Effects of granisetron and lorazepam, alone and in combination, on psychometric performance

TERRY J. LEIGH, CHRISTOPHER G. G. LINK & GRAEME L. FELL

Human Pharmacology Unit, SmithKline Beecham Pharmaceuticals, Medicinal Research Centre, Coldharbour Road, Harlow, Essex CM19 5AD

The effects of granisetron ($160 \mu\text{g kg}^{-1}$ body weight) and lorazepam (2.5 mg) on psychometric performance were investigated in a randomised, single-blind, crossover, placebo controlled study of twelve healthy male volunteers. There was strong evidence that lorazepam impaired psychometric performance. In contrast there was very little evidence to suggest that granisetron had any impact on performance or that there was any interaction between the two compounds. The findings from this study suggest that granisetron does not impair psychometric performance and that it can be co-administered with lorazepam without producing unwanted synergistic effects.

Keywords granisetron psychometric performance 5-HT₃ receptors

Introduction

A number of drugs are used alone and in combination to treat emesis associated with cancer chemotherapy. Metoclopramide is currently widely in use as an anti-emetic and evidence has accumulated suggesting that this action is related to antagonism of 5-HT₃ receptors at peripheral and possibly central sites (Miner & Sanger, 1986).

Granisetron (BRL 43694) is a novel compound which has been shown to be more effective than chlorpromazine plus dexamethasone in controlling the nausea and vomiting associated with various emetogenic cytostatic regimens (Marty, 1989). Structurally, granisetron is one of a series of azabicyclic compounds. It is a potent and selective 5-HT₃ receptor antagonist which lacks dopamine receptor antagonist activity and is therefore expected to be better tolerated than metoclopramide (Fake *et al.*, 1987).

Often, antiemetics need to be prescribed concomitantly with a benzodiazepine. The commonest reasons for the concomitant treatment include psychological distress, sleep disorders and adjuvant therapy for refractory nausea and vomiting. It is therefore possible that granisetron will be prescribed concomitantly with e.g. lorazepam, a compound known to affect central receptors. The impact of these compounds, alone and in combination, on psychometric performance needs to be investigated. The safety implications of impaired psychometric performance on machine operation and driving are well known. The objectives of the present study were to assess the effects of granisetron and lorazepam on psychometric performance and to assess whether there was any interaction between the two compounds.

Methods

Twelve male volunteers aged 19–46 (mean 32) years participated in the study. All had passed a comprehensive medical examination, including medical history, clinical examination, electrocardiography, haematology, clinical chemistry and urinalysis. Volunteers gave informed consent and the study was approved by an independent ethics committee. With the exception of one volunteer, who received 2 g paracetamol on one study day for a headache, volunteers abstained from medications for 2 weeks before the start of the study until its completion. Subjects were also required to abstain from alcohol for 24 h before dosing until 24 h after dosing on each study day.

The study was conducted according to a randomised, single-blind, crossover, placebo controlled design. Each volunteer attended on 4 separate days, a minimum of 1 week apart, and received an oral capsule followed 30 min later by an intravenous infusion over 3 min. All treatments were matched in order to maintain the blindness of the study. The treatments received on the four study sessions were as follows:

Capsule	Infusion
Placebo	Placebo
Placebo	Granisetron ($160 \mu\text{g kg}^{-1}$)
Lorazepam (2.5 mg)	Placebo
Lorazepam (2.5 mg)	Granisetron ($160 \mu\text{g kg}^{-1}$)

The dose of granisetron selected was the maximum likely to be used in clinical practice, hence optimising the chance of demonstrating any interaction.

On each study day, a full battery of psychometric tests were carried out at -1 h (pre-dose), $+1.5$ h, $+3$ h, $+6$ h

and at +24 h (times relative to start of infusion). These tests were carried out using a CUBE microprocessor system in an inner room with constant artificial lighting. An outline of the tests is given below.

Subjective assessments

Sixteen bipolar visual analogue scales based on those developed by Bond & Lader (1974) were presented one at a time on a visual display unit (VDU) as a 15 cm line bisected in the centre by a 2 cm line which acted as a cursor. Data were presented as hundredths of the total length of the line. The ends of each line were labelled alert/drowsy, calm/excited, strong/feeble, muzzy/clear-headed, well-coordinated/clumsy, lethargic/energetic, contented/discontented, tranquil/troubled, mentally slow/quick-witted, tense/relaxed, attentive/dreamy, incompetent/proficient, happy/sad, antagonistic/friendly, interested/bored, withdrawn/sociable. Volunteers were asked to move the cursor line to a point on each scale that represented how they felt at that moment, with the extremes of the scales representing the 'most' they had ever experienced.

Choice reaction time

Two coloured response buttons with adjacent light-emitting diodes (LEDs) were mounted at an equal distance from a control button. Upon illumination of one of the LEDs, volunteers were asked to move their preferred digit from the control button to the button adjacent to the lit LED as quickly as possible and then return the digit to the control button until one of the LEDs was illuminated again. Two timings were recorded—(a) time taken to release the control button (response time) and (b) time taken to move and then depress the appropriate button adjacent to the illuminated LED (movement time).

During this task volunteers wore headphones, through which a warning tone was emitted prior to the illumination of one of the two LEDs. This tone was of two different pitches, each pitch associated with one of the LEDs 80% of the time. There were a total of 100 stimuli, presented in a pseudorandom sequence, such that the stimuli, both with and without auditory misdirection, were evenly distributed between the two LEDs.

Time estimation

Volunteers pressed a button to both initiate and then terminate their estimate of a 1 min period of elapsing time.

Flash fusion threshold

A LED was mounted at the end of a sealed oscilloscope viewing hood. This LED was illuminated twice, the interval between the flashes varying in an apparently random fashion, under microprocessor control. The volunteer pressed one button if he perceived one flash and another button if two flashes were perceived. A total of 100 presentations were made which covered a range of interflash intervals of 25 to 124 ms.

Tapping rate

Volunteers were asked to tap a morse key as fast as possible for 1 min.

Motor control and coordination

Volunteers used large forceps to transfer 36 glass beads (1.5–2 mm diameter), one at a time, from a Petri dish into individual wells of a microtitre plate. The volunteers themselves pressed a button to both start and complete this task.

Rapid information processing task

This task required the volunteers to sustain a continuous level of performance over a period of 400 s. Volunteers were presented, on a VDU, in pseudorandom sequence, five different letters of the alphabet, in both lower and upper cases (A, B, D, E and H). Four hundred presentations were made at the rate of one per second, on display for 0.1 s. There were 20 occasions when the same letter in the same case was presented consecutively, and 20 with the same letter but different case. Volunteers were required to depress a response button as soon as they had identified consecutive presentations of the same letter, irrespective of case.

Statistical analysis

The data were subjected to a repeated-measures analysis of variance which enabled evaluation of six planned significance tests. The first test compared granisetron with placebo, the second lorazepam with placebo and the third evaluated whether there was a significant interaction effect between granisetron and lorazepam. Tests 4 and 5 evaluated whether the time profiles of granisetron and lorazepam were significantly different from placebo. Test 6 examined whether there was a drug interaction effect which varied over time. Where appropriate, degrees of freedom for *F* tests were adjusted using the Greenhouse-Geisser correction (Greenhouse & Geisser, 1959). Hypothesis testing was performed at the 5% significance level in accordance with usual practice.

Analyses were carried out using the procedure GLM of the SAS statistical package, version 5.16, on a DEC VAX 8550 computer.

Results

Statistically significant lorazepam vs placebo and granisetron vs placebo effects are detailed in Tables 1 and 2 respectively.

Subjective assessments

Lorazepam produced statistically significant increases in drowsiness, feebleness, muzziness, clumsiness, lethargy, mental slowness, relaxation, dreaminess, incompetence, sadness and withdrawal. Granisetron produced statistically significant increases in clumsiness and attentive-

Table 1 Statistically significant lorazepam vs placebo effects

Variables	Direction	Significant lorazepam effect
<i>Subjective assessments</i>		
Drowsiness	Increased	Main effect, $P = 0.002$; time profile difference, $P < 0.001$
Feebleness	Increased	Main effect, $P = 0.002$; time profile difference, $P = 0.003$
Muzziness	Increased	Main effect, $P = 0.005$; time profile difference, $P < 0.001$
Clumsiness	Increased	Main effect, $P < 0.001$; time profile difference, $P < 0.001$
Lethargy	Increased	Main effect, $P = 0.003$; time profile difference, $P < 0.001$
Mental slowness	Increased	Main effect, $P = 0.045$; time profile difference, $P < 0.001$
Relaxation	Increased	Time profile difference, $P = 0.046$
Dreaminess	Increased	Main effect, $P = 0.015$; time profile difference, $P < 0.001$
Incompetence	Increased	Main effect, $P = 0.024$; time profile difference, $P = 0.007$
Sadness	Increased	Main effect, $P = 0.035$
Withdrawal	Increased	Time profile difference, $P = 0.037$
<i>Choice reaction time</i>		
Total number of correct responses	Decreased	Time profile difference, $P = 0.01$
Number of correct responses (correct cue)	Decreased	Time profile difference, $P = 0.024$
Mean response time of correct responses (correct cue)	Increased	Main effect, $P = 0.002$; time profile difference, $P < 0.001$
Mean response time of correct responses (incorrect cue)	Increased	Main effect, $P = 0.006$; time profile difference, $P < 0.001$
Mean movement time of correct responses (correct cue)	Increased	Main effect, $P < 0.001$; time profile difference, $P < 0.001$
Mean movement time of correct responses (incorrect cue)	Increased	Main effect, $P = 0.002$; time profile difference, $P < 0.001$
<i>Flash fusion threshold</i>	Increased	Main effect, $P < 0.001$; time profile difference, $P < 0.001$
<i>Tapping rate</i>	Decreased	Main effect, $P < 0.001$; time profile difference, $P < 0.001$
<i>Motor control and coordination (task time)</i>	Increased	Main effect, $P = 0.002$; time profile difference, $P < 0.001$
<i>Rapid information processing task</i>		
Total number of correct responses	Decreased	Main effect, $P < 0.001$; time profile difference, $P < 0.001$
Total number of errors	Increased	Main effect, $P = 0.01$; time profile difference, $P < 0.001$
Number of correct responses (letters of the same case)	Decreased	Main effect, $P < 0.001$; time profile difference, $P < 0.001$
Number of correct responses (letters of different case)	Decreased	Main effect, $P < 0.001$; time profile difference, $P < 0.001$
Mean response time of correct responses (letters of the same case)	Increased	Time profile difference, $P = 0.002$
Mean response time of correct responses (letters of different case)	Increased	Main effect, $P = 0.004$; time profile difference, $P < 0.001$

Table 2 Statistically significant granisetron vs placebo effects

Variables	Direction	Significant granisetron effect
<i>Subjective assessments</i>		
Clumsiness	Increased	Time profile difference, $P = 0.002$
Attentiveness	Increased	Main effect, $P = 0.023$
<i>Tapping rate</i>	Increased	Main effect, $P = 0.04$; time profile difference, $P = 0.004$
<i>Rapid information processing task</i>		
Mean response time of correct responses (letters of different case)	Decreased	Main effect, $P = 0.034$

ness. There were no statistically significant treatment interaction effects.

Choice reaction time

Lorazepam produced statistically significant impairments in six of the seven choice reaction time variables measured. Granisetron produced no statistically significant changes in any of these variables. There were no statistically significant treatment interaction effects.

Time estimation

There were no statistically significant treatment effects for this variable.

Flash fusion threshold

Lorazepam produced a statistically significant increase in the flash fusion threshold. There were no statistically significant granisetron or treatment interaction effects.

Tapping rate

Lorazepam produced a statistically significant reduction in tapping rate, whereas granisetron produced a statistically significant increase in tapping rate. Lorazepam produced large reductions in tapping rate from +1.5 h to +6 h. This effect was nullified at +3 h and +6 h when granisetron was administered concomitantly, giving rise to a statistically significant granisetron $\times$ lorazepam $\times$ time interaction effect ($P = 0.008$).

Motor control and coordination

Lorazepam produced a statistically significant increase in the time taken to complete this task. There were no statistically significant granisetron or treatment interaction effects.

Rapid information processing task

Lorazepam produced statistically significant impairments in all six rapid information processing variables measured. Granisetron produced a statistically significant improvement in one of the six rapid information processing variables measured. There were no statistically significant treatment interaction effects.

Discussion

There was little evidence that granisetron had any impact on subjective feelings. Although granisetron produced statistically significant increases in clumsiness and attentiveness, it should be pointed out that a large number of assessments were used and the changes observed were in opposite directions. Lorazepam, as

expected, produced statistically significant impairments in most of the assessments. There was no evidence from the subjective data of any interaction effect between granisetron and lorazepam.

There was little evidence that granisetron affected objective psychometric performance. Only two of the 17 variables measured were significantly affected by granisetron; both indicated an improvement of performance. Lorazepam, as expected, produced a marked impairment of objective psychometric performance, producing statistically significant impairment in most of the variables measured. There was little evidence from this data of any interaction effect between granisetron and lorazepam. Of all the variables measured, only tapping rate exhibited a statistically significant granisetron $\times$ lorazepam $\times$ time interaction effect.

The findings from this study suggest that granisetron does not impair psychometric performance and that it can be co-administered with lorazepam without producing unwanted synergistic effects.

The authors would like to thank Dr G. R. McClelland for the development of the test battery, Mr D. Thompson for his statistical advice, Sister C. Potter for her help in conducting the study and Miss J. Rowley for her careful preparation of the manuscript.

References

- Bond, A. J. & Lader, M. H. (1974). The use of analogue scales in rating subjective feelings. *Br. J. med. Psychol.*, **47**, 211–218.
- Fake, C. S., King, F. D. and Sanger, G. J. (1987). BRL 43694: A potent and novel 5HT₃ antagonist. *Br. J. Pharmacol.*, **91**, 335P.
- Greenhouse, S. W. & Geisser, S. (1959). On methods in the analysis of profile data. *Psychometrika*, **32**, 95–112.
- Marty, M. (1989). Granisetron compared with chlorpromazine plus dexamethasone in patients receiving other emetogenic chemotherapy. In *The Treatment of Cytostatic Drug-Induced Emesis* (Official Satellite to ECCO 5) Cheshire, U.K.: Adelphi Communications Ltd.
- Miner, W. D. & Sanger, G. J. (1986). Inhibition of cisplatin-induced vomiting by selective 5-hydroxytryptamine M-receptor antagonism. *Br. J. Pharmacol.*, **88**, 497–499.

(Received 23 July 1990,
accepted 31 October 1990)