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Papers

The Real Costs of Emesis—An Economic Analysis of Ondansetron vs. Metoclopramide in Controlling Emesis in Patients Receiving Chemotherapy for Cancer

D. Cunningham, M. Gore, N. Davidson, M. Miocevich, M. Manchanda and N. Wells

The cost effectiveness of ondansetron was compared with that of metoclopramide in the prevention of acute emesis due to highly emetogenic chemotherapy in an open, randomised, parallel group pilot study. Ondansetron was given as three 8 mg intravenous doses (0, 4 and 8 h) and metoclopramide as an intravenous loading dose (3 mg/kg) followed by a maintenance dose of 0.5 mg/kg/h for 8 h. Therapeutic outcomes and full utilisation costs, that is nursing time, material costs, in addition to drug acquisition prices were recorded for each antiemetic for 24 h following chemotherapy. The cost per successfully treated patient (≤ 1 emetic episode and no adverse events) was £95.20 for ondansetron and £92.18 for metoclopramide. The results of the study therefore suggest that for the control of acute emesis due to highly emetogenic chemotherapy ondansetron and metoclopramide are equally cost-effective treatments.
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INTRODUCTION

PATIENTS RECEIVING chemotherapy for cancer have ranked nausea and emesis as the most serious of the side-effects associated with such treatment [1]. For some patients these side-effects are so severe that they may refuse further courses of therapy [2]. Medication that is effective in controlling emesis can therefore be expected to play an important role in helping to reduce the distress that many patients suffer whilst receiving cytotoxic agents.

Chemotherapy-induced emesis (CIE) also has resource implications for the National Health Service (NHS). Caring for patients who experience this side-effect may not only draw significantly upon nursing time but may also require the use of additional material items, for example, clean bed linen, which also incur additional costs. It may be predicted that the magnitude of these costs will be inversely related to the effectiveness of the medication employed to control emetic responses to cytotoxic chemotherapy.

Therapeutic efficacy and full "utilisation" costs, i.e. nursing time and material costs in addition to basic drug prices, are important components of economic analyses which seek to quantify the overall resource consequences of choosing between alternative therapeutic regimens. Confining attention to drug acquisition costs alone will result in incomplete resource usage information, which, if employed in isolation to guide drug selection, may lead to an inefficient use of NHS funds.

Against this background, the present paper reports the results of a pilot study undertaken to explore the therapeutic outcomes and the total resource costs of ondansetron, one of a new class of agents which act by selective 5-HT_3 receptor antagonism, and metoclopramide in the prevention of acute emesis associated with highly emetogenic chemotherapy.

PATIENTS AND METHODS

The study was an open, multicentre randomised, parallel group study. The duration of the study was 24 h; all patients were hospitalised for this period. Patients were eligible for the study if they were aged 18 years or over and were receiving their first course of cisplatin (50–120 mg/m^2) or other highly emetogenic chemotherapy. Patients who had previously received chemotherapy treatment were also eligible for the study as long as they had not experienced chemotherapy-induced emesis on a previous course.

Patients were excluded if they had: a severe concurrent illness other than neoplasia; gastrointestinal obstruction; central nervous system metastases; received antiemetic therapy in the 24 h prior to chemotherapy; experienced vomiting in the 24 h prior to chemotherapy; experienced chemotherapy and/or radiotherapy-induced nausea and vomiting in previous courses of therapy; a known sensitivity to ondansetron. Patients were also excluded if they were thought or known to be pregnant or if they were receiving concurrent medication with benzodiazepines, except when given for night sedation or concurrent medication with antiemetics (corticosteroids were allowed if they were part

Correspondence to D. Cunningham.
D. Cunningham is at the Royal Marsden Hospital, Downs Road, Sutton, Surrey SM2 5PT; M. Gore is at the Royal Marsden Hospital, Fulham Road, Chelsea, London SW3 6JJ; N. Davidson is at the North Middlesex Hospital, Sterling Way, Edmonton, London N18 1QX; and M. Miocevich, M. Manchanda and N. Wells are at Glaxo Laboratories Limited, Stockley Park West, Uxbridge, Middlesex UB11 1BT, U.K.
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Table 1. *Resources*

Resource	Description
Antiemetic administration	Disposable materials used in the administration of the antiemetic, i.e. swab, needle, syringe, intravenous giving set and saline for injection.
Materials	Items consumed after an emetic episode or adverse event, i.e. mouthwash, linen, clothing.
Additional drugs	Drugs used for rescue antiemetic medication or in the treatment of adverse events.
Additional drug administration	Materials used in the administration of additional drugs.
Nursing staff	The time spent by nursing staff dealing with emetic episodes, adverse events and comforting patients. The following data were recorded as appropriate: time taken to administer and empty vomit bowl; administer bed bath; change linen; change patient's clothes and clean floor.
Medical staff	The time spent by medical staff dealing with emesis and adverse events.

Drug costs were derived from the Monthly Index of Medical Specialities February 1991 and the British National Formulary No. 19.
Staff average hourly rates—Department of Health.
Material costs—Health Service Costing Returns 1986/1987, with adjustments for inflation.

of the chemotherapy regimen or if they were for physiological supplementation).

The study was approved by the ethical committees of the participating hospitals and all patients gave written informed consent.

Patients were randomised to receive either ondansetron (8 mg intravenous at 0, 4 and 8 h postchemotherapy) or metoclopramide (3 mg/kg intravenous loading dose, followed by 0.5 mg/kg/h intravenous for 8 h).

The number of emetic episodes and details of adverse events were recorded by nursing staff. In addition the nursing staff recorded details of all materials used in the administration of the antiemetic; materials and "rescue" medication used to deal with emesis not controlled by the study drugs; medication used to treat adverse events; time spent caring for patients experiencing emesis and adverse events (Table 1). An emetic episode was defined as a single vomit or retch or any number of continuous vomits or retches. Emetic episodes were separated by the absence of vomiting or retching for at least 1 min.

Assessment of therapeutic outcome

The therapeutic outcome of antiemetic therapy was based on whether or not patients experienced (a) significant emesis and (b) an adverse event to the study medication. Significant emesis was defined as more than one emetic episode during the 24 h period. Combining these two criteria generated four mutually exclusive possible outcomes of treatment (Fig. 1). The most favourable outcome was that identified as pathway 1 where patients experienced no significant emesis and no adverse events. Patients were regarded as having been successfully treated if they achieved this outcome.

Utilisation costs

Full drug utilisation costs for ondansetron and metoclopramide were obtained by combining the acquisition price for each study drug with the expenditure on those items required to administer the two drugs, with the prices and administration costs of "rescue" medication and medication used to treat adverse events and finally with the material and nursing and medical time costs involved in caring for patients experiencing emesis or adverse events.

Cost per successfully treated patient

The cost per successfully treated patient was obtained for ondansetron and metoclopramide by dividing the mean drug utilisation cost per patient for each of the study antiemetics by the probability of being successfully treated (as defined above).

RESULTS

32 patients entered the study, 14 received ondansetron and 18 metoclopramide. Patients' characteristics are given in Table 2. The majority of patients in each treatment arm were men: 75% in the ondansetron arm and 72% in the metoclopramide arm. The groups were similar with respect to mean age and weight.

The results of treatment with ondansetron and metoclopramide in terms of the outcome pathways identified in Fig. 1 are shown in Table 3. 7 of the 14 (50%) patients who received ondansetron were successfully treated, that is they experienced at most, one emetic episode and no adverse events to the antiemetic (pathway 1, Fig. 1). In contrast, only 4 of the 18 (22%) patients who received metoclopramide were defined as successfully treated cases.

The median number of emetic episodes suffered by the ondansetron treatment group as a whole was one (range zero to seven) compared with four (range zero to nine) for those receiving metoclopramide.

2 of the 14 (14%) patients receiving ondansetron experienced

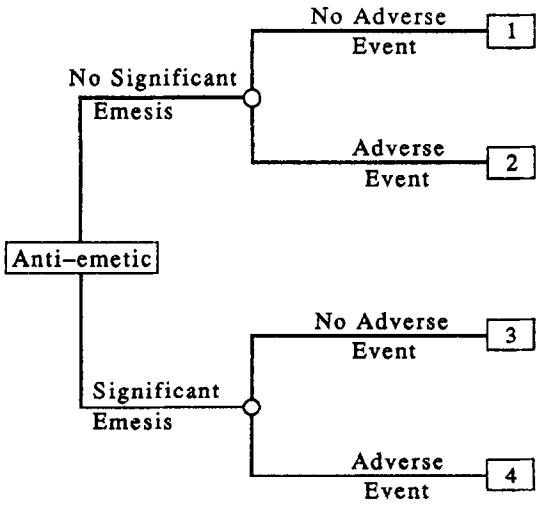

Fig. 1. Possible outcomes from antiemetic treatment.

Table 2. Patients' characteristics

	Ondansetron (n = 14)	Metoclopramide (n = 18)
Sex (male/female)	11/3	13/5
Mean age	49.8	55.7
Mean weight (kg)	74.6	68.0
Primary tumour*		
Haematopoietic	4	6
Lymphoma	2	2
Gastrointestinal	2	6
Skin	3	0
Head and neck	1	4
Gynaecological	0	1
Bone or soft tissue	1	0
Other	1	0
Chemotherapy		
Melphalan	4	5
Cisplatin alone	2	3
Cisplatin + others	7	9
Dacarbazine	1	0
Doxorubicin	0	1
Concurrent steroids	4	4

* Two primary tumours were recorded in 1 patient.

adverse events compared with 5 out of 18 (27%) in the metoclopramide group. In the ondansetron group, 1 patient suffered diarrhoea and a tingling sensation in the hands and arms and the other experienced tremor prior to vomiting. In the group that received metoclopramide 1 had abdominal cramps, 2 suffered diarrhoea—one of whom also had spasms through the legs and arms. A fourth patient was constipated and a fifth suffered transient hypertension, headache and photophobia.

Utilisation costs

The utilisation costs associated with ondansetron and metoclopramide are shown in Table 4. The mean utilisation cost associated with ondansetron treatment was £47.60; the corresponding figure for metoclopramide treatment was £20.28. The single most costly item in both groups was the cost of the antiemetic drug (£44.57/ondansetron patient; £11.91/metoclopramide patient). The administration costs of the antiemetic and the costs related to the nursing time spent caring for patients who experienced emesis and or adverse events were significant items of expenditure in the metoclopramide group.

Cost per successfully treated patient

The cost per successfully treated patient was £95.20 and £92.18 for the ondansetron and metoclopramide groups, respectively (Table 5).

Table 3. Outcome of antiemetic treatment for acute chemotherapy-induced emesis

Outcome	Ondansetron (n = 14)	Metoclopramide (n = 18)
1	7	4
2	0	2
3	5	9
4	2	3

Table 4. Mean drug utilisation cost in the first 24 h following chemotherapy

Resource item	Ondansetron (£) (n = 14)	Metoclopramide (£) (n = 18)
Antiemetic drugs	44.57	11.91
Antiemetic administration	0.26	3.74
Materials	0.73	0.59
Additional drugs	0.19	0.46
Additional drug administration	0.01	0.06
Nursing staff	1.84	3.34
Medical staff	0.00	0.18
Total	47.60	20.28

DISCUSSION

The aim of the present pilot study was to compare the cost effectiveness of ondansetron 8 mg intravenous (three doses) with metoclopramide 3 mg/kg intravenous loading dose followed by an 8-h intravenous maintenance infusion (0.5 mg/kg/h) in the prevention of acute emesis associated with highly emetogenic chemotherapy. The results of the study suggest that ondansetron and metoclopramide are equally cost-effective antiemetics.

A straightforward comparison of the basic NHS price of the daily doses of ondansetron and metoclopramide used in this study (8 mg intravenous three doses and 3 mg/kg intravenous loading, 0.5 mg/kg/8-h infusion, respectively) yields a price ratio of 3.7:1.0. This comparison dose not, however, take account of the wider ranging costs associated with the use of each agent. These broader utilisation costs comprise, in addition to basic drug prices, expenditure on the items employed in administering the antiemetic agents as well as the costs of the nursing time, materials and other drugs which arise when treatment fails and patients experience emesis and/or side-effects requiring intervention. When these additional resource requirements are taken into account the revised cost ratio between ondansetron and metoclopramide falls to 2.3:1.0.

The next stage in the analysis is to calculate cost-effectiveness ratios by relating the costs of using the two antiemetic agents to their associated therapeutic outcomes. The results of the present study demonstrate that the probability that an individual patient will be successfully treated, i.e. will experience no more than one episode of emesis in the 24 h following the administration of cisplatin or, similarly, emetogenic cytotoxic agents as well as no adverse responses to the antiemetic medicines, is 50% for ondansetron and 22% for metoclopramide. Dividing the full utilisation costs for the two antiemetic agents by these probabilities yields costs per successfully treated patient of £95.20 and £92.18 for ondansetron and metoclopramide, respectively. Consequently, the revised "true" cost ratio becomes 1.03:1.00.

Table 5. Cost-effectiveness ratios

	Ondansetron	Metoclopramide
Percentage of patients successfully treated	50	22
Cost per patient	£47.60	£20.28
Cost per successfully treated patient	£95.20	£92.18

These results indicate that the differential in acquisition price between ondansetron and metoclopramide was compensated for by the superior efficacy, lower incidence of adverse events, lower antiemetic administration costs and lower nursing staff and material costs associated with treatment with ondansetron. Moreover, the acquisition price of ondansetron, in this study, was based on three 8 mg intravenous doses. In patients receiving cisplatin (50–120 mg/m^2) containing chemotherapy, two recent studies have demonstrated that a single 8 mg intravenous dose is effective in controlling acute emesis [3, 4], thereby shifting the cost-effectiveness calculations positively in favour of ondansetron.

From a strictly economic viewpoint embracing all potential resource costs and therapeutic outcomes associated with the use of ondansetron and metoclopramide, the present study shows that the NHS would neither lose nor gain by selecting one of the antiemetic agents in preference to the other. However, the analysis does not take into account the very real benefits to patients of avoiding emesis, the side-effect identified by many individuals as the most distressing of those caused by cytotoxic chemotherapy. In this respect the findings of the present study indicate that ondansetron offers significant advantages over metoclopramide: patients receiving the former agent have a probability of successfully avoiding significant emesis that is more than twice that for individuals given metoclopramide.

Furthermore, analysis of the group of patients who experienced significant emesis with or without adverse events indicates that the ondansetron-treated patients experienced emesis to a lesser extent than the metoclopramide group: the median number of emetic episodes suffered by the ondansetron "failures" was only three compared with five for the "failed" metoclopramide cases.

Although conducted in a relatively small sample of patients, the present study has reiterated the need to assess the costs of different treatment options in the light of the outcomes they achieve if NHS resources are to be used efficiently.

Specifically, the study has shown that ondansetron and metoclopramide emerge as equally cost-effective antiemetic options when all utilisation costs and outcomes are taken into account, even though ondansetron carries a higher basic NHS price.

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Marginal Surgery and Postoperative Radiotherapy in Soft Tissue Sarcomas

The Scandinavian Sarcoma Group Experience

Tom A. Wiklund, Thor A. Alvegård, Henning T. Mouridsen, Anders Rydholm and Carl P. Blomqvist

In a randomised Scandinavian Sarcoma Group study (n=240) on the effect of postoperative adjuvant doxorubicin in high grade adult soft tissue sarcoma, 26 patients were treated with marginal surgery and postoperative radiotherapy. The protocol dose was 51 Gy in 17 fractions, or equivalent. Local recurrence occurred in 6 patients. Two local failures were geographical misses. Salvage treatment was ultimately successful in 3 of 4 attempted cases. 15 patients had complications, which in 3 cases necessitated amputation. These 3 patients had received the protocol fractionation and doxorubicin. However, other factors possibly responsible for the complication were also present.
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INTRODUCTION

CONSERVATIVE SURGERY combined with radiotherapy has been increasingly used in the management of soft tissue sarcomas (STS). Local control is achieved in 80–95% [1–3].

We report on a well-defined group of patients, included in a trial on adjuvant chemotherapy in high grade STS conducted by the Scandinavian Sarcoma Group (SSG) [4]. Patients with marginal surgical margins received postoperative radiotherapy. The recommended target dose was 51 Gy in 17 fractions over 24 days, or an equivalent dose based on CRE (cumulative radiation effect) formalism. This formula takes into account the total dose, the number of fractions and the total time of the radiotherapy.

The higher than conventional radiation dose per fraction was