The cost-effectiveness of misoprostol in preventing serious gastrointestinal events associated with the use of nonsteroidal anti inflammatory drugs

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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
Using misoprostol to prevent nonsteroidal anti-inflammatory drug (NSAIDs)-induced complications in patients with rheumatoid arthritis (RA) who were taking NSAIDs.

Type of intervention
Secondary prevention.

Economic study type
Cost-effectiveness analysis.

Study population
Patients (over 52 years old) with RA and who were taking NSAIDs.

Setting
Clinical practice. The economic study was carried out in Ontario, Canada.

Dates to which data relate
Effectiveness and resource use data were collected between July 1991 and August 1993. The fiscal year was 1994.

Source of effectiveness data
Effectiveness data were derived from a single study (Silverstein, 1995).

Link between effectiveness and cost data
Costing was performed on the same patient sample as that used in effectiveness analysis.

Study sample
Power calculations were used to determine the sample size: with an estimate of 2% per year for the incidence of serious NSAID-induced upper gastrointestinal complications, 40 to 50% difference in complication rate, 30 to 40% withdrawal rate, and an alpha less than 0.05 and power greater than 0.8, at least 7,500 patients were required in the study. A total of 8,843 patients were randomly assigned in blocks to either the misoprostol group (n=4,404) with an average (SD) age of 67.6 (6.9) or the placebo group (n=4,439) with an average (SD) age of 67.6 (7.0).

Study design
This was a randomised, placebo-controlled, double-blind trial, carried out in 664 centres. Patients were randomized in
blocks of four. The duration of the study was 6 months. The withdrawal rate was 42% in the misoprostol group versus 36.4% (p<0.001) in the placebo group.

**Analysis of effectiveness**
The principle used in the analysis of effectiveness was intention to treat. The health outcome measures were the rate of definite upper gastrointestinal complications, the rate of adverse events (diarrhoea, abdominal pain, dyspepsia, nausea, vomiting, or flatulence), the rate of serious upper gastrointestinal complications in subgroups of patients at higher risk. The study groups were shown to be comparable in terms of demographic and clinical features. A logistic regression was performed to identify the risk factors in relation to the occurrence of serious upper gastrointestinal complications.

**Effectiveness results**
The misoprostol group had a 0.57% rate of definite upper GI complications versus 0.95% in the placebo group, resulting in a 40% reduction with misoprostol (odds ratio 0.598; 95% CI: 0.364 - 0.982; p=0.049). The rate of adverse events (diarrhoea, abdominal pain, dyspepsia, nausea, vomiting, or flatulence) was 55% in the misoprostol group versus 41% in the placebo group. The patients at medium risk because of previous peptic ulcer disease (PUD) had a 0.93% rate of definite upper GI complications (6 from 643) in the misoprostol group versus 2.82% (18 of 638) in the placebo group. The corresponding rates for the subgroup at high risk because of age (over 75 years) and previous PUD were 1.48% (2 of 135) and 5.74% (7 of 122), respectively.

**Clinical conclusions**
In older patients with rheumatoid arthritis, misoprostol reduced serious NSAID-induced upper gastrointestinal complications by 40% compared with placebo.

**Modelling**
A decision tree model was used to estimate the costs and effects associated with each study arm.

**Measure of benefits used in the economic analysis**
The benefit measure was definite upper GI complications averted.

**Direct costs**
Costs were not discounted due to the short study period (less than one year). Quantities were not systematically reported separately from the costs, but the cost items were reported separately. The cost analysis covered the costs of misoprostol and its dispensing fees, inpatient surgical and medical management of a serious or suspected GI event, outpatient treatment with and without endoscopy of the upper GI tract, and management of side effects. The perspective adopted in the cost analysis was that of a provincial health care plan. The source of inpatient cost data was the Ontario Case Cost Project (OCCP) database. The source of outpatient cost data was a study published in 1993. The consumer price index was used to update the outpatient cost data from 1990 to 1994. 1994 price data were used.

**Indirect Costs**
Not considered.

**Currency**
Canadian dollars (Can$).

**Sensitivity analysis**
A probabilistic sensitivity analysis was performed using Monte Carlo simulations, choosing values from the 95% CIs of
Estimated benefits used in the economic analysis
The number of GI events averted per 1000 patients was 3.8 for the baseline population over a 6 month period. The corresponding figures for patients at medium and high risk were 18.9 and 42.6, respectively.

Cost results
Using baseline estimates, the total cost per 1000 patients was Can$419,490 with prophylaxis versus Can$59,380 with no prophylaxis. The corresponding values for patients at medium risk were Can$447,949 and Can$165,522. The values for patients at high risk were Can$470,102 (prophylaxis) and Can$295,383 (no prophylaxis).

Synthesis of costs and benefits
The cost per GI event averted was regarded as the measure of cost-effectiveness: Can$94,766 (95% CI: Can$60,286 - Can$137,146) for the baseline population over a 6-month period. The corresponding figures for those patients at medium and high risk were Can$14,943 (95% CI: Can$10,912 - Can$32,157) and Can$4,101 (95% CI: Can$-220 - Can$18,146).

Authors' conclusions
Prescribing misoprostol for all patients with RA who are aged 52 or older costs Can$94,766 for each additional GI event averted. However, when patients at higher risk are specifically selected, the cost per averted GI complication is markedly reduced. These results, based on actual serious event rates and actual data on endoscopies and upper GI series, hospitalisations, and surgeries, provide a better estimate of the true cost-effectiveness of misoprostol than previous analyses based on endoscopic data and modelling of all resource utilization.

CRD COMMENTARY - Selection of comparators
The reason for the choice of placebo as the comparator is clear, as at that time there was no evidence that other agents could reduce the incidence of NSAID-induced GI lesions.

Validity of estimate of measure of benefit
The estimates of benefit are likely to be internally valid given the use of a double-blind randomised design and a very large sample, the size of which was determined using power calculations.

Validity of estimate of costs
Resource utilization was not systematically reported separately from the costs. However, adequate details of methods of cost estimation were given. Costing was carried out retrospectively from the viewpoint of the provincial health care plan in Canada. As acknowledged by the authors, the study considered only direct costs, while costs to patients and others in society were not included. Cost results may not be generalisable to other settings or countries.

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