Anti-Cancer Drugs 1995, **6**, pp. 243–249

Cost effectiveness of 5-hydroxytryptamine$_3$ receptor antagonists: a retrospective comparison of ondansetron and granisetron

Neil Johnson[1] and Nick Bosanquet[2]

[1]Cambridge Pharma Consultancy, 1 Quayside, Bridge Street, Cambridge CB5 8AB, UK. Tel: (+44) 223 350553; Fax: (+44) 223 315115. [2]St Mary's Hospital Medical School, Imperial College of Science, Technology and Medicine, University of London, Norfolk Place, London, UK.

As clinical and economic analyses to date have shown clear benefits of using the new 5-hydroxytryptamine$_3$ receptor antagonists (5-HT$_3$RAs) over traditional antiemetics, the choice between them may necessitate the assessment of comparative cost-effectiveness. This paper presents the results of an assessment of the relative cost-effectiveness of two current 5-HT$_3$RAs: ondansetron and granisetron. The analysis was based on a retrospective assessment of the cost and effectiveness (defined as no vomiting and no worse than mild nausea) of these new antiemetics. Efficacy data were based on the results of two recently published directly comparative clinical studies of ondansetron versus granisetron in the treatment of chemotherapy-induced emesis following both single-dose and fractionated chemotherapy. The cost of treatment was derived by combining clinical data from these studies with manufacturers' drug prices, and published costs of drug administration and emetic episodes. Costs for inpatient stay and side-effects were assumed to be equal across both treatment alternatives. The results were expressed in terms of the total cost per patient of emetic treatment and the cost per well-controlled patient. On this basis, granisetron was found to be more than 50% more cost-effective than ondansetron. This result was robust to variation in key assumptions concerning efficacy and cost, although ondansetron would become the more cost-effective if the dose was reduced to one 8 mg i.v., with no concomitant loss of efficacy.

Key words: Antiemetics, cost-benefit analysis, economics, granisetron, ondansetron.

Introduction

Over the last few years, there has been considerable debate concerning the merits of the new generation of antiemetics: 5-hydroxytryptamine$_3$ receptor antagonists (5-HT$_3$RAs).[1–4] Three 5-HT$_3$RAs have been launched to date in Europe: ondansetron, granisetron and tropisetron. Although the use of these compounds is becoming widespread, comparative evaluation of their costs and benefits has yet to be conducted.

Clinical trials have shown that these agents are, in certain circumstances, more efficacious and less toxic than more traditional treatments, such as metoclopramide, in reducing nausea and vomiting following cytotoxic therapy.[5–7] Such agents therefore confer a significant benefit on the patient in terms of improved quality of life.[8,9] Thus, although the drugs are more costly to acquire, if used appropriately the increased efficacy and improved quality of life for the patient ensures the additional benefit of these new drugs outweighs the additional cost.[1,4,10–15]

Given that the use of 5-HT$_3$RAs is cost-additive to hospital budgets, decision makers need to know how these new and important drugs can be used in the most cost-effective manner.[16] Decisions over which drug to use, at which dose and when, requires comparative studies of *both* the clinical and economic aspects of these new therapies. With the recent publication of comparative *clinical* trials, it is now important that comparative *economic* studies are conducted of these new antiemetics.[17–20]

A comparative economic evaluation should consider the full resource implications of drug use. In the case of 5-HT$_3$RAs, it is therefore inappropriate to limit comparison to the acute emetic phase over the first 24 h, as there is evidence that there is significant potential resource utilization in days subsequent to chemotherapy.[3] In view of this, clinical studies of acute emesis alone do not provide sufficient data for a full economic evaluation to be conducted.

The primary objective of this paper was to take a broad overview of the relative cost-effectiveness of the two market leaders, ondansetron and granisetron. The analysis was based on published effec-

Financial support for this research was provided by SmithKline Beecham Pharmaceuticals.

Correspondence to N Johnson

tiveness and cost data, allowing comparability and providing the first step towards assessing the *relative* value of these two drugs. Sensitivity analysis was used to assess the applicability of the results at different European prices, and to test the robustness of the results to possible variation in dose and efficacy.

Methods

Effectiveness

The effectiveness measure used for analysis was the degree to which each therapy completely controlled nausea and vomiting (defined as no vomiting and no worse than mild nausea). Analysis was not conducted by nausea or vomiting alone, nor at less than complete control, as it was felt that, clinically, complete control was the most appropriate endpoint.[16]

The effectiveness of each drug at particular dosages was based on two recently published directly comparative clinical studies comparing ondansetron and granisetron; one study was independently financed[17] and the other was financed by Glaxo, the manufacturer of ondansetron.[18] These studies are described below briefly.

As the analysis was intended to provide a broad overview of the cost-effectiveness of ondansetron and granisetron, the primary criteria for choosing these two studies was that one study considered single-dose chemotherapy and one fractionated. As mentioned earlier, the possibility of significant resource utilization in days subsequent to chemotherapy meant that it was important that the single-dose chemotherapy study covered a full 5 days, and not just the initial 24 h. Two other recently published comparative clinical trials could therefore not be considered in the analysis, as they only assessed emesis over a 24 h period.[19,20]

Bonneterre and Hecquet (henceforth Bonneterre) conducted a randomized cross-over study comparing ondansetron and granisetron as antiemetic therapy in 175 chemotherapy naive patients receiving their two first cycles of single dose moderately emetogenic drugs.[17] The study population was predominantly female. Treatment and incidence of nausea and vomiting was assessed over a 5 day period. Ondansetron was administered as an initial dose of 8 mg i.v., then 8 mg orally every 8 h for 3 days (a total of nine tablets), while granisetron was administered as a single dose of 3 mg i.v. These doses followed the approved regimen for France (which for ondansetron have subsequently been reduced by one oral dose per day). Two groups were used in the analysis: complete responders (no nausea or vomiting) and non-responders (all others). A total of 150 patients completed the study. There was no statistically significant difference in treatment compliance between the groups. Over the 5 day period, complete control of nausea and vomiting was achieved in 56.7% of ondansetron-treated patients and in 59.4% of granisetron-treated patients.

Noble *et al.* (henceforth Noble) conducted a double-blind, randomized cross-over study also comparing ondansetron and granisetron as antiemetics in cancer chemotherapy.[18] Patients receiving two cycles of identical chemotherapy fractionated over 5 days were given either ondansetron (8 mg three times daily) or granisetron (3 mg plus two placebo infusions daily) on each day of chemotherapy, administered i.v. A total of 359 patients were recruited from 46 centers in six countries, predominantly France. Of these patients, 309 completed the crossover trial, with primary efficacy defined as complete response (no vomiting, no worse than mild nausea and no rescue medication) over 5 days. The study population was predominantly male. Each intravenous infusion lasted 15 min and was given initially 5 min prior to chemotherapy. Further doses of ondansetron or placebo were then administered at 8 and 16 h. The results showed that, averaged over the 5 days, complete control of nausea and vomiting was achieved in 39.8% of ondansetron-treated patients and in 44% of granisetron-treated patients.

In both these studies the difference in efficacy between ondansetron and granisetron was not statistically significant. Although equal efficacy is addressed in the sensitivity analysis, the numerical difference was used in the evaluation of cost-effectiveness as a pragmatic means to address the costs of failure. This is described in more detail below.

Costs

The average total cost, per patient, of each antiemetic treatment comprises the cost of: antiemetic drugs; intravenous administration; inpatient stay; attending and treating side-effects; and attending and treating failures (those with breakthrough emesis). The unit costs, expressed in French Francs (FF), of each of these items used in the analysis is outlined below.

Antiemetic drug costs were based on French prices, as presented in Table 1. French prices were

used as the basis for analysis as the patient populations upon which the effectiveness data were based were predominantly French. As manufacturers' list prices were used, the relative cost-effectiveness of the treatment options will be influenced by differentials across European markets, both in terms of the list price and discounts which may be available for different products. Thus, manufacturers' list price for eight European markets is presented in Table 1, and assessment of the impact of these price differentials, and differentials in discount, is provided in the sensitivity analysis.

The unit cost of administering an i.v. dose was considered to be FF2.17. This estimate comprises disposable materials used in the administration, such as swab, needle, syringe and intravenous giving set.[12,21] Although this cost is based on an assessment made for ondansetron, it was assumed that administering granisetron would cost (at least) no more, as it is a lower dose drug. A zero cost was assumed for administering oral ondansetron.

Inpatient stay was not included in the cost of treatment; there is no reason to assume that the proportion of patients requiring inpatient stay would be different between the two treatments. Similarly, in the studies providing the basis for the efficacy data, the proportion of patients experiencing side-effects was found not to be significantly different across treatments.[17,18] Thus, the cost of treating side-effects was also assumed to be equal across treatments.

Ideally, failures (patients who experience *any* vomiting) should be assessed by the average number of emetic episodes per patient per treatment. However, there are insufficient data to perform such analyses in either paper considered.[17,18] Bonneterre does not consider the number of emetic episodes explicitly and Noble only reports that proportion experiencing zero or more than four vomits. From these data it is assumed for the analyses presented here that, where emesis occurs, patients will experience, on average, two emetic episodes in each 24 h period. There is no difference assumed in the number of episodes between treatments.

For these emetic episodes, there are two costs to be considered: attending the emetic episode and administering further drugs to treat the emesis. The unit cost of attending an emetic episode was considered to be FF250. This comprises the medical and nursing time required, for example, to administer and empty a vomit bowl, consumables such as linen, mouthwash and clothing, and the probability of extra days stay in hospital.[11,12] It does not include any additional cost incurred in administering further antiemetic drugs to treat breakthrough emesis. There is little available information concerning such additional doses in either of the above studies.[17,18] Although, for example, the *proportion* of patients requiring rescue medication may be equal between treatment groups, the *number* of doses used for breakthrough may not be. Consequently, the use of additional medication is only addressed in the sensitivity analysis, where the impact of one or two additional doses per treatment day is assessed.

Results

There are two sets of results concerning the cost and effectiveness of each antiemetic: those using Bonneterre as the basis for analysis and those using Noble.

The average total cost per patient (Table 2, column 1) is derived by multiplying the unit price of

Table 1. Manufacturers' list price for each antiemetic by market

Country	Unit price (FF)			Exchange rate for french francs
	Ondansetron (8 mg)		Granisetron (3 mg)	
	i.v.	oral	i.v.	
France	**150**	**90**	**265**	—
Austria	144	81	240	0.48
Italy	79	49	140	0.003
The Netherlands	191	100	191	3.040
Portugal	124	68	182	0.033
Spain	101	63	175	0.041
Switzerland	140	65	192	4.004
UK	98	59	262	8.33

Table 2. Average total cost per treated and per well-controlled patient

Study/period	Cost/treated patient		Efficacy rate (%)		Cost (FF)/well-controlled patient	
	ondansetron	granisetron	ondansetron	granisetron	ondansetron	granisetron
Bonneterre	1236	507	57	59	2179	854
Noble	3787	2735	40	44	9515	6217

each drug (as shown in Table 1) by the dose used. This is then combined with the cost of administering a dose and of treating those patients experiencing breakthrough emesis.

For example, for the analysis based on Bonneterre, the cost of antiemetic medication is simply one 3 mg dose of granisetron (FF265) or one 8 mg i.v. dose plus nine 8 mg oral doses of ondansetron (FF960). As each only requires one i.v. administration, this cost is the same for each (FF2.17). The average cost of attending emesis is calculated from the proportion of patients experiencing emesis, multiplied by the cost of attending to two emetic episodes. Thus, for ondansetron the proportion of patients experiencing emesis is 54.7%, and so the average cost of emesis per patient is therefore FF273 (0.547 multiplied by FF500). (For granisetron, the cost of emesis is FF240.)

The average total cost per patient for those treated with ondansetron is therefore FF1236, and for granisetron is FF507. This means that, for instance, if 100 patients were treated then, based on Bonneterre, the total cost of treating these patients would be FF123600 if treated with ondansetron and FF50700 if treated with granisetron.

However, not all these patients will be well controlled and as such it will cost more to attain a well-controlled patient with each treatment option. To assess this, the total cost per treated patient was combined with efficacy rates (Table 2, column 2) to assess the cost per *well-controlled* patient (no vomiting and no worse than mild nausea). This is shown in the third column of Table 2. The cost per well-controlled patient is simply the cost per treated patient divided by the efficacy rate. This calculation therefore distributes the total cost across that proportion of patients successfully treated. For instance, at an efficacy rate of 50%, in order to achieve a well-controlled patient, two patients will require treating, on average. Thus, the cost per well-controlled patient would be twice that of the cost per treated patient (as it is the average total cost per patient divided by 0.5).

In the analyses presented here, granisetron is more cost-effective than ondansetron. Based on Bonneterre, the cost to achieve a well-controlled patient with granisetron is less than half that of using ondansetron. Based on Noble, granisetron is more than 20% less costly than ondansetron in achieving a well-controlled patient.

Sensitivity analyses

The results of the cost-effectiveness analyses are dependent on the efficacy of each drug in controlling nausea and vomiting, and the cost of treatment with each drug therapy. With respect to the relative costs of ondansetron and granisetron, there are four main variables of influence: (i) differences in the list prices of each drug in different countries; (ii) differences in the discounted price of these drugs for individual hospitals or purchasing groups; (iii) differences in the dosing schedule of each drug; and (iv) differences in the number of additional doses required to deal with breakthrough emesis.

The robustness of the results, and their applicability to clinical practice, was tested in relation to independent changes in all the above variables.

Relative efficacy

The relative efficacy of each drug in achieving complete control of nausea and vomiting is subject to some variation in published clinical studies.[22–24] At the efficacy rates reported in Bonneterre and Noble, granisetron is more cost-effective than ondansetron. However, as neither study showed a statistically significant difference in efficacy, equal efficacy for ondansetron and granisetron was considered. This was achieved by holding the efficacy of granisetron constant and increasing the efficacy of ondansetron. This reduces the cost per well-controlled patient using ondansetron. However, the magnitude of this reduction is small. For the Bonneterre study, the cost per well-controlled patient using ondansetron falls from FF2179 to FF2080. For the Noble study, the reduction is from FF9515 to FF8607. In each case, granisetron is still the most cost-effective option.

Drug list price

The impact of different list prices was tested by assessing the relative cost-effectiveness of the two drugs at a range of current European list prices (Table 1). Table 3 shows the *additional* cost, above costs for granisetron, to achieve a well-controlled patient with ondansetron. One can see that, at prices in all countries considered, granisetron was found to be more cost-effective than ondansetron.

Price discounts

Differential discounts in the purchase price of these drugs would have an impact on their relative cost-effectiveness. However, for both analyses, even if the hospital list price for ondansetron is discounted by 50% *more* than the discounted price for granisetron, granisetron will still be more cost-effective.

Dosing schedule

The conclusions of the analysis change with variation in the dosing schedule. Such variation may be due to change in the daily dose of each antiemetic, and/or a change in the length of treatment. Here the analysis is presented for a reduction in the daily dose of ondansetron relative to granisetron. Table 4 illustrates the variation in dosages considered for ondansetron (holding granisetron constant) and the resultant cost per well-controlled patient. In each case granisetron remains the most cost-effective option until the dose of ondansetron falls to just one 8 mg i.v. dose, with no reduction in efficacy.

This result raises issues concerning the efficacy of different doses of ondansetron. There is mixed evidence concerning both the relative efficacy of 8 versus 32 mg of ondansetron, and the relative efficacy of 8 mg of ondansetron versus 3 mg of granisetron.[5,19,20,25–27] Whether lower doses of ondansetron are as efficacious as higher doses, or 3 mg of granisetron, is debatable. If efficacy does fall with reduction in dose, then whether ondansetron becomes more cost-effective depends on the relative rate of decline of efficacy and dose levels.

Table 3. Extra costs (FF) of achieving a well-controlled patient with ondansetron over granisetron across Europe

Country	Bonneterre	Noble
France	**1325**	**3298**
Austria	1214	3356
Italy	760	2043
The Netherlands	1681	5684
Portugal	1070	3262
Spain	962	2474
Switzerland	1034	3751
UK	747	1373

Use of rescue medication

The costs of treatment will also depend on the use of additional antiemetic doses to treat breakthrough emesis. Here the use of one and two extra doses was considered. For both ondansetron and granisetron, an extra i.v. dose was considered to be administered. For analysis based on Bonneterre, the doses were all assumed to be administered on day 1. For Noble, they were assumed to be administered on each day of treatment. The results are presented in Table 5. Granisetron remains the most cost-effective antiemetic whether one or two extra doses are administered.

Discussion

The clinical approach to chemotherapy-induced nausea and vomiting has been significantly altered by the introduction of 5-HT_3RAs. The efficacy of these agents in acute emesis is clear (although this benefit has yet to be shown in delayed emesis) and it is the economic impact of the alternative therapies that will largely determine their acceptance.[16] Our analysis has shown that, based on the dosages used in recent clinical studies, granisetron is more cost-effective than ondansetron; a result which is robust to variation in key assumptions concerning efficacy and cost.

The variable of critical concern to the analysis is the dosing schedule. In the analysis presented here,

Table 4. Cost per well-controlled patient at different doses of ondansetron

Study	Dose of ondansetron	Cost (FF)/well-controlled patient
Bonneterre	8 mg i.v. plus six 8 mg doses orally	1703
	8 mg i.v. plus three 8 mg doses orally	1227
	8 mg i.v. only	751
Noble	8 mg i.v. twice daily	7630
	8 mg i.v. daily	5746

Table 5. Cost per well-controlled patient with one and two extra doses of antiemetic per day to treat breakthrough emesis.

Study/period	Cost/well-controlled patient (FF)			
	one extra dose		two extra doses	
	ondansetron	granisetron	ondansetron	granisetron
Bonneterre	2447	1303	2716	1753
Noble	11 426	9252	13 338	12 288

ondansetron becomes the more cost-effective antiemetic if the dose is reduced to one 8 mg i.v.; with this being conditional on efficacy being retained. However, the effectiveness of these drugs is dependent on a range of extraneous factors, such as the patients age and sex, previous susceptibility to motion sickness and/or sickness in pregnancy, and emetogenicity of cytotoxic treatment. Thus, treatment efficacy for each patient cannot be predicted accurately and choosing the optimal emetic dose is difficult. There is conflicting evidence, for example, over the relative efficacy of varying doses of ondansetron.[5,16,19,20,25,26] In this case it is likely that doses at the higher end of the recommended range should be used in clinical practice.[28]

In making a comparative assessment of these different treatments, there are two additional important considerations which have not been considered in the analysis.

First, the use of dexamethasone in conjunction with either drug has not been considered.[29] It is assumed that any increased efficacy that could be achieved with dexamethasone would result in a similar increase in the cost-effectiveness of both drugs. Further clinical study is required in this area before it can be built in to any economic assessment.

Second, we have not considered patients' preference over treatment alternatives. Two recent studies have found that a preference was expressed for granisetron.[18,19] One reason postulated for this is a more convenient dosage schedule for granisetron.[19] One may expect this preference to be amplified by routine clinical practice, where granisetron would be given as a single injection and ondansetron may involve multiple injections. However, patient preference cannot as yet be incorporated in an economic evaluation of antiemetic therapy, as there is no indication of the *strength* of such preference.[30] As granisetron has been shown in this analysis to be the more cost-effective antiemetic, the addition of patient preference in a quantifiable way will simply serve to reinforce this economic advantage.

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(Received 16 December 1994; accepted 18 January 1994)