Letter to the Editor

Acute hypotensive effects of oral cisapride and erythromycin in healthy subjects

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Erythromycin, a motilin agonist, and cisapride, a 5-HT₄ receptor agonist, enhance gastrointestinal motility [1]. Although cisapride is no longer marketed in Europe and USA because of the risk of fatal arrhythmias, the drug is still available in USA to patients who have failed all standard therapeutic modalities [2]. Erythromycin may also cause cardiotoxicity [2].

Although the pro-kinetic effects of erythromycin and cisapride are well characterized, few data are available on their acute haemodynamic effects [3–5]. We studied the acute blood pressure (BP) and heart rate (HR) effects following a single oral dose of erythromycin and cisapride in healthy subjects ($n = 10$, M:F = 4 : 6; 54.9 ± 7.5 years, mean $\pm$ s.e.mean) and compared them to a group of historical controls of similar age receiving placebo ($n = 26$, M:F = 19 : 7, 48.5 ± 5.0 years). No subject was receiving drugs affecting gastric emptying or BP. The study was approved by the Local Research Ethics Committee. Each subject gave written informed consent prior to the study.

The effects of cisapride and erythromycin were assessed in two separate sessions, 24 h apart. Sitting and standing BP and HR (Dinamap® 8100 Monitor, Critikon, Tampa, Florida, USA) were measured at baseline and after oral cisapride (10 mg, Janssen-Cilag Ltd, UK) or erythromycin (250 mg, Abbott Laboratories Ltd, UK) every 15 min for 210 min in a randomised, double-blinded, crossover study. On the second study day, the same procedures were performed after each subject received the second pro-kinetic. In the placebo group, studied in the same laboratory during the same period of the day, BP and HR were measured every 60 min. Changes in BP and HR were assessed by ANOVA for repeated measurements with Bonferroni's correction for multiple comparisons. The effect of age on haemody-

namic responses was assessed by ANCOVA (SPSS for Windows, SPSS Inc, Chicago, IL, USA). A P -value less than 0.05 indicated statistical significance.

One subject did not complete the cisapride arm because of symptomatic hypotension. Compared to placebo, erythromycin and cisapride induced a significant reduction in systolic BP (Figure 1). The maximal effects were observed 1.5–2.5 h after erythromycin (sitting Δ SBP erythromycin vs. placebo -10 ± 9 mmHg, 95%CI -8 to -29) and 1–2 h after cisapride (sitting Δ SBP cisapride vs. placebo -12 ± 5 mmHg, 95%CI -2 to -22 ; standing Δ SBP cisapride vs. placebo -14 ± 6 mmHg, 95%CI -1 to -26). Although the effects of cisapride and erythromycin on SBP were similar, there was a trend towards a greater overall hypotensive effect of cisapride on standing SBP ($P = 0.12$). The hypotensive effects were independent of age.

To our knowledge, no studies have specifically investigated the acute haemodynamic effects of erythromycin and cisapride in humans. Although there are isolated reports of hypotension induced by these drugs [3–5].

The mechanisms responsible for the hypotension following erythromycin and cisapride remain largely unknown. In healthy subjects, a significant increase in plasma motilin concentrations was observed after intravenous erythromycin [6]. Intravenous [Leu13] motilin in dogs produces transient decreases in BP and induces endothelium-dependent relaxation [7], thus potentially explaining the acute hypotension following erythromycin. In the rat, intravenous cisapride produces significant hypotensive effects that are partially abolished by pretreatment with atropine, suggesting that the hypotensive effect might be mediated by the cholinergic system [5].

The hypotension induced by erythromycin and cisapride might have important clinical implications because a substantial proportion of subjects receiving these pro-kinetics suffer from autonomic nervous system dysfunction and blood pressure instability [8, 9]. Moreover, the hypotensive effects of cisapride and erythromycin might worsen postprandial hypotension, which is related to the rate of gastric emptying [10].

The limitations of our study are its relatively small sample size and the comparison with a group of historical controls receiving placebo. Larger randomised con-

Figure 1

Mean systolic blood pressure, diastolic blood pressure, and heart rate changes after cisapride, erythromycin, and placebo. SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate. Placebo (n = 26) (▲); erythromycin (n = 10) (◆); cisapride (n = 10) (■), *p < 0.05 **p < 0.01 vs. baseline Means ± SEM

trolled trials are warranted to confirm these preliminary findings.

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Received

17 November 2003

Accepted

26 January 2004

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