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ORIGINAL ARTICLES

5-HT_3 antagonist ondansetron—an effective outpatient antiemetic in cancer treatment

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Abstract

Thirty children aged 2–16 years with malignant tumours who were receiving chemotherapy were treated with the 5-HT_3 antagonist ondansetron. Each received a single intravenous dose (5 mg/m^2) followed by oral doses (2–4 mg depending on surface area) every eight hours for five days. Chemotherapy regimens comprised: carboplatin alone, carboplatin plus etoposide, cisplatin plus etoposide; adriamycin (doxorubicin) plus cyclophosphamide, or ifosfamide. Twelve patients received ondansetron with their first course of chemotherapy and the other patients were poor responders to previous antiemetic treatment. Efficacy was assessed by a questionnaire documenting the incidence of vomiting and severity of nausea. In a 24 hour period after starting chemotherapy a complete or major response (less than two vomiting episodes) was achieved in 87% of children. Although ondansetron was effective for early antiemesis after cisplatin or ifosfamide, delayed vomiting, retching, or nausea reduced responses to 50% and 20%, respectively. We conclude that in children ondansetron is an effective, well tolerated, oral antiemetic enabling simple administration in the outpatient setting. In the present schedule it was of limited efficacy against cisplatin or ifosfamide induced emesis.

Severe vomiting in adults receiving cancer chemotherapy is often a dose limiting factor and may influence treatment compliance. Although the latter is less of a problem with children, the impact of vomiting on quality of life is of major importance. Intensification of treatment regimens over the last decade, with the widespread use of highly emetic regimens with drugs such as cisplatin or ifosfamide, has brought this issue to the fore. Although some regimens may be given as an outpatient this is often impossible because of the stress imposed on the family by having to manage a child with intractable vomiting at home. Oral antiemetics are of limited value and the most effective regimens have, in general, to be given intravenously. The most widely used combination is intravenous dexamethasone combined with intravenous metoclopramide. High dose metoclopramide is of proved efficacy in platinum induced vomiting but severe extrapyramidal side effects are a particular problem in children. There is a great need, therefore, for an effective orally administered antiemetic that would facilitate outpatient administration of chemotherapy and also improve the tolerability of inpatient regimens.

Agents such as chlorpromazine, chlorpheniramine, and lorazepam may be effective but this is usually at doses that produce considerable sedation. Frequently, the child dislikes the sedative effect and may, ultimately, prefer to vomit and be done with it. It has been suggested that the efficacy of high dose metoclopramide is less related to its activity as a dopamine antagonist than to a separate effect of serotonin receptors. Recently, specific 5-HT_3 receptor antagonists have been developed that have been shown to prevent vomiting in animals[1] and also in adults receiving platinum or non-platinum containing regimens.[2 3] The drug has been well tolerated in adults, the only concern being a transient rise of liver transaminases. Minor symptoms such as headaches and dizziness have also been reported in a small number of patients.

The present pilot study sought to determine the tolerance of this agent in children and evaluate its antiemetic efficacy after both platinum and non-platinum containing drug regimens.

Patients and methods

Thirty patients with solid tumours were studied. Their age, diagnosis, and treatment regimens are shown in table 1. Treatment regimens are classified in three broad groups: those containing (i) cisplatin (60–100 mg/m^2) (group A); (ii) adriamycin (doxorubicin) (40–60 mg/m^2) plus cyclophosphamide (400–1000 mg/m^2) or ifosfamide (6–9 g/m^2) (group B); and (iii) carboplatin (5–600 mg/m^2) (group C).

An initial loading dose (5 mg/m^2) was infused over 15 minutes, followed by an oral dose every eight hours, for five days. The oral dose was related to the surface area: $<0{\cdot}3$ m^2, 1 mg; $0{\cdot}3$–$0{\cdot}6$ m^2, 2 mg; $0{\cdot}6$–$1{\cdot}0$ m^2, 3 mg; and $>1{\cdot}0$ m^2, 4 mg. All patients were admitted for the first 24 hours for clinical evaluation. Twelve had not received any prior chemotherapy and the others had previously been treated with standard antiemetic regimens such as metoclopramide, dexamethasone, and lorazepam with which vomiting had been poorly controlled. One patient was studied on two occasions after different chemotherapy regimens.

Serum urea, creatinine, and electrolyte concentrations and liver function were checked before drug administration, and 24 hours and seven days later.

Antiemetic efficacy was assessed by a simple

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Table 1 Patient details

Patient No	Sex	Age	Other drugs	Malignancy
Group A: cisplatin				
1	F	9	Vincristine	Neuroblastoma
2	M	12	Etoposide	Rhabdomyosarcoma
3	F	12	Etoposide, bleomycin	Squamous cell lung carcinoma
4	F	9	Adriamycin	Osteosarcoma
5	M	15	Etoposide	Ewing's sarcoma
6*	F	12	Etoposide	Rhabdomyosarcoma
Group B: adriamycin+cyclophosphamide or ifosfamide				
Cyclophosphamide:				
7	F	4	Vincristine	Rhabdomyosarcoma
8	F	12	Vincristine, prednisolone	Non-Hodgkin's lymphoma
9	F	5	Vincristine	Nasopharyngeal carcinoma
10	M	13	Vincristine	Rhabdomyosarcoma
11*	F	12	Vincristine	Rhabdomyosarcoma
12	F	6	Vincristine	Rhabdomyosarcoma
13	M	8	Vincristine	Rhabdomyosarcoma
14	M	15	Vincristine, prednisolone	Non-Hodgkin's lymphoma
Ifosfamide:				
15	F	16	Vincristine	Ewing's sarcoma
16	F	11	Vincristine	Ewing's sarcoma
17	M	12	Vincristine	Ewing's sarcoma
18	M	15	Vincristine	Ewing's sarcoma
19	M	14	Vincristine	Ewing's sarcoma
Group C: carboplatin				
20	M	8	—	Neuroblastoma
21	M	6	—	Astrocytoma
22	M	2	—	Astrocytoma
23	F	4	—	Neuroblastoma
24	M	4	—	Wilms' tumour
25	M	5	—	Neuroblastoma
26	F	15	Etoposide, bleomycin	Ovarian teratoma
27	M	15	Etoposide, bleomycin	Testicular teratoma
28	F	6	Etoposide	Medulloblastoma
29	F	8	Etoposide, bleomycin	Ovarian teratoma
30	M	9	Etoposide, bleomycin	Cerebral germinoma
31	M	2	Etoposide	Ependymoma

*Patient No 6 and 11 are the same child.

Table 2 Questionnaire

Day number:
(1) How would you assess your child's level of activity today?
Please grade as:
More active than usual
Same—as active as usual
Less active than usual
Very lethargic
(2) Please grade overall nausea as:
1=Not sick at all
2=A bit sick
3=Very sick
(3) How many times has your child vomited (been sick) today?
(4) How many times has your child retched (been sick without bringing anything up) today?
(5) How was your child's appetite today?
Please grade as:
1=Better than usual
2=As usual
3=Some solids
4=Liquids only
(6) Have any other symptoms upset your child today? If Yes, please explain.

Complete response=no vomiting, retching, or nausea. Major response=two or fewer episodes of vomiting, retching, or nausea. Minor response=three to five episodes of vomiting, retching, or nausea. Failure=more than five episodes of vomiting, retching, or nausea.

questionnaire given to the patient or family which documented the incidence of vomiting and severity of nausea (table 2). This evaluated symptoms daily for five days after starting treatment. Vomiting was evaluated and classified as a complete response (no vomiting), major response (one to two emetic episodes), minor response (three to five episodes). If there were five or more vomiting episodes in a 24 hour period ondansetron was regarded as having failed and alternative antiemetic treatment was given. Nausea, appetite, and general level of activity were documented over the next five days and scored as shown in table 2.

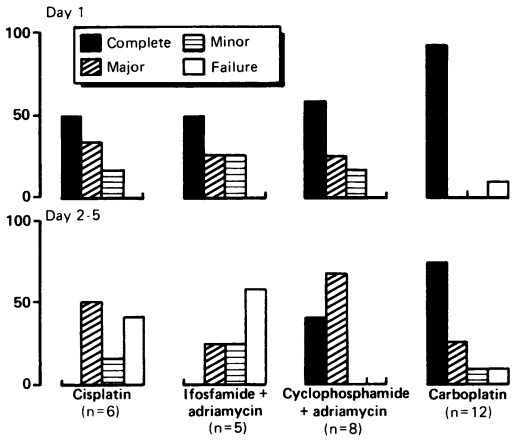
Written consent was obtained from patients after discussion concerning the experimental nature of the study and description of the potential side effects as reported in adults. The protocol was approved by the ethical committee of the Royal Marsden Hospital.

Results

Within the first 24 hour period after starting chemotherapy 11 out of 12 patients receiving carboplatin had a complete or major response, as did seven of the eight receiving adriamycin with cyclophosphamide. Three of six receiving cisplatin and four of five receiving ifosfamide/adriamycin had a complete or major response (figure). Beyond 24 hours antiemetic efficacy was maintained in the cyclophosphamide/adriamycin and carboplatin groups, but not with cisplatin or ifosfamide (figure). Significant vomiting and nausea developed in these patients despite continuing ondansetron. Three of six children on cisplatin and four of five on ifosfamide had 'late' emesis with three or more episodes of vomiting, retching, or nausea. Overall in 27 children (87%) ondansetron had a useful effect (complete or major effect) on day 1, whereas nine (30%) had significant emesis on days 2–5.

Adverse events are as listed in table 3. These were all regarded as minor and the relation to ondansetron was unclear due to the high incidence of similar non-specific symptoms in children after cancer chemotherapy.

There were transient rises in liver enzymes in



Percentage of patients responding with regard to time and treatment regimen.

Table 3 Symptoms reported on diary cards

Patient No	*Symptom*	*Day recorded*
	Group A: cisplatin	
1	Stomach cramp, diarrhoea	2
		2
3	Dizziness, weakness,	2
	sleepiness	2–3
		3
5	Diarrhoea, dizzy spells	3
		4
	Group B: adriamycin+cyclophosphamide or ifosfamide	
15	Headache	4
8	Headache	6
16	Abdominal pain	2–3
10	Withdrawn and quiet	2
	Group C: carboplatin	
20	Loose bowel movements	3

three patients (alanine aminotransferase 71 IU/l, alanine aminotransferase 130 IU/l, and γ glutamyltransferase 34 IU/l, respectively). A fourth child developed hepatitis while on chemotherapy with raised enzymes and bilirubin. The timing was not related to the administration of ondansetron and although no viral pathogen was isolated, this seems the likely cause. The liver dysfunction was transient.

Discussion

Ondansetron selectively binds to the 5-HT_3 functional receptor for 5-hydroxytryptamine (serotonin). These receptors are found predominantly in the gastrointestinal tract but have also been shown in the central nervous system. The antiemetic activity of 5-HT_3 antagonists has been demonstrated in the ferret and is probably a consequence of action on the intestinal tract.[4] The drug appears to be devoid of the classical extrapyramidal reactions associated with dopamine antagonists.

In addition to ondansetron two other 5-HT_3 antagonists have been studied in preliminary clinical trials. ICS205-930 (Sandoz) has been shown to have efficacy in patients receiving combination chemotherapy including cisplatin.[5] BRL43694 (Beecham) has similiarly been shown to produce complete abolition of emesis in about 50% of patients studied.[6 7] As with ondansetron the side effects reported in both adult volunteers and initial clinical studies were mild comprising mild sedation and occasional headaches. There has, however, been one case report of severe diarrhoea and flushing after ICS205-930.[8]

Cunningham *et al* first reported antiemetic activity in adults receiving anthracycline based regimens who were refractory to first line antiemetics.[2] Of 15 patients studied only one did not have a complete response. Several subsequent studies in adults have confirmed the efficacy of this drug and with most chemotherapy regimens a complete response rate in the region of 60% has been reported.[9–12] As might be predicted complete response rates have been somewhat lower for cisplatin based regimens.

A number of studies have evaluated the scheduling of ondansetron and a wide range of doses from 0·01 mg/kg to 0·48 mg/kg have been given as continuous infusions or pulsed administration with from three to eight hours between doses.[9 13–15] There have to date been no studies that clearly show which regimen is superior. There is evidence that doses of 0·18 mg/kg are superior to 0·01 mg/kg,[16] but further escalation seems to add little to efficacy.[15]

Pharmacokinetic studies in adults have shown a mean half life of four hours and mean bioavailability of an oral dose in the region of 70%.[10 13] In the present paediatric study an initial intravenous loading dose, similar to that given by Cunningham *et al*, was used and a subsequent oral dose every eight hours was given based upon surface area within limitations of tablet size. A total of five days' duration was chosen to try and avoid delayed vomiting as there were suggestions from preliminary studies in adults that despite good control during the first 24 hours late vomiting could occur.

The present study demonstrates the good tolerance of this agent with no sedation, no neurological side effects, and a high compliance rate. A transient rise in liver enzymes occurred in three patients but, because of the chemotherapy, it is impossible to be sure that this was related to ondansetron. There does seem to be evidence from healthy volunteers, however, that transient rises in liver transaminases may occur in a small proportion of patients.

The efficacy of the drug in treatment regimens given over a single day was very encouraging, with almost complete abolition of nausea and vomiting in most of those receiving the weekly VAC regimen ('Rapid VAC': vincristine, adriamycin, and cyclophosphamide) or single dose carboplatin, and in these patients delayed emesis was not a problem. Although the doses of adriamycin (40 mg/m^2) and cyclophosphamide (400 mg/m^2) are comparatively low, the 'Rapid VAC' regimen is usually emetogenic. Similarly, though carboplatin is usually better tolerated than cisplatin, in a number of patients vomiting had previously been poorly controlled with conventional antiemetic regimens.

The activity in cisplatin or divided dose ifosfamide regimens was disappointing. Although the antiemetic effect was reasonable, ~50%, during the first 24 hours, delayed symptoms were an important problem. This finding emphasises the importance of following

up patients beyond the first day after chemotherapy. Antiemetic studies often only report the activity of new drugs during this early period. For example, ondansetron (4–8 mg, every six hours) was shown to be effective in 10/12 adults receiving ifosfamide (4–6 g/m^2, infused over 24 hours) but follow up ended less than 24 hours after the end of chemotherapy.[17] This study design may give a false impression of the clinical usefulness of the agent as 'out of sight—out of mind'.

Whether changes in route or scheduling might improve the efficacy with cisplatin or ifosfamide regimens remains to be demonstrated. It has been suggested that the addition of dexamethasone may have value in refractory vomiting.[18]

Randomised studies in adults have suggested that ondansetron compared favourably with conventional and high dose metoclopromide in cyclophosphamide and cisplatin based regimens.[19 20] This pilot study indicates encouraging activity, particularly with single day regimens, and randomised studies in this group of patients are planned.

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