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THE EFFECT OF ONDANSETRON ON RADIATION-INDUCED EMESIS AND DIARRHOEA

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Fractionated radiotherapy of malignancies in the abdomen induces nausea and vomiting in approximately 50% of the patients. During abdominal irradiation the damaged gastrointestinal mucosa releases 5-HT with ensuing activation of 5-HT_3 receptors which may explain the nausea and vomiting. Ondansetron is a new 5-HT_3-antagonist with antiemetic properties. In this consecutive study, 33 patients receiving fractionated upper abdominal irradiation ($\geq$100 cm^2, 1,8-4 Gy daily dose for a mean of 13 days) were treated with ondansetron (8 mg t.d.s. p.o.). Emesis was completely controlled in 26/33 (79%) patients throughout their radiation course, which embraced 628 (94%) treatment days. Ondansetron was well tolerated. Eleven patients developed mild constipation. No patients experienced diarrhoea (a common distressing side-effect of abdominal irradiation). It is suggested that ondansetron can be of value in preventing emesis in patients receiving fractionated radiotherapy. The possible beneficial effect in preventing diarrhoea must be further evaluated.

Radiotherapy of malignancies in the abdomen induces nausea and vomiting in a significant number of patients. The intensity varies depending on the dose schedule, the irradiated volume and the site of treatment (1, 2). Approximately 50% of the patients subjected to fractionated irradiation of upper abdomen (e.g. radiotherapy of lymphoma in the stomach) or treated with larger volumes (paraortic irradiation in testicular carcinoma) and up to 80% of the patients receiving radiotherapy with high single fractions develop nausea and vomiting. Current available anti-emetics (e.g. metoclopramide or nabilone) have been shown to control these problems in about 50% of patients during prolonged radiotherapy courses (3). Chlorpromazine or levonantradol seemed to be of some value in reducing nausea/vomiting in patients subjected to high-dose irradiation due to symptomatic neoplasias in the abdomen (4). However, these drugs are regularly associated with sedation and extrapyramidal sensations partially due to interaction with dopamine receptors (5). Ondansetron, a novel and highly selective 5-hydroxytryptamine 3 receptor (5-HT_3) antagonist is devoid of dopamine receptor interaction and thus gives the opportunity to more specific management of the radiation-induced emesis (6, 7). The present paper describes the results from an open non-randomized study in which ondansetron was given to 33 consecutive patients subjected to radiotherapy of malignancies in the abdomen.

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Material and Methods

Patients and irradiation. Thirty-three patients (15:18, female:male; age 24–82 years) subjected to fractionated irradiation of malignancies in the abdomen were consecutively included in the study and prospectively monitored for the development of nausea and vomiting during the period October 1989–October 1990 at the Department of Oncology, University Hospital, Umeå, Sweden. The patients had given their informed consent and the study followed the local ethical guidelines. The criteria of inclusions with regard to irradiation were: megavoltage radiotherapy, opposed or single anterior or posterior fields,

which included an area of $\geqslant 100\,cm^2$ between the level of the upper border of the 11th thoracic vertebrae and the lower border of third lumbar vertebrae and a minimum dose of 1.8 Gy per fraction at the midplane of the treated volume. Treatment was given for a minimum of five days and the mean number of fractions was 14, range 5–23. A detailed description of the patients, diagnosis and schedule of radiotherapy are given in Table 1.

Drug administration. Ondansetron was administered orally 8 mg three times daily from the first day of irradiation and up to two days following the last radiation-treatment. No other anti-emetic therapy was allowed 24 h prior to the start or during the study. All other concomitant medication was recorded.

Evaluation. Nausea and emesis were consecutively registered during ondansetron delivery. The patients completed a diary card daily throughout the radiotherapy course including weekends and recorded the number of vomits, retches, and grade of nausea (none, mild, moderate or severe). The number of ondansetron tablets were registered. In addition clinical assessment was performed weekly, any side-effects noted and the compliance checked. Routine laboratory status was followed throughout the ondansetron medication. The response on emesis was defined according to Gralla (8); complete response (no emetic episode), major response (1–2 emetic episodes) minor response (3–5 emetic episodes) or failure (>5 emetic episodes or rescue anti-emetic therapy required per 24 h). One emetic episode signifies any episode of vomiting or retching.

Results and Discussion

The results are summarized in Table 2 (a and b). The worst experience of nausea and vomiting are given expressed either in relation to the number of patients or to the number of irradiation sessions. The majority of the patients displayed no or only minor discomfort with nausea/vomiting during the radiotherapy courses. Eleven of the patients experienced mild constipation, which was easily managed by lactulose. None of the patients suffered from diarrhoea. Three patients developed transient itching erythemal reaction that was not associated to the radiation

Table 1

Diagnosis and radiotherapy schedule

Diagnosis (Number of patients)	Fraction dose (Gy)	Total dose (Gy)
Ventricular lymphoma (9)	1.8	42–44
Other lymphoma (2)	1.8	42–44
Testicular carcinoma (7)	1.8	32–35
Palliative radiotherapy of different malignancies (15)	1.8–4.0	24–42
Total (33)		

Table 2

The degree of emesis, vomiting and/or retching and grade of nausea to ondansetron following fractionated radiotherapy. Number of patients = 33

	Worst day* n (%)	Total treatment days** n (%)
Emesis (response)		
Complete	26 (79)	628 (94)
Major	3 (9)	35 (5)
Minor	3 (9)	7 (1)
Failure	1 (3)	1 (<1)
Nausea (degree)		
None	15 (46)	502 (75)
Mild	8 (24)	125 (19)
Moderate	6 (18)	36 (5)
Severe	4 (12)	8 (1)

* This signified each individual patient's worst day regarding emesis (vomiting and retching) or nausea during ondansetron treatment.

** Ondansetron treatment during 456 radiotherapy days. The remaining days were either days of rest or postradiotherapy days (at most 2 days/patient). The total ondansetron treatment days were 671).

treatment, i.e. outside the treatment field. There were no sex differences in any of the parameters analyzed. There were no obvious correlations between the nausea/vomiting and the delivered radiation dose or field size regarding the patients in this study.

It is evident that ondansetron offers a new approach in managing radiotherapy-induced emesis. In addition to our study, Priestman et al. (9, 10) reported ondansetron to be more effective than metoclopramide in patients undergoing single high-dose upper abdominal irradiation. Ondansetron was highly effective in approximately 90% of the patients as compared to 45% of those treated with metoclopramide. Furthermore, other studies regarding chemotherapy have convincingly shown the beneficial effects of ondansetron and of other 5-HT_3 receptor antagonists, both in minimizing emesis, and also in minimizing distressing side-effect such as sedation and extra-pyramidal symptoms associated with e.g. metoclopramide (11). The most commonly occurring adverse event associated with ondansetron is constipation and headache (12).

In current clinical practice patients undergoing fractionated radiotherapy are not given regular emesis-prophylaxis, partially since the length of the radiotherapy course increases the risk of unwanted side-effects of the anti-emetics currently used. Nevertheless, it is important to recall the fact that the distress to the patient during fractionated irradiation may be particularly pronounced since the treatment can comprise up to 40 sessions. If untreated, emesis may persist throughout this period and cause physiologic changes, e.g. dehydration, electrolyte imbalance and/or malnutrition which in turn can hamper the quality of life and the final goal for the treatment.

Finally, one interesting implication from our results is the observation that ondansetron seemed to reduce the problem with diarrhoea. Diarrhoea is a common discomfort associated with radiotherapy to the abdomen (13). Thus, the known 'adverse effect' of ondansetron with increase in bowel transit time (14) and constipation can be of benefit in this group of patients.

One major problem in evaluating the present results is that there only exists limited information on the actual frequency and severity of radiation-induced emesis, correlated to fraction size, treatment volume and duration. Most available figures derive from non-controlled estimates and experience. A more correct evaluation both with regard to ondansetron's effect in reducing emesis induced by fractionated radiotherapy and its possible preventing effect on diarrhoea demands a randomized, double-blind, placebo-controlled study. Such a study is in progress. It is also of interest to evaluate the effects of a reduced onsansetron intake, i.e. twice daily as is now recommended for chemotherapy-treated patients.

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