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ONDANSETRON AND TROPISETRON WITH DEXAMETHASONE IN THE PROPHYLAXIS OF ACUTE VOMITING INDUCED BY NON-CISPLATIN-CONTAINING CHEMOTHERAPY

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Forty-seven patients receiving non-cisplatin-containing chemotherapy were entered in a prospective study in which the efficacy of ondansetron plus dexamethasone and tropisetron plus dexamethasone in the prophylaxis of acute vomiting was evaluated. Thirty-nine patients were evaluable for cross-over analysis. During the 24 hours following the start of chemotherapy, 97% of patients on ondansetron plus dexamethasone reported total control of vomiting compared with 82% of those on tropisetron plus dexamethasone ($p = 0.026$). Thus, both 5-HT_3- receptor antagonists combined with dexamethasone were highly effective in controlling acute vomiting induced by non-cisplatin-containing chemotherapy. The observed difference between the treatments may be caused by different dose schedules of ondansetron and tropisetron. A double-blind design with equal number of placebo-controlled administrations is needed to ascertain whether there is a significant pharmacological difference between ondansetron and tropisetron.

Acute nausea and vomiting are the most common side-effects of cytotoxic chemotherapy (1). The pathophysiology of vomiting is still partly unclarified. Recent research has emphasised the importance of serotonin receptors in controlling emesis. The release of serotonin by cytotoxic agents may activate the vomiting reflex via 5-HT_3-receptors located on vagal afferent nerves or in the area postrema (2). Ondansetron (GR38032F) and tropisetron (ICS 205–930) are highly selective 5-HT_3-receptor antagonists with demonstrated antiemetic activity in patients receiving cisplatin- (3, 4) and non-cisplatin-containing regimens (5, 6). Particular improvement in the prophylaxis of emesis has been shown during the first 24 h after the administration of chemotherapy (5, 7). The combination of dexamethasone and ondansetron has been reported to give an even better antiemetic control than ondansetron alone in cisplatin-containing chemotherapy (8). Doses and schedules of ondansetron have varied in different antiemetic trials. Oral ondansetron given every 8 h has been effective in the prophylaxis of acute cisplatin-induced vomiting (8). Tropisetron has been given as a single daily dose of 5 mg intravenously (i.v.) or orally. Constipation and headache have been the main adverse events in patients receiving 5-HT_3-antagonists. Since 5-HT_3-receptors are found in the gut, constipation most probably is due to the drugs. We report the results from an open, randomized cross-over study of ondansetron or tropisetron, both together with dexamethasone, in the prophylaxis of acute vomiting induced by non-cisplatin-containing chemotherapy.

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Material and Methods

Both outpatients and inpatients were eligible for the study provided they were designated to receive two similar courses of non-cisplatin-containing chemotherapy separated by at least 14 days. Patients with brain metastases or signs of bowel obstruction were excluded. Also patients

who had experienced vomiting within 12 h before starting the study were excluded. Patients entered the study consecutively and were randomly assigned to receive either ondansetron plus dexamethasone or tropisetron plus dexamethasone with their first course of chemotherapy, crossing over to the other treatment during their second course. Informed consent was received from every patient.

Forty-seven patients were entered into the study. Characteristics of the patients are given in Table 1. Chemotherapy comprising cyclophosphamide (>500 mg/m^2) with mitoxantrone, doxorubicin, epirubicin or methotrexate was given to 27 patients. Eight patients were not evaluable for emesis. Six of these received cytotoxic combination at a reduced dose during the second course due to haematological toxicity, and in two patients the chemotherapy regimens was changed due to progression of the malignant disease.

Patients were given 10 mg dexamethasone i.v. prior to every course of chemotherapy. Either 8 mg ondansetron or 5 mg tropisetron was given to patients by slow i.v. injection after dexamethasone and immediately before chemotherapy. The loading dose of ondansetron was followed by 8 mg ondansetron given orally twice at 8-h intervals. In the hospital the number of vomits and retches during the first 24 h after the start of chemotherapy was recorded by nurses. The same data were recorded on follow-up cards by outpatients. Control of vomiting during the first 24 h was scored as Total: no vomiting, Partial: 1–4 vomits and Failure: more than 4 vomits. Nausea was not recorded as an evaluation criteria.

Table 1

Patient characteristics

No. of patients	47
Males/females	14/33
Median age (years)	
Males	58.3
Females	49.5
Age range	30–75
Previous chemotherapy	
Yes	25
No	22
Primary tumour	
Breast	26
Lung	8
Melanoma	4
Other	9
Cytotoxic chemotherapy	
CNF	13
CMF	8
CEF	3
VAC	3
Carboplatin-containing	7
DTIC-containing	5
Epirubicin-containing	3
MTX-5-FU	3
MMM	2

Patients were only included in the cross-over analysis of response if they received the cytostatics in the planned doses. The number of emetic episodes during the consecutive courses was analysed by log-linear modelling with the SPSS/PC+ software. The proportion of success was compared between treatments by the Mantel-Haenszel χ^2-test.

Results

The response to antiemetic therapy is shown in Table 2. Ondansetron was superior to tropisetron in the total control of vomiting during the first 24 h ($p = 0.026$). Only two of the patients, who had no previous chemotherapy, did not achieve total control with either antiemetic treatment. Only one patient experienced severe vomiting during both chemotherapy courses. There was evidence of interaction between antiemetic treatment and course number when the emesis was assessed in the log-linear analysis. All the patients expressing any degree of failure (i.e. partial control or total failure) to the antiemetic treatment experienced it during the first course of treatment. Only one of the study patients vomited also during the second course of treatment. There was no evidence of any other interaction in the log-linear analysis. When asked for preference, 19 (49%) patients out of 39 expressed no difference, 13 (33%) preferred ondansetron and 7 (18%) preferred tropisetron. Constipation occurred in 14 (36%) patients receiving ondansetron and 7 (18%) patients receiving tropisetron. This difference was not statistically significant. Headache was reported by 7 (18%) patients receiving ondansetron and 7 (18%) receiving tropisetron.

Table 2

Grade of control of vomiting during the first 24 h

Grade of control of vomiting	Ondansetron plus dexamethasone n (%)	Tropisetron plus dexamethasone n (%)
Total control	38 (97)	32 (82)
Partial control	0	6 (15)
Failure	1 (3)	1 (3)

Discussion

To our knowledge, this is the first study in which the compound effect of tropisetron and dexamethasone is evaluated. Ondansetron and dexamethasone together in the antiemetic therapy with cisplatin-containing chemotherapy have been previously evaluated (8). Similar evaluations have not been published of non-cisplatin-containing chemotherapy.

Ondansetron and tropisetron have a very similar profile of adverse events, among which constipation and headache are typical. In the present study constipation occurred more often with ondansetron but the difference was not

statistically significant and there was an equal number of patients complaining of headache with the two antiemetic treatments. However, the large number of patients complaining of constipation may also be due to the fact, that a number of them were using opioid analgesics while under treatment.

A cross-over design is an applicable method in antiemetic studies since using patients as their own controls reduces the variance for a given sample size. However, there exists the potential problem that the efficacy of the treatment may vary with the treatment courses due to, for example, anticipatory vomiting or altered clinical status. In the present study there was evidence of interaction between antiemetic treatment and course number in the log-linear analysis when the response to treatment was assessed. The course number appeared to be a confounding factor which has to be taken into consideration when the results are judged. If the antiemetic response of the first course only is analysed, the antiemetic response rate for ondansetron was 93% and for tropisetron 75%, a difference which is statistically significant at $p = 0.05$ level.

Both ondansetron and tropisetron seem to provide effective and safe antiemetic treatment in all kinds of emetogenic chemotherapy. The adverse events are similar, well tolerated and reversible. In the present study 19 (49%) of the patients were unable to state a preference for any of the two antiemetic treatments. Ondansetron was preferred by 13 and tropisetron by 7 patients. The preference correlated with the emetic control.

Combining dexamethasone with a 5-HT$_3$-antagonist results in an improvement in antiemetic efficacy at least in cisplatin-containing chemotherapy (8). Dexamethasone also has adverse events. A feeling of transitory itching after i.v. administration of dexamethasone is very common. Many patients also experience hot flushes and facial erythema within 24 h after i.v. dexamethasone. In the present study some of the patients complained of itching, but none experienced hot flushes or facial erythema.

The study demonstrated that both ondansetron and tropisetron together with dexamethasone are highly effective in preventing vomiting during the first 24 h after non-cisplatin-containing chemotherapy. Total control of vomiting was obtained more often with ondansetron. However, the observed difference may be due to the placebo effect caused by different dosing schedules of ondansetron (three times a day) and tropisetron (once a day). The frequent administrations may have increased the placebo effect of ondansetron. It is also possible that a single daily dose of tropisetron in some patients may not result in high enough plasma levels to produce the maximum anti-emetic protection. A double-blind design with equal number of placebo-controlled administrations is needed to ascertain whether there is a significant pharmacological difference between ondansetron and tropisetron.

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