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Studies with abanoquil (UK-52,046) a novel quinoline α_1-adrenoceptor antagonist: I. Effects on blood pressure, heart rate and pressor responsiveness in normotensive subjects

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1 Abanoquil (UK 52,046) is a novel, quinoline-derivative, α_1-adrenoceptor antagonist which, on the basis of animal studies, possesses antiarrhythmic activity at doses which have little or no effect on blood pressure.

2 In two placebo-controlled, double-blind, crossover studies the α_1-adrenoceptor antagonist activity (phenylephrine pressor responses) and the effects on blood pressure and heart rate (in the presence and absence of concomitant β-adrencoeptor blockade) have been investigated in healthy, normotensive subjects following the intravenous administration (i.v.) of abanoquil.

3 In the first study, abanoquil at a dose of 0.4 $\mu g\ kg^{-1}$ i.v. (as a bolus or by increments) produced significant α_1-adrenoceptor antagonism (with rightward shifts of more than two-fold in the phenylephrine pressor dose-response curves) but no significant effects on supine or erect blood pressure and heart rate.

4 In the second study, a dose of 0.5 $\mu g\ kg^{-1}$ i.v. had no significant effect on supine or erect blood pressure but pre-treatment with atenolol promoted a small fall in erect blood pressure without causing significant orthostatic hypotension.

5 In conclusion, significant α_1-adrenoceptor antagonism without marked reflex tachycardia or profound postural hypotension suggest that abanoquil has a different haemodynamic profile from that of 'classical' peripheral α_1-adrenoceptor antagonists.

Keywords abanoquil UK-52,046 α_1-adrenoceptor antagonist

Introduction

A population of myocardial α_1-adrenoceptors has been clearly demonstrated in both animal and human myocardium by radioligand binding and functional studies (Bruckner *et al.*, 1985). These cardiac α_1-adrenoceptors are implicated in the pathogenesis of ventricular arrhythmias arising in association with ischaemia and increased catecholamine release. In man, such arrhythmias are most likely to occur in the course of acute myocardial infarction or during reperfusion after acute myocardial ischaemia. In animal models these ischaemia- and reperfusion-induced ventricular arrhythmias can effectively be suppressed by α_1-adrenoceptor antagonist drugs (Manning & Hearse, 1984; Wilber *et al.*, 1987; Riemersma, 1982) but in clinical practice application of this antiarrhythmic approach has so far been precluded by the predominant peripheral vascular effects of conventional α_1-adrenoceptor antagonist drugs and their potentially adverse haemodynamic consequences, particularly orthostatic hypotension and reflex tachycardia.

Abanoquil (UK-52,046) (4-amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydro-6,7-dimethoxyisoquinol-2-yl) quinoline methanesulphonate) is a potent and selective antagonist at cardiac and peripheral α_1-adrenoceptors in a variety of *in vitro* and *in vivo* studies (Aubry *et al.*, 1988). It has been shown to modify cellular electrophysiology in the ischaemic guinea-pig heart and its antidysrhythmic properties have been clearly demonstrated in different animal models (Aubry *et al.*, 1988; Flores & Sheridan, 1988; Uprichard *et al.*, 1988). In animal models effective 'cardio-protection' against ventricular arrhythmias (provoked by intravenous adrenaline or by myocardial ischaemia) has been obtained with abanoquil without compromising central or

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peripheral haemodynamics. This has been interpreted as indirect evidence that abanoquil has a relative selectivity for cardiac rather than peripheral vascular α_1-adrenoceptors (Aubry *et al.*, 1988).

To investigate the α_1-adrenoceptor effects and the haemodynamic profile of abanoquil in humans a series of studies has been performed in healthy males.

Methods

Subjects

All studies were undertaken in young, healthy, normotensive, male volunteers who had no clinical, electrocardiographical, haematological or biochemical evidence of disease at pre-study evaluation. Biochemical and haematological screening was repeated prior to and about 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 protocols had been approved by the institutional Research and Ethics Committee.

Study I: Dose-finding study

This was a placebo-controlled, double-blind, randomised, crossover study to identify an intravenous (i.v.) dose of abanoquil which produced a significant degree of peripheral vascular α_1-adrenoceptor antagonism as assessed by a rightward shift of the pressor dose-response curve to phenylephrine, a selective α_1-adrenoceptor agonist.

Six volunteers were studied (age 22 ± 1 years; weight 75 ± 7 kg; height 181 ± 7 cm). On 3 study days, not less than 7 days apart, subjects received the following treatments:

Treatment 1 A total i.v. dose of 0.4 μg kg^{-1} abanoquil in escalating steps of three bolus doses of 0.1, 0.1 and 0.2 μg kg^{-1}.

Treatment 2 A single i.v. bolus dose of 0.4 μg kg^{-1} which was preceded by two placebo injections.

Treatment 3 Three injections of placebo as 0.9% saline.

The three individual bolus doses of drug or placebo were administered at 0, 1.5 and 3 h and phenylephrine pressor responsiveness was measured at 30 min after each administration (thus, at 0.5, 2 and 3.5 h) (Figure 1).

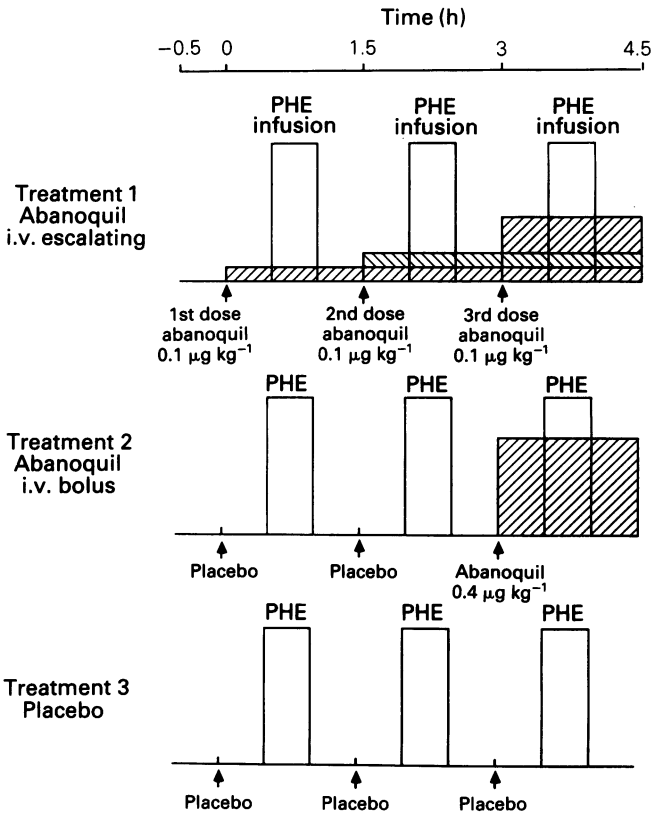

Figure 1 Design of study 1 (Dose-finding study). PHE = phenylephrine.

Study II: Effects of concomitant β-adrenoceptor blockade

This was a double-blind, randomised, crossover study to examine the effect of concomitant β-adrenoceptor antagonist treatment (3 days pre-treatment with atenolol) on the blood pressure and heart rate responses to a single i.v. dose of 0.5 μg kg^{-1} of abanoquil and to assess the safety and tolerability of such a combination. Six volunteers (age 24 ± 7 years; weight 70 ± 5 kg; height 174 ± 5 cm) entered this study but one subject (for incidental, personal reasons) did not complete the study and his data have been excluded from the analysis. Subjects undertook 3 study days, not less than 7 days apart, to receive the following treatments:

Treatment 1 A single i.v. dose of 0.5 μg kg^{-1} abanoquil after 3 days oral pretreatment with atenolol, 100 mg daily.

Treatment 2 Abanoquil (as above) after 3 days oral pretreatment with matching placebo.

Treatment 3 A single i.v. dose of placebo (0.9% saline) after 3 days oral pretreatment with atenolol.

On each study day 1 h after the supervised administration of that day's oral medication, subjects were dosed with i.v. abanoquil or i.v. placebo (Figure 2). Measurements of blood pressure and heart rate were made at frequent intervals throughout the 8 h study day and again at 24 h post-dosing.

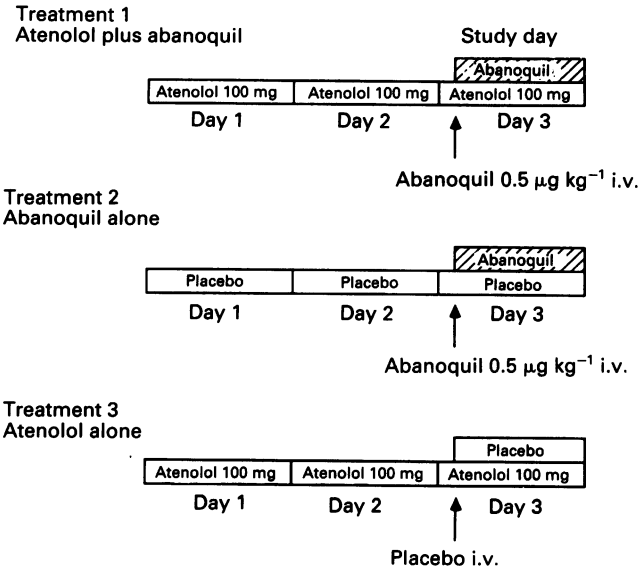

Figure 2 Design of study 2 (β-adrenoceptor blocker study).

Blood pressure and heart rate

Supine blood pressure and heart rate were measured in duplicate, after not less than 10 min recumbency, using a semi-automatic device (Datascope Accutorr 2 and 2A) and erect recordings were carried out after subjects had been standing for 2 min.

Phenylephrine pressor responses

The selective α_1-adrenoceptor agonist, phenylephrine, was administered by controlled intravenous infusion with at least three incremental dose steps within a dose range of 0.5–10 $\mu g\ kg^{-1}\ min^{-1}$. Pressor responsiveness was described in terms of:

a) *PD_{15}-values*: i.e. the dose of phenylephrine ($\mu g\ kg^{-1}\ min^{-1}$) required to elevate mean blood pressure by 15 mm Hg.

b) *PD-ratios*: i.e. the ratio of the PD_{15}-values in the presence and absence of the antagonist abanoquil. This method has been described in detail previously (Sumner *et al.*, 1982; Sumner & Elliott, 1987).

Statistical methods

The repeated measurements of supine and erect blood pressure and heart rate were statistically evaluated by analysis of variance (ANOVA) in Study I and by analysis of co-variance (ANCOVA) in study II, using baseline blood pressure and heart rate as co-variates to take account of the effects of the pretreatment with atenolol. Pressor responses were compared by repeated measures analysis of variance of the PD-values (ANOVA). 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 between treatment differences.

Results throughout are expressed as mean ± s.d.

Results

Study I: Dose-finding study

α_1-adrenoceptor antagonism From the individual PD_{15}-values for the phenylephrine dose response studies individual dose ratios were derived and these are summarised in Table 1. There was no consistent effect with 0.1 $\mu g\ kg^{-1}$ but 0.2 $\mu g\ kg^{-1}$ of abanoquil produced a rightward shift in five of the six subjects, on average by 1.4 fold. With 0.4 $\mu g\ kg^{-1}$ abanoquil, either by increments or as a single bolus injection, there were significant overall 2–3 fold rightward shifts of the phenylephrine pressor dose response: the PD_{15} increased from 1.91 ± 0.48 $\mu g\ kg^{-1}\ min^{-1}$ after placebo to 4.29 ± 0.94 with incremental dosing and to 5.41 ± 3.92 $\mu g\ kg^{-1}\ min^{-1}$ after the single bolus dose of abanoquil, giving rise to mean PD_{15}-ratios of 2.3 and 2.8 respectively (95% CI for the mean difference between placebo and the single bolus dose: 0.84 to 6.20 $\mu g\ kg^{-1}\ min^{-1}$).

Table 1 Study I: Dose-finding study
Individual PD_{15} ratios (relative to placebo)
A PD_{15}-ratio greater than 1 indicates a rightward shift of the phenylephrine pressor response.

	Dose of abanoquil ($\mu g\ kg^{-1}$)			
Subject	*0.1*	*0.2 escalating*	*0.4 escalating*	*0.4 bolus*
1	0.94	1.56	2.57	2.73
2	0.85	0.76	2.08	5.14
3	0.69	1.61	1.82	1.08
4	0.98	1.21	3.24	2.89
5	2.13	1.73	2.33	2.79
6	1.40	1.50	1.81	1.92
Mean ± s.d.	1.17 ± 0.53	1.40 ± 0.36	2.31 ± 0.54	2.76 ± 1.36

Blood pressure and heart rate There were no significant effects on supine and erect blood pressure or heart rate following any treatment with abanoquil although there was a consistent trend, albeit small and statistically non-significant, for both supine and erect heart rates to increase after a total dose of 0.4 $\mu g\ kg^{-1}$. The time profiles for erect blood pressure and heart rate are shown in Figure 3.

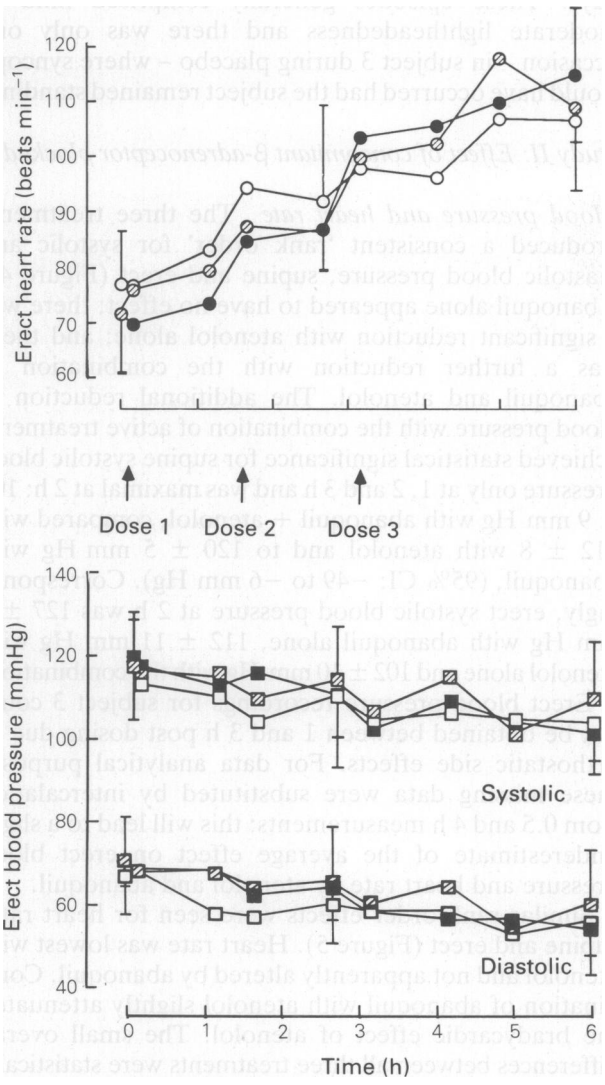

Figure 3 Profiles of erect blood pressure and heart rate in the dose-finding study: placebo (○,□), escalating doses of abanoquil (⊘,⊡) and bolus abanoquil (●,■).

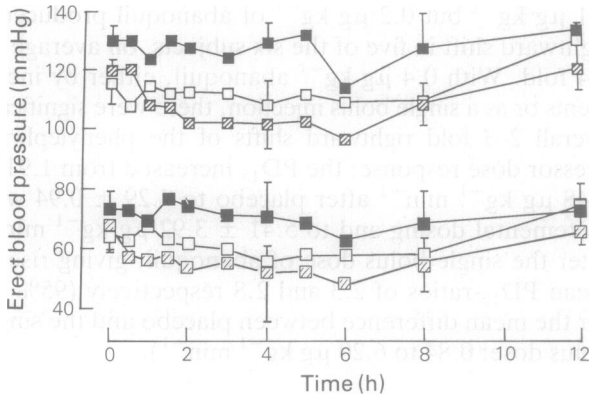

Figure 4 Profile of erect blood pressure in study II (β-adrenoceptor blocker study): abanoquil alone (■), atenolol alone (□) and abanoquil plus atenolol (▨).

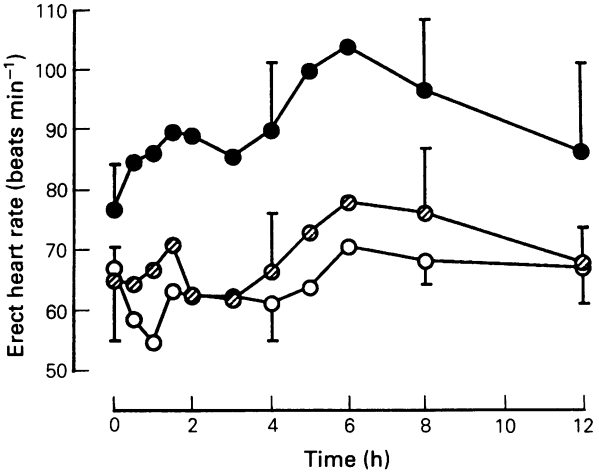

Figure 5 Profile of erect heart rate in study II (β-adrenoceptor blocker study): abanoquil alone (●), atenolol alone (○) and abanoquil plus atenolol (⊘).

Adverse events In total there were only six episodes where subjects reported symptoms suggestive of postural hypotension. Two of these reports occurred on the placebo day (Subjects 1 and 3) and the remaining four reports were all by subject 4 on both of his abanoquil days. These episodes generally comprised mild to moderate lightheadedness and there was only one occasion – in subject 3 during placebo – where syncope would have occurred had the subject remained standing.

Study II: Effect of concomitant β-adrenoceptor blockade

Blood pressure and heart rate The three treatments produced a consistent 'rank order' for systolic and diastolic blood pressure, supine and erect (Figure 4). Abanoquil alone appeared to have no effect; there was a significant reduction with atenolol alone; and there was a further reduction with the combination of abanoquil and atenolol. The additional reduction in blood pressure with the combination of active treatments achieved statistical significance for supine systolic blood pressure only at 1, 2 and 3 h and was maximal at 2 h: 100 ± 9 mm Hg with abanoquil + atenolol, compared with 112 ± 8 with atenolol and to 120 ± 5 mm Hg with abanoquil, (95% CI: −49 to −6 mm Hg). Correspondingly, erect systolic blood pressure at 2 h was 127 ± 5 mm Hg with abanoquil alone, 112 ± 11 mm Hg with atenolol alone and 102 ± 10 mm Hg with the combination.

Erect blood pressure recordings for subject 3 could not be obtained between 1 and 3 h post dosing due to orthostatic side effects. For data analytical purposes these missing data were substituted by intercalation from 0.5 and 4 h measurements: this will lead to a slight underestimate of the average effect on erect blood pressure and heart rate by atenolol and abanoquil.

Similar rank order effects were seen for heart rate, supine and erect (Figure 5). Heart rate was lowest with atenolol and not apparently altered by abanoquil. Combination of abanoquil with atenolol slightly attenuated the bradycardic effect of atenolol. The small overall differences between all three treatments were statistically significant, with 95% CI of 2 to 8 beats min^{-1} for the mean difference between atenolol alone and the combination.

Adverse events The incidence of volunteered orthostatic symptoms (as a percentage over all time points) was 0% on atenolol alone, 4% on abanoquil alone and greatest with 16% after the combination of abanoquil and atenolol. In most instances subjects reported that they felt syncope would have occurred had they not resumed supine posture and subject 2 in particular was unable even to sustain sitting between 1 and 3 h post dosing. These symptoms resolved after 3 h post dosing and there were no long-term sequelae.

Discussion

In the dose-finding study, substantial 2–3 fold rightward shifts of phenylephrine pressor dose-responses were obtained with abanoquil at a dose of 0.4 μg kg^{-1}. These rightward shifts of the phenylephrine pressor response curves are indicative of an antagonist effect on human α_1-adrenoceptors (Sumner *et al.*, 1987) and are consistent with the results of the earlier animal studies (Aubry *et al.*, 1988) and with the results from other human studies (Schafers *et al.*, 1991; Tomlinson *et al.*, 1989).

Despite this evidence of significant α_1-adrenoceptor blockade, abanoquil had no significant effect on supine blood pressure and, more importantly, on erect blood pressure and there was only an associated slight acceleration of heart rate. Similar results were obtained in a second series of studies with 0.5 μg kg^{-1} (Schafers *et al.*, 1991) in which neither supine nor erect blood pressure showed any significant reductions despite the presence of an effective and relatively long lasting (12 h) antagonism of phenylephrine pressor responses. Thus, abanoquil, which is a quinoline derivative, appears to show some haemodynamic differences from the 'conventional' quinazoline derivative α_1-adrenoceptor antagonists, prazosin and doxazosin. In several analogous studies undertaken in this Department, both prazosin and doxazosin have produced similar degrees of α_1-adrenoceptor blockade (as assessed by pressor responsiveness

to phenylephrine) but both have produced significant falls in erect blood pressure in healthy, normotensive, male volunteers (Elliott *et al.*, 1981, 1982a, 1988; Vincent *et al.*, 1983). The potential physiological relevance of this discrepancy between the effect of abanoquil on phenylephrine pressor responses and the absence of an effect on erect blood pressure is not inconsistent with a 'cardioselective' mode of α_1-adrenoceptor blockade by abanoquil.

The effectiveness of α_1-adrenoceptor antagonist drugs against ischaemia and reperfusion induced ventricular arrhythmias has been recognised for some time and blockade of myocardial α_1-adrenoceptors is thought to be the underlying mechanism (Manning & Hearse, 1984).

Furthermore, synergistic antidysrhythmic activity between abanoquil and β-adrenoceptor blockade with the cardioselective β-adrenoceptor blocker atenolol has been observed in animal models (Uprichard *et al.*, 1988). However, previous studies in normotensive volunteers and hypertensive patients with prazosin, the 'classical' α_1-adrenoceptor antagonist, have reported a potentiation of the orthostatic hypotensive response to this drug when combined with a β-adrenoceptor antagonist (Elliott *et al.*, 1981; Seidemann *et al.*, 1982) and such an effect could potentially offset any therapeutically useful synergistic antidysrhythmic activity. In this present study the combination of abanoquil and atenolol promoted only a relatively small additional reduction in both supine and erect blood pressure. In contrast, in a similar study with prazosin (Elliott *et al.*, 1981), the magnitude of the blood pressure reduction produced by prazosin in combination with β-adrenoceptor blockade by both cardioselective (prizidolol) and non-selective agents (propranolol) was significantly increased and the incidence of serious orthostatic symptoms (88 and 80% for the two combinations, respectively) was far higher. Nevertheless, whilst allowance might be made for some degree of individual susceptibility, the observations in subject 3 in this study with abanoquil suggest that it is not completely devoid of such potential hypotensive effects.

It is possible that the hypotensive potential of abanoquil only escaped detection because of the (presumably) compensatory increases in heart rate, such that the drug – although quantitatively different – is qualitatively similar to the quinazoline derivatives as a peripheral α_1-adrenoceptor antagonist/vasodilator. These slight increases in both supine and erect heart rate appear to be consistent phenomena: although statistical significance was not achieved in this (dose finding) study with 0.4 $\mu g\ kg^{-1}$ it was achieved for both supine and erect heart rate in the follow-up series of studies involving an i.v. dose of 0.5 $\mu g\ kg^{-1}$ (Schafers *et al.*, 1991). The results of the atenolol study also lend some support to this interpretation since concomitant β-adrenoceptor blockade (and attenuation of any baroreflex-mediated increase in heart rate) apparently 'unmasked' a vasodilating effect of abanoquil leading to a fall in blood pressure additional to that produced by atenolol alone. Again, there appear to be differences between abanoquil and the quinazoline drugs, since both prazosin and doxazosin as single agents are associated with falls in erect blood pressure in young, normotensive males, *despite* a substantial reflex tachycardia (Elliott *et al.*, 1981, 1982a,b, 1988; Vincent *et al.*, 1983).

In summary, these studies confirm that abanoquil produces significant α_1-adrenoceptor antagonism in human volunteers without producing significant orthostatic hypotension or reflex tachycardia. In combination with cardioselective β-adrenoceptor blockade, there was only slight potentiation of the hypotensive effect and blunting of the bradycardic effect of the β-adrenoceptor blocker alone. These results suggest that abanoquil has a different haemodynamic profile from that of 'classical' peripheral α_1-adrenoceptor antagonists and therefore warrants further clinical investigation.

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