distribution. Electrocardiographical intervals and baroreflex slopes were statistically compared by paired *t*-test. A *P* value of less than 0.05 was regarded as statistically significant. 95% Bonferroni confidence intervals (CI) were calculated to assess the magnitude of the differences between abanoquil and placebo.

Results

Duration of α_1-adrenoceptor antagonist activity

The pressor dose-responses at 1 h post dosing showed maximal α_1-adrenoceptor blockade and could be appropriately described as a set of two parallel curves for all but one subject. (There were technical difficulties for subject 2 on the placebo study day). The individual dose ratios derived from this fit are summarised in Table 2. The rightward shifts of the dose-response curves were closely comparable for systolic and diastolic blood pressure at respectively 3.2 ± 1.4 and 3.4 ± 1.0.

Thereafter at 6, 12 and 25 h there was a gradual, progressive decline in the extent of the α_1-adrenoceptor antagonism: at 12 h post dosing, the PD_{20}-ratio for systolic blood pressure was 1.3 (95% CI: 1.5 to 0.98) and the PD_{15}-ratio for diastolic blood pressure was 1.5 (95% CI: 2.2 to 1.1: $P < 0.05$) indicating significant α_1-adrenoceptor antagonism. These data are summarised in Table 3 and Figure 1.

Table 2 Individual dose-ratios derived from the reduced quadratic 'parallelism' model for systolic (SBP) and diastolic (DBP) blood pressure for the 1 h pressor infusion

	Dose-ratio	
Subject	*SBP*	*DBP*
1	1.65	1.84
2	—	—
3	4.73	4.23
4	2.51	3.76
5	2.97	4.46
6	2.34	2.70
7	5.14	3.26
Mean	3.22	3.38
± s.d.	1.40	0.99

The 'parallelism' dose-ratio defines the parallel shift of the pressor dose response in the presence of the antagonist. It is the same at every part of the dose-response curve.

Table 3 Mean PD-ratios and 95% Bonferroni confidence intervals for systolic and diastolic blood pressure at 1, 6, 12 and 25 h following 0.5 μg kg^{-1} abanoquil i.v.

Time post-dosing (h)	*PD_{20}-systolic ratio* Mean	95% CI	*PD_{15}-diastolic ratio* Mean	95% CI
1	2.8	3.9 to 2.1	3.2	4.5 to 2.2
6	1.5	2.0 to 1.1	1.7	2.3 to 1.2
12	1.3	1.8 to 0.98	1.5	2.2 to 1.1
25	1.1	1.4 to 0.8	0.9	1.2 to 0.6

Blood pressure and heart rate

Abanoquil had no significant effect on supine or erect blood pressure but there were slight and statistically significant increases in supine and erect heart rates. The time profiles for erect blood pressure and heart rate are shown in Figure 2. The 95% CI for the mean overall difference in erect heart rate between placebo and abanoquil was −15 to −4 beats min^{-1}.

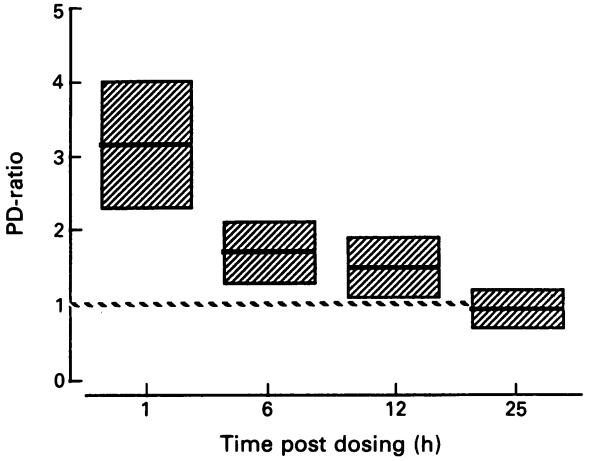

Figure 1 PD-ratios for mean arterial pressure at 1, 6, 12 and 25 h post-dosing: mean values and 95% Bonferroni confidence intervals are shown.

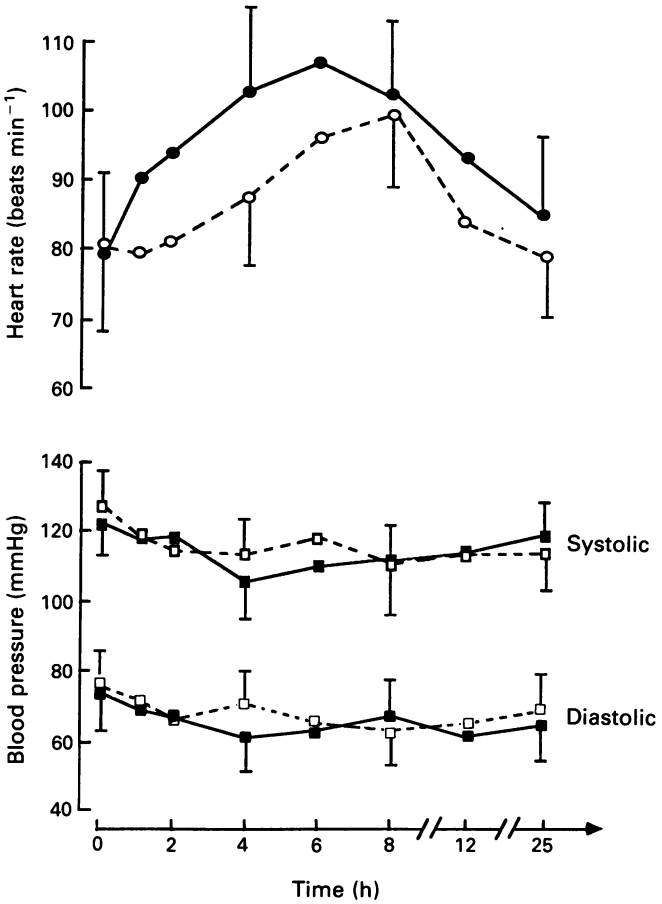

Figure 2 Erect blood pressure and heart rate following placebo (○---○) and following abanoquil (●——●). Heart rate was increased significantly following abanoquil ($P < 0.05$, repeated measures ANOVA).

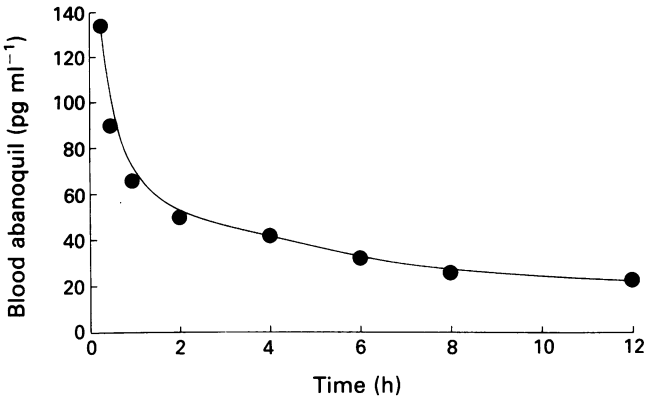

Figure 3 Representative concentration-time profile for abanoquil.

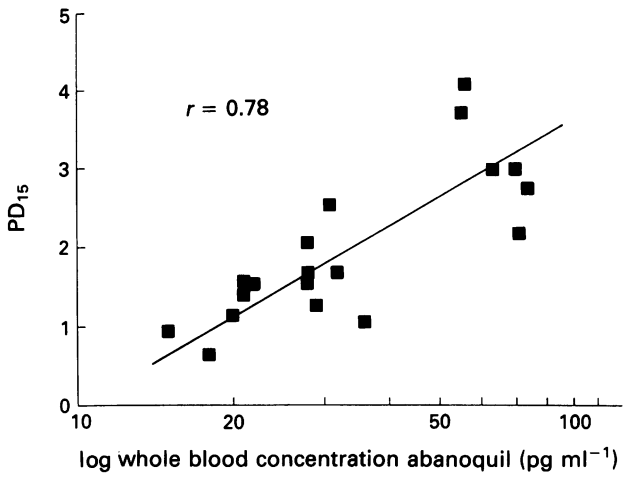

Figure 4 Correlation between the extent of α_1-adrenoceptor antagonism (for diastolic blood pressure) and the whole blood concentration of abanoquil.

Pharmacokinetics

In one subject (no. 4) an interfering substance was present in all samples such as to confound any analysis of drug concentrations and hence any pharmacokinetic analysis in this subject was precluded. In all remaining subjects the most appropriate pharmacokinetic fit was by a two-compartment open model, as illustrated by a representative concentration-time profile (Figure 3). From this a mean whole blood clearance of 63 ± 11 l h^{-1}, a mean volume of distribution at steady state of 479 ± 76 l and a mean terminal elimination half-life of 5.9 ± 1.4 h were calculated (Table 4). In none of the subjects was drug detected 25 h after the intravenous injection and in only one subject were drug concentrations above the limit of detection (20 pg ml^{-1}) at 12 h following drug administration.

Pharmacokinetic-dynamic relationship

For the group data there was a significant correlation between the log whole blood concentrations at 1, 6 and 12 h post dosing and the extent of α_1-adrenoceptor antagonism (as assessed by the phenylephrine PD-ratios as shown in Figure 4) ($r = 0.57$, $P < 0.05$ for systolic blood pressure and $r = 0.78$, $P < 0.007$ for diastolic blood pressure).

Heart rate vs *blood pressure relationship*

The heart rate *vs* blood pressure relationship was also investigated during the time of maximum α-adrenoceptor blockade i.e. during the 1 h pressor infusion. The fall in heart rate per unit increase in both systolic and diastolic blood pressure was examined in each individual subject (the data for subject 2 were incomplete and therefore excluded). There was no consistent change of the linear slope, m, for either systolic or diastolic blood pressure after treatment with abanoquil (Table 5).

Abanoquil had no significant effect on the surface electrocardiographic intervals: mean values respectively for placebo and for abanoquil were 0.17 ± 0.03 and 0.16 ± 0.04 s for PR interval; 0.10 ± 0.01 and 0.10 ± 0.01 s for QRS duration; 0.42 ± 0.04 and 0.41 ± 0.03 s for QT interval; 60 ± 13 and 64 ± 9 beats min^{-1} for heart rate.

Adverse experiences

There were three episodes of symptoms suggestive of postural hypotension, all of them occurring in subject 7, comprising mild to moderate lightheadedness. Two occurred 2 and 8 h respectively following administration of abanoquil and the third one on his placebo day during the 8 h recording. This corresponds to an incidence of

Table 4 Individual pharmacokinetic parameters following intravenous abanoquil (0.5 μg kg^{-1})
Parameter estimates derived from analysis of drug concentration time profile on the basis of the equation:
$C = Ae^{-\alpha t} + Be^{-\beta t}$

	Fitted pharmacokinetic parameters				*Derived pharmacokinetic parameters*			
Subject	*A* (pg ml^{-1})	α (h^{-1})	*B* (pg ml^{-1})	β (h^{-1})	*CL* (l h^{-1})	V_{ss} (l)	V_c (l)	$t_{½,z}$ (h)
1	160.7 ± 33.1	3.4 ± 1.1	76.7 ± 6.0	0.16 ± 0.018	80.5	460	179	4.3
2	224.3 ± 4.4	2.5 ± 0.1	60.0 ± 2.1	0.13 ± 0.007	64.3	430	128	5.5
3	88.4 ± 6.0	2.4 ± 0.4	54.0 ± 2.6	0.092 ± 0.010	60.2	617	263	7.5
5	170.5 ± 32.1	9.1 ± 0.9	75.2 ± 1.1	0.16 ± 0.005	69.5	415	137	4.3
6	268.7 ± 16.9	2.9 ± 0.3	66.3 ± 4.3	0.10 ± 0.012	50.3	436	112	6.8
7	79.9 ± 6.5	3.0 ± 0.4	57.6 ± 1.7	0.099 ± 0.007	53.8	516	236	6.9
Mean					63.1	479	176	5.9
± s.d.					11.0	76	62	1.4

Table 5 Slope 'm' (beats min^{-1} mm Hg) of each individual linear regression analysis i.e. changes in heart rate per unit increase in systolic and diastolic blood pressure

	Systolic BP		*Diastolic BP*	
Subject	*Placebo*	*Abanoquil*	*Placebo*	*Abanoquil*
1	-0.87*	-0.79	-0.86	-0.80
2	—	—	—	—
3	-0.51*	-0.20	-0.86*	-0.36*
4	-0.39*	-0.63*	-0.79*	-1.02*
5	-0.31*	-0.24*	-1.16*	-0.36*
6	-0.55*	-0.40*	-0.68*	-0.59*
7	-0.09	-0.34	-0.18	-0.31
Mean	-0.45	-0.43	-0.76	-0.57
± s.d.	0.26	0.23	0.32	0.29

*These individual values are significantly different from 0 ($P < 0.05$).

orthostatic symptoms of 2% during placebo and 4% during treatment with abanoquil.

Discussion

This study confirms and extends the results of previous studies with abanoquil (Schafers *et al.*, 1991) with rightward shifts of the phenylephrine dose-responses, maximal at 1 h but detectable for up to 12 h after a single intravenous dose.

The preliminary pharmacokinetic analysis suggests that the whole blood concentration-time profile of intravenous abanoquil is most appropriately described by a two-compartment model as has previously been found for both prazosin and doxazosin (Meredith *et al.*, 1985), with a mean terminal elimination half-life of around 6 h. In the studies with prazosin and doxazosin the measured blood concentrations were around 10 ng ml^{-1} i.e. about 150 times higher than the mean whole blood concentration of about 66 pg ml^{-1} measured 1 h after dosing in this study i.e. at about the time of maximal α_1-adrenoceptor blockade with abanoquil. Although circulating concentrations of these drugs do not necessarily reflect their actual concentrations at the site of action (i.e. peripheral vascular or myocardial α_1-adrenoceptors) this more than 100 fold difference suggests that abanoquil has a higher potency than the quinazoline drugs. Thus, this series of studies with intravenous doses of 0.4 $\mu g\ kg^{-1}$ and 0.5 $\mu g\ kg^{-1}$ have consistently produced evidence that abanoquil causes significant α_1-adrenoceptor antagonism but no significant effect on either supine or erect blood pressure.

For the group as a whole, the extent of the α_1-adrenoceptor antagonism showed a significant correlation with the circulating whole blood concentrations of abanoquil. Similar correlations between the antagonistic effect on phenylephrine pressor dose-responses and circulating plasma concentrations of prazosin have been reported previously in healthy, normotensive volunteers (Elliott *et al.*, 1988; von Bahr *et al.*, 1982) and a relationship has also been described for doxazosin in terms of the calculated concentration of doxazosin in the so-called 'effect compartment' (Vincent *et al.*, 1983).

The correlations which have been identified between drug concentration, hypotensive activity and α_1-adrenoceptor antagonism for both prazosin and doxazosin (Bateman *et al.*, 1979; Elliott *et al.*, 1981, 1988; Meredith *et al.*, 1985; Vincent *et al.*, 1983) have been interpreted as *in vivo* evidence in 'intact man' (albeit inferential evidence) that the hypotensive efficacy of these quinazolines is mediated *via* α_1-adrenoceptor antagonism as has long been suggested by classical *in vitro* experiments in various animal tissues (Alabaster *et al.*, 1986; Cambridge *et al.*, 1977) as well as in human vascular preparations (Jauernig *et al.*, 1978). In contrast, the results of these studies with abanoquil suggest that the α_1-adrenoceptor antagonism—as assessed by phenylephrine pressor responses—does not necessarily provide a direct correlate with the blood pressure lowering action in healthy, normotensive volunteers. Thus, the mode of action of abanoquil appears to differ from the conventional α_1-adrenoceptor antagonist activity of the quinazoline derivatives.

Further preliminary evidence in man to suggest that abanoquil is qualitatively different comes from a comparative study involving phenylephrine pressor responses and tilting responses (Tomlinson *et al.*, 1989). In that study, for a similar degree of inhibition of the systolic pressor response to phenylephrine, diastolic pressor responsiveness was more suppressed by prazosin than by abanoquil. On the *assumption* that the phenylephrine induced increase in systolic blood pressure may preferentially reflect its effect on cardiac α-adrenoceptors, whereas its effect on diastolic blood pressure is more closely related to stimulation of vascular α-adrenoceptors, this may be interpreted as an indirect reflection of the 'cardioselectivity' of abanoquil. However, the data from the phenylephrine responses in this present study do not corroborate this finding since the PD-ratios for systolic and diastolic blood pressure were very similar and, more importantly, there was no consistent difference between the parallelism dose ratios for systolic and diastolic blood pressure.

A further possibility is that the acute postural hypotensive effect on prazosin is attributable to an effect on capacitance rather than on resistance vessels (Jauernig *et al.*, 1978; Khatri *et al.*, 1985) and, in contrast, the lack of such an acute hypotensive effect with abanoquil is the result of a relative selectivity for arterial rather than for venous α-adrenoceptors. Thus, if peripheral arterial vasodilatation induces a compensatory increase in heart rate, a fall in blood pressure may not be detectable in young, healthy subjects. The results of our previous study (Schafers *et al.*, 1991) seem to support such an interpretation to some extent, since concomitant β-adrenoceptor blockade with atenolol apparently 'unmasked' a vasodilating effect of abanoquil leading to a reduction in blood pressure. However, although there have been slight and statistically significant increases in both supine and erect heart rate consistent with compensatory baroreflex mediated increase in sympathetic nervous system activity, there also consistently has been an early and transient rise in supine heart rate within 10–15 min of intravenous dosing and it is noteworthy that β-adrenoceptor blocker treatment with atenolol did not prevent this increase (Schafers *et al.*, 1991). Overall, the blood pressure and heart rate results suggest

that abanoquil is not devoid of peripheral vascular α_1-adrenoceptor antagonist activity but that it is quantitatively different from quinazoline derivatives.

Abanoquil had no apparent effects on surface electrographic intervals or on baroreflex sensitivity. Although the relatively insensitive methodologies in this study cannot exclude an effect on cardiac cellular electrophysiology as has, for example, been found in guinea pig isolated perfused hearts during ischaemia (Flores & Sheridan, 1988), these negative findings are entirely consistent with those reported from more detailed studies (Barin *et al.*, 1990; McKaigue & Harron, 1990).

In summary, this study confirms that abanoquil has α_1-adrenoceptor antagonist activity in man which is related to drug concentrations and is detectable for up to 12 h post dosing following a single intravenous dose of 0.5 $\mu g\,kg^{-1}$. Since there is more recent pharmacokinetic information, using a more sensitive assay, to suggest that the terminal elimination half-life exceeds 24 h (D. Cox, personal communication) it seems likely that twice, or once daily, dosage regimens will be appropriate, assuming that the results obtained in healthy volunteers translate to patients.

It was not possible in the present study to provide definitive proof of 'cardioselectivity' but the absence of orthostatic hypotension and profound reflex tachycardia suggests that abanoquil displays a haemodynamic profile which differs from that of the α_1-adrenoceptor antagonists of the quinazoline class and thus warrants further clinical investigation as an antiarrhythmic agent.

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