Br. J. Cancer (1992), **66**, Suppl. XIX, S64–S67

Economic evaluation of ondansetron: preliminary analysis using clinical trial data prior to price setting

M.J. Buxton[1] & B.J. O'Brien[2]

[1]*Health Economics Research Group, Brunel University, Uxbridge, Middlesex, UB8 3PH, UK;* [2]*Department of Clinical Epidemiology and Biostatistics, McMaster University, Hamilton, Ontario, Canada L85 3Z5.*

Summary This study combines secondary analysis of efficacy and side-effect data from a randomised controlled trial with estimates of resource use to evaluate the likely economic effects of the new antiemetic agent ondansetron. Costs, effects and cost-effectiveness of ondansetron in the prophylaxis of acute nausea and vomiting induced by chemotherapy are assessed relative to antiemetic therapy with metoclopramide. Superior efficacy of ondansetron is quantified both in terms of significant emesis avoided and emesis management costs avoided. A simple cost analysis, with the metoclopramide dosage priced at £10, indicates that therapy with ondansetron would give equivalent net treatment costs, at a price ratio (ondansetron/metoclopramide) of 2.3 to 1. If therapeutic success is defined as the avoidance of emesis and antiemetic side-effects, then the two therapies would be equally cost-effective at a drug price ratio of 5 to 1. We conclude that, (i) economic evaluation prior to price setting is feasible and informative; (ii) such models can indicate prospective data collection priorities.

It is now widely accepted that the economic implications of new therapies need to be considered and that health care systems need to ensure that the scarce resources available to them are used effectively and efficiently. An increasing number of economic evaluations of health care interventions have been published, including studies relating to pharmaceutical products in general (e.g. Oster & Epstein, 1987; O'Brien *et al.*, 1990; Buxton *et al.*, 1991) and to the screening and treatment of cancer in particular (Levine *et al.*, 1985; Hillner & Smith, 1991).

The typical context of economic evaluation for a new pharmaceutical is when the product has been both approved by regulatory authorities (i.e. demonstrated safety and efficacy) and marketed at a particular price. In contrast to this post-marketing assessment, it is possible to undertake pre-marketing economic evaluation where the price of the new product has not yet been set, but data exist on other aspects of treatment costs and effects. An obvious use of such pre-marketing data is as an input into the process of determining appropriate pricing or reimbursement levels for the new drug, recognising that its cost-effectiveness, relative to the best alternative therapy is, in part, a function of its price.

This paper presents an example of a simple pre-marketing economic evaluation of the antiemetic ondansetron. The study combines secondary analysis of data from a large randomised trial with estimates of emesis management costs to determine the costs, effects and cost-effectiveness of ondansetron relative to metoclopramide in the prophylaxis of chemotherapy-induced emesis. These data are used to explore the relationship between the costs and cost-effectiveness of ondansetron and its price relative to metoclopramide.

Materials and methods

Available data on effects and side-effects

Data were available from a multicentre double-blind cross-over study by Marty *et al.* (1990) which compared the efficacy and safety of ondansetron versus metoclopramide in the prophylaxis of acute nausea and vomiting induced by cancer chemotherapy regimens containing cisplatin. The trial was a randomised crossover design with two treatment periods separated by a 3–4 week interval. Ondansetron was given intravenously in a loading dose (8 mg) before cisplatin administration and then in a continuous infusion (1 mg per hour) for 24 h. Metoclopramide was given intravenously in a loading dose (3 mg kg^{-1} body weight) before cisplatin and infused (0.5 mg kg^{-1} per hour) for 8 h; placebo was infused for the next 16 h. Cisplatin (80 to 100 mg per square metre) was given over a one-hour period, 30 min after the loading dose of the antiemetic.

Patients were of both sexes, hospitalised, aged 29–69, and had cancers with a variety of primary tumour sites. An interim analysis indicated superior efficacy of ondansetron and the trial was stopped early: a total of 76 patients who had received both drugs were available for analysis. The main measure of outcome was the frequency of emetic episodes (vomits plus wretches) in the first 24 h. As indicated in Table I, 57 of 76 treatments (75%) with ondansetron resulted in complete (no episodes) or nearly complete (one or two episodes) control of emesis compared to 32 of 76 treatments (42%) with metoclopramide, a difference that was statistically significant ($P < 0.001$). The incidence of adverse effects such as headache, sedation and diarrhoea was low and similar in both therapy groups.

Constructing a probability tree

Original patient-specific data from the trial were re-analysed for the purpose of constructing a simple probability tree for each therapy group: a diagram combining clinical and treatment events with their observed frequency of occurrence in the trial. Such schematic structuring of clinical problems is common in the literature of clinical decision analysis (Weinstein & Fineberg, 1980).

Table I Control of emesis in 76 patients by ondansetron and metoclopramide

Emetic Control	*Number of treatments (per cent)* *Ondansetron*	*Metoclopramide*
Complete (no episodes)	35 (46)	12 (16)
Nearly complete (1 or 2 episodes)	22 (29)	20 (26)
Partial (3–5 episodes)	8 (11)	16 (21)
None (>5 episodes)	11 (14)	28 (37)

Source: Marty, M. *et al.* (1990).
Note: Thus treatment with ondansetron results in complete or nearly complete control of emesis in 57/76 (75%) of treatments and hence in Figure 1 the probability of no significant emesis is 0.75.

Correspondence: M.J. Buxton.

The probability trees for ondansetron and metoclopramide are presented in Figure 1. These diagrams indicate the four criteria for partitioning each therapy data set are:

(i) the probability of suffering significant emesis (defined as greater than two episodes within 24 h);
(ii) the probability of suffering at least one significant antiemetic side-effect (includes all side-effects other than those rated as mild/minor effects by investigators);
(iii) the probability of this side-effect being treated (i.e. the proportion treated in the trial);
(iv) the probability that the side-effect is resolved (with or without treatment).

Applying these criteria partitions each antiemetic therapy group into ten mutually exclusive sub-groups corresponding to the branch endpoints of the trees, E1 to E10. Moving from left to right on each tree the total of 76 patients are progressively subdivided at each chance node (represented by circles). For example, on the ondansetron tree the endpoint E4 represents the two patients who experienced significant emesis, a significant side-effect which was not treated but did resolve. Therefore, based on this trial, there is a probability of 0.026 (2/76) that a patient will follow this course. Conversely it can be seen that the most probable outcome (probability = 0.67) is that a patient will experience no significant emesis or side-effect with ondansetron (endpoint E6).

Economic evaluation methods

The differential costs of managing chemotherapy-induced emesis with either ondansetron or metoclopramide are of two sorts: (i) costs which all patients incur such as the cost of the antiemetic drug itself; (ii) cost which occur for some but not all patients (i.e. are probabilistic). These latter costs are due to two general types of event: (i) response to individual emetic episodes; (ii) response (which may include additional prescribed therapy) to side-effects from antiemetic therapy.

Based on the regimens described in Gralla *et al.* (1987), the ex-manufacturer price for the metoclopramide-based course in this study is approximately £10. At this time no empirical data exist on the costs of managing emetic episodes. In the absence of reliable information, various cost assumptions have been made based, in part, on good nursing practice guidelines for emesis management (see Note 1). Explicit cost

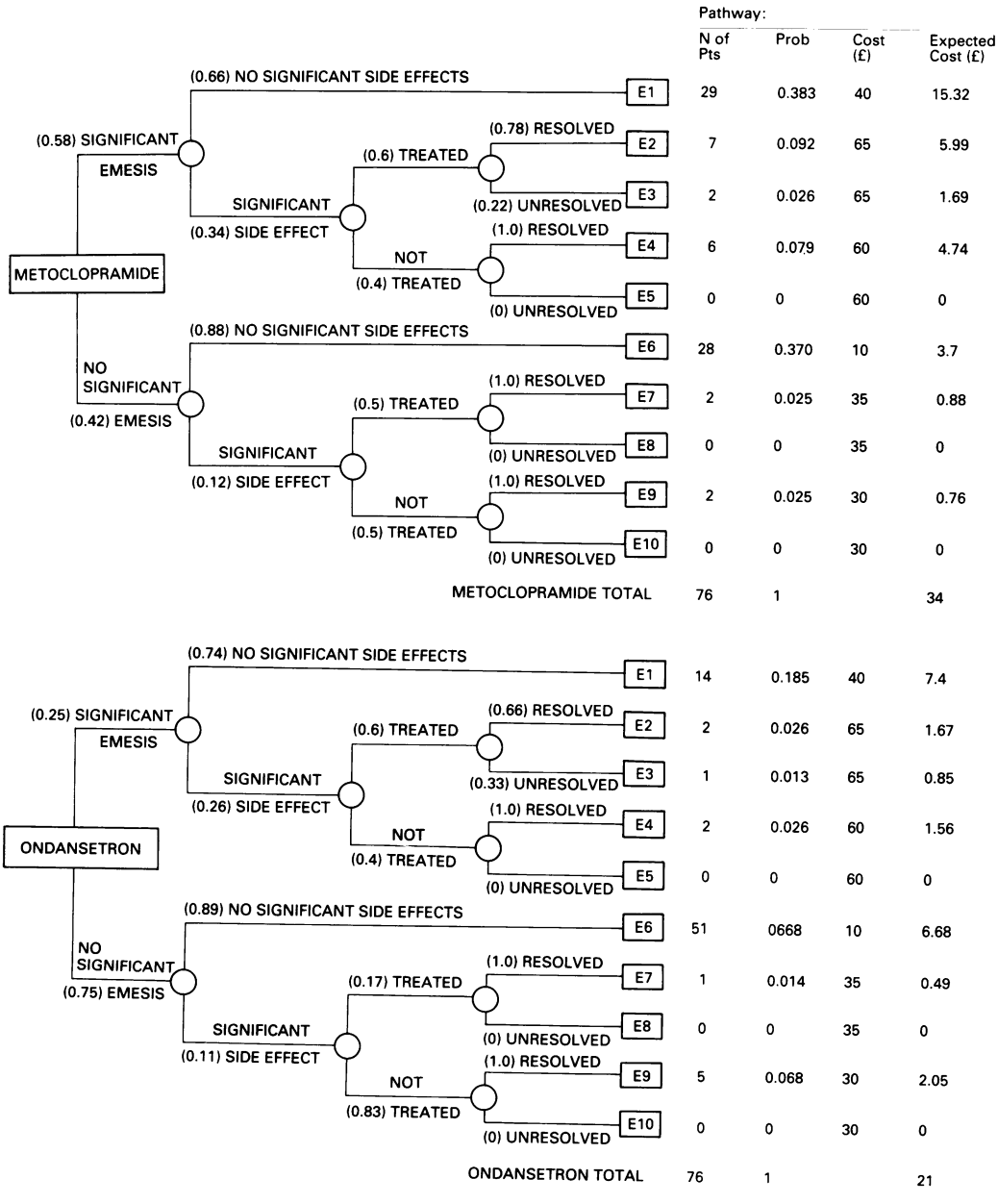

Figure 1 Probability trees for metoclopramide and ondansetron therapies. Seventy-six patients enter each therapy probability tree and are subdivided at chance nodes (0). The probabilities of events at chance nodes are figures in brackets which always sum to one.

assumptions are detailed (see Note 2) and these suggest: (i) the patient care cost of responding to significant emesis is approximately £30; (ii) the patient care cost of responding to a significant antiemetic side-effect is approximately £20; (iii) the cost of treating an antiemetic side-effect is approximately £5.

By combining estimates of the various costs associated with emesis and its management with incidence data embodied in the probability trees it is possible to determine the expected cost of emesis therapy for each group. Expected costs are simply costs weighted by their probability of occurrence or incidence. Thus in the metoclopramide probability tree a person reaching endpoint E4 will have incurred the costs of metoclopramide (£10) + the costs of emesis (£30) + the costs of side-effects (£20) = £60. However, the trial data indicate that the probability of this experience for any one patient receiving this drug is only 0.079 (six patients out of 76) and hence the expected cost for this branch is £4.74 (60 × 0.079). Summing the expected costs over all ten endpoints gives the total expected cost for antiemetic therapy with metoclopramide.

It should be noted that in the ondansetron tree, Figure 1, the cost of ondansetron has initially been assumed equal to metoclopramide (£10). Thus the observed difference in total therapy cost is simply a function of the costs of emesis and side-effect management.

There are various distinct forms of economic evaluation available (Drummond *et al.*, 1987). Two approaches were appropriate here. The first was a simple cost analysis. A threshold price for ondansetron was calculated at which price the expected costs of the two therapy groups are equal. At this price the extra cost of ondansetron itself, balances its savings from the costs associated with its lower level of emesis and side-effects.

The second method was cost-effectiveness analysis which compares therapies in terms of their cost per unit of effect. The expected costs for each therapy are defined as before. Therapeutic success (effectiveness) is defined here in two alternative ways: (i) as the number of patients with no significant emesis; (ii) more restrictively, as the number of patients with no significant emesis and no significant side effects. For each definition of effectiveness the price of ondansetron is found where the ratio of cost to effect for metoclopramide and ondansetron are equal.

Results

Cost analysis

Define the expected costs of antiemetic therapy with ondansetron, C_o, and metoclopramide, C_m, as the sum of antiemetic drug cost, $C(d)_o$, $C(d)_m$, (with ondansetron initially assumed equal to metoclopramide at £10), and the costs of emesis management, $C(em)_o$, $C(em)_m$, which vary according to the differential probabilities of events and their associated costs as detailed in Figure 1. Thus therapy costs can be expressed in two simple equations:

$$C_o = C(d)_o + C(em)_o \ (= £10 + £11) \text{ from Figure 1} \quad (1)$$

$$C_m = C(d)_m + C(em)_m \ (= £10 + £24) \text{ from Figure 1} \quad (2)$$

Holding emesis management costs and metoclopramide costs constant but allowing the price of ondansetron to vary, the problem is to find the drug cost ratio, R*, (ondansetron/metoclopramide), and implicitly the threshold cost of ondansetron, $C(d)_o$*, which equates treatment costs between the two groups ($C_m = C_o$). Rearranging equations 1 and 2:

$$R^* = \frac{C(d)_o + (C(em)_m - C(em)_o)}{C(d)_m} = \frac{C(d)_o}{C(d)_m} = 2.3 \quad (3)$$

Thus the drug price ratio (R*) which equates total costs for the two therapy groups is 2.3:1. Hence the use of ondansetron would be cost reducing up to the point where it was priced at 2.3 times that of metoclopramide at £10.

Cost-effectiveness

Using the same cost definitions, measures and notation, cost-effectiveness analysis is used to calculate the ratios of cost to effect (C/E) for the two therapy groups. Two alternative measures of effectiveness or therapeutic success are analysed: (i) with effectiveness defined as the number of patients, in each therapy group who did not experience significant emesis. Thus for ondansetron $E_o = 57$ (of 76) patients and for metoclopramide $E_m = 32$ (of 76) patients. When drug prices are equal ($C(d)_o = C(d)_m$) then the ratio of cost per unit effect is greater for metoclopramide. As before, the problem is to find the drug price ratio, $R^* = C(d)_o^*/C(d)_m$ which equates the ratios of cost to effect for the two therapies. Algebraically this can be expressed:

$$\frac{C(d)_o^* + C(em)_o}{E_o} = \frac{C(d)_m + C(em)_m}{E_m} \quad (4)$$

and hence

$$\frac{C_o}{E_o} = \frac{C_m}{E_m} \quad (5)$$

Substituting values into equation 4 and solving for the unknown $C(d)_o$*, and hence R*, yields a price ratio (ondansetron/metoclopramide) of 5.0:1 which achieves the equality in equation 5.

(ii) with effectiveness defined as the number of patients, in each therapy group who do not experience significant emesis and do not experience significant side-effects, for ondansetron $E_o = 51$ (of 76) patients and for metoclopramide $E_m = 28$ (of 76) patients. Performing the same calculations as in (i) the price ratio which equalises the ratios of cost to effect is marginally higher at 5.1.

These results are summarised in Table II. This table also gives details of how sensitive estimates are to alternative assumptions about the costs of emesis management. High estimates reflect a doubling of all cost assumptions (i.e. cost of responding to emesis of £60 rather than £30) and low estimates a halving of these assumptions.

Discussion

The results of these cost and cost-effectiveness analyses suggest that, given the therapeutic superiority of ondansetron in the avoidance of chemotherapy-induced emesis, ondansetron could be priced considerably higher than metoclopramide and still offer lower or equal net treatment costs, and at a still higher price ratio can offer lower or equal cost per unit of effect. This analysis provides preliminary estimates of these ratios and confirms that this approach offers a useful tool for pre-marketing economic evaluation.

The present estimates of the magnitude of the differences in net treatment costs, at various drug price levels, are sensitive to assumptions made about the costs of managing emetic episodes and treatment side-effects. The study used crude estimates, but empirical data are now being collected in a number of countries to cost more accurately emesis and associated effects. Additionally it would be important and

Table II Drug price ratios which give (i) net treatment cost equivalence and (ii) equalise ratios of cost per unit effect

		Price-ratios (R) (Ondansetron: Metoclopramide)*		
		Base case	*High costs*	*Low costs*
(i)	Cost minimisation:	2.3	3.5	1.6
(ii)	Cost-effectiveness:			
	Cost per success: no emesis	5.0	8.0	3.3
	Cost per success: no emesis and no side-effects	5.1	8.2	3.4

relatively easy to establish whether similar results would be produced from subsequent trials of ondansetron versus metoclopramide. Until the necessary trials are undertaken it would be difficult to establish the extent to which similar cost-effectiveness ratios hold true when the comparator is not a single agent, but the common practise of using antiemetics in combination.

This study does not embody any information about patient preferences for the avoidance of emesis and/or the side-effects of antiemetic therapy. Implicit in the definition of success for the cost-effectiveness analysis is the assumption that the avoidance of emesis is of equal value to patients as the avoidance of antiemetic side-effects. A more comprehensive study design would be cost-utility analysis where patient preferences would be elicited concerning the relative desirability of the various therapeutic pathways.

An interesting extension of the cost-effectiveness analysis would be to extend the focus of the study. Although patients may not view emesis as being the worst of all chemotherapy side-effects, some clinicians have argued that a bad emetic experience may reduce a patient's willingness to complete a sequence of therapies (Smyth, 1988). If longitudinal data were available on the relationship between non-completion due to emesis and long term survival then it might be possible to undertake cost-effectiveness analysis with deaths averted or life-years gained as the measure of effect.

This work was undertaken with financial support from Glaxo Holdings, and the authors thank Nick Wells for his helpful comments on earlier drafts.

Notes

(1) Hallet (1988) suggests that 'with each episode of vomiting the nurse must immediately supply a clean receptacle, a tooth brush and a mouthwash, a bowl for washing and often a change of bed linen and nightwear. Sometimes it is necessary to actually physically support a weak and drowsy patient. Protracted vomiting is in itself exhausting and may leave the patient dependent upon the nurse for help with all physical activities'.

(2) The detailed cost assumption are as follows:

Additional cost of dealing with emesis (per patient with significant emesis):	£
2 h of nursing time	10
Linen, disposables etc	5
20 min of junior doctor's time	3
0.1 probability of additional day's stay	12
Total	30

Additional cost of dealing with side-effects (per patient with significant side-effects):	£
1 h of nursing time	5
20 min of junior doctor's time	3
0.1 probability of additional day's stay	12
Total	20

Additional cost of treating side-effects (per patient who receives treatment):	£
20 min of junior doctor's time	3
Drug costs	2
Total	5

References

BUXTON, M.J., DUBOIS, D.J., TURNER, R.R., SCULPHER, M.J., ROBINSON, P.A. & SEARCY, C. (1991). Cost implications of alternative treatments for aids patients with cryptococcal meningitis. *J. Infect.*, **23**, 17–31.

DRUMMOND, M.F., STODDART, G.L. & TORRANCE, G.W. (1987). *Methods For Economic Evaluation of Health Care Programmes*, Oxford University Press: Oxford.

GRALLA, R.J., TYSON, L.B., KRIS, M.G. & CLARK, R.A. (1987). The management of chemotherapy induced nausea and vomiting. *Med. Clin. North Amer.*, **71**, 289–300.

HALLETT, N. (1988). Vomiting – a nurse perspective. *Clinician*, **6**, 22–25.

HILLNER, B.E. & SMITH, T.J. (1991). Efficacy and cost-effectiveness of adjuvant chemotherapy in women with node-negative breast cancer. *New Engl. J. Med.*, **324**, 160–168.

LEVINE, M.N., DRUMMOND, M.F. & LABELLE, R.J. (1985). Cost-effectiveness in the diagnosis and treatment of carcinoma of unknown primary origin. *Can. Med. Assoc. J.*, **133**, 977–987.

MARTY, M., POUILLART, P., SCHOLL, S. *et al.* (1990). Comparison of the 5-Hydroxytryptamine$_3$ (serontonin) antagonist ondansetron (GR38032F) with high-dose metoclopramide in the control of cisplatin-induced emesis. *New Engl. J. Med.*, **322**, 816–821.

O'BRIEN, B.J., BUXTON, M.J. & KHAWAJA, H.T. (1990). An economic evaluation of transdermal glyceryl trinitrate in the prevention of intravenous infusion failure. *J. Clin. Epidemiol.*, **43**, 757–763.

OSTER, G. & EPSTEIN, A.M. (1987). Cost-effectiveness of antihyperlipemic therapy in the prevention of coronary heart disease. *JAMA*, **258**, 2381–2387.

SMYTH, J.F. (1988). The problem of emesis induced by cancer chemotherapy. *Clinician*, **6**, 2–12.

WEINSTEIN, M.C. & FINEBURG, H.V. (1980). *Clinical Decision Analysis*, W.B. Saunders: Philadelphia.