« Cost Effectiveness of Ondansetron and Metoclopramide in the Treatment of Post-Operative Nausea and Vomiting in Patients Undergoing Elective Surgery »

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ABSTRACT

The cost effectiveness of intravenous ondansetron 4mg and intravenous metoclopramide 10 mg in the treatment of post-operative nausea and vomiting (PONV) was assessed in a prospective, randomised, double-blind, parallel-group study in 60 hospital centres in France. Seven hundred and forty-six adult in-patients who experienced PONV within six hours of recovery from general anaesthesia were recruited. The incidence of PONV and the direct medical resources used to treat it were collected for 24 hours after administration of treatment. The primary outcome measure was the incremental cost-effectiveness of ondansetron (additional cost of successful treatment). Mean cost effectiveness (the mean cost of successful PONV management) was also calculated for both treatments. Successful treatment was defined as no symptom of PONV. Costs were evaluated from the hospital perspective. The mean cost of successful PONV management per patient was 87.98 FF for ondansetron and 70.86 FF for metoclopramide. Incremental cost effectiveness demonstrated that an additional 17.12 FF will give each patient a 15.1% improved chance of complete control of nausea and vomiting. This is less than the difference in the acquisition cost (52.11 FF) between the two drugs. The mean cost effectiveness ratio was 190.43 FF for ondansetron and 227.85 FF for metoclopramide. The cost effectiveness ratio was lower for ondansetron because the improved effectiveness and lower cost of PONV management outweighed the increased drug acquisition cost.

Keywords : ondansetron, metoclopramide, nausea and vomiting, surgery, cost-effectiveness.

INTRODUCTION

Post operative nausea and vomiting (PONV) is a significant problem[1] which causes distress to the patient, and in some cases, for instance ophthalmic surgery, can even compromise surgery[2]. Severe complications related to PONV are relatively rare, but some, such as aspiration pneumonia, can be fatal. PONV, particularly in children, can cause dehydratation and electrolyte imbalance. As a result, there are economic consequences to PONV for example, additional care required. With the increasing pressure on institutions to justify expenditure, economic studies examining all of the costs and consequences of illness and its treatment from the institutional perspective are becoming more important in the decision making process. In particular, the benefits of a new treatment or policy which improves the care of patients with PONV, and which has resource consequences for the institution, should be assessed using economic as well as clinical criteria.

Ondansetron is a $5HT_3$ antagonist which has demonstrated superior efficacy compared with metoclopramide in the prevention[3] and treatment[4] of PONV. Two studies, both in adults[3,5], have investigated the cost-effectiveness of ondansetron in the prevention of PONV and found that ondansetron is more cost effective than metoclopramide. A third study in children whowed that ondansetron reduces resource use due to PONV[6]. Hoever, there have been no published reports evaluating the cost-effectiveness of ondansetron versus metaclopramide in the treatment of PONV.

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This economic analysis is based on the results of a multicentre study at 60 sites in France, comparing ondansetron and metoclopramide in the treatment of PONV. The efficacy and safety results from this study have already been reported[4]. This economic component of the study investigated the extent to which the greater cost of ondansetron, compared with metoclopramide, can be offset by reductions in other direct medical costs in patients with established PONV. It also evaluated whether the differences in treatment costs for PONV were justified by the differences in the rate of successful treatment. The primary objective was to measure the cost of improving effectiveness by using ondansetron for each successfully treated patient (i.e. the incremental cost effectiveness).

MATERIALS AND METHODS

This was an economic analysis of direct medical costs and consequences associated with the treatment of PONV with ondansetron of metoclopramide during the first 24 hours after surgery. The primaty outcome measure was the incremental cost effectiveness of ondansetron from the payers perspective. The study, conducted at 60 sites in France, was a randomised, double-blind, parallel-group comparison of the two anti-emetic treatments, ondansetron 4mg and metoclopramide 10mg, both administered intravenously.

- **Study Procedures**

Seven hundred and forty-six patients were randomised to treatment qith either ondansetron 4mg i.v. or metoclopramide 10mg i .v. administered over five minutes. They were recruited from an in-patient population who had undergone elective surgery requiring general anaesthesia. They were expected to stay in hospital more than 24 hours. All patients had experienced nausea lasting at least five minutes or had vomited at least once during the first six hours after recovery.

Patients were monitored for 24 hours after receiving study medication. To allow time for the study medication to take effect, any episodes of nausea and vomiting which occurred during the first 15 minutes after dosing were excluded from the analysis. After this initial period of 15 minutes, investigators recorded details of procedures and resources used to manage nausea and vomiting.

The following data for each patient were collected : time spent caring for patients by staff, i.e. doctor, staff nurse or auxiliary nurse ; any materials used, for example clean bedlinen, vomit bowls and paper towels ; and rescue medication administered to treat breakthrough nausea and vomiting.

- **Effectiveness Measure**

The measure of effectiveness was based on the number of emetic episodes and severity of nausea over the 24-hour study period. In this economic evaluation, the criterion for successful treatment was complete protection from nausea and vomiting.

- **Resources Used**

The time staff spent with patients, details of any materials and medications used to treat PONV (including study medication), and details of any treatment for adverse events as a result of study medication were recorded.

The following assumptions were made when evaluating resource use for individual episodes of nausea and vomiting : materials were not re-used for subsequent episodes ; the time taken to administer drugs was included in the overall time taken to treat an individual episode.

Where more than one member of staff attended a patient, resource use was based on a nurse being in attendance for the whole recorded attendance time : if the members of staff were a staff nurse and one doctor, it was assumed that the staff nurse was present for the total attendance time and the doctor for five minutes ; if the members of the staff were a staff nurse and auxiliary nurse, then it was assumed that the staff nurse was present for the whole time and the cost of the auxiliary nurse was not included ; if the members of staff were a staff nurse, auxiliary nurse and a doctor, it was assumed that the staff nurse was present for the whole of the attendance time, that the doctor was present for five minutes and the cost of the auxiliary nurse was not included.

- **Adverse events**

Any adverse events reported during the study attributable to the study medication were included in the economic evaluation.

- **Sensitive Analysis**

Where patients dropped out of the study because they had severe nausea and vomiting, it was assumed that they had experienced five emetic episodes. This allocation of five episodes was agreed by an expert panel before the start of the study and defined in the protocol. These emetic episodes were allocated a cost as follows : the mean cost per emetic episode (from patients in the treatment group who did not drop out) multiplied by five. This gave a more realistic estimate of the actual costs of treating PONV and is referred to as the upper estimate.

Two analyses were performed in the sensitivity analysis. The first used data where no allowance was made for additional resources which could have consumed by patients who dropped out (the lower estimate). The second analysis was performed using the upper estimate, where an allowance was made for each patient who dropped out.

Analysis of the primary outcome, the incremental cost effectiveness of ondansetron, and the secondary outcome, mean cost effectiveness, was based on the upper estimate of resource use.

- **Cost of Treatment**

The cost of managing PONV was calculated from the direct costs, i.e. the sum of the drug costs, the materials used and staff time managing PONV. No allowance was made for fixed or indirect costs. Since ptients were not followed-up until discharge from hospital, no data were collected as to how PONV could impact on length of stay in hospital. The cost of medicines and materials were based on the purchase price for the Assistance Publique des Hôpitaux de Paris (AP-HP). The AP-HP is the largest hospital group in France. The laundry costs for bedlinen were based on the total annual costs of laundry and the mean daily number of launderings (corrected for 251 working days per year). Staff costs were full employment costs, i.e. inclusive of social security contributions made by the employer to the government. These costs were used to calculate a mean net cost for each treatment group (Table I).

Table I : Cost of medicines, materials and staff

ITEM	COST (French Francs)
Study Treatment :	**Unit Cost**
Ondansetron : 2ml ampoule of 4mg	52.579
Metoclopramide 2ml ampoule of 10mg	0.475
Rescue medicines	Cost price to AP-HP
Materials :	**Unit cost**
Gloves (pair)	0.438
Use of kidney basin	0.429
Paper towel	0.031
Change of nightgown	9.163
Change of bedlinen	10.858
Respiration cannula	15.200
Surgical cover	2.370
Draw sheet	1.580
Sterile compress	0.203
Non-sterile compress	0.071
Disposable rubber gloves	0.395
Theatre clothing	17.800
Aspiration cannula	1.010
Cellulose sheet	0.088
Staff Costs	**Cost per Minute**
Doctor	4.050
Nursing Sister	2.484
Nurse	2.014
Auxiliary Nurse	1.621

- **Cost-effectiveness Analysis**

Two measures of cost effectiveness were employed. The first measure, incremental cost effectiveness, addresses the question, « How much extra will it cost to get the additional effectiveness from the more expensive treatment ? ». The equation used to calculate incremental cost effectiveness is the difference in the mean net cost of treatment, divided by the difference in effectiveness. The second measure, mean cost effectiveness, addresses the question « On average, how much does it cost to successfully treat a patient with a given therapy ? ». The equation used to calculate mean cost effectiveness for each treatment is the mean net cost divided by the effectiveness.

- **Statistical Analysis**

The study was designed to have an 80% power to detect a 10% difference in effectiveness, defined as no episodes of nausea of vomiting, between ondansetron and metaclopramide. It was estimated that 768 pateints could be required to achieve this.

Statistical analysis of effectiveness was performed using a Chi-square test. The test was two-sided with significance determined at the 5% level.

RESULTS

There were 746 patients randomised to treatment of whom 64 were male and 682 were female. The mean age was 45 ± 12 years and the mean weight 63 ± 11 kg. Three hundrer and eighty patients received ondansetron and 366 patients received metoclopramide. There were no significant differences in the demographic characteristics between the treatment groups.

The majority of patients (52%) underwent gynaecological procedures with gastrointestinal procedures (12 %) and ear, nose and throat (10 %) procedures being the next most common.

Eleven of the 746 patients were excluded from the economic analysis for the following reasons : four patients were lost to follow-up ; no data were collected for three patients ; and there were errors in data collection for four patients.

- **Effectiveness**

A significantly greater percentage of patients had complete control (no nausea of vomiting) in the ondansetron treatment group (172/372, 46.2%) compared with the metoclopramide treatment group (113/363, 31.1%), ($p < 0.0001$). Where patients experienced nausea or vomiting folliwing study treatment, the median time to the first episode was five hours for metoclopramide and over 24 hours for ondansetron.

- **Resource Use**

Overall, the mean staff time spent per patient treating the symptoms of nausea and/or vomiting was shorter for the ondansetron treatment group (18.7 minutes) compared with the metoclopramide treatment group (26.5 minutes).

Patients who received rescue medication and who did not drop out of the study required more support from staff because their nausea and vomiting was more severe. The additional time was also partly due to the time required to administer rescue medication. Fewer patients in the ondansetron treatment group received rescue medication compared with patients in the metoclopramide treatment group (Table II). In addition, fewer patients in the ondansetron treatment group were prescribed multiple rescue treatments compared with the metoclopramide treatment group.

Table II : Number of patients who required rescue medications

	Ondansetron N (%)	Metoclopramide N (%)
No rescue treatment	283 (74.48)	223 (60.92)
One treatment	76 (20.00)	109 (29.78)
Two treatments	21 (5.52)	27 (7.38)
Three or more treatments	0 (0.00)	7 (1.92)

The most commonly prescribed rescue medication was intravenous metoclopramide, which was administered to 222 (73%) of the patients who required rescue medication.

A greater percentage of patients treated with metoclopramide (69.4%) required materials compared with patients treated with ondansetron (57.3%). There was a difference in the number of kidney basins used (median : 1 with ondansetron and 2 with metoclopramide) and paper towels used (median : 1 with ondansetron and 2 with metoclopramide). There were no significant differences in the number of night-gowns, PVC gloves or bed changes required.

Three patients in the metoclopramide treatment group received treatment for adverse events considered related to study medication. None received such treatment in the ondansetron group.

- **Cost of PONV Management**

The cost of PONV management was based on all patients included in the economic evaluation. The mean cost of treating PONV per patient is summarized in Table III.

Table III : Cost differences by category

	Ondansetron mean cost in FF	Metoclopramide mean cost in FF	Difference
Total population	n = 372	n = 363	
Acquisition cost of study medication	52.58	0.47	52.11
Staff costs	31.45	56.16	-24.71
Material costs	2.91	4.17	-1.26
Cost of rescue treatment	1.04	2.56	-1.52
Cost of treatment for adverse events	0	7.5	-7.5
Total PONV management cost	87.98	70.86	17.12

Drug acquisition and staff costs represented the major cost components. Ondansetron 4mg iv cost 52.11 FF more than metoclopramide 10mg iv, however, this difference was reduced to 17.12 FF when the mean global costs per patient were compared. This is because patients in the ondansetron treatment group incurred fewer staff costs for the treatment of nausea and vomiting, required less rescue treatment, had fewer adverse events and consumed fewer materials.

- **Cost effectiveness**

Incremental cost effectiveness (i.e. the extra cost of successfully providing, to one extra pattient, the additional protection from nausea and vomiting by ondansetron) was 113.88 FF (Table IV). Expressed differently, for an additional 17.12 FF per patient, there is an additional 15.1% likelihood of complete control of nausea and vomiting with ondansetron.

Table IV : Incremental cost effectiveness ratio

Drug	Mean cost	Cost difference (C)	Probability of successfully treatment	Difference in effectiveness (E)	Incremental cost effectiveness ratio (C/E)
Ondansetron	87.98 FF	17.12 FF	0.462	0.151	113.38 FF
Metoclopramide	70.86 FF		0.311		

Mean cost effectiveness (i.e. the mean cost of successful treatment with ondansetron and metoclopramide) was 190.43 FF for ondansetron and 227.88 FF for metoclopramide. The cost effectiveness ratio was less for ondansetron because the efficacy rate less for ondansetron because the efficacy rate was higher and fewer treatment costs were incurred over and above the drug adquisition costs.

- **Sensitivity Analysis**

Fifty-four patients in the ondansetron group and 76 patients in the metoclopramide group dropped out of the study. All of these patients had experienced emetic episodes and had received rescue treatment. The allowance made for drop-outs did not significantly affect the results with an incremental cost-effectiveness for ondansetron of 172.38 FF (lower estimate) and 113.38 FF (upper estimate).

DISCUSSION

In economic evaluations, there are two ways of measuring cost-effectiveness : the first, incremental cost-effectiveness, measures the cost per unit effectiveness of switching from one treatment to a new treatment ; the second, mean cost-effectiveness, measures the cost per unit of effectiveness for different treatments independently of each other. Incremental cost-effectiveness is potentially valuable to institutions making policy decisions on fund allocation for different therapies and diseases. Mean cost effectiveness is a useful comparison for similar therapies in situations where budget is available to buy a new therapy.

In this study, we demonstrated that an additional 17.12 FF will give each patient a 15.1% improved chance of complete control of nausea and vomiting. It could be that 17.12 FF over-estimated the additional cost of improved effectiveness with ondansetron because the cost of managing patients with PONV may have been underestimated. This underestimation may be due to the following : fistly, patients were evaluated over 24 hours and there was no follow-up to see whether further treatment for PONV was required and therefore, whether further costs were incurred. Secondly, there is evidence that PONV is associated with an increased length of stay in hospital[7,8]. In this study, no data were collected to see whether there was a correlation between the incidence of PONV and the length of stay in hospital. Finally, the impact of PONV from the patient's perspective was not specifically measured. PONV causes patients significant distress and it is rated as the most undesirable post-operative consequence of surgery. Patients are willing to suffer dysphoria, decreased mental acuity and increased pain to avoid PONV[2].

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The mean cost effectiveness ratios in this study demonstrated that ondansetron is more cost effective than metoclopramide (190.43 FF versus 227.88 FF). More patients in the ondansetron treatment group had complete control of nausea and vomiting compared with patients treated with metoclopramide and therefore, they required fewer resources and requiring less staff time.

In conclusion, the results of this study suggest that the treatment of PONV with ondansetron is better value for money that treatment with metoclopramide. While ondansetron costs more than metoclopramide, the extra cost of PONV management with ondansetron is considerably smaller than the difference in the drug acquisition cost. In addition, the cost and efficacy results from this study demonstrated superior cost effectiveness for ondansetron in the treatment of established PONV.