Comparative efficacy of a single oral dose of ondansetron and of buspirone against cisplatin-induced emesis in cancer patients

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Summary Buspirone, an agonist of the 5-HT1A subtype of serotonin receptors, has shown antiemetic activity in animal models. However, in cancer patients treated with cisplatin, ondansetron, given either i.v. (one 8-mg dose 30 min after cisplatin) or orally (one 16-mg dose at the end of cisplatin infusion) was superior (P<0.001) to buspirone (60 mg p.o. at the end of cisplatin and 60 mg p.o. 30 min later), in all parameters of antiemetic efficacy. These results are in favour of 5-HT3 receptors, but against the participation of 5-HT1A receptors in acute emesis associated with cisplatin chemotherapy.

Keywords: serotonin; emesis; cisplatin; buspirone; ondansetron; serotonin receptors

Serotonin plays an important role in the pathogenesis of nausea and vomiting (Cubeddu et al., 1990, 1992; Andrews and Davis, 1993). Emesis induced by anti-cancer chemo- and radiotherapy, post-operative emesis and ipecac-induced emesis are ameliorated by selective antagonists of 5-HT3 receptors (see Andrews and Davis, 1993, and Andrews, 1994, for review). Recent studies indicate that, in addition to 5-HT3 receptors, other serotonin receptor subtypes may play a role in emesis. In laboratory animals, activation of 5-HT1A receptors by a single dose of 8-hydroxy-2-(di-n-propyl amino)tetralin(8-OH-DPAT), buspirone or other 5-HT1A agonists suppresses emesis induced by motion sickness, cisplatin, α1-adrenergic receptor agonists, nicotine, veratrine, copper sulphate or stimulation of vagal afferents (Lucot and Crampton, 1987, 1989; Milano and Gregot, 1992; Okada et al., 1994). The antiemetic effects of 5-HT1A receptor agonists have not been explored in humans. In this study, we investigated the antiemetic effect of buspirone, an agonist of 5-HT1A receptors, in human cancer patients treated with cisplatin.

Recent studies designed to simplify treatment and to reduce pharmacy and nursing costs related to antiemetic therapy demonstrated that ondansetron can be given in a single i.v. dose with no loss of its antiemetic efficacy (Beck et al., 1992; Seynaeve et al., 1992). Although oral ondansetron has been used for non-cisplatin chemotherapy (Cubeddu et al., 1994), no information is available on whether oral ondansetron could control emesis associated with cisplatin treatment. The antiemetic efficacy of one i.v. and of one oral dose of ondansetron was compared with that of oral buspirone. Dose administration was timed to achieve highest antiemetic levels at the peak of emesis.

Patients and methods

Design

A three-arm, randomised, double-blind, parallel group study design was employed. One group received a single 8 mg i.v. dose of ondansetron, dissolved in 50 ml of D5/W (dextrose 5% in water), and given as a 15 min infusion, starting 30 min after completing the 1 h cisplatin infusion. Another group of patients received a single 16 mg dose of ondansetron administered orally at the end of the cisplatin infusion. The buspirone group received two oral doses of buspirone, one

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Results

The demographics characteristic of the patients are shown in Table I. Patients were similar with regard to age, weight and dose of cisplatin administered to the three study groups. However, a higher proportion of females was present in the oral ondansetron-treated group (P<0.01, based on the chi-square test).

Results for the control of acute emesis are shown in Table II and Figure 1. In pairwise treatment comparisons, both single dose oral and single dose i.v. ondansetron were statistically superior to buspirone for all measured efficacy parameters. Compared with buspirone, patients treated with a single dose of oral or i.v. ondansetron experienced a greater proportion of complete treatment responses (i.e. no emesis) (P<0.01), fewer emetic episodes (P<0.01) and a lower proportion of treatment failures (P<0.01). Further, the number of patients requiring rescue antiemetic was significantly greater after buspirone than after either of the ondansetron treatments (Figure 1). There were no differences in the measurements of antiemetic efficacy between oral ondansetron and i.v. ondansetron. Ondansetron (8 mg i.v.), given as rescue antiemetic, effectively controlled vomiting in buspirone-treated patients, since there were no additional emetic episodes after its administration.

Discussion

Recent studies in laboratory animals indicate that 5-HT1A receptor agonists (buspirone, 8-OH-DPAT, flesinoxan, gepirone) have antiemetic activity against emetic stimuli acting via different pathways (Lucot and Crampton, 1987, 1989; Milano and Gregot, 1992; Okada et al., 1994). High concentrations of 5-HT1A binding sites and of receptor mRNA have been found in the nucleus tractus solitarius, an important brain area in the control of emesis (Lucot, 1992). Although part of the antiemetic action of 5-HT1A agonists observed in animals may be mediated through the nucleus tractus solitarius, it is possible that these agents could act at the vomiting centre. In this study, we explored whether buspirone, a 5-HT1A agonist with anxiolytic properties, was effective against cisplatin-induced emesis in cancer patients. Buspirone is completely absorbed after oral administration, peak plasma levels are achieved within 40–90 min of dosing and elimination half-life averages 4 h. Recommended initial dosage for antiemetic effects is of 10–15 mg day⁻¹ and maintenance dosage of 15–30 mg day⁻¹, given in 2–3 divided doses. The manufacturer recommends not to exceed 60 mg day⁻¹ (see American Hospital Formulary Services, 1993 for review). In this study, buspirone, in doses much higher than required for anxiolytic activity failed to protect cancer patients from the acute (initial 24 h) emetic action of cisplatin. The complete, major and minor response rates and the failure rates in buspirone-treated patients were similar to those previously described for placebo-treated patients (Cubeddu et al., 1990). These results suggest that buspirone at the dose-regimen employed (three to four times higher than the daily doses required for anxiolytic effects) is devoid of clinically significant antiemetic activity against the cisplatin-induced emesis. The lack of effect of buspirone could be explained by the reported differences in the degree of involvement of 5-HT1A receptors in emesis, within species. For example, buspirone was less effective in the ferret than in the cat against cisplatin-induced emesis (Wells et al., 1993). Our study suggests that the drug may not be very effective in humans. Additional studies on repeated (or even higher) doses of buspirone on cisplatin-induced acute and delayed emesis (we only evaluated acute emesis) and on nausea and emesis associated with other chemotherapeutic drugs are required.

Intravenous ondansetron, given either in repeated doses or as a continuous infusion, antagonises vomiting associated with cisplatin treatment (Cubeddu et al., 1990; Beck et al., 1992; Seynaeve et al., 1992). These regimes have high pharmacy and nursing costs, and often lengthen the duration of hospitalisation. Recent studies showed that a single 8 mg i.v. dose of ondansetron was as effective as the more complicated regimes (Beck et al., 1992; Seynaeve et al., 1990). Although our study is based on a small number of patients, the complete response (67%), complete plus major response (89%) and the failure (0%) rates obtained in this trial with a single 8 mg i.v. dose of ondansetron (given 30 min after cisplatin) were similar to those observed by Beck et al. (1992), employing a single 32 mg dose of i.v. ondansetron, given 30 min before cisplatin.

Table I Patient demographics

| Buspirone i.v. ondansetron Oral ondansetron |
|-------------------------------------------|
| No. of patients | 10 | 9 |
| Age (years)      | 51 ± 3 | 45 ± 5 | 48 ± 5 |
| Sex (M:F)        | 7:3 | 8:1 | 2:7 |
| Weight (kg)      | 59 ± 2 | 62 ± 3 | 63 ± 3 |
| Cisplatin dose   | 81 ± 4 | 89 ± 4 | 85 ± 4 |

Table II Comparative antiemetic activity of buspirone and ondansetron

| Treatment responses | Buspirone i.v. ondansetron | Oral ondansetron |
|---------------------|-----------------------------|------------------|
|                     | (n = 10)                    | (n = 9)          |
| Complete            | 0 (0%)                      | 6 (67%)          | 5 (56%)          |
| Major               | 1 (10%)                     | 2 (22%)          | 3 (33%)          |
| Minor               | 3 (30%)                     | 1 (11%)          | 1 (11%)          |
| Failure             | 6 (60%)                     | 0 (0%)           | 0 (0%)           |

Complete response, no emetic episodes; major, one or two emetic episodes; minor, three or four emetic episodes; failure, ≥ 5 emetic episodes or administration of rescue antiemetics. Significantly different from buspirone at *0.002, *0.008 and *0.006. P-values are based on Mantel–Haenszel test for complete response and for failures.

Figure 1 Need for rescue antiemetics after prophylactic treatment with buspirone or ondansetron in patients treated with cisplatin chemotherapy. The percentage of patients requiring rescue antiemetics after cisplatin-based chemotherapy over the 24 h study period for each of the three treatment groups is shown. Both ondansetron groups were significantly different from buspirone (P<0.01) based on Mantel–Haenszel test. Buspirone; ondansetron.
The antiemetic efficacy of a single oral dose of ondansetron against moderate to high-dose cisplatin had not been studied. In previous trials, repeated doses of oral ondansetron were administered only after an i.v. loading dose of 8 mg (see Cooke and Mehra, 1994 for review). Since the bioavailability of oral ondansetron is nearly 50%, the oral dose of ondansetron employed in this study was twice the i.v. dose. In addition, oral ondansetron was given at the end of the cisplatin infusion, to achieve higher levels at the time of the emesis peak. In this work, oral ondansetron proved as effective as i.v. ondansetron, indicating that a single prophylactic 16 mg oral dose of ondansetron can be used to cover effectively the period of acute emesis associated with cisplatin treatment.

In summary, in this study we demonstrated that the acute period of emesis associated with cisplatin chemotherapy, can be treated either with one oral or one i.v. dose of ondansetron. These simplified regimens facilitate compliance and reduce cost and patient discomfort. However, further studies in larger numbers of patients are required to determine whether a single 16 mg oral dose of ondansetron (8 mg i.v.) was highly effective in stopping vomiting when administered as rescue antiemetic. Finally, acute dosing with oral buspirone did not protect against acute emesis induced by cisplatin. Our results support the role of 5-HT3 receptors but are against the participation of 5-HT1A receptors in acute emesis associated with treatment using cisplatin in cancer patients.

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