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Duration of action and effect on baroreflex function of the anti-arrhythmic α_1 antagonist UK-52,046

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Abstract—The effects of acute and chronic oral administration of UK-52,046 (25 $\mu g\ kg^{-1}$) on baroreflex function and its duration of action, were studied in conscious dogs. It was found that UK-52,046 had no effect on blood pressure and heart rate following acute and chronic administration. UK-52,046 shifted the phenylephrine dose response curve to the right, and the PE50 (measure of α_1-adrenoceptor antagonism) was increased ($P < 0.05$) compared to placebo on day 1 (2, 4, 8 and 24 h) and day 8 (2, 4, 8 and 12 h). The antagonism was increased ($P < 0.05$) on day 8 (0, 8 and 12 h) compared with day 1. Evaluation of the effects of UK-52,046 on baroreflex function using phenylephrine to increase blood pressure indicated no significant difference from placebo. It was concluded that at an anti-arrhythmic dose, UK-52,046 has no effect on blood pressure, heart rate or baroreflex function. The pressor response curve was shifted to the right indicating a duration of action of at least 12 h on chronic oral administration.

During myocardial ischaemia α_1-adrenoceptor responsiveness is enhanced (Sheridan et al 1980) and has been correlated to an increase in the number of α_1-adrenoceptors present (Corr et al 1981). It has been postulated that the malignant arrhythmias accompanying myocardial ischaemia are primarily mediated by α_1-adrenoceptors (Benfey 1982; Sheridan & Culling 1985). In cardiovascular diseases baroreflex function is depressed (Chapleau et al 1988, review) and if therapy produces additional depression of baroreflex function, further untoward haemodynamic consequences may result.

UK-52,046 (4-amino-6,7-dimethoxy-2-(1,2,3,4-tetrahydro-6,7- dimethoxyisoquinol-2-yl) quinoline methanesulphonate) is an α_1-adrenoceptor antagonist which is thought to act predominantly on myocardial α_1-adrenoceptors, abolishing arrhythmias in experimental models, with little effect on blood pressure and heart rate in animals (Uprichard et al 1988) and man (McKaigue et al 1989). As the α_1-adrenoceptor antagonists prazosin, indoramin and alfuzosin have been shown to decrease baroreflex sensitivity in animals (Harron et al 1984a) and man (Sasso & O'Connor 1982; Deering et al 1988; McKaigue et al 1989), the present study investigated the effects of an anti-arrhythmic dose of UK-52,046 (25 $\mu g\ kg^{-1}$ orally) on baroreflex function and its duration of action on α_1-adrenoceptors during acute and chronic administration in conscious dogs.

Materials and methods

Adult greyhounds of either sex (29·0 ± 1·2 kg, mean ± s.e.m. n = 5) were restrained in the supine position in a temperature controlled laboratory at the same time each day.

Arterial blood pressure was measured using an intra-arterial catheter connected to a pressure transducer (Bell & Howell, type 4-422-000) and heart rate (Lead II electrocardiogram) was simultaneously recorded on a Lectromed MX 216 two-channel recorder. A cannula was inserted into the cephalic vein for vasoactive drug administration (phenylephrine).

Following 30 min quiet rest, increasing doses of phenylephrine (1–128 $\mu g\ kg^{-1}$) were administered at intervals to progressively increase the systolic blood pressure by > 50 mmHg. This was repeated at 2, 4, 8, 12 and 24 h on day 1 and day 8 after administration of UK-52,046 (25 $\mu g\ kg^{-1}$) or placebo as single oral doses daily for eight days. Treatments were randomized and seven days apart.

The duration of action of UK-52,046 was assessed from the phenylephrine dose response curves by calculating that dose of phenylephrine at each time interval required to increase the systolic blood pressure by 50 mmHg (PE50).

Baroreflex function was evaluated by relating the systolic blood pressure to the RR interval of the subsequent cardiac cycle (Smyth et al 1969; Deering et al 1987). The slope of the regression line of RR interval vs systolic blood pressure is taken as a measure of baroreflex sensitivity (ΔRR ms $mmHg^{-1}$), and was calculated at the maximum shift in the phenylephrine dose response curve.

Statistical analysis

Comparisons were made between placebo and UK-52,046 on all test days using Friedman's ANOVA, Mann Whitney U-test (blood pressure and heart rate) and Wilcoxon's signed rank test for matched pairs (PE50).

Results

Following placebo no change occurred in systolic (SBP) and diastolic (DBP) blood pressure or heart rate (HR) on day 1 and day 8 (8 h: day 1 SBP 156·5 ± 5·6; DBP 79·5 ± 7·1; HR 62·3 ± 8·1; day 8 SBP 160·7 ± 7·9; DBP 76·8 ± 6·9; HR 64·1 ± 10·7; Table 1). These values were not significantly different from those following UK-52,046 at any time interval (8 h: day 1 SBP 161·8 ± 6·9; DBP 76·5 ± 6·2; HR 61·6 ± 10·2; day 8 SBP 157·4 ± 6·7; DBP 89·2 ± 7·4; HR 65·0 ± 9·7; Table 1).

The duration of action calculated from the PE50 indicated that on placebo no change occurred on either day 1 or day 8. UK-52,046 increased ($P < 0.05$) the PE50 at 2, 4, 8, and 24 h on day 1 (maximum at 4 h: 22·6 ± 2·4 $\mu g\ kg^{-1}$; Fig. 1) and at 2, 4, 8, and 12 h on day 8 (maximum at 8 h: 44·6 ± 7·9 $\mu g\ kg^{-1}$; Fig. 1). The PE50 during UK-52,046 administration on day 8 was greater ($P < 0.05$) than on day 1 at 0, 8 and 12 h (maximum difference at 8 h: 44·6 ± 7·9 (day 8) vs 22·5 ± 0·9 $\mu g\ kg^{-1}$ (day 1); Fig. 1).

Evaluation of baroreflex sensitivity at the time of maximum shift of the phenylephrine dose response curve indicated no change in the slope of the regression line (ΔRRms $mmHg^{-1}$) with placebo or UK-52,046 on either day (8 h: day 1 24·4 ± 5·8 (placebo) vs 30·8 ± 12·7 (UK-52,046); day 8 21·6 ± 4·4 (placebo) vs 26·3 ± 7·9 (UK-52,046)) nor were the intercepts different (Fig. 2).

Discussion

In the present study following acute and chronic oral administration of UK-52,046 there was no effect on systolic and diastolic blood pressure and heart rate at a dose which is anti-arrhythmic in experimental models. This is in accordance with previous

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Table 1. Effect of chronic oral administration of UK-52,046 (25 $\mu g\ kg^{-1}$) and placebo on blood pressure and heart rate in conscious dogs (mean ± s.e.m.; n = 5).

Systolic blood pressure (mmHg)						
Time (h)	0	2	4	8	12	24
Day 1						
Placebo	154·0 ± 9·6	157·7 ± 8·1	160·1 ± 6·7	156·5 ± 5·6	156·5 ± 5·7	157·2 ± 7·7
UK-52,046	152·2 ± 9·1	163·9 ± 9·9	154·2 ± 6·6	161·8 ± 6·9	160·4 ± 8·4	142·7 ± 9·2
Day 8						
Placebo	157·7 ± 6·2	171·1 ± 4·8	167·8 ± 7·1	160·7 ± 7·9	168·6 ± 6·9	156·4 ± 8·8
UK-52,046	142·6 ± 7·7	150·3 ± 7·7	151·2 ± 5·1	157·4 ± 6·7	150·4 ± 4·3	142·4 ± 5·0
Diastolic blood pressure (mmHg)						
Day 1						
Placebo	89·3 ± 9·0	82·3 ± 7·5	80·9 ± 5·3	79·5 ± 7·1	80·1 ± 3·7	91·4 ± 4·3
UK-52,046	82·3 ± 6·7	81·0 ± 10·5	73·3 ± 8·7	76·5 ± 6·2	81·4 ± 8·2	81·2 ± 0·7
Day 8						
Placebo	86·5 ± 5·6	81·4 ± 7·0	84·7 ± 5·3	76·8 ± 6·9	86·8 ± 7·2	89·3 ± 4·8
UK-52,046	89·9 ± 9·7	86·2 ± 8·8	83·8 ± 9·8	89·2 ± 7·4	90·1 ± 3·4	86·4 ± 6·9
Heart rate (beats min^{-1})						
Day 1						
Placebo	78·9 ± 5·6	62·3 ± 6·0	66·1 ± 8·5	62·3 ± 8·1	74·2 ± 10·5	81·0 ± 6·7
UK-52,046	74·5 ± 7·8	65·8 ± 11·1	72·9 ± 13·3	61·6 ± 10·2	88·6 ± 20·1	78·7 ± 8·4
Day 8						
Placebo	84·3 ± 6·7	61·6 ± 6·9	65·5 ± 10·3	64·1 ± 10·7	68·9 ± 14·6	81·6 ± 5·9
UK-52,046	71·7 ± 8·7	54·2 ± 3·2	64·9 ± 14·5	65·0 ± 9·7	68·7 ± 10·6	72·6 ± 9·2

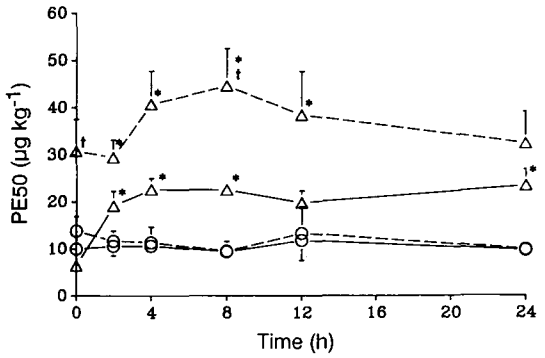

FIG. 1. Effect of acute and chronic oral administration of UK-52,046 (25 $\mu g\ kg^{-1}$) and placebo on PE50 (phenylephrine dose $\mu g\ kg^{-1}$ required to increase systolic blood pressure by 50 mmHg) over 24 h (mean ± s.e.m.; n = 5). O——O placebo day 1. Δ——Δ UK-52,046 day 1. O - - - O placebo day 8. Δ - - - Δ UK-52,046 day 8. * $P < 0.05$ drug vs placebo. † $P < 0.05$ drug day 1 vs drug day 2.

studies in animals (Aubury et al 1988; Uprichard et al 1988). UK-52,046 did not affect baroreflex function (either slope or intercept) to increases in blood pressure with phenylephrine, confirming results occurring in man (McKaigue et al 1989).

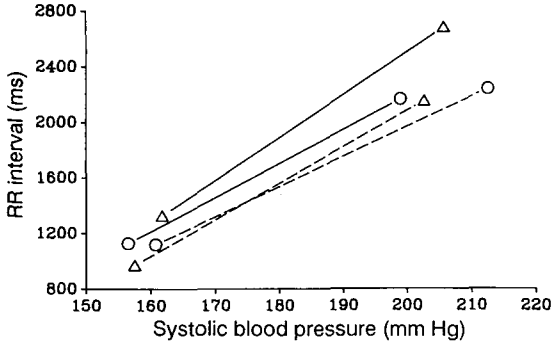

FIG. 2. Effect of acute and chronic oral administration of UK-52,046 (25 $\mu g\ kg^{-1}$) and placebo on baroreflex function (mean ± s.e.m.; n = 5). O——O placebo day 1. Δ——Δ UK-52,046 day 1. O - - - O placebo day 8. Δ - - - Δ UK-52,046 day 8.

However, it did shift the phenylephrine dose response curve to the right on day 1 and day 8 compared with placebo, in keeping with competitive α_1-antagonism.

On day 1 of the UK-52,046 treatment (Fig. 1) the PE50 (measure of α_1-antagonism) was increased ($P < 0.05$) at 2, 4, 8 and 24 h, indicating a duration of action of at least 24 h following a single oral dose of UK-52,046. In man a single intravenous dose of UK-52,046 has a duration of action up to 12 h (Meredith et al 1989). On chronic treatment (day 8) UK-52,046 increased ($P < 0.05$) the PE50 at 2, 4, 8 and 12 h. Compared with acute administration, chronic administration of UK-52,046 increased ($P < 0.05$) PE50 at 0, 8 and 12 h confirming a 12-24 h duration of action from a single oral dose. This is of interest as the study indicates α_1-antagonism without an accompanying reduction in blood pressure. This is in contrast to prazosin and indoramin which shift the phenylephrine dose response curve to the right at anti-arrhythmic doses, and reduce blood pressure (Alps et al 1971; Sumner et al 1982; Benfey et al 1984; Harron et al 1984b).

α_1-Adrenoceptors have been identified in the heart (Benfey 1982), at baroreceptor nerve endings (Goldman & Saum 1984; Munch et al 1987) and throughout the peripheral vasculature. Peripheral α_1-adrenoceptors mainly occur postsynaptically on arteries (De Mey & Vanhoutte 1981), while venous smooth muscle contains both α_1- and α_2-postsynaptic adrenoceptors (Horn et al 1982). It has been suggested that myocardial α_1-adrenoceptors only play a physiological role under abnormal conditions (Wagner & Brodde 1978).

Phenylephrine (α_1-agonist) increases blood pressure by peripheral α_1-adrenoceptor mediated vasoconstriction (Sheldon et al 1983) and by increasing myocardial inotropy. Several studies show that the positive inotropic effect is solely mediated by α-adrenoceptors (Wenzel & Su 1966; Govier 1967; Verma & McNeill 1976; Schumann et al 1978). Others suggest it is mediated by α-adrenoceptors at low concentrations of phenylephrine and by β-receptors at higher concentrations (Endoh et al 1976, 1982). Hartmann et al (1988) showed that in isolated feline ventricular myocytes, propranolol decreased the phenylephrine induced contractility from 201 ± 28% to 130 ± 8%, the residual contractility being inhibited by prazosin. Therefore myocardial and/or peripheral α_1-antagonism could shift the phenylephrine pressor response curve to the right. From analysis of phenylephrine pressor responses Bruckner et al (1985) have

suggested that the diastolic response is more dependent on peripheral α_1-adrenoceptor stimulation while the systolic response is dependent on cardiac α_1-adrenoceptor stimulation. Work with prazosin has shown greater inhibition of the diastolic than systolic phenylephrine pressor response (Singleton et al 1982) suggesting preferential binding to peripheral sites. Further work by Tomlinson et al (1989) comparing equipotent doses of UK-52,046 and prazosin in the above manner, has shown less inhibition of the diastolic pressor response by UK-52,046 than by prazosin suggesting that UK-52,046 preferentially blocks myocardial α_1-adrenoceptors in comparison to prazosin.

With regard to baroreflex function, α_1-adrenoceptor blockade may modify the discharge rate by blockade of the baroreceptor nerve endings (Munch et al 1987) or by decreasing vessel wall distensibility (Bergel et al 1980), either of which may decrease baroreflex function. It is therefore plausible that UK-52,046 which may preferentially antagonise myocardial α_1-adrenoceptors would not affect baroreflex function, as is seen (Fig. 2). This is in contrast to prazosin which depresses baroreflex function (Sumner et al 1982).

In conclusion, UK-52,046 at a dose which is anti-arrhythmic has a long duration of action and no effect on blood pressure, heart rate and baroreflex function. However, like prazosin and indoramin it competitively shifts a phenylephrine dose response curve, although in contrast to these drugs, it may be due to a predominant effect on the myocardium as compared to the peripheral vasculature.

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