A randomized trial comparing omeprazole, ranitidine, cisapride, or placebo in Helicobacter pylori negative, primary care patients with dyspepsia: the CADET-HN Study

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 omeprazole (20 mg once daily), ranitidine (150 mg twice daily) and cisapride (20 mg twice daily) with placebo in the treatment of dyspepsia among Helicobacter pylori (H. pylori)-negative patients.

Type of intervention
Treatment.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised patients aged 18 years and older presenting with epigastric pain or discomfort, with or without additional symptoms of heartburn, acid regurgitation, excessive burping or belching, increased abdominal bloating, nausea, sensation of abnormal digestion, or early satiety. To be included in the study, the patients needed to be suitable for empiric treatment and to have negative serological and breath tests for H. pylori.

The following categories of patient were excluded:

those who had undergone investigation by upper endoscopy or gastrointestinal barium study in the preceding 6 months, or twice in the preceding 10 years;

those who had a diagnosis of suspected irritable bowel syndrome or gastroesophageal reflux disease (GERD), a diagnosis of GERD being assumed if the patient had isolated symptoms of heartburn and/or regurgitation;

those who displayed alarm symptoms warranting endoscopy (such as vomiting, bleeding, inadvertent weight loss or dysphagia), a previous diagnosis of GERD by endoscopy or X-ray, or reported heartburn or regurgitation without epigastric pain; and

those who fulfilled the Manning criteria (3 or more from 6) for irritable bowel syndrome.

Setting
The setting was primary care. The economic study was conducted in Canada.

Dates to which data relate
The effectiveness and resource use data were gathered between September 1998 and February 2001. The cost data were taken from published and electronic sources relating to 1995 to 1999. A common price year for the costs was not stated.

Source of effectiveness data
NHS Economic Evaluation Database (NHS EED)
The evidence for the effectiveness outcomes was derived from a single study.

**Link between effectiveness and cost data**
The costing was undertaken prospectively on the same patient sample as that used in the effectiveness study.

**Study sample**
A power calculation established that a sample size of 135 patients per group was required, assuming a 2-tailed alpha error rate of 0.05 and a power of 80% with a 15% drop-out rate during screening. Patients who were eligible and consented to enter the study were randomly assigned to one of the four groups. Of 705 patients enrolled in the study, 27.4% did not proceed to randomisation. This comprised 2.4% who either withdrew consent or were lost to follow-up, 24.5% who did not fulfil the study criteria, and 0.5% who were non-compliant or lost to attrition. A total of 512 patients were randomised, with 135 allocated to omeprazole, 139 to ranitidine, 105 to cisapride and 133 to the placebo. Enrollment and treatment in the cisapride group was prematurely terminated in January 2000 after published reports of rare, serious, cardiac side effects.

**Study design**
The study was a randomised controlled trial that was carried out in 35 centres. Randomisation was performed using a computer-generated list stratified for each centre in blocks of four. Patients, study personnel and investigators were all blinded to treatment allocation throughout the study. Dummy tablets were used in conjunction with the omeprazole dose to facilitate concealment of group allocation. Baseline observations were made in the 2 weeks prior to the study commencing. Patients received 4 weeks of empiric treatment with the assigned drug or placebo, followed by 5 months of on-demand treatment with the same medication. Patients could use antacid tablets (Mylanta) up to 4 times per day as a rescue medication.

The follow-up was by clinic visits at 4, 12 and 24 weeks and by telephone at 8, 16 and 20 weeks. At 4 weeks, 4 patients were lost to follow-up, 16 had discontinued treatment and 2 had not received treatment. Follow-up was completed by 131 (97%) of the omeprazole group, 135 (97%) of the ranitidine group, 94 (89.5%) of the cisapride group, and 130 (97.7%) of the placebo group. At 6 months, a further 10 patients were lost to follow-up and 42 had discontinued treatment. Follow-up at 6 months was completed by 120 (88.9%) of the omeprazole group, 123 (88.5%) of the ranitidine group, 84 (80%) of the cisapride group, and 111 (83.5%) of the placebo group. The reasons for discontinuing treatment were non-compliance, personal problems, criteria not fulfilled, adverse events, early termination, consent withdrawn, disease deteriorated, moved, pregnancy, lack of efficacy and time constraints. Compliance was assessed by pill counts and was defined as at least 75% of the dispensed tablets being taken.

**Analysis of effectiveness**
The primary health outcome was treatment success. This was defined as a Global Overall Severity (GOS) score of 1 or 2 after 4 weeks and 6 months of treatment. The GOS measured dyspepsia over the preceding 4 weeks using a 7-point Likert scale that ranged from "1, no problem" to "7, very severe problem - cannot be ignored and markedly limits daily activities and often requires rest". A secondary outcome measure was the proportion of patients who became completely asymptomatic (GOS=1). Other reported outcome measures were the severity of specific dyspeptic symptoms, and quality of life as measured by the quality of life in reflux and dyspepsia instrument, gastrointestinal symptoms rating scale, and overall treatment effect.

Sub-group analyses were performed, although the study was not powered for these. The authors stated that the analysis of the clinical study was conducted on an intention to treat basis. At baseline, the four groups were shown to be comparable in terms of the patients' demographic characteristics and dyspeptic symptoms.

**Effectiveness results**
At 4 weeks, the treatment success rate was 51.1% (95% confidence interval, CI: 43 - 60) with omeprazole, 36% (95% CI: 28 - 44) with ranitidine, 30.5% (95% CI: 22 - 39) with cisapride and 23.3% (95% CI: 16 - 31) with placebo.
Omeprazole was significantly better than all other treatments, (p<0.05).

At 4 weeks, the percentage of patients who were completely asymptomatic (GOS=1) was 23.7% (95% CI: 16.5 - 30.9) with omeprazole, 10.8% (95% CI: 5.6 - 15.9) with ranitidine, 7.6% (95% CI: 2.5 - 12.7) with cisapride and 3.8% (95% CI: 0.5 - 7.0) with placebo. Omeprazole was significantly better than all other treatments, (p<0.05).

Sub-group analyses were performed, although the study was not powered for these. For patients with at least mild heartburn and/or regurgitation (score >/= 3) at baseline (n = 211), omeprazole was more effective than the other treatments.

In those patients who had either no or minimal heartburn and/or regurgitation at baseline (n=301), omeprazole and ranitidine were superior to placebo.

At 6 months, the treatment success rate was 44% (95% CI: 36 - 53) with omeprazole, 41% (95% CI: 33 - 49) with ranitidine, 40% (95% CI: 31 - 49) with cisapride and 35% (95% CI: 27 - 43) with placebo. There was no statistically significant difference between the treatments.

The authors also reported that the proportion of patients who were successfully treated at 4 weeks and remained so at 6 months was significantly different between the groups. The differences between omeprazole and both cisapride and placebo were statistically significant, (p=0.001), whereas the difference between omeprazole and ranitidine was not, (p=0.053). Adverse effects were frequent but generally mild. The mean number of on-demand tablets and rescue antacid used was comparable between the groups.

Clinical conclusions
The authors concluded that omeprazole provided superior symptom relief in comparison with ranitidine, cisapride and placebo in the treatment of dyspepsia in H. pylori-negative patients.

Measure of benefits used in the economic analysis
The measure of health benefit used was the proportion of successfully treated patients at 4 weeks. Discounting was not applied to the benefits.

Direct costs
Both the direct costs to the health service and to the patient were included in the analysis. These comprised the dyspepsia-related costs of hospitalisation, visits to health care professionals (general practitioners, gastroenterologists, surgeons and nurses), investigations (endoscopy, upper gastrointestinal barium meal, 13C-urea breath test, laboratory tests, X-rays) and medicines (prescription and over-the-counter).

Health care resource use was measured prospectively at monthly intervals by questionnaire. The method for collecting and aggregating the other direct costs was not reported here, but it was described in two other published papers (Chiba et al. 2002 and 2004, see 'Other Publications of Related Interest' below for bibliographic details). The hospitalisation costs were obtained from the Canadian Coordinating Office for Health Technology Assessment. The physician costs were taken from the Ontario Health Insurance Plan, as were the costs of most investigations. The exception was the 13C-urea breath test which was sourced from MDS Laboratories. The cost of other health professionals visits were obtained from McMaster University. The prescription drug costs were taken from the Ontario Drug Benefit Formulary and the Medis Distributing Catalogue, and were evaluated as the purchase price plus a 10% dispensing charge. Over-the-counter medicine costs were based on amounts reported by participants.

The cost estimates were reported separately from resource use, but data were not presented for all items. Discounting was not applied, even though the costs were incurred during more than 2 years. The cost data were taken from published and electronic sources relating to 1995 to 1999. It was unclear whether a common price year was used for the costing. The authors stated that the costs for study protocol visits and the urea blood test, which all patients underwent, were not included.
Statistical analysis of costs
The costs were treated deterministically. No statistical analysis of the costs was reported.

Indirect Costs
The indirect costs were included, which was appropriate given the societal perspective of the analysis. The indirect costs comprised the days missed from work for employed patients and the days lost from usual activities for unemployed and senior patients, owing to dyspepsia. These were evaluated according to the human capital approach, using national statistics relating to 1996. The number of days lost was self-reported by the study participants. The value of each day and the number of days lost in each group were presented separately, which will enhance replication of the analysis in other settings. Discounting was not applied. The authors also reported that transportation costs were included in the indirect cost analysis, but no details were given. Therefore, it was unclear whether transportation costs were related to the transport time, which would be appropriate, or the direct costs of transportation, which would not be appropriate.

Currency
Canadian dollars (Can$). Conversion rates to US dollars ($) and UK pounds sterling (\(\)) were reported. These were Can$1 = $0.60 = 0.43.

Sensitivity analysis
A probabilistic sensitivity analysis was used to estimate the 95% CIs around the cost-effectiveness ratios and to create cost acceptability curves. A bootstrapping method was used but further details, such as the distributional assumptions and the number of iterations, were described elsewhere (Chiba et al. 2004).

Estimated benefits used in the economic analysis
At 4 weeks, the effectiveness of treatment was 0.31 for cisapride, 0.36 for ranitidine, 0.51 for omeprazole and 0.23 for placebo. The side effects of treatment were not considered in the analysis.

Cost results
The mean total societal cost per patient for 6 months was Can$371 for cisapride, Can$225 for ranitidine, Can$364 for omeprazole and Can$152 for placebo. The costs were not discounted. The cost of adverse events due to treatment was not specifically addressed.

Synthesis of costs and benefits
The costs and benefits were summarised in the form of an incremental cost-effectiveness ratio (ICER). The incremental cost at 6 months was divided by the incremental benefit at 4 weeks, and then multiplied by six to obtain the additional cost per month free of symptoms. The ICER of omeprazole compared with ranitidine was Can$154. No other ICERs were reported. A cost-effectiveness acceptability curve of omeprazole and ranitidine, created by bootstrapping, was presented.

The authors also calculated cost-effectiveness ratios for each drug compared with the placebo, and then applied bootstrapping methods to calculate 95% CIs around the estimates. The results of this analysis were Can$2,988 (95% CI: -4,365 - 143,487) for cisapride, Can$574 (95% CI: -140 - 4,057) for ranitidine and Can$762 (95% CI: 421 - 1,425) for omeprazole.

Authors' conclusions
Omeprazole was significantly more efficacious as a first-line treatment for dyspepsia in Helicobacter pylori (H. pylori)-negative patients in primary care than ranitidine, cisapride or placebo. Omeprazole was also the most successful in patients who rated epigastric pain or heartburn as their most bothersome symptom. The cost-effectiveness analyses
suggested that omeprazole became cost-effective over ranitidine at a relatively high cost of $154 per symptom-free month. The cost-effectiveness of omeprazole versus ranitidine for on-demand treatment in H. pylori-negative, uninvestigated dyspepsia was not established.

CRD COMMENTARY - Selection of comparators
Although no explicit justification was given for the comparators used, they appear to have represented current practice in the authors' setting. You should decide if the comparators represent current practice in your own setting.

Validity of estimate of measure of effectiveness
The analysis was based on a randomised controlled trial, which was appropriate for the study question. The method of sample selection suggested that the study sample was representative of the study population. In addition, the patient groups were shown to be comparable at baseline. The methods of randomisation, blinding, length of study and loss to follow-up were all reported, suggesting that the internal validity of the study is likely to be good. The outcomes were analysed on an intention to treat basis. A power calculation was reported but an adequate sample size was not achieved for each treatment group.

Validity of estimate of measure of benefit
The authors selected the outcomes at 4 weeks as the estimate of benefit to be synthesised with the costs. This estimate was obtained directly from the effectiveness analysis. The choice of the measure was justified on the basis that on-demand treatment was unlikely to be initiated if symptoms were not resolved after 4 weeks of continuous treatment.

Validity of estimate of costs
The analysis of the costs was performed from a societal perspective. It appears that all the relevant categories of costs have been included in the analysis. Although some costs were omitted from the analysis, such as the cost of relatives and carers time, their omission is unlikely to have affected the authors' conclusions. Only a selection of the costs and the resource use were reported separately, which will limit the reproducibility of the study in other settings. No statistical analysis of the quantities used was performed. The costs were treated deterministically, and the authors did not report either any measures of variance or the results of any statistical analysis. Bootstrapping was used to create 95% CIs around the cost-effectiveness ratios. Discounting was not applied despite costs being incurred in more than 2 years. It was unclear whether costs or charges were reported. A common price year was not reported, which will make future comparisons with other studies difficult.

Other issues
The authors compared their findings with those from other studies, and reported that their results generally agreed with those of published studies. They did not directly address the issue of the generalisability of the results to other settings. However, generalisability of the effectiveness results was enhanced by avoidance of entry criteria based on endoscopic investigation. The results were presented selectively, with the authors failing to report the proportion of patients that became completely asymptomatic at 6 months. The study enrolled patients who were H. pylori negative and this was reflected in the authors' conclusions. The authors noted that some criteria for defining dyspepsia now exclude symptoms of heartburn and acid regurgitation as they are considered to be part of GERD. The current study included patients with symptoms of heartburn and acid regurgitation, but only in the presence of moderate severity epigastric pain.

The authors calculated cost-effectiveness ratios for each drug in relation to the placebo. These allowed the active value of the treatments to be evaluated, but were incorrectly described as the ICERs. Standard economic evaluation practice is to rank alternative treatments in terms of their relative ICER. For the synthesis of costs and benefits the authors combined the effectiveness data at 4 weeks with the cost data at 6 months, despite having complete data at both times. This combined the outcomes of the continuous treatment with the costs related to both the continuous and on-demand treatment.
Implications of the study
The authors stated that, in view of the efficacy and cost results, the decision whether to initiate treatment with an H2-agonist such as ranitidine, or a proton-pump inhibitor such as omeprazole, should be made after discussions between the physician and patient. They recommended that further studies be undertaken to explore the cost-effectiveness of omeprazole compared with ranitidine as an on-demand medication, and to explore the discrepancy between incomplete symptom control and patient preference for on-demand therapy.

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