Comparison of the neurokinin-1 antagonist GR205171, alone and in combination with the 5-HT_3 antagonist ondansetron, hyoscine and placebo in the prevention of motion-induced nausea in man

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Aims In man a neurokinin-1 (NK_1) receptor antagonist has previously been shown to be ineffective in the prevention of motion-induced nausea. The antiemetic efficacy of NK_1 receptor antagonists against chemotherapy-induced emesis is, however, enhanced when combined with a 5-HT_3 receptor antagonist. Hence the efficacy of the NK_1 antagonist GR205171 in combination with the 5-HT_3 antagonist ondansetron (Zofran™) was assessed in motion-induced nausea.

Methods GR205171 25 mg i.v., with and without concomitant administration of ondansetron 8 mg i.v., and hyoscine hydrobromide 0.6 mg orally (positive control) were compared with placebo in a model of motion-induced nausea. The study was performed to a four-period, randomized, balanced, double-blind, crossover design in 16 healthy subjects. The end-point was the exposure to the motion stimulus required to produce moderate nausea in the subjects.

Results The motion stimulus required to produce moderate nausea was significantly greater for the positive control than placebo ($P<0.001$). There was no significant difference between either GR205171 or GR205171 plus ondansetron and placebo ($P=0.648$ and 0.342, respectively).

Conclusions The enhancement of NK_1 receptor antagonist antiemetic activity through combination with a 5-HT_3 receptor antagonist is not replicated in motion-induced nausea.

Keywords: 5-HT_3 receptor antagonist, hyoscine, motion sickness, NK_1 receptor antagonist

Introduction

Motion-induced nausea and vomiting is a common problem for which the most frequently used drug treatments are anticholinergics, e.g. scopolamine, or antihistamines, e.g. cinnarizine. Although effective, such treatments are also associated with undesirable side-effects such as drowsiness. The 5-HT_3 receptor antagonist antiemetics are nonsedating and highly effective in managing both chemotherapy-induced emesis (CIE) and postoperative nausea and vomiting (PONV) but have proved ineffective in the control of motion-induced nausea in man [1]. In animal studies neurokinin-1 (NK_1) receptor antagonists, including GR205171, have been shown to be effective antiemetic agents against a wide range of emetogens [2, 3], including motion [3, 4]. In man, one NK_1 receptor antagonist, L-758,298, has been shown to be ineffective in preventing motion-induced nausea [5]. However, there is increasing evidence in man that the antiemetic activity of NK_1 antagonists against CIE is significantly enhanced, possibly in a synergistic fashion, when an NK_1 antagonist is given in conjunction with a 5-HT_3 antagonist [6–8]. Hence this study was performed to assess the effectiveness of the NK_1 receptor antagonist GR205171 alone and in combination with the 5-HT_3 antagonist ondansetron (Zofran™) in an established model

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of motion-induced nausea [1, 5, 9]. As ondansetron has previously been demonstrated as being ineffective in preventing nausea in this model [1] any synergistic activity between the NK_1 and 5-HT_3 antagonists should be readily discernible.

Methods

Subjects

Sixteen healthy male (8) and female (8) volunteers aged between 18 and 50 years took part in the study. Subjects had a body mass index between 19 and 29 kg m^{-2}, were not taking any medication and were nonsmokers. Written informed consent was obtained from all subjects and approval for the study was granted by the DERA Centre for Human Sciences Research Ethics Committee. Each subject's general practitioner was consulted about the suitability of the subject for inclusion in the study prior to enrolment. At screening, subjects had a familiarization session with the motion stimulus, without any treatment, during which the subject's susceptibility to motion-induced nausea was confirmed.

Design

The experiment was performed to a double-blind, double-dummy, balanced, randomised, four-period crossover design with two test treatments and placebo and active controls. The test treatments were GR205171 25 mg i.v. and GR205171 25 mg i.v. plus ondansetron 8 mg i.v. The positive control was hyoscine hydrobromide 0.6 mg orally. Oral treatments were administered with 150 ml water 90 min prior to the motion challenge. I.v. treatments were administered sequentially over 2 min each starting 30 min prior to the motion challenge. Subjects consumed a standard breakfast before attending the facility on each dosing occasion. The dose of hyoscine is the standard dose for prevention of motion sickness and the doses of GR205171 and ondansetron were the same as have been shown to be effective against high-dose cisplatin induced emesis [8]. The ondansetron dose is also that shown to be ineffective when used alone in a motion-induced nausea model [1]. There was a washout period of at least 1 week between treatment arms.

Motion challenge and nausea rating

The method used was similar to that reported elsewhere [1, 5, 9]. Subjects were seated immediately over the axis of rotation of a servo-controlled rotating chair, fully enclosed in a cabin to prevent viewing of the external world. A video camera permitted observation of the subject and a microphone and speaker system enabled communication. The angular velocity of the chair was set initially at $1.5^\circ\ s^{-1}$ and was increased in $1.5^\circ\ s^{-1}$ increments every 30 s up to a maximum of $120^\circ\ s^{-1}$. At each angular velocity the subject made a sequence of head movements through approximately 45°, forwards and backwards in pitch and left and right in roll. Movements were carried out in response to prerecorded commands such that the four head movements occurred in a random order in each sequence. The subject was asked to rate their level of malaise at the end of each sequence of head movements on the following scale: 1 = 'No symptoms'; 2 = 'Any symptom but no nausea'; 3 = 'Mild nausea'; and 4 = 'Moderate nausea; stop motion challenge'. The challenge was stopped when a malaise score of '4' or a maximum angular velocity of $120^\circ\ s^{-1}$ (reached after 40 min) was attained.

As has been reported previously [1, 5], a measure of exposure to the motion stimulus was obtained by summing the products of the angular velocity of the chair (in rev min^{-1}) and the number of head movement sequences made at that velocity, for each angular velocity experienced during the experimental period (i.e. until the subject reported a malaise level of 4). The value recorded for exposure to the motion stimulus was directly proportional to the total number of revolutions of the turntable during the period of head movement. The motion stimulus measure strictly has units of rev min^{-1}. However, as this could be misleading, the values are quoted without units. If a subject had not assessed his/her malaise level as 4 by the end of the challenge, the exposure to motion at 40 min was recorded.

Statistics

The analysis was performed using a mixed model ANOVA on the log(motion exposure) values. The covariate of primary interest was treatment, and subject was fitted as a blocking covariate. The results of the analysis give the difference between the geometric mean values for the each test treatments and placebo on a logarithmic scale. When back transformed to the original scale, the resultant difference between the geometric means is a ratio. The geometric mean motion exposure values (plus 95% CI) and the ratio of test to placebo motion exposure values (plus 95% CI) are presented.

Results

A summary of the motion exposure required to reach moderate nausea for each of the treatments together with the comparisons between the two test treatments (GR205171 25 mg and GR205171 25 mg plus ondansetron 8 mg) and positive control (hyoscine hydrobromide 0.6 mg) and placebo is shown in Table 1. The mean motion exposure required to produce moderate nausea

Table 1 Summary of the exposure to motion stimulus required to develop moderate nausea for each treatment and comparisons between test treatments, positive control and placebo.

	Geometric mean (95% CI)	*Ratio test/placebo (95% CI)*	P *value*
GR205171 25 mg	200.4 (134.2, 299.5)	1.05 (0.8, 1.3)	0.648
GR205171 25 mg + Ondansetron 8 mg	212.3 (154.6, 291.6)	1.12 (0.9, 1.4)	0.342
Hyoscine 0.6 mg	313.6 (229.7, 428.2)	1.65 (1.3, 2.1)	<0.001
Placebo	190.1 (131.8, 274.3)	–	–

was significantly greater for hyoscine than placebo (314 *vs* 190, $P<0.001$). The mean motion exposures required to produce moderate nausea in the GR205171 and GR205171 plus ondansetron arms were 200 and 212, respectively. There was no significant difference between either of the NK_1 receptor antagonist arms and placebo ($P=0.648$ and 0.342). Three subjects, all of whom had received the positive control treatment, had not reported a malaise level of 4 on reaching the maximum angular velocity. These subjects were all assigned a motion exposure value of 806. Although this will have censored the data for this treatment, it does not affect the outcome of the study or conclusions reached.

Discussion

The significantly greater exposure to motion required to achieve moderate nausea in the hyoscine arm of the study in comparison with the placebo arm is consistent with previous studies and confirms the potential of the model to assess putative treatments for motion sickness. Additionally, the absolute motion exposure values are very similar to those reported previously using the same methodology (placebo 190 and 192 and hyoscine 314 and 333 in this study and Reid *et al.* [5], respectively) suggesting good reproducibility. In contrast to the positive control data, the lack of any significant difference in motion exposure values between either of the test treatments and placebo mirrors the previous negative findings with an NK_1 receptor antagonist in this model [5]. In addition, the apparent synergy demonstrated between NK_1 and 5-HT_3 receptor antagonists in cisplatin-induced nausea and vomiting was not replicated here with motion-induced nausea. Although only a single dose of the NK_1 antagonist was studied here, the good efficacy seen using the same dose regimen against cisplatin-induced emesis combined with the lack of any significant effect in this model suggests that these results were not due simply to too small a dose being used.

It might be considered striking that a class of drug which has demonstrated excellent efficacy against emesis in various animal species and a number of models, including motion-induced emesis, has no prophylactic effect against motion-induced nausea in man. These differences could simply be due to species differences in the neuronal pathways mediating nausea and vomiting or in the role of substance P within those pathways. Alternatively, these differences may derive from the fact that in animal studies the subjective sensation of nausea cannot be assessed adequately. Instead a reduction in the number of retches or vomits and increase in the latency to vomiting are used to assess efficacy. Thus the NK_1 receptor antagonists may be less effective in prophylaxis against nausea than the animal data, derived from retching or vomiting endpoints, would suggest. This is consistent with the relatively low efficacy in man of the NK_1 antagonists when given alone in the management of CIE [10–13] and may be particularly relevant in healthy volunteer models or clinical situations where nausea is the primary response.

Whatever the cause of the apparent species differences in the antiemetic efficacy of the NK_1 antagonists, the lack of effect of 5-HT_3 antagonists, NK_1 antagonists or a combination of the two in motion-induced nausea highlights the differences in aetiology and pathogenesis between this and chemotherapy-induced emesis or post-operative nausea and vomiting.

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