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Antiemetic activity of the NK_1 receptor antagonist GR205171 in the treatment of established postoperative nausea and vomiting after major gynaecological surgery

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In this double-blind, randomized, parallel group study, we have investigated the antiemetic activity of the potent and selective NK_1 receptor antagonist GR205171 25 mg i.v. compared with placebo in the treatment of established postoperative nausea and vomiting (PONV) in patients after major gynaecological surgery performed under general anaesthesia. The incidence of PONV in the study population was 65%. Thirty-six patients were treated with placebo or GR205171 (18 patients per group). GR205171 produced greater control of PONV than placebo over the 24-h assessment period. The stimuli for emesis after PONV are multifactorial and the efficacy of GR205171 in this study supports the broad spectrum potential for NK_1 receptor antagonists in the management of postoperative emesis. GR205171 was well tolerated and no adverse events were reported that would preclude the further development of this agent.

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Postoperative nausea and vomiting (PONV) are considered very unpleasant side effects of the postoperative period and some patients regard them as the worst features of recovery. PONV are known to be multifactorial in aetiology. The incidence of PONV is 10–80%, depending on the patient, type of surgery and anaesthetic involved; the incidence can be as high as 73% after certain gynaecological procedures, such as abdominal and vaginal hysterectomy.[1] In addition, many patients are administered opioids for postoperative pain and this is associated with a significant incidence of nausea and vomiting, contributing to the overall pattern of emesis during recovery.

Extensive research in animals has implicated substance P and neurokinin$_1$ (NK_1) receptors in the regulation of emesis. Binding studies using radiolabelled substance P have demonstrated neurokinin receptors, including NK_1 receptors, in the nucleus of the solitary tract and dorsal motor nucleus of the vagus nerve of the ferret and rat.[2] Indeed, NK_1 receptor antagonists demonstrated broad spectrum antiemetic activity in a range of animal species.[3] GR205171 is a potent and selective NK_1 receptor antagonist with high affinity for the human NK_1 receptor and *in vivo* antiemetic activity in animal models of emesis (e.g. emesis induced by cisplatin (acute and delayed), cyclophosphamide, x-irradiation, ipecacuanha, copper sulphate, opioid and motion).[3] NK_1 receptor antagonists demonstrate a broader antiemetic spectrum than $5HT_3$ receptor antagonists in animals. This profile of GR205171, if translated into humans, would provide a major advance in the clinical management of emesis.

GR205171 has been demonstrated to be safe and well tolerated in healthy male and female volunteers after a single infusion over 15 min (Glaxo Wellcome, data on file). These studies also showed that GR205171 had acceptable pharmacokinetic properties with high clearance (1177 ml min^{-1}), a large volume of distribution (588 litre) and a moderate to long half-life (8.3 h).[4]

The aim of this pilot study was to evaluate the efficacy and safety of a single 25 mg i.v. dose of GR205171 in the treatment of established nausea and/or emesis after major gynaecological surgery performed under general anaesthesia. The postoperative setting was selected for this clinical study as the multifactorial stimuli for nausea and vomiting in this situation provide a model to evaluate the broad

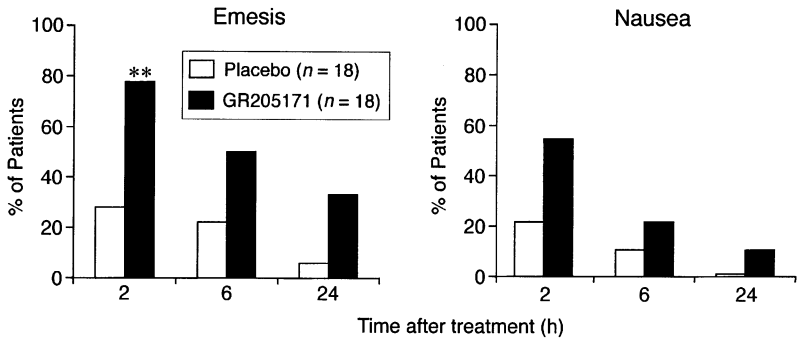

Fig 1 Percentage of patients experiencing complete control of emesis and nausea during the 24 h following treatment with GR205171 25 mg i.v. or placebo. $^{**}P<0.01$ *vs* placebo (exact two-sided Fisher's test).

spectrum antiemetic activity of GR205171. Preliminary data from this study have been presented previously.[5]

Methods and results

Three centres in France participated in this double-blind, randomized, parallel group study. After obtaining approval from the Local Ethics Committee, written informed consent was obtained from female patients (18–65 yr) undergoing abdominal or vaginal hysterectomy or ovariectomy, performed under general anaesthesia. In addition, patients received adequate analgesic medication to control pain and received at least one dose of opioid within 6 h of surgical recovery. Patients who experienced nausea and/or vomiting within 6 h of surgical recovery were treated with a single i.v. dose of either GR205171 25 mg or placebo and were assessed for number of emetic episodes (vomits and/or retches), nausea and pain (four-point graded scale: none, mild, moderate or severe; worst episode during the assessment period) for the subsequent 24 h. In addition, safety (adverse event monitoring, clinical chemistry and haematology, urinalysis and vital signs) was assessed for the subsequent 72 h. Rescue medication was available for patients who did not respond to the study medication.

We studied 57 patients, of whom 36 experienced nausea and/or vomiting within 6 h of surgical recovery (incidence of PONV 65%). Thirty-six patients were treated with GR205171 ($n=18$) or placebo ($n=18$). The two groups were comparable in sex (all female), age, ethnic origin, weight and surgical procedure. For the GR205171 group, a higher proportion of patients were of child-bearing potential (67% compared with 44% in the placebo group) and a lower proportion of patients were post-menopausal (17% compared with 39% in the placebo group).

The proportion of patients who experienced complete control of emesis or nausea (Fig. 1), with neither rescue medication nor premature withdrawal, was greater in the GR205171 group than in the placebo group. These effects were maintained at all times over the 24 h. In addition, the GR205171 group experienced fewer emetic episodes by 2 h ($P=0.006$) and less severe nausea at all times ($P\leqslant0.025$, exact Wilcoxon rank sum test) than the placebo group. The proportion of patients requiring rescue medication was less for the GR205171 than for the placebo group by 6 h (44% *vs* 67%) and by 24 h (61% *vs* 83%).

There was no difference between the GR205171 and placebo groups in terms of control of pain ($P=1.0$, exact Fisher's test) and severity of pain ($P>0.243$, exact Wilcoxon rank sum test). In addition, there was no difference in the incidence of adverse events between the GR205171 group (seven events in five patients) and the placebo group (12 events in six patients) and there were no reports of adverse events that would preclude the further clinical development of GR205171.

Comment

Using PONV as a model with multifactorial stimuli for emesis, we have demonstrated the clinical antiemetic efficacy of GR205171. A single i.v. dose of GR205171 25 mg administered to treat established nausea and/or emesis was well tolerated and provided better control of PONV than placebo in patients undergoing the highly emetogenic stimulus of major gynaecological surgery performed under general anaesthesia.

Preliminary data reporting the effects of another NK_1 receptor antagonist, CP122,721, on PONV were presented recently.[6] CP122,721 200 mg orally produced better control of vomiting than ondansetron 4 mg i.v. alone, but in contrast with our study using GR205171, there was no control of nausea. In addition, a combination of CP122,721 and ondansetron provided no further control of vomiting or nausea.

NK_1 receptors have been implicated in the neurotransmission of pain.[7] Our study did not demonstrate the analgesic efficacy of GR205171 in postoperative pain, although it is realized that the study was not designed to assess analgesic efficacy as a primary end-point.

This is the first clinical study to demonstrate the antiemetic efficacy (control of both nausea and vomiting) of an NK_1 receptor antagonist when administered as a single agent in the treatment of established PONV and supports the broad spectrum antiemetic potential of this class of agents. The results of this study suggest that GR205171

has clinical benefit in PONV and further studies will aim to optimize the dose and schedule for GR205171 in the management of emesis.

Acknowledgement

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