Acute haemodynamic effects of cromakalim in patients with angina pectoris

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1 We studied the acute haemodynamic effects of cromakalim, a vasodilator which activates smooth muscle potassium channels, in 11 patients with ischaemic heart disease undergoing routine cardiac catheterisation. A similar group of six patients given placebo were studied under identical conditions.

2 There were no significant differences in baseline haemodynamic parameters between the two groups.

3 Following intravenous cromakalim ($15 \mu\text{g kg}^{-1}$) cardiac output increased by 30% ($P < 0.05$ vs placebo) while systolic arterial pressure decreased by 8% ($P < 0.05$), systemic vascular resistance decreased by 29% ($P < 0.01$) and pulmonary vascular resistance decreased by 24% ($P < 0.01$) at plasma concentrations of the (+)- and (–)-enantiomers of cromakalim of $6.2 \pm 0.5 \text{ ng ml}^{-1}$ and $10.0 \pm 1.0 \text{ ng ml}^{-1}$ respectively.

4 There were no significant differences in diastolic arterial pressure, left ventricular dP/dt and stroke volume between the two groups. Heart rate increased by 11% following cromakalim but this did not achieve significance.

5 These findings confirm that cromakalim acts primarily as an arteriolar vasodilator producing an improvement in cardiac performance. Cromakalim may be of benefit in the treatment of patients with ischaemic heart disease.

Keywords vasodilator cromakalim ischaemic heart disease

Introduction

Cromakalim, BRL34915, is a structurally novel, orally active vasodilator with antihypertensive properties (Ashwood *et al.*, 1984; Buckingham *et al.*, 1984, 1986a). It is a benzopyran derivative, ($\pm$)-6-cyano-3,4-dihydro-2,2-dimethyl-trans-4-(2-oxo-1-pyrrolidyl)-2H-benzo[b]pyran-3-ol, consisting of a 50:50 racemic mixture of the (+)- and (–)-enantiomers (BRL38226 and BRL38227 respectively). *In vitro* and *in vivo* studies have shown that the biological activity is primarily present in the (–)-enantiomer (Buckingham *et al.*, 1986b). Cromakalim relaxes vascular smooth muscle by opening potassium channels, thereby holding the membrane potential at or close to the potassium equilibrium potential (E_{K}). It

therefore exhibits physiological antagonism offsetting the depolarising action of excitatory agents by its hyperpolarising properties (Hamilton *et al.*, 1986). Initial work suggests that the effects of cromakalim are unrelated to changes in intracellular calcium availability (Howlett, 1987).

The antihypertensive properties of cromakalim have been confirmed in animal models and in man. In conscious animals oral antihypertensive doses of cromakalim (0.01 – 1 mg kg^{-1}) are 10–30 times lower than those of nifedipine (Buckingham *et al.*, 1986a). Cromakalim has a reproducible pattern of response with absence of cumulative effects. It has not been shown to

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have rebound effects on withdrawal and lacks tachyphylaxis. Whereas nifedipine slightly reduces renal blood flow and markedly increases femoral blood flow, cromakalim has been shown to increase renal flow and to have little effect on femoral flow in anaesthetised normotensive cats: potentially beneficial characteristics for an antihypertensive agent. In addition coronary vasodilator effects have been demonstrated *in vitro* (Cain & Nicholson, 1988). The arteriolar vasodilator properties of cromakalim, and lack of significant venodilator effects, have been confirmed in man (Benjamin *et al.*, 1988) and its blood pressure lowering action has been described in hypertensive patients (Van den Burg *et al.*, 1986).

The combination of systemic arteriolar vasodilatation and possible coronary vasodilatation suggests that cromakalim may be beneficial in the treatment of angina pectoris. We therefore assessed the detailed haemodynamic response to a single intravenous dose of cromakalim in patients with ischaemic heart disease.

Methods

Seventeen male patients of mean age 53 years (range 40–65 years) were recruited to the study. Their mean height was 172 cm (range 155–187 cm) and mean weight was 78 kg (range 58–96 kg). All had stable angina pectoris of mean duration 38 months (range 3–120 months) and seven had sustained myocardial infarctions at least 6 months prior to the study; none had evidence of congestive heart failure. A diagnosis of ischaemic heart disease was made from the clinical history and the presence of ischaemic changes on treadmill exercise testing. Subsequent coronary angiography confirmed the presence of coronary artery disease in all patients. Prior to the study eight patients were receiving β -adrenoceptor antagonists, five were receiving long-acting nitrate preparations, six were receiving calcium antagonists and six were taking aspirin. All regular medication was stopped for at least 24 h prior to the study but patients were allowed to take sublingual glyceryl trinitrate as required. Diazepam 10 mg orally was given 1 h before the study.

All patients were studied supine during routine cardiac catheterisation prior to coronary angiography and left ventriculography. Written informed consent was obtained for the additional study procedures which were approved by the hospital ethics committee. Following an overnight fast catheters were introduced under local anaesthesia. A sheath was inserted into the

femoral artery for measurement of systemic arterial pressures and, through it, a catheter-tipped manometer (Sentron) was introduced retrogradely into the left ventricle for measurement of left ventricular pressures and left ventricular dP/dt. A thermodilution Swan-Ganz catheter was inserted into the pulmonary circulation via the femoral vein for measurement of pulmonary arterial pressures and estimation of cardiac output. Heart rate was taken from a simultaneous electrocardiogram.

The study was of single-blind design: eleven patients received the active drug and six patients received placebo. Two successive baseline recordings of all parameters were obtained 15 min before the study commenced and their means calculated. Cromakalim ($15 \mu\text{g kg}^{-1}$ made up to a total volume of 20 ml with physiological saline) or 20 ml of physiological saline as placebo was then infused over 10 min through a peripheral vein. Haemodynamic measurements were recorded every 5 min for 30 min following the onset of the infusion. Blood samples were also collected from the Swan-Ganz catheter prior to and at 5 min intervals for 30 min following the onset of infusion. Further samples were obtained at 1, 2, 3, 4, 6, 8 and 24 h following the infusion. Each 5 ml sample was placed in a tube containing EDTA, gently shaken and then centrifuged at $3000 \text{ rev min}^{-1}$ for 15 min. The plasma was then stored at -20°C until drug assay.

Drug assay

Simultaneous quantification of each of the enantiomers of cromakalim was undertaken on the plasma samples using chiral capillary gas chromatography-mass spectrometry as described by Gill *et al.* (1988a).

Statistical methods

Baseline haemodynamic parameters in the two groups were compared using Student's *t*-test. Haemodynamic parameters at each 5 min interval following cromakalim were compared with those following placebo using repeated measures of analysis of variance and, where appropriate, applying the *t*-test. The level of significance was taken as $P < 0.05$.

Results

Haemodynamic parameters

The acute effects of cromakalim and placebo on haemodynamic parameters are shown in

Figure 1 Changes in haemodynamic parameters in the cromakalim treated group (solid lines) and in the placebo treated group (broken lines). Each point represents mean $\pm$ s.e. mean. Baseline values were not significantly different in the cromakalim and placebo groups.

Significance of changes in the cromakalim group with respect to the placebo group: * $P < 0.05$; ** $P < 0.01$.

HR, heart rate; SAP, systemic arterial pressure (systolic, mean and diastolic pressure); CO, cardiac output; SV, stroke volume; MPAP, mean pulmonary arterial pressure; LVEDP, left ventricular end-diastolic pressure; LV dP/dt, left ventricular dP/dt; SVR, systemic vascular resistance; PVR, pulmonary vascular resistance.

Figure 1. One patient in the active treatment group had incomplete haemodynamic recordings and was excluded from the analysis. There was no significant difference in any baseline haemodynamic parameter between cromakalim and placebo treated groups. The most significant effects of cromakalim were on cardiac output (+30%), systolic arterial pressure (−11%), systemic vascular resistance (−29%) and pulmonary vascular resistance (−24%) at 10 to 15 min following the onset of infusion.

Heart rate increased following cromakalim and remained elevated throughout the 30 min study period but values were not significantly different from those following placebo. Systolic systemic arterial pressure decreased following the onset of infusion of cromakalim and was significantly different from placebo at 10 min (−11%, $P < 0.01$) and 15 min (−8%, $P < 0.05$) and remained lower than baseline throughout the study ($P < 0.01$ vs placebo at 30 min).

Diastolic systemic arterial pressure was slightly lower than baseline throughout the study in the cromakalim treated group but this was not significantly different from placebo. Mean arterial pressure was lower in the cromakalim treated group at 10, 25 (both $P < 0.05$) and 30 min ($P < 0.01$).

Cromakalim increased cardiac output throughout the study period, reaching a peak at 15 min following the onset of infusion (8.2 ± 0.5 vs 6.3 ± 0.5 l min⁻¹, $P < 0.01$ vs placebo at 15 min). Although stroke volume rose concomitantly the changes were not statistically significant, possibly related to the greater variation in response following infusion. Left ventricular stroke work was unchanged throughout the study period (126 ± 13 vs 118 ± 7 g m/beat at 10 min and 134 ± 14 vs 123 ± 10 g m/beat at 15 min, both $P = \text{NS}$). Total left ventricular work was slightly elevated following cromakalim but this did not achieve statistical significance (8518 ± 849 vs

$7647 \pm 863 \text{ g m min}^{-1}$ at 10 min and 8699 ± 853 vs $7809 \pm 705 \text{ g m min}^{-1}$ at 15 min, both $P = \text{NS}$).

There were significant decreases in systemic vascular resistance following cromakalim: -19% at 5 min ($P < 0.05$ vs placebo), -27% at 10 min, -29% at 15 min (both $P < 0.01$), -17% at 20 min and -23% at 30 min (both $P < 0.05$). Pulmonary vascular resistance was also decreased: -19% at 10 min, -24% at 15 min and -25% at 30 min (all $P < 0.01$). Cromakalim produced little change in pulmonary arterial pressure or left ventricular end-diastolic pressure (see Figure 1), although there were significant differences when compared with the placebo group since in the latter both parameters rose slightly. Left ventricular dP/dt was slightly elevated following cromakalim but changes were also observed in the placebo treated group.

Adverse effects

No adverse effects were reported during or following the study.

Plasma drug values

Peak plasma drug concentrations for both enantiomers of cromakalim occurred at 5 min of infusion (see Figure 2). Plasma levels of the $(-)$ -enantiomer tended to be higher than those of the $(+)$ -enantiomer throughout the study period.

At maximal effect on cardiac output and systemic vascular resistance (15 min following the onset of infusion) plasma levels of cromakalim were $6.2 \pm 0.5 \text{ ng ml}^{-1}$ and $10.0 \pm 1.0 \text{ ng ml}^{-1}$ for the $(+)$ - and $(-)$ -enantiomers respectively.

Discussion

This study demonstrates that cromakalim has arteriolar vasodilator properties in patients with ischaemic heart disease and may therefore be of benefit in the treatment of patients with angina pectoris. The most profound effects were on left ventricular afterload, systemic vascular resistance fell by 17–29%, and on

Figure 2 Mean (s.e. mean) plasma cromakalim concentrations over 24 h (following $15 \mu\text{g kg}^{-1}$) in the 11 study patients. $(+)$ -enantiomer: solid line; $(-)$ -enantiomer: broken line. $\blacksquare$ represents the duration of the infusion.

cardiac performance, cardiac output increased by 19–30%. Pulmonary vascular resistance was also reduced (19–24%). Cromakalim may thus have a direct pulmonary arteriolar vasodilator action in addition to its systemic action. Since pulmonary arterial pressures were little changed following cromakalim, the decrease in pulmonary vascular resistance was balanced by the increase in cardiac output.

These changes were accompanied by a reflex tachycardia (up to 11% increase or +7 beats min^{-1} at 10 min). Although stroke volume was improved by up to 17% this failed to reach statistical significance because of the large standard error of the mean of values post-infusion. It is possible that with a larger patient population this would have achieved significance. The large increase in stroke volume suggests that this component accounts for most of the improvement in cardiac output and that this is secondary to the afterload-reducing properties of cromakalim. It is unlikely that cromakalim has a direct positive chronotropic effect since a reflex tachycardia commonly accompanies acute systemic arteriolar vasodilatation, for example following nifedipine (Dargie *et al.*, 1980; McLeay *et al.*, 1983).

Left ventricular stroke work, derived from the product of stroke volume and the difference between mean arterial pressure and left ventricular end-diastolic pressure, was not significantly altered in the two groups. Since preload appeared to be unaffected by the drug, changes in afterload were approximately balanced by changes in stroke volume. Although there was a slight increase in heart rate following cromakalim, total left ventricular work was not significantly increased compared with placebo. Evaluation of cromakalim as a potential anti-anginal agent should include further investigation of its effect on cardiac work, especially during chronic therapy.

Left ventricular end-diastolic pressure and pulmonary arterial pressure remained constant following cromakalim. However, there was a slight increase in both parameters in the placebo group resulting in a significant difference between the two groups especially at 30 min following infusion. These increases may be a response to the supine position and it is possible that any tendency for increase in the active treatment group was offset by cromakalim, suggesting that the drug may have a mild effect on preload and pulmonary pressures.

Left ventricular dP/dt , a measure of contractility, was increased following cromakalim, albeit modestly. The increase is likely to reflect the increase in heart rate and conclusions concerning

the possible inotropic properties of cromakalim cannot be made from this study. Isolated tissue studies have suggested that in usual doses cromakalim lacks significant cardiac stimulating or depressing activity, although in high doses (up to 100 times the vasodilating dose) depression of contractility has been observed (Cain & Metzler, 1985). Further investigation of a potential inotropic effect of cromakalim in man should be performed in the presence of β -adrenoceptor antagonism, to offset the reflex tachycardia, while pacing, as previously described in haemodynamic investigations of calcium antagonists in man (Culling *et al.*, 1984; Sheridan & Thomas, 1987).

The increase in heart rate following single intravenous dosing with cromakalim in this study is similar in magnitude to that observed in an initial study of the antihypertensive action of cromakalim in man (Van den Burg *et al.*, 1986). Nevertheless, in the present study there was no significant difference in values between the cromakalim treated and placebo treated groups. It is possible that a residual β -adrenoceptor antagonist effect was present in those patients receiving long-acting preparations despite the drugs being discontinued at least 24 h prior to the study; this may have lessened the magnitude of the heart rate response following cromakalim. In the study of Van den Burg *et al.* (1986) an increase in supine heart rate of 13% (+10 beats min^{-1}) was observed 4 h following oral dosing with cromakalim (0.5–1.5 mg). A similar heart rate response is also observed following supine oral dosing with nifedipine and, on chronic dosing with the latter the effect diminishes, perhaps related to baroreceptor resetting (McLeay *et al.*, 1983). In animal studies reflex tachycardia has been observed in spontaneously hypertensive rats following single doses of cromakalim but is not observed after chronic dosing (Buckingham *et al.*, 1986a). A persistent reflex tachycardia following arteriolar vasodilatation increases cardiac work and is therefore likely to be disadvantageous in the longterm management of patients with angina pectoris. The presence of a persistent tachycardia following chronic dosing with the arterial vasodilators minoxidil and hydralazine prevents the routine use of these agents in the management of patients with angina pectoris. The effect of cromakalim on heart rate during the longer-term management of patients with ischaemic heart disease is necessary to evaluate its potential role in this condition.

In this study, following intravenous cromakalim $15 \mu\text{g kg}^{-1}$ (mean dose 1.2 mg, range 0.9–1.4 mg), maximum plasma concentrations of

both enantiomers were obtained 5 min following dosing. Plasma levels remained reasonably stable for both enantiomers between 1 and 6 h post-dosing but levels of the (–)-enantiomer were higher. In a pharmacokinetic study of oral cromakalim at four dose levels (0.5, 1, 1.5 and 2 mg) (Gill *et al.*, 1988b), maximum plasma concentrations of the (–)-enantiomer tended to occur earlier than those of the (+)-enantiomer and again were found to be higher. The maximum plasma levels obtained following 1 mg orally were similar to those obtained in our study at the equivalent time post-dosing, viz. for the (+)-enantiomer $2.3 \pm 0.4 \text{ ng ml}^{-1}$ at $4.5 \pm 1.3 \text{ h}$ and for the (–)-enantiomer $6.3 \pm 2.0 \text{ ng ml}^{-1}$ at $3.0 \pm 0.8 \text{ h}$. The terminal elimination half-life for each enantiomer is similar for both oral and intravenous routes and there is no evidence that the route of administration affects the metabolism of either enantiomer (personal communication, Beecham Research Laboratories).

Cromakalim is a member of a new group of orally active antihypertensive agents, the benzopyran derivatives (Ashwood *et al.*, 1984). It opens smooth muscle potassium channels, thereby maintaining the transmembrane potential near the K_{eq} (Hamilton *et al.*, 1986). This action resembles that of the cyanoguanidine derivative, pinacidil (Cook *et al.*, 1988), and the nitrovasodilator, nicorandil (Weir & Weston, 1986), although unlike the latter the action of cromakalim does not appear to increase intracellular cyclic GMP concentrations (Newgreen *et al.*, 1988) or to decrease intracellular calcium availability (Howlett, 1987). The mechanism by which potassium channel activation relaxes smooth muscle has not been fully elucidated but

is likely to vary depending on the tissue (Bolton *et al.*, 1985) and the pharmacological agent. It is possible that those tissues most sensitive to cromakalim are those where membrane depolarisation plays a major role in excitation.

The action of cromakalim in different vascular beds is also variable: it has renal vasodilator activity but lacks effects on femoral blood flow (Buckingham *et al.*, 1986a). The latter may prevent dependent oedema developing, an advantage compared with nifedipine, while the former effect would be advantageous in hypertension. At high doses ($0.1\text{--}0.3 \text{ mg kg}^{-1}$) cromakalim has also been shown to have diuretic and kali-natriuretic effects but it is uncertain whether these are related to intrarenal potassium channel activation or other mechanisms, such as vasopressin release (Dumez *et al.*, 1988). In addition cromakalim has other actions, for example it appears to sensitise baroreceptors to pressor challenges, unlike pinacidil, and since baroreceptor sensitivity is altered in hypertension this too may be advantageous (Clapham & Cooper, 1988). Cromakalim also opens potassium channels in guinea pig papillary muscle, decreasing the action potential duration, but appears to have little mechanical effects except at high dose (Cain & Metzler, 1985). Preliminary data in man has confirmed its specific arteriolar vasodilator effect and antihypertensive action (Benjamin *et al.*, 1988; Van den Burg *et al.*, 1986).

This study confirms the arteriolar vasodilator action of cromakalim in patients with angina pectoris. Further investigation of the role of this compound in the management of ischaemic heart disease is indicated.

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(Received 18 April 1989,
accepted 9 November 1989)