A prospective randomized trial of the antiemetic efficacy and cost-effectiveness of intravenous and orally disintegrating tablet of ondansetron in children with cancer

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The study compared orally disintegrating tablets (ODT) and intravenous (IV) formulations of ondansetron in controlling nausea and vomiting in children receiving chemotherapy regimens without cisplatin. The oral formulation (ZOFRAN ZYDIS tablet; GlaxoSmithKline) was administered at a dose of either 4 mg (body surface area <= 0.8 m²) or 8 mg (body surface area > 0.8 m²). The IV formulation (ZOFRAN ampoule; GlaxoSmithKline) was administered at a dose of 5 mg/m² every 12 hours.

Type of intervention
Prevention.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised children and adolescents with cancer who were receiving chemotherapy. Patients with other underlying disorders causing emesis (e.g. gastrointestinal disease, brain tumours and brain metastases) and/or having courses containing cisplatin were excluded.

Setting
The setting for the study was not explicitly stated. However, given the health technology involved it is likely to have been secondary care. The economic study was carried out in Izmit-Kocaeli, Turkey.

Dates to which data relate
The effectiveness data were gathered between October 2003 and March 2004. The resource use data appears to have been collected during the same period. The price year was not reported.

Source of effectiveness data
The effectiveness data were derived from a single study.

Link between effectiveness and cost data
The costing was undertaken on the same patient sample as that used in the effectiveness study. It was not explicitly stated whether the costing was performed prospectively or retrospectively.

Study sample
Patients were eligible if they met the inclusion criteria (see 'Study Population'), and were receiving their first course of
chemotherapy, or had no nausea or vomiting during previous chemotherapy courses. Those receiving antiemetics during the preceding 24 hours were excluded. A total of 22 children and adolescents were enrolled in the study. No details on how the sample size was determined, the method of sample selection, or those who refused to participate, were provided. The number of patients allocated to each regimen was not reported. However, it was reported that there were 95 courses of chemotherapy, of which 56 were allocated to the IV arm and 36 to the ODT arm.

Study design
The study was a randomised controlled trial (RCT) that was carried out in a single institution. The patients were consecutively randomised to either the ODT or IV formulation arm of ondansetron, during their admission to the unit to receive chemotherapy. Only the supervisor nurse was aware of the randomisation. At the end of each chemotherapy day, a paediatric oncologist who was unaware of the randomisation recorded the drug efficiency, along with adverse events and changes in the daily activity and appetite. The duration of follow-up was not explicitly stated, although it was likely that the patients were followed up for the duration of their chemotherapy. No loss to follow-up was reported.

Analysis of effectiveness
It was not stated whether the analysis of the clinical study was conducted on an intention to treat basis or for treatment completers only. However, assuming that there was no loss to follow-up, the two methods would provide the same results. The primary health outcome was the control of nausea and vomiting. The outcome was divided into four categories:

- complete control (no vomiting or nausea);
- major control (1 to 2 vomits or nausea);
- minor response (3 to 5 vomits and/or less than 5 hours of nausea);
- complete failure (more than 5 vomits and/or at least 5 hours of nausea, and generally indicating the administration of another antiemetic therapy).

A paediatric oncologist assessed the outcomes through interviews with patients, parents and the observing nurse. Notes on the diary cards, as recorded by the parents and the observing nurse, were also evaluated. Changes in daily activities and appetite were also noted as a health outcome. The patients in the two groups were reported to be similar in age, gender, body surface area and emetogenic grade of their chemotherapy courses.

Effectiveness results
The overall antiemetic response rates of the courses were 83% complete, 8% major, 4% minor and 5% failure. Complete response rates were not significantly different between boys and girls, (p=0.102).

The two treatment groups did not differ in complete response rates (82% in the IV group versus 85% in the ODT group), (p=0.981), appetite (same as usual: 59% in the IV group and 72% in the ODT group), (p=0.141), and daily activities (same as usual: 55% in the IV group and 54 % in the ODT group), (p=0.525).

The complete response rate was 94% in patients younger than 10 years and 69% in patients aged 10 years or older, (p=0.004). However, differences between IV versus ODT formulations in patients under 10 years and patients aged at least 10 years were not statistically significant.

In 56 courses with Grade III and IV emetogenicity, the complete response rates were no different for IV (75%) or ODT formulations (80%), (p=0.931). There was also no difference in the appetite and daily activities between the two treatment arms, (p=0.272 and p=0.140, respectively).

A total of 231 chemotherapy days were evaluated during the study. Daily response rates and appetites were no different between the two treatment arms, (p=0.728 and p=0.054, respectively). However, patients in the ODT arm showed less reduction in daily activities, (p=0.041).
The complete response rates were higher for courses containing corticosteroids (39/41) than for courses without corticosteroids (40/54), (p=0.006).

**Clinical conclusions**

The ODT and IV formulations were equally effective in controlling acute emesis of children. The control of emesis was greater for children receiving courses containing corticosteroids and for children younger than 10 years old.

**Measure of benefits used in the economic analysis**

The measure of benefit used was the number of courses and days with complete antiemetic control (no nausea or vomiting). This was obtained directly from the effectiveness analysis.

**Direct costs**

The direct costs included were the cost of each tablet consumed by the patient in the oral group and the cost of every ampoule (even if the whole content was not used) for the IV group. No other costs were included. It would appear that data on resource quantities were obtained from the single study used for the effectiveness analysis, while the cost data might have been collected from the authors' own setting. The date to which the costs related was not reported. Discounting was not performed but, given the short timeframe involved (less than one month), this seems appropriate. The costs estimated were the average costs.

**Statistical analysis of costs**

The authors reported that either the Kruskal-Wallis test or the Mann-Whitney test were used for continuous variables. However, they did not report whether the costs were regarded as a continuous variable.

**Indirect Costs**

No indirect costs were included.

**Currency**

US dollars ($). The authors did not report the conversion rate used to convert Turkish liras (YTL) into US dollars.

**Sensitivity analysis**

The authors do not appear to have performed any sensitivity analysis.

**Estimated benefits used in the economic analysis**

See the 'Effectiveness Results' section.

**Cost results**

For the whole group, the mean cost of one course was $83.0 (+/- 65.9), which was $99.6 (+/- 74.5) in IV courses and $59.2 (+/- 41.6) in ODT courses, (p=0.004).

In the whole group, the daily antiemetic cost was $34.8 (+/- 11.2). The daily costs were $43.6 (+/- 6.11) for the IV formulation and $23.9 (+/- 4.7) for the ODT formulation, (p<0.001).

**Synthesis of costs and benefits**

In the IV group, complete response was achieved in 46 courses (106 days) with a total antiemetic cost of $5,581.2. In the ODT group, complete response was achieved in 39 courses (87 days) with a total antiemetic cost of $2,464.8.
The mean cost per successfully controlled course was $121.3 for the IV formulation and $63.2 for the ODT formulation. The costs per successfully controlled day were $52.6 (IV) and $28.3 (ODT), respectively.

Authors' conclusions
The orally disintegrating tablet (ODT) formulation of ondansetron was as effective as intravenous (IV) ondansetron. Therefore, ODT ondansetron was shown to be a safe, well-tolerated and cost-effective antiemetic for children receiving moderately and highly emetogenic chemotherapy without cisplatin.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was given for the comparator used, IV ondansetron would appear to represent current practice in the authors' setting. You should decide if it is a widely used health technology in your own area.

Validity of estimate of measure of effectiveness
The analysis was based on an RCT, which was appropriate for the study question. It was unclear from the paper if the study sample was representative of the study population. In addition, there were no details on why or how the study sample was chosen from the study population. The randomisation method used to allocate the patients to the different arms was not reported, and there were no details of how participants differed from non-participants. The patient groups were shown to be comparable at analysis. The study population comprised 22 patients and 95 chemotherapy courses. Given that no details were provided about the sample size necessary to detect a significant difference between the two groups, it was unclear whether the non significant differences in effectiveness between the two groups were due to insufficient sample size or to a real equivalence between the two technologies. Some of the chemotherapy courses involved the same participants, but it was unclear whether the authors accounted for this non-independence of courses during the analysis.

Validity of estimate of measure of benefit
The estimation of benefits was obtained directly from the effectiveness analysis. This limits the comparability of the study results to those studies evaluating similar interventions and considering similar measures of health benefit.

Validity of estimate of costs
The authors did not report the perspective adopted for their study, thus it is impossible to tell whether all the relevant costs were included. Only the specific costs of the drugs were included in the analysis. The authors acknowledged that the exclusion of the cost of inpatient stay, IV preparation consumables and nursing time is likely to lead to an underestimation of the true cost of the IV formulation. Therefore, their inclusion in the cost estimation would not change the conclusions of the study.

Other issues
The authors made appropriate comparisons of their findings with those from other studies. There was a short discussion about other studies that had investigated the cost or effectiveness of oral and IV ondansetron and seemed to have reported similar conclusions to those in the present study. The authors discussed the variations in response rates found in various studies. They noted that their response rates were higher and put forward a number of possible explanations. For example, the exclusion of cisplatin-containing regimens, the mild to moderate emetogenicity of some courses, or a lack of emesis in young children.

The issue of generalisability to other settings was not addressed. The cost estimates and efficacy data appear to have been derived from Turkish estimates and evidence, which may limit the generalisability of the study beyond Turkey. This is especially true given the lack of any sensitivity analysis. The authors did not present their results selectively. The study considered young patients undertaking all grades of chemotherapy and this was reflected in the authors' conclusions.
Implications of the study
The authors acknowledged that the study may encourage paediatric oncologists to try ODT formulations in combination with dexamethasone in cisplatin-containing chemotherapy.

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Other publications of related interest


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