A comparison of the gastric and central nervous system effects of two substituted benzamides in normal volunteers

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1 Eight healthy male volunteers participated in a single-blind, random allocation, crossover, comparison of intravenous metoclopramide (10 mg), the peripherally acting, gastrointestinal stimulant BRL 20627 (10 mg) and saline.

2 The central nervous system effects were assessed by quantitative electroencephalography (EEG) and by visual analogue scales. Gastric motility and emptying were assessed by epigastric impedance.

3 Metoclopramide increased the EEG amplitude by 10.4% (a statistically significant, $P < 0.05$, effect) and increased frequencies above 22 Hz, whereas both BRL 20627 and placebo had only minor effect on the EEG frequencies and slightly decreased the EEG amplitude. Ratings on visual analogue scales showed that metoclopramide caused statistically significant ($P < 0.01$ difference from placebo) restlessness and slight but significantly less ($P < 0.05$ difference from placebo) feeling of happiness.

4 Epigastric impedance changes indicated that both metoclopramide and BRL 20627 increased gastric contractile activity, but the rate of gastric emptying was not significantly altered by either drug although it tended to be shortened following metoclopramide but not BRL 20627 treatment.

5 It is concluded that since the published animal data show that BRL 20627 has only weak dopamine antagonistic properties this study further implicates dopamine receptor blockade in the akathisia but not in the gastric effect of metoclopramide.

Keywords metoclopramide quantitative EEG akathisia gastric emptying gastric motility

Introduction

Metoclopramide is a substituted benzamide which is used widely to promote gastrointestinal activity and as an antiemetic (Harrington *et al.*, 1983). The sites and mechanisms by which metoclopramide exerts these effects remain obscure. The four main hypotheses which may, either alone or in a combination, account for the therapeutic properties of metoclopramide, involve a peripheral enhancement of cholinergic (Fontaine & Reuse, 1978; Kilbinger *et al.*, 1982; McClelland & Sanger, 1982), serotonergic (Masso & Roberts, 1980) or dopamine antagonist activity

(Roman, 1982) or a central enhancement of cholinergic activity (Costall *et al.*, 1983).

Metoclopramide produces few unwanted effects at usual therapeutic doses but transient extrapyramidal reactions have been reported in approximately 1% of patients (Robinson, 1973) which are thought to result from blockade of central dopaminergic receptors involved in motor function (Tarsy *et al.*, 1975; Bateman, 1983). The main evidence for this mechanism is the similarity between the extrapyramidal effects of phenothiazine and butyrophenone antipsychotics

(Giger, 1975). On the other hand the incidence of tardive dyskinesias after metoclopramide is much lower than after antipsychotic treatment (Kane & Smith, 1982; Wiholm *et al.*, 1984), and metoclopramide has been used to treat tardive dyskinesias associated with antipsychotics such as haloperidol and prochlorperazine (Karp *et al.*, 1981). Therefore, despite the common central dopaminergic blockade, metoclopramide apparently has a different distribution of activity within the central nervous system.

BRL 20627, like metoclopramide, is a substituted benzamide (Figure 1), which increases gastrointestinal activity in animals (McClelland *et al.*, 1983; McClelland & Sanger, 1983) and man (Bateman, 1984).

Pharmacologically BRL 20627 has a peripheral profile like metoclopramide since both compounds similarly increase gastric motility and emptying in the rat (McClelland *et al.*, 1982); increase gastric motility in the dog (McRitchie *et al.*, 1984); increase cholinergic responses in the rat isolated stomach (McClelland & Sanger, 1983); and guinea pig isolated stomach, gall bladder and urinary bladder (Costall *et al.*, 1984). BRL 20627 is considerably less potent than metoclopramide as a dopaminergic antagonist since in contrast to metoclopramide, BRL 20627 does not significantly elevate plasma prolactin concentration in the rat, and is considerably less potent than metoclopramide in the central nervous system, at inhibiting apomorphine induced climbing behaviour in the mouse (McClelland *et al.*, 1982).

This study was designed to compare the activity of BRL 20627 and metoclopramide in human volunteer subjects by examining both central nervous system and gastric functions simultaneously. Central nervous system effects were examined objectively by EEG and subjectively

by visual analogue scales. The effects of these two compounds on stomach emptying and contractility were assessed using the novel method of epigastric impedance. This is a simple, inexpensive and non-invasive method which has been developed to assess drug effects in normal volunteers (McClelland & Sutton, 1985a). When compared simultaneously with scintigraphy it produced comparable results to this established method (Sutton *et al.*, 1984). Epigastric impedance has proved capable of detecting more rapid gastric emptying after both intravenous (Sutton & McClelland, 1983) and oral (McClelland & Sutton, 1985b) metoclopramide without the need artificially (e.g. pharmacologically) to retard gastric emptying. It will detect also gastric contractile activity which is quantifiable by Fourier analysis. Thus, the increase in 1–5 cycles per min activity which occurs after a liquid meal is enhanced when metoclopramide has been given before the meal (McClelland & Sutton, 1985a).

Methods

The use of BRL 20627 in volunteer studies and clinical trials had received ethical approval from an established review panel of independent experts in medicine and pharmacology. Volunteers were experienced members of an established panel who discussed fully the experiment before giving consent to participate.

Eight healthy male volunteers (aged 20–34 years, mean 29.4) were included. Volunteers who required any medicine during the study period, or who had taken an investigational new drug in the 3 months prior to the study were excluded. The subjects were instructed to drink no alcohol from 24 h before dosage. At intervals of at least 1 week the volunteers were given 10 mg metoclopramide hydrochloride (Maxolon®, Beecham Research Laboratories) or 10 mg BRL 20627 or normal saline in a random order, single-blind crossover design. Drugs were administered intravenously as five boluses of 2 ml spread over 1–1.5 min.

The EEG was recorded for 30 min before and after dosing including a 15 min period with eyes closed on either side of dosing. Silver/silver chloride electrodes were placed on the scalp according to the International Federation 10–20 system at O₂, A₂, FP₁ and FP₂. The signals from O₂–A₂ and FP₁–FP₂ were recorded on ambulatory EEG recorders (Oxford Medical Systems) with the O₂–A₂ recording later replayed through a bandpass filter (Kemo) at 1 and 50 Hz into a PDP 11/40 minicomputer for analysis. The pre-

Figure 1 Chemical structure of metoclopramide and BRL 20627.

and post-dose recording periods each comprised five samples of 32 s duration. The FP₁-FP₂ recording was used to identify non-cerebral activity (artefact) for exclusion from analysis. Recordings were analysed by the methods previously described (McClelland & Raptopoulos, 1984; McClelland & Sutton, 1985c). Primary wave analysis, derived from zero-crossing, was performed and portrayed as percent time in each 2 Hz bands up to 30 Hz. Zero crossing analysis was performed also on the first derivative of the EEG and displayed in 4 Hz bands up to 60 Hz. The power spectrum, in 2 Hz bands up to 30 Hz, was derived from a Fast Fourier Transform of the EEG. Mean frequency and amplitude were obtained also. The ratio of post- to pre-dose values for each subject was calculated and the ratios after each treatment were then averaged to give a geometric group mean and standard error. The frequency and amplitude data was analysed statistically by analysis of variance and differences between treatments assessed by Duncan's multiple range test.

One hour after dosing the volunteers completed visual analogue scales designed to assess symptoms that have been reported after metoclopramide administration. These scales consisted of 100 mm lines which the subjects marked at the point which corresponded to their feelings over the previous hour. The ends of the scales were labelled: drowsy/alert, feel hot/feel cold, restless/calm, happy/sad, fidgety arms/heavy arms, fidgety legs/heavy legs, dizzy/no dizziness, nausea/no nausea, anxious/contented, desire to get up/desire to continue lying down. The data were analysed by the Friedman test and where this disclosed a significant ($P < 0.05$) treatment effect, by Friedman's multiple comparison test.

The epigastric impedance method has been described previously (McClelland & Sutton, 1985a). Thirty minutes before dosing silver/silver chloride electrodes were placed on the abdomen, one at a point one third of the distance from xiphisternum to umbilicus, another a further one third below and one third to the left. Two electrodes were placed on the back in a parallel,

reciprocal position. A current of 4 mA peak-to-peak at 100 KHz was applied to one pair through the abdomen, and the voltage variations acquired by the other pair recorded on chart and magnetic tape. Volunteers lay still and semi-recumbent at 45°, legs stretched out on the couch throughout recordings. Exactly 5 min after drug treatment they swallowed 750 ml orange squash; the impedance deflection above baseline was designated 100% (Figure 2). The remaining deflection was measured at 1 min intervals for 30 min and expressed as a percent of the maximum increase after the 'meal'. The curve of best fit (mono-exponential) was computed and the 50% emptying times calculated from the resultant equation. These half-times were statistically analysed by analysis of variance after logarithmic transformation.

To provide a measure of gastric motility the impedance output was recorded on magnetic tape (Racal) and processed by a minicomputer (PDP 11/40) for display on a VDU whence 5 min samples of trace from immediately before and after consumption of the meal were selected by a light pen. The two samples were analysed by Fourier Analysis and the data from 0 to 5 cycles min⁻¹ presented in 0.2 cycles min⁻¹ bands thus including the known stomach contraction rate of approximately 3 min⁻¹ (Alvarez, 1922). Ratios of post- to pre-meal power in this waveband were calculated in similar fashion to the ratios of EEG activity.

Results

Metoclopramide caused a mean increase in the EEG amplitude of 10.4%, while BRL 20627 and placebo decreased amplitude by 7.4% and 5.7% respectively. This was a statistically significant ($F = 4.17$, $P < 0.05$) drug effect, with metoclopramide treatment significantly different from both BRL 20627 and placebo treated groups. There were no statistically significant drug effects on the mean EEG frequency.

Figure 2 Typical epigastric impedance recording.

Both BRL 20627 and placebo produced slight decreases in alpha activity (8–12 Hz) and increases in most other frequencies (Figure 3). In contrast, metoclopramide decreased almost all activity below 22 Hz and increased all faster activity. After metoclopramide the power spectrum increased in all frequencies, an effect not produced by BRL 20627 or placebo. EEG from one BRL 20627 subject was lost due to equipment malfunction.

Visual analogue scales showed a statistically significant restlessness reported after metoclopramide (Figure 4), and a slight but statistically significant feeling of less happiness: the metoclopramide group median was 1.5 mm below the mid-point of the visual analogue scale, while after placebo it was 6 mm above it. Effects which were reported but failed to achieve statistical significance were fidgety arms and legs, and a desire to get up after metoclopramide treatment.

One volunteer was excluded from analysis of gastric emptying due to a consistently small deflection after consumption of the liquid meal. Both metoclopramide and BRL 20627 increased markedly the amount of post-meal gastric motility while placebo treated subjects did not (Figure 5).

Gastric half-emptying times after metoclopramide tended to diminish (geometric mean 8.6, s.d. 2.2 min) compared with placebo (12.3 s.d. 1.9 min), however there was no statistically significant difference between treatments ($F =$

0.92, $P > 0.05$; Table 1). There was no change in gastric emptying rate after BRL 20627.

Discussion

In this study metoclopramide produced statistically significant, quantifiable increases in the EEG amplitude and fast activity above 22 Hz. This contrasts with the finding of Nakra *et al.* (1975) who showed no such increases after 0.3 and 0.15 mg kg⁻¹ given orally. Furthermore, they reported increased slow wave activity (2.4–4.0 Hz) 2.5–5 h after 0.3 mg kg⁻¹ although not after 0.15 mg kg⁻¹. The different EEG profiles obtained may be due to different routes of administration or to other numerous experimental differences, such as electrode positions.

The EEG profile obtained here with metoclopramide is very similar to that reported after oral administration of the substituted benzamides sulpiride and sultopride (Saito, 1981). The latter compounds are potent dopamine antagonists in the central nervous system. Sulpiride does however produce two very different EEG profiles at different doses (Itil, 1982) and in different normal subjects (Saito *et al.*, 1982). In this respect metoclopramide may be similar to sulpiride, with a different EEG profile after intravenous administration to that reported previously by Nakra *et al.* (1975) after oral administration.

Figure 3 Effect of placebo, metoclopramide (10 mg) and BRL 20627 (10 mg) on the mean (s.e. mean) quantitative EEG changes immediately after intravenous administration.

Figure 4 Effect of intravenous metoclopramide (10 mg), BRL 20627 (10 mg) and placebo on the median and interquartile range of visual analogue scales ($n = 8$).

Friedman Test $P < 0.05$ for calm/restless and sad/happy.

* $P < 0.05$, ** $P < 0.01$ —metoclopramide vs placebo, $\diamond P < 0.05$ metoclopramide vs BRL 20627 (Friedman multiple comparison test)

Figure 5 Effect of placebo, metoclopramide (10 mg) and BRL 20627 (10 mg) on the mean ($\pm$ s.e. mean) gastric contractile activity changes, as measured by epigastric impedance in the first 5 min after intravenous administration.

Since BRL 20627 has been shown in animal experiments to possess only weak dopamine antagonistic properties (McClelland *et al.*, 1982) it is possible that the EEG effects of metoclopramide, sulpiride and sultopride are a consequence of dopamine receptor antagonism in the central nervous system.

The visual analogue scales represent an attempt to elucidate the impressions of volunteers in previous studies who would report vaguely unpleasant experiences which were visible externally by their fidgety limbs and desire to get up. These symptoms have been reported previously (Bateman *et al.*, 1978; Barnes *et al.*, 1982; Jungmann & Schoffling, 1982) but our additional scales of anxious/contented, happy/sad and alert/drowsy represent symptoms that have not been reported and were intended as

Table 1 50% gastric emptying times (min) after intravenous metoclopramide (10 mg), BRL 20627 (10 mg) and placebo

Volunteer	Placebo	Metoclopramide 10 mg	BRL 20627 10 mg
1	15.8	9.4	29.6
2	16.7	26.2	13.8
3	6.6	12.5	3.8
4	11.4	16.1	26.5
5	36.5	2.5	15.5
6	10.5	5.5	14.5
7	5.5	5.3	11.7
Geometric mean	12.3	8.6	14.1
log mean	1.089	0.937	1.148
log s.d.	0.275	0.343	0.292

distractors. These self-ratings produced wide variations for heavy/fidgety limbs and desire to get up/continue lying down, and though trends emerged they were not statistically significant. These variations did not preclude a significant result for restless/calm. The sensitivity of happy/sad was somewhat surprising as a difference of 7.5 mm between metoclopramide and placebo was significant. Hence, by looking for mood changes in some depth we have detected subtle effects which may escape notice in busy or demanding circumstances for patients and doctors. This partly explains our incidence of seven of eight volunteers with akathisia to its most mild degree when clinical reports quote figures of 20–25% (Jungmann & Schöffling, 1982; Strum *et al.*, 1983). The incidence of akathisia in the present study is similar to the six out of seven subjects who experienced akathisia in the study by Bateman *et al.* (1978).

Although EEG changes and subjective restlessness were both produced by metoclopramide but not BRL 20627, this does not necessarily indicate a cause-and-effect relationship, or even a common pharmacological origin. These are both, however, indications of an effect on the central nervous system by metoclopramide but not BRL 20627.

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