Clinical Note

Use of Ondansetron in Palliative Medicine

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Abstract
Ondansetron was the first of several selective 5- hydroxytryptamine (5-HT_3) antagonists to be available as an antiemetic. Its uses in the setting of highly and moderately emetogenic chemotherapy and radiotherapy are well established. Ondansetron has also been used to manage nausea and vomiting in other patients. We report a retrospective analysis of its use in all 16 patients who were commenced on ondansetron after admission to our institution for nausea and/or vomiting over a 4-year period. Nine patients had advanced human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS), and seven had malignancy. These patients were not undergoing disease-modifying treatment and had inadequate responses to therapeutic doses of standard antiemetics, used either singly or in combination. Responses were independently reviewed and graded by two investigators. Response was judged at 48 hr after commencing therapy. Potential causes of nausea were also reviewed. Overall, 13 of 16 [81%, 95% confidence interval (CI) 54%–96%] derived benefit. Twelve of 15 patients (80%) with nausea had a demonstrable improvement, and ten of 14 patients (71%) with vomiting also improved. Eight of ten patients (80%) admitted with nausea and/or vomiting as one of their presenting problems had the symptom controlled within 48 hr of ondansetron therapy. Treatment with ondansetron was well tolerated, onset of action was rapid, and response rates were high and sustained over time. Seven of the 16 patients continued ondansetron therapy for more than 10 days. With minimal reductions in inpatient bed stays, the total costs of ondansetron could be met while at the same time better supporting patients remaining in the community. J Pain Symptom Manage *1997;13:302–307.* © *U.S. Cancer Pain Relief Committee, 1997.*

Key Words
Ondansetron, palliative medicine, AIDS, vomiting, nausea

Introduction

Nausea and vomiting are frequently encountered symptoms in palliative medicine. Palliation can be difficult, and despite combinations of antiemetics, some degree of failure is frequent.

Ondansetron is the first of several selective 5-hydroxytryptamine (5-HT_3) antagonists available as an antiemetic. Its use in the settings of acute nausea and vomiting associated with highly and moderately emetogenic chemotherapy and radiotherapy to the upper abdomen are now well established.[1–3] More

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recently, randomized controlled trials have demonstrated its efficacy in single preoperative doses in the control of postoperative nausea and vomiting.[4] There are isolated case reports in the literature of good symptomatic responses to ondansetron in palliative patients who have not responded to standard antiemetics.[5–7] There are more recent reports of benefit in patients with pruritus secondary to cholestasis not responding to antihistamines or cholestyramine.[8]

Ondansetron is generally well tolerated. The main side effects are constipation and dose-related headache. Significantly, dystonic reactions are rare,[9] and sedation is absent. In short-term use, there is antiemetic synergism between ondansetron and dexamethasone when used following emetogenic chemotherapy.[10] There is no established role yet for the long term use of ondansetron.

Although not approved for use in a palliative setting, its use in these patients occurred in an inpatient setting for one of three reasons: a variety of antiemetics had been used without appreciable success, the patients themselves requested it having had a previous good experience with it during chemotherapy or radiotherapy, or it had been continued from a period of acute treatment elsewhere.

Methods

This study took place at the Sacred Heart Hospice, a 100-bed hospice in central Sydney associated with St. Vincents Hospital, a teaching hospital with major cancer and human immunodeficiency virus/acquired immunodeficiency syndrome (HIV/AIDS) units. The Hospice admitted 782 patients in 932 separate admissions in 1994 and saw 480 new patients through its community outreach service that same year. All medications were dispensed through a central pharmacy so that patients prescribed ondansetron were traced through pharmacy billing records.

The study had institutional Ethics Committee approval. Two investigators (D.C. and N.C.) independently reviewed the medical and nursing notes in the medical records of all patients identified as receiving ondansetron. This identified likely causes and graded nausea and/or vomiting at the time ondansetron was commenced and 48 hr after the first dose. The figure of 48 hr was chosen as an arbitrary figure based on our early clinical experience that those who were seen to derive benefit from ondansetron did so rapidly after treatment was initiated.

Fifty-three patients received ondansetron at our institution between its introduction in Australia in April 1991 and September 1995. Twenty-eight were admitted or commenced on ondansetron for previously accepted indications (moderate or highly emetogenic chemotherapy or radiotherapy to the upper gastrointestinal tract). Twenty-five patients (nine with malignancy and 16 with HIV/AIDS) were not receiving disease-modifying treatment, such as chemotherapy or radiotherapy.

We report here all 16 patients (seven with malignancy and nine with HIV/AIDS) who were commenced on ondansetron while in the Hospice. Complete data were available on all patients. All patients reviewed had received and were continuing various combinations of standard antiemetics. There were no reversible causes for the nausea, such as untreated hypercalcaemia or untreated cerebral metastases.

Costs were calculated as of June 1995. One inpatient bed-day in the hospice costs Aud $363. The price of ondansetron was the wholesale price to the hospital pharmacy of Aud $15.99 per 8 mg tablet.

Results

HIV Patients

Patient characteristics are summarized in Table 1, including previous treatment, likely causes of nausea and vomiting, and outcomes. All of these patients were on medications previously identified as being associated commonly with nausea and/or vomiting, and all had other factors that could not be excluded as causes for their symptoms.

All patients were receiving other antiemetics up to the time that ondansetron was commenced and all continued on at least one antiemetic with the ondansetron. In each case, combination antiemetics were tried before the use of ondansetron.

The dosage of ondansetron was a median of 16 mg per 24 hr in two or three divided doses (range, 8–24 mg). Therapy was continued for a median of 9 days (range, 4–110 days). Sur-

Table 1
Human Immunodeficiency Virus Patients

Age in years (median, 40.5; range, 31–57), all male	34	41	40	31	57	47	46	35	46
Identified as a problem on admission: 1. nausea and/or vomiting, 2. none	2	1	1	1	2	2	1	1	1
Factors thought to contribute to nausea: 1. drugs, 2. cerebral disease, 3. GIT pathology, 4. endocrinopathy, 5. uremia, 6. sepsis	1	1,3	1,6	1,3	1,3,6	1,2,3	1,3	1,3,4	1,3
Antiemetic therapy used: 1. prochlorperazine, 2. metoclopramide, 3. haloperidol, 4. meclozine, 5. domperidone, 6. cisapride, 7. thiethylperazine, 8. cyclizine,									
Therapeutic doses	1	4,5,6	4,6,7	4,5,7	2	1,2,3,4	2,3,4,5	1,2,3,4	1,2,3,6,8
As ondansetron commenced	1	5,6	4	4,7	2	2,3,4	3,4	1	3,8
Concomitant/continuing	1	6	4	6,4	3	3	3	1	3,8
Nausea/vomiting: 0–absent, 1–mild, 2–moderate, 3–severe									
Nausea before ondansetron	2	1	2	1	1	3	1	2	3
Nausea after ondansetron	1	0	0	1	1	0	0	1	1
Vomiting before ondansetron	1	2	2	2	1	3	1	1	3
Vomiting after ondansetron	1	1	1	2	1	0	0	0	1
Total 24-hr dosage ondansetron (mg), two to three divided doses	16	16	24	24	12	8	8	24	16
Duration of ondansetron (days) (median, 9 days; range, 4–110 days)	110	7	42	8	4	80	4	>17	11
Survival from commencing therapy (days) (median, 28 days; range, 8–245 days)	111	21	60	8	20	80	18	>245	35

GIT, gastrointestinal.

vival from the time of commencing ondansetron was a median of 28 days (range, 8–245 days).

Overall, seven of nine AIDS patients had improvement in their nausea. Six of the nine patients had improvement in their vomiting within 48 hr of commencing therapy. Two patients had no improvement in mild nausea or vomiting. Six of these patients had nausea and/or vomiting as one of their presenting complaints. Of the six, five had nausea and vomiting improve within 48 hr of commencing ondansetron.

Two of these patients had previous severe extrapyramidal reactions to antiemetics; one to both metoclopramide and prochlorperazine and the other to haloperidol. No adverse effects were attributable to ondansetron in this patient group, other than constipation in one patient.

Patients with Malignancy

Patient characteristics are summarized in Table 2. Again, the cause of the nausea was usually multifactorial. In one patient, morphine and flucloxacillin were commenced and coincided with the onset of nausea. Of the other six patients, five were on medications associated with nausea. Three patients had cerebral metastases. Four patients had significant gastrointestinal tract pathology that could have contributed to their nausea and/or vomiting. One patient was uremic and another had sepsis unresponsive to appropriate antibiotics.

All patients had tried at least two previous antiemetics alone and in combination at appropriate therapeutic doses before ondansetron was commenced. All continued at least one other antiemetic after commencing ondansetron. Three were on combination antiemetics when ondansetron was commenced.

The dosage of ondansetron was a median of 14 mg per 24 hr (range, 4–24 mg/24 hr) in one to three divided doses. The median duration of therapy in this group was 3 days (range, 3–42 days). Survival in this group from the time treatment commenced was a median of 4 days (range, 3–56 days).

Of the six patients with malignancy who had nausea, five improved after ondansetron was added. One patient had no improvement in mild nausea. Five patients with malignancy

Table 2
Malignancy Patients

Age in years, gender (median, 59; range, 47–84)	47F	84F	71M	49F	74M	52F	66F
Primary diagnosis	breast	pancreas	stomach	ovary	prostate	breast	ovary
Identified as a problem on admission: 1. nausea and/or vomiting, 2. none	1	2	1	1	1	2	2
Factors thought to contribute to nausea: 1. drugs, 2. cerebral disease, 3. GIT pathology, 4. endocrinopathy, 5. uremia, 6. sepsis	1,2	1,3	1,3,9	1,2,3	1	1,2	3,5
Antiemetic therapy used: 1. prochlorperazine, 2. metoclopramide, 3. haloperidol, 4. meclozine, 5. domperidone, 6. thiethylperazine, 7. cyclizine, 8. dexamethasone, 9. prednisolone							
Therapeutic doses	2,3,4,5,8	1,4	3,4,7	1,2,3,8	1,2,3	3,5,6,7,8	2,4
As ondansetron commenced	5,8	1	3,7	1,3,8	3	8	4
Concomitant/continuing	1,8	9	7	3,8	3	8	4
Nausea/vomiting; 0–absent, 1–mild, 2–moderate, 3–severe							
Nausea before ondansetron	1	0	1	1	1	1	2
Nausea after ondansetron	0	0	1	0	0	0	0
Vomiting before ondansetron	2	1	1	2	0	0	1
Vomiting after ondansetron	0	0	1	1	0	0	0
24-hr dosage ondansetron (mg) one to three doses	4	8	16	24	24	12	16
Duration of therapy (days) (median, 3 days; range, 3–42 days)	42	9	3	11	3	3	3
Survival from commencing therapy (days) (median, 4 days; range, 3–56 days)	56	13	3	13	4	4	4

GIT, gastrointestinal.

had vomiting, four of whom improved. Two patients had no vomiting, and one had no improvement in mild vomiting.

Four patients with malignancy had nausea and/or vomiting as a symptom on admission. All had been on at least three other antiemetics before commencing ondansetron, and three improved within 48 hr of commencing treatment.

No adverse events were noted in this group of patients on ondansetron.

Overall

This was a heterogeneous group of patients with advanced life-threatening illnesses. All had nausea and/or vomiting as a difficult-to-control symptom despite the use of routine therapies, alone and in combination, in therapeutic doses. Thirteen of 16 patients [81%; 95% confidence interval (CI) 54%–96%] derived benefit. Of the 15 patients with nausea as a symptom, 12 improved (80%; 95% CI, 52%–96%). Of the 14 patients with vomiting, ten improved (71%; 95% CI, 42%–92%). Eight of ten patients (80%; 95% CI, 44%–98%) admitted with nausea and/or vomiting as one of their presenting problems had the symptom controlled later within 48 hr of ondansetron treatment.

Despite relatively long-term usage (seven of 16 patients received ondansetron for more than 10 days), the treatment was well tolerated with no untoward events. Two patients discontinued treatment because they no longer had symptoms without the underlying cause of their nausea being definitely identified. Both had nausea return promptly and responded again when retreated with ondansetron.

The patients with HIV/AIDS in this study occupied 283 bed-days (Table 3). The total cost of their ondansetron was Aud $8752. Cancer patients had a total of 74 bed-days and incurred a cost of AUD $1415 for ondansetron.

Discussion

This group of patients had derived inadequate benefit from standard single or combi-

Table 3
Costs

Total bed-days of patients in series	Cost (Aud $) of bed-days (Aud $363/day)	Total cost (Aud $) of ondansetron (Aud $15.99/8 mg)	Ondansetron cost as a percentage of bed-day costs
HIV/AIDS patients 283	$102,729	$ 8752	8.5%
Malignancy patients 74	$ 26,862	$ 1415	5.2%
Total 357	$129,591	$10,167	7.8%

HIV, human immunodeficiency virus; AIDS, acquired immunodeficiency syndrome.

nation antiemetics. Treatment with ondansetron was well tolerated, and response rates were rapid, high, and sustained over time. There were no modifications to dose due to side effects despite the comparatively high maintenance doses used over long periods of time.

Published data have largely been concerned with ondansetron given as short courses for treating chemotherapy-induced nausea and vomiting. This retrospective study supports a role for this class of antiemetic medication in the management of nausea and/or vomiting in the palliation of patients with advanced cancer and HIV/AIDS, especially those who do not derive benefit from standard antiemetic agents in combination.

Cost is of concern with ondansetron, but cost must be interpreted in the widest possible sense.[11] In this group of patients, oral ondansetron was the only preparation used. Given the response rate, control of nausea and/or vomiting in the community will always be a far less expensive option than admitting someone to an inpatient unit. The total cost of ondansetron in HIV/AIDS patients was equivalent to the cost of 24.1 bed- days in our institution. If ondansetron could avoid one median stay in this patient group, or result in an overall reduction of bed stay of 8.5%, then this would pay for the use of ondansetron of the whole group. The total cost of ondansetron in cancer patients was equivalent to 3.9 bed-days (or equal to the shortest admission in this group). If there was a 5.2% decrease in bed-days because of more rapid symptom control of nausea and/or vomiting in this group, then this would pay for the use of ondansetron.

In this study, ondansetron was used as third- or fourth-line therapy. Given the response rate, its earlier introduction, even while patients are at home, may lead to substantial savings in inpatient costs. A prospective outpatient study is warranted using earlier intervention with ondansetron for nausea and/or vomiting in patients with life-threatening illnesses.

Conclusion

Although retrospective, this study captures accurate data as these facts are routinely and carefully recorded in the ongoing medical records of all patients admitted to our institution. Our experience suggests that ondansetron has a role to play in the treatment of difficult-to-manage nausea during life-threatening illnesses. It had a rapid onset of action in those patients who derived benefit from it (13 of 16), was well tolerated, and can be cost effective. There is a case for further studies of ondansetron in patients with nausea and/or vomiting at an earlier stage in their presentations, rather than as third- or fourth-line therapy when other combinations have failed.

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