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Cardiovascular effects of cromakalim (BRL 34915) in healthy volunteers

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1 The effect of oral doses of cromakalim 0.5, 1.0, 1.5 and 2.0 mg on several cardiovascular parameters was studied in healthy male volunteers.
2 In the first study, no dose of cromakalim reduced systolic or diastolic blood pressure in the supine or standing position. Reductions of diastolic blood pressure after exercise ($P < 0.01$) were observed 4 h after administration of 2.0 mg.
3 There was a trend towards increased heart rate after 2.0 mg at all time intervals, and significant changes were observed in supine and standing heart rate at 2 and 4 h ($P < 0.01$). No significant change was observed in exercise heart rate.
4 In the second study small increases in forearm blood flow were observed from 3 h to 5 h after oral administration of 1.0 and 2.0 mg of cromakalim. Forearm vascular resistance was significantly reduced after 2.0 mg ($P < 0.025$) when compared with placebo. No change was observed in forearm venous capacitance after either dose of cromakalim, or placebo. Supine heart rate was significantly increased 4 h after 2.0 mg of cromakalim ($P < 0.025$).
5 These results show that oral administration of cromakalim decreases diastolic blood pressure and forearm vascular resistance. A hypotensive effect is probably attenuated by reflex tachycardia.

Keywords cromakalim BRL 34915 cardiovascular effects

Introduction

Cromakalim (6-cyano-3,4-dihydro-2,2-dimethyl-*trans*-4-(2-oxo-1-pyrrolidyl)-2H-benzo-[b] pyran-3-ol) is a novel antihypertensive agent which has been shown to reduce blood pressure in experimental animal models (Buckingham *et al.*, 1986). It has been reported to act via a mechanism involving hyperpolarization of the cell membrane mediated by the activation of membrane potassium channels (Hamilton *et al.*, 1986).

The aim of the present studies was to determine the effect of four doses of cromakalim on heart rate and blood pressure in healthy volunteers and subsequently to examine the effect of two of those doses on forearm blood flow and venous capacitance.

Methods

The studies were carried out in healthy male volunteers according to protocols approved by the Ethical Committee of Queen's University, Belfast. Written consent was received from each subject prior to his entry to the study.

Study 1

This study investigated the effect of oral administration of cromakalim 0.5, 1.0, 1.5, 2.0 mg and placebo on heart rate and blood pressure in eight healthy volunteers aged 19–38 years (mean age 25 ± 6 years) and weighing 54.8–90.6 kg (mean weight 71 ± 9 kg). There was an interval of at least 1 week between treatments.

On each study day subjects presented to the laboratory at 08.00 h after a light breakfast and an indwelling cannula was inserted in a forearm vein. After baseline observations had been taken, cromakalim was administered in a double-blind dose escalating design, with random inclusion of a placebo. Observations were made at 2, 4, 6, 8, 10 and 24 h after drug administration. At each time, heart rate and blood pressure were measured after the subject had rested supine for 15 min, remained standing for 3 min, and undertaken an exercise step test which entailed stepping on and off a platform 46 cm high at a rate of 34 times min^{-1} for 3 min. Heart rate was measured from a direct writing electrocardiograph by recording five successive R-R intervals. If sinus arrhythmia was present,

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the heart rate was counted over a 1 min period. Exercise heart rate was recorded immediately on cessation of exercise, counting the first five R-R intervals. Blood pressure was measured with a Hawksley random zero sphygmomanometer. Diastolic blood pressure was recorded using phase 4.

Statistical analysis was by Friedman's analysis of variance accepting ($P < 0.05$) as significant to reject the null hypothesis. The differences between groups were compared by a multiple comparison test (Conover, 1980). The level of significance was reduced to $P < 0.01$ for Study 1 where four groups were compared with placebo.

Study 2

The effect of cromakalim on heart rate, blood pressure, forearm blood flow (FBF) and venous capacitance (VC) was examined in a further 12 volunteers aged 19–28 years (mean age 22 ± 2 years) weighing 63.5–79.5 kg (mean weight 71 ± 6 kg). Subjects attended the laboratory in the morning after a light breakfast and an indwelling cannula was inserted in a vein in the left forearm. They then rested supine for at least 1 h in a constant temperature (22 ± 1° C). Baseline observations were made after 30 and 50 min. Cromakalim 1.0 and 2.0 mg and placebo were administered as single oral doses in a double-blind randomised design with at least 1 week between treatments. Observations were taken every hour for 5 h after dosing. Heart rate was measured from a direct writing electrocardiograph as above, and blood pressure using a Hawksley random zero sphygmomanometer. Diastolic blood pressure was taken at phase 4. FBF and VC were measured by venous occlusion plethysmography using an indium in silastic strain gauge attached to the right forearm. At each observation time, VC was measured using the equilibration method at an occlusion pressure of 30 mm Hg and FBF was taken as the mean of 10 measurements of blood flow at an occlusion pressure of 60 mm Hg. Forearm vascular resistance was calculated at each observation time as mean arterial pressure (diastolic blood pressure + one third pulse pressure)/forearm blood flow. Statistical analysis was as described previously, but a level of $P < 0.025$ was considered significant for the multiple comparison test as only two groups were compared with placebo.

Results

Study 1

No change in supine systolic (range 103–112 mm Hg) or diastolic blood pressure (range 74–83 mm Hg) was observed after administration of placebo. No dose of cromakalim had a significant effect on supine systolic or diastolic blood pressure when compared with placebo. The values observed after the 1.5 mg and 2.0 mg doses are shown in Table 1. After 2.0 mg, an increase ($P < 0.01$) in supine heart rate was observed at 2, 4 and 10 h after drug administration (Table 1). There was a trend towards increased heart rate after lower doses of cromakalim at 2, 4, 6, 8 and 10 h, but these changes were not statistically significant.

No changes in standing blood pressure were observed after placebo (Table 2). Small reductions of blood pressure

Table 1 The effect of two doses of BRL 34915 (1.5 mg and 2 mg) and placebo on supine resting systolic (SBP) and diastolic blood pressure (DBP, mm Hg) and heart rate (HR, beats min^{-1}). Mean and 95% confidence limits are shown

	0 h	*2 h*	*4 h*	*6 h*	*8 h*	*10 h*	*24 h*
Placebo							
SBP	114.3 (109.4–119.1)	108.4 (102.3–114.4)	103.4 (98.6–108.2)	110.1 (103.3–117.0)	107.0 (102.5–111.5)	109.9 (104.8–115.0)	112.3 (106.9–117.6)
DBP	83.6 (77.9–89.4)	78.5 (73.5–83.5)	74.6 (69.0–80.3)	77.5 (72.4–82.6)	76.4 (71.2–81.5)	78.1 (72.6–83.6)	80.5 (73.0–88.0)
HR	59.0 (53.6–64.4)	60.4 (53.7–67.0)	61.6 (53.9–69.3)	68.0 (56.7–79.3)	66.3 (59.0–73.5)	68.9 (60.5–77.2)	61.6 (57.7–65.5)
BRL 34915 1.5 mg							
SBP	113.1 (107.8–118.5)	111.0 (104.2–117.8)	106.0 (97.6–114.4)	107.5 (103.4–111.6)	106.9 (100.4–113.3)	108.4 (102.0–114.8)	112.0 (100.2–123.8)
DBP	77.0 (71.7–82.3)	77.3 (74.5–80.0)	72.3 (65.4–79.1)	73.1 (69.8–76.5)	75.3 (67.4–83.1)	74.5 (69.6–79.4)	78.4 (69.9–86.8)
HR	59.5 (53.5–65.5)	66.4 (55.1–77.6)	71.6 (57.1–86.1)	74.0 (60.1–87.9)	70.1 (56.8–83.4)	74.5 (61.5–87.5)	61.4 (53.7–69.0)
BRL 34915 2 mg							
SBP	114.9 (108.0–121.7)	113.8 (108.3–119.2)	107.3 (100.9–113.6)	107.6 (100.3–114.9)	107.4 (97.4–117.4)	113.4 (105.4–121.3)	113.1 (106.1–120.2)
DBP	74.5 (71.2–77.8)	74.6 (70.0–79.2)	71.1 (67.6–74.7)	72.0 (70.4–73.6)	72.6 (67.4–77.8)	73.0 (63.2–82.8)	73.1 (67.6–78.6)
HR	63.4 (57.2–69.6)	77.1* (62.6–91.7)	78.5* (61.9–95.1)	83.0 (68.9–97.1)	79.6 (66.8–92.5)	84.1* (71.0–97.2)	68.5 (63.1–73.9)

* = $P < 0.01$ compared with placebo.

Table 2 The effect of two doses of BRL 34915 (1.5 mg and 2 mg) and placebo on standing systolic (SBP) and diastolic blood pressure (DBP, mm Hg) and heart rate (HR, beats min^{-1}). Mean and 95% confidence limits are shown

	0 h	*2 h*	*4 h*	*6 h*	*8 h*	*10 h*	*24 h*
Placebo							
SBP	110.9 (107.6–114.2)	105.4 (98.6–112.1)	103.4 (98.9–107.9)	102.0 (97.4–106.6)	103.6 (99.1–108.1)	108.1 (103.1–113.2)	112.4 (109.4–115.4)
DBP	85.9 (80.9–90.9)	81.5 (73.8–89.2)	81.0 (73.4–88.6)	79.1 (71.7–86.5)	80.3 (71.7–88.8)	83.3 (74.6–91.9)	86.4 (80.0–92.7)
HR	75.1 (70.3–79.9)	78.5 (67.8–89.2)	84.9 (75.9–93.9)	91.4 (80.7–102.0)	86.5 (77.3–95.7)	87.3 (78.2–96.3)	75.9 (70.9–80.9)
BRL 34915 1.5 mg							
SBP	110.9 (101.9–119.8)	105.5 (98.8–112.2)	99.8 (86.6–112.9)	97.4 (87.0–107.7)	99.5 (87.4–111.6)	103.0 (94.0–112.0)	111.3 (98.9–123.6)
DBP	85.6 (78.2–93.0)	81.1 (73.1–89.1)	76.3 (64.5–88.0)	76.5 (66.1–86.9)	74.3 (62.9–85.6)	77.6 (70.6–84.7)	81.6 (70.3–93.0)
HR	78.0 (67.3–88.7)	95.5* (79.8–111.2)	99.4 (83.8–115.0)	96.6 (78.8–114.4)	90.5 (68.7–112.3)	92.3 (75.1–109.4)	80.0 (68.1–91.9)
BRL 34915 2 mg							
SBP	112.6 (101.5–123.7)	102.0 (95.2–108.8)	94.5 (84.9–104.1)	98.3 (88.3–108.2)	96.1 (85.7–106.5)	109.0 (99.9–118.1)	109.9 (101.5–118.2)
DBP	82.8 (75.3–90.2)	78.6 (71.9–85.3)	71.4 (56.7–86.0)	75.4 (67.5–83.3)	75.4 (65.8–84.9)	83.1 (73.7–92.5)	79.0 (72.8–85.2)
HR	83.8 (75.7–91.8)	108.0* (93.4–122.6)	105.8* (86.3–125.2)	105.3 (87.4–123.1)	103.6 (88.3–119.0)	100.8 (86.9–114.6)	83.3 (77.1–89.4)

* = $P < 0.01$ compared with placebo.

were observed after 2.0 mg when compared with placebo. Significant increases in heart rate were observed 2 and 4 h after 2.0 mg ($P < 0.01$) and 2 h ($P < 0.01$) after 1.5 mg. No changes in blood pressure or heart rate were observed after 0.5 mg or 1.0 mg.

Cromakalim at the doses used had no effect on systolic blood pressure or heart rate following exercise, but a significant fall in diastolic blood pressure was observed 4 h after 2.0 mg ($P < 0.01$) (Table 3).

Cromakalim was well tolerated by the eight subjects in this study. Mild headache was reported after 1.5 mg (two subjects) and 2.0 mg (four subjects), occurring between 4 and 8 h after administration.

Study 2

The supine systolic blood pressure was unchanged throughout the study period after 1.0 and 2.0 mg cromakalim. Diastolic blood pressure was reduced 4 h after both 1.5 mg ($P < 0.01$) and 2.0 mg ($P < 0.025$) and 5 h after 2.0 mg when compared with placebo ($P < 0.025$) (Table 4). An increase in heart rate was observed 4 h after administration of 2.0 mg of cromakalim ($P < 0.025$). The changes in forearm blood flow observed after placebo, 1.0 mg and 2.0 mg are shown in Figure 1. No change was statistically significant. Forearm vascular resistance was reduced at 5 h after 1.0 and 2.0 mg ($P < 0.025$) compared with placebo (Figure 2). No change in venous capacitance was observed.

Of the 12 volunteers, four complained of slight to moderate headache, one after 1.0 mg and three after 2.0 mg. One volunteer also complained of nausea beginning approximately 6 h after 2.0 mg.

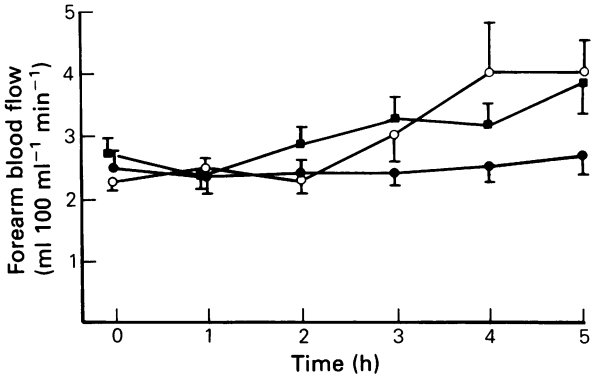

Figure 1 Changes in forearm blood flow after oral administraton of placebo (●) and cromakalim 1.0 mg (■) and 2.0 mg (○) to 12 volunteers. Mean ± s.e. mean values are shown.

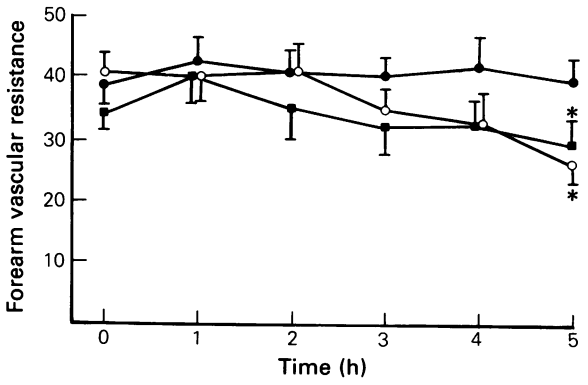

Figure 2 Changes in forearm vascular resistance after oral administration of placebo (●) and cromakalim 1.0 mg (■) and 2.0 mg (○) to 12 volunteers. Mean ± s.e. mean values are shown. * = $P < 0.025$ compared with placebo.

Table 3 The effect of two doses of BRL 34915 (1.5 mg and 2 mg) and placebo on systolic (SBP) and diastolic blood pressure (DBP, mm Hg) and heart rate (HR, beats min^{-1}) during exercise. Mean and 95% confidence limits are shown

	0 h	*2 h*	*4 h*	*6 h*	*8 h*	*10 h*	*24 h*
Placebo							
SBP	150.0 (136.1–163.9)	149.0 (139.8–158.2)	150.4 (141.2–159.5)	149.4 (136.9–161.8)	150.0 (140.9–159.1)	152.0 (139.0–165.0)	149.6 (140.1–159.1)
DBP	55.7 (47.3–64.1)	56.8 (45.0–68.5)	57.6 (47.9–67.4)	56.9 (47.3–66.4)	55.6 (44.9–66.4)	60.1 (50.7–69.5)	61.9 (52.5–71.2)
HR	153.5 (145.5–161.5)	158.5 (147.1–170.0)	157.0 (149.1–164.9)	155.3 (144.6–165.9)	158.3 (147.8–168.7)	159.5 (150.0–169.0)	151.5 (143.8–159.2)
BRL 34915 1.5 mg							
SBP	144.4 (136.4–152.3)	144.4 (133.0–155.7)	143.1 (135.0–151.2)	144.1 (131.1–157.2)	149.8 (135.6–163.9)	148.8 (135.7–161.8)	152.5 (144.4–160.6)
DBP	58.1 (51.5–64.7)	58.1 (47.3–69.0)	51.3 (41.7–60.8)	55.6 (42.7–68.6)	55.1 (48.4–61.9)	58.3 (46.7–69.8)	55.0 (45.9–64.1)
HR	147.3 (135.0–160.0)	156.0 (142.5–169.5)	156.0 (144.0–168.0)	157.5 (145.8–169.2)	156.0 (142.9–169.1)	156.6 (144.6–168.5)	150.9 (138.4–163.4)
BRL 34915 2 mg							
SBP	148.8 (139.2–158.3)	143.8 (134.9–152.6)	138.8 (125.2–152.3)	135.6 (120.9–150.3)	142.5 (127.9–157.1)	151.3 (139.5–163.0)	145.0 (136.1–153.9)
DBP	46.3 (40.1–52.4)	46.3 (37.2–55.3)	41.9* (35.3–48.5)	50.6 (42.4–58.8)	43.8 (34.5–53.0)	49.4 (38.2–60.5)	52.5 (42.9–62.1)
HR	147.3 (140.3–154.2)	162.6 (151.8–173.4)	161.6 (149.5–173.8)	161.5 (149.7–173.3)	160.5 (150.8–170.2)	164.1 (153.2–175.0)	159.1 (149.3–169.0)

* = $P < 0.01$ compared with placebo.

Table 4 The effect of two doses of BRL 34915 (1 mg and 2 mg) and placebo on supine systolic (SBP) and diastolic blood pressure (DBP, mm Hg) and heart rate (HR, beats min^{-1}) in 12 volunteers. Mean and 95% confidence limits are shown

	0 h	*1 h*	*2 h*	*3 h*	*4 h*	*5 h*
Placebo						
SBP	114.0 (108.9–119.1)	115.1 (110.5–119.7)	115.7 (110.2–121.2)	115.8 (110.6–121.1)	115.8 (111.1–120.5)	116.7 (111.8–121.6)
DBP	73.5 (68.4–78.6)	76.6 (71.5–81.7)	78.6 (73.9–83.3)	78.3 (72.9–83.6)	78.9 (74.7–83.1)	81.8 (76.9–85.3)
HR	66.7 (60.7–72.7)	62.9 (57.5–68.3)	64.7 (59.8–69.5)	63.8 (59.3–68.3)	63.5 (59.0–68.0)	65.8 (60.7–70.8)
BRL 34915 1.0 mg						
SBP	116.2 (112.2–120.1)	115.3 (110.4–120.1)	113.9 (109.0–118.8)	114.3 (108.9–119.7)	114.2 (109.1–119.3)	115.1 (109.7–120.5)
DBP	73.6 (70.4–76.8)	72.5 (69.2–75.8)	73.8 (69.6–77.9)	72.9 (68.0–77.9)	73.9** (70.0–77.8)	74.8 (71.2–78.3)
HR	68.8 (61.1–76.6)	70.7 (60.6–80.8)	68.6 (59.9–77.3)	69.2 (59.7–78.7)	67.2 (60.2–74.2)	70.8 (62.9–78.8)
BRL 34915 2.0 mg						
SBP	116.4 (109.7–123.2)	117.8 (109.2–126.4)	115.6 (108.4–122.7)	116.9 (110.1–123.8)	116.8 (109.9–123.7)	116.2 (111.4–120.9)
DBP	74.8 (67.6–82.1)	73.6 (65.9–81.3)	71.8 (64.1–79.4)	74.1 (67.2–81.0)	73.8* (67.8–79.9)	73.9* (66.1–81.7)
HR	66.3 (61.4–71.1)	73.2 (64.6–81.7)	70.4 (64.4–76.5)	70.5 (63.8–77.2)	72.3* (66.4–78.1)	73.6 (67.6–79.6)

* = $P < 0.025$, ** = $P < 0.01$ compared with placebo.

Discussion

Cromakalim is a novel agent which has been shown to cause dose-related reductions in blood pressure in canine and feline models (Buckingham *et al.*, 1986) and is currently being evaluated for the treatment of mild hypertension. It has been postulated that cromakalim exerts its hypotensive effect via a hyperpolarisation of cells in the vasculature. Studies on animal isolated tissues (Hamilton *et al.*, 1986; Weir & Weston, 1986a, b) have provided evidence for the opening of membrane potassium channels thereby shifting the membrane potential towards the potassium equilibrium potential (Hamilton *et al.*, 1986), thus making the membrane less sensitive to circulating excitatory agents.

The current studies were designed to examine the effect of cromakalim on heart rate, blood pressure and vascular flow parameters in healthy volunteers. Cromakalim was shown to have little effect on supine systolic or diastolic blood pressure. There was a tendency for both standing systolic and diastolic blood pressure to fall between 4 and 8 h after 2.0 mg, but with the limited numbers in this study we cannot exclude the possibility that a true reduction in pressure occurred. An increase in heart rate was observed in both postures which may serve to minimise any tendency towards a fall in blood pressure in healthy subjects. No change in heart rate was observed after exercise at any dose of cromakalim, but there was a tendency towards a reduction in systolic and diastolic blood pressure between 4 and 8 h after 2.0 mg. The reduction in diastolic blood pressure was significant at 4 h. Pharmacokinetic studies in healthy male volunteers showed that the mean maximum observed plasma concentration occurred 2–6 h after oral administration of cromakalim and increased in a dose dependent fashion from 0.5 mg to 2.0 mg (Davies *et al.*, 1988). The pharmacodynamic results from this study would support this.

At 24 h after administration there was a trend towards reduction of supine and standing diastolic blood pressure and increase in heart rate in the same postures although this failed to reach statistical significance. These findings would be consistent with a proposed plasma elimination half-life for cromakalim of 22.5 h (Davies *et al.*, 1988).

Cromakalim was shown to decrease forearm vascular resistance in healthy subjects after 2.0 mg. This effect was manifest from 3 to 5 h after drug administration and reached significance at 5 h. No change in venous capacitance was observed, which would suggest that the action of cromakalim is mainly on the arteriolar bed.

The observed tachycardia suggests that a reflex mechanism to compensate for the initial hypotensive effect of cromakalim may be operative. It is possible that administration of cromakalim in combination with a β-adrenoceptor blocking drug may increase its efficacy as an antihypertensive agent by counteracting this initial reflex tachycardia. Early animal studies showed that the tachycardia was prevented by β-adrenoceptor blockade. In oral repeat dose studies in animal models (Buckingham *et al.*, 1986) no evidence was recorded of tachyphylaxis or rebound hypertension on cessation of drug treatment. Further studies will be required to see if cromakalim is effective in the treatment of hypertension alone or with a β-adrenoceptor antagonist.

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