Points of View

Economic evaluation of gastric ulcer prophylaxis in patients with arthritis receiving non-steroidal anti-inflammatory drugs

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Summary: This study assesses the economic benefits of misoprostol in the prophylaxis of gastric ulcers larger than 0.3 cm in patients with osteoarthritis receiving non-steroidal anti-inflammatory drugs. Independent epidemiological data were obtained for patients in Scotland and the West Midlands. Co-diagnosis of arthritis with gastric ulcer recorded in the routine data was substantially less (4% Scotland, 10% West Midlands) than the 21% found at case review. These data were combined with cost and patient management data in a decision analysis model to explore whether prophylactic use of misoprostol altered substantially the average cost of managing gastric ulcer. Using conservative assumptions and a daily dose of 400 µg, cost savings per patient to the National Health Service of £5–£8 over a 3-month period are expected in the groups of patients studied, while at the 800 µg dose there would be a net cost of £23–£25. Sensitivity analysis showed that under many assumptions misoprostol is expected to be cost saving or cost neutral.

Introduction

In the United Kingdom prescriptions for non-steroidal anti-inflammatory drugs (NSAIDs) have risen by 64% over the last 8 years to some 24 million annually¹ and now account for approximately 5% of all National Health Service (NHS) prescriptions.^{2,3} There is a risk of developing gastrointestinal (GI) complications when taking these drugs. The precise extent of this is uncertain but may be increasing.^{4–6} Approximately 38–50% of these patients may report dyspepsia,^{7,8} but of greater importance is the incidence of major complications such as haematemesis or perforation which have been reported to occur in around 1% to 2% of patients taking NSAIDs.^{6,9,10}

Misoprostol, a synthetic prostaglandin E₁ analogue, is effective in preventing gastric mucosal lesions associated with NSAID administration¹¹ and also in reducing blood transfusion requirements following upper GI bleeding.¹² Endoscopically proven gastric ulcers (GU) have been shown to be present in between 12%¹³ and 28%¹⁴ of patients taking regular NSAIDs. However, the use of an additional drug to prevent some of the GI complications associated with NSAID

treatment is controversial.^{15,16} Do the costs outweigh the benefits? The economic consequences of various activities within the NHS have received much emphasis recently and concerns have been raised regarding resources used for the management of NSAID-induced ulcers.^{1, 15–19}

An economic evaluation has been undertaken of the prophylactic use of misoprostol for GU in patients with arthritis receiving NSAIDs. The technique of decision analysis^{20–22} was used to model the costs and outcomes for patients under differing assumptions. The economic evaluation^{23–25} compared the additional cost of 3 months' misoprostol prophylaxis with the savings in other health care resources, through reductions in diagnostic investigations, hospital admissions and ambulatory care.

Methods

Probabilities

A controlled clinical trial of misoprostol prophylaxis¹¹ was used to provide cumulative 3-month rates for GU over 0.3 cm in size. The rates for an intention to treat analysis were: control group 21.7% (30 ulcers in 138 patients entering the trial),

400 µg/day 5.6% (8 ulcers in 143 patients) and 800 µg/day 1.4% (2 ulcers in 140 patients). For ulcers over 0.5 cm the rates were 12.3%, 4.2% and 0.7%. The corresponding rates for an evaluable cohort analysis, from which withdrawals for protocol deviations and losses to follow-up are excluded, were 24.6%, 6.3% and 1.6%.

The proportion of patients free of abdominal pain at the end of the trial was reported to be 'over 70%' for both misoprostol groups and 57% in the control group.¹¹ These were used as estimates for the relative proportions of patients with persistent or transient symptoms as figures from a larger study²⁶ were similar at 71% and 58%, a highly significant difference.

The proportion of patients developing ulcers who were referred to hospital (5.34%) was estimated from the National Morbidity Survey for England and Wales.²⁷ The probabilities of events associated with GU admission, for example, the proportion of patients undergoing surgery and their mortality rates, were obtained by combining 3 years of data from the Scottish Morbidity Records (SMR1) hospital returns for Scotland. A similar exercise in the West Midlands (WMRHA), using Hospital Activity Analysis (HAA) data, provided comparable information for a second population of similar size (5 million). These databases pro-

vided information on two specific groups: those patients in whom a co-diagnosis of arthritis was recorded although the prime diagnosis was GU, and patients over 60 years old, regardless of arthritis status. These were chosen to represent the principal users of NSAIDs.

Decision tree

The possible outcomes for patients with abdominal pain on NSAIDs are shown in a decision tree (Figure 1). Not all patients are investigated as, in many, the pain remits either spontaneously or on treatment. Patients with persistent symptoms are more likely to be investigated and followed up carefully. Many will not have evidence of ulcer and, together with those having transient symptoms who receive minimum supervision, form the 'no ulcer' group. Some will be found to have GU and will be supervised in hospital outpatient departments; a few will develop complications with or without preceding complications, such as haematemesis, requiring hospital admission for either medical or surgical care. The key decision, at node 1, is whether or not to give misoprostol. If effective, prophylaxis leads to different probabilities at chance nodes M and N, with consequent effects on the number of patients following particular branches.

Figure 1 Schematic decision tree showing the outcome of patients on NSAIDs. *In the sensitivity analysis of drug compliance the misoprostol branch is divided into two – representing compliant and non-compliant cases – the rest of the tree being repeated as in the no misoprostol section. The figures indicate the proportion in the branches for the Scottish data using 1,000 patients as an example and with a silent ulcer rate of 0%.

ches of the tree – as shown in Figure 1 for groups of 1,000 patients.

Efficacy data from clinical trials may not be reflected by clinical practice in which compliance might be lower than implicit when using intention to treat results. The no compliance arm was used to assess this effect.

Resource utilization

Data on hospital length of stay for medical and surgical admissions for GU (ICD code 531) were obtained from SMR1 in Scotland and HAA in the West Midlands. Detailed data on the frequency of diagnostic investigations, the proportion of hospital stay in intensive care and frequency of transfusions were obtained by case reviews as a random sample consisting of 718 patients with GI disease (ICD 531.0 to 535.9, 536.8 and 578) and an additional 60 with a coded co-diagnosis of arthritis (ICD 710.0 to 724.9), admitted to Glasgow hospitals in 1987. Arthritis severity was graded at case review as mild, moderate, severe, based on predefined limitation of activity. Attendance at rheumatology clinics was noted and operations for arthritis were recorded.

Data on general practitioner management of GI disease were obtained by structured interviews conducted by telephone with random samples of general practitioners (GP) in Glasgow and Birmingham in July and September 1989. The surveys were stopped when over 80% of the sample had been contacted. General practitioners were asked about their typical management of a 65 year old patient with no history of peptic ulcer, who was on NSAIDs for arthritis and who developed 'dyspepsia'. Details were obtained of actions taken and patterns of investigation for patients with symptoms, for situations with and without diagnostic evidence of GU.

Cost estimates

The costs were expressed in 1988 prices, inflating by an appropriate health service price index where base estimates were from different years.²⁸ The treatment costs of managing patients in each setting were calculated by combining the resource utilization data with those of the unit costs of each resource. The daily 'hotel' component of hospital cost was taken from published sources.²⁹ Investigations, blood transfusions and operating theatre staff were costed by detailed surveys in Glasgow hospitals (full details of these methods are available from the authors). The costs of biopsy were included once for all patients with ulcers. Operating theatre, recovery room and intensive care costs were not readily available from the NHS and were estimated from local private sector

charges. However, the daily cost of intensive care estimated by this method was lower than that in another NHS costing exercise³⁰ and is therefore conservative.

The costs of GP visits, ambulance journeys and outpatient attendances were obtained from routinely available statistics.^{29, 31–33} The costs of drugs were obtained from MIMS. No adjustment was made to drug costs on the grounds that pharmacists' percentage on-cost and dispensing fees were balanced by the discounts available to the NHS.

The base case costs were those for Scotland, since these were estimated from the most homogeneous data set. However, calculations were also made for the West Midlands, substituting local data on length of hospital stay, GP management, proportion of patients undergoing surgery and, where appropriate, English unit cost data.

Sensitivity analysis

A number of key estimates and assumptions were varied in order to assess the sensitivity of the study results to such changes. Among the varied parameters were: the size of lesion taken to be an ulcer, the proportion of patients having investigations and the proportion of patients hospitalized. It is unlikely, in routine practice, that all symptomatic patients would be endoscoped as in the trial,¹¹ and some would have undetected ulcers (sometimes called 'silent ulcers'³⁴) incurring the lower costs of those with persistent symptoms; the proportion was varied in the sensitivity analysis, however the total admitted with complications was kept constant.

Results

Demographic and clinical data

Data on the ambulatory care by GPs of patients on NSAIDs with dyspepsia are shown in Table 1. Patients with symptoms would first have their NSAID stopped or changed and an antacid (Maalox) used. If symptoms proved to be transient the cost would be that of the antacid plus GP visits in the first 4 weeks. Patients with persistent symptoms in addition would have an X-ray or an endoscopy, implying both GP visits and, depending upon availability of open access endoscopy, some outpatient visits. Patients with confirmed GU would stop misoprostol and have 6 weeks' treatment with an H₂ antagonist and extra follow-up. Patients with a negative investigation would have less follow-up; however, some GPs may arrange a check endoscopy if symptoms continued. Those admitted to hospital would also have follow-up

care, comprising an average of 1.3 outpatient visits after a surgical admission and 1.6 after a medical admission in Glasgow. The corresponding figures for Birmingham were 1.0 and 1.5 respectively.

Data on hospitalization are shown in Table II. It can be seen that lengths of stay are generally higher in the West Midlands and that a greater proportion of cases have surgery. This is consistent with the findings that annual GU admission rates are lower in the West Midlands (202 per million compared with 252 per million in Scotland), that annual hospital mortality from GU is higher (17.9 per million compared with 13.5 per million in Scotland) and that co-diagnosis of arthritis in routine returns was 10% and 4% respectively. These data suggest a greater illness severity of ulcer cases admitted in the West Midlands.

Females comprised 45% of all the Glasgow study cases, 55% of GUs and 67% of GUs over 60. The study showed that a total of 21% (adjusted for sampling) had arthritis recorded in the clinical notes indicating substantial under-coding (4%) in the routine Scottish data. The additional cases were less likely to have attended a rheumatology clinic (27% *vs* 70%), and be graded moderate or severe (72% *vs* 94%). However, both groups had identical rates for arthritis operation of 19%.

Cost estimates

The unit costs for the key resource items used in the calculation of costs for Scotland and England are given in Table III. These were obtained either from

the detailed survey in Glasgow, or from nationally available sources.

The data in Tables I-III were used to calculate the cost of managing patients corresponding to each branch of the decision tree (Table IV). Therefore a patient with symptoms and evidence for a GU would first incur some costs in ambulatory care. There would be a small probability of admission to hospital for medical or surgical care.

Balance of cost and benefits

The data in Table IV were combined with the probabilities in order to calculate the expected cost of care with and without misoprostol prophylaxis* (Table V). The base case analysis (assuming a 400 µg dose, modelling the clinical trial results for lesions larger than 0.3 cm and incorporating an undetected ulcer rate of 30%), shows a net saving of £6.10 in Scotland over the expected 3 monthly cost of care without prophylaxis which is £100.80 per case; thus the full cost of misoprostol is not only

*The expected value (EV) for 1,000 patients on misoprostol using the data in Figure 1, 100% compliance, undetected ulcer rate of 0%, cost codes I-V (Table IV) and adding the cost of misoprostol is $(53 \times 334.53) + (2.234 \times 1327.87) + (0.766 \times 1546.54) + (944 \times 80.38) = £97,760$. For a similar group not given misoprostol the EV is $(205.41 \times 315.03) + (8.62 \times 1308.37) + (2.97 \times 1527.04) + (783 \times 42.68) = £113,942$.

Table I Management by GPs of patients on NSAIDs with dyspepsia

	Survey results	
	Glasgow	Birmingham
Number of GPs	13	17
A Initial symptoms		
Visits to surgery in first 4–6 weeks	2.1	2.4
B Symptoms persist		
Refer for X-ray after initial surveillance period	9 (69.2%)	8 (47.0%)
Refer for endoscopy after initial period	4 (30.8%)	9* (51.5%)
Associated initial outpatient attendances	0.6	0.7
Number of surgery visits in 1 month during investigations	2.1	1.8
C X-ray or initial endoscopy – GU		
Follow up of first endoscopy – outpatient attendance	0.7	1.0
Follow-up endoscopy (after X-ray or initial endoscopy)	1.2	0.6
Associated outpatient attendances	1.4	0.7
Number of surgery visits per month	2.2	1.4
D X-ray or initial endoscopy – negative		
Number of surgery visits per month	1.4	1.3
Endoscopy within 3 months after negative X-ray	33%	44%

*One additional GP would investigate only 75% of patients. Effectively, 8.75 out of 17 (51.5%). Resource utilization for a GU case is the sum of A + B + C, for the no ulcer group it is a weighted average of A, and A + B + D.

Table II Hospitalization for gastric ulcer

		<i>SCOTLAND 1985-87</i> 1986 Population 5.12 million Total SMR1 discharges* 2,043,616 Total GU discharges 3867		<i>ENGLAND (West Midlands)</i> 1984-86 1985 Population 5.18 million Total HAA discharges* 1,508,752 (Ref 32) Total GU discharges 3134	
		<i>Arthritis as co-diagnosis</i>	<i>Over 60s</i>	<i>Arthritis as co-diagnosis</i>	<i>Over 60s</i>
Cases used		156	2659	309	2268
Average age		71.3	73.1	70.1	72.7
Mean length of stay	Medical	16.22	11.71	23.81	11.98
	Surgical	11.90	10.82	12.96	12.63
% Surgical admissions		25.6	40.3	50.48	44.09

*Excludes day cases, psychiatric and obstetric cases.

Table III Unit costs of key resource items (Scotland)

<i>Item</i>	<i>£</i>
GP visit	6.07 (6.89*)
Outpatient attendance	13.58 (32.40*)
Endoscopy	84.46
X-Ray	
Ba meal	36.88
Ba enema	56.03
Transfusion	88.68
Biopsy (at first endoscopy when GU present)	43.93
Surgical operations for GU (in addition to investigations, day cost & follow-up costs)	352.04
Medical admissions for GU (in addition to investigations, day cost & follow-up costs)	51.89
Daily ward cost (general care)	51.35
Daily ward cost (intensive care)	330.00
H ₂ antagonist (6 weeks) (Ranitidine)	44.62
Misoprostol (3 months)**	
400 µg daily	39.00
800 µg daily	78.00
Antacid (Maalox)	3.70
Ambulance (double journey)	33.33 (38.60*)

*Unit cost figures for England; **Patients with ulcer are assumed to incur only half the cost of 3 months' treatment.

recovered but there are additional savings. The equivalent result for England is £8.40. The net savings for all patients with GU over 60 years were slightly lower at about £5 in Scotland and England. The sensitivity analysis (Table V) shows that, under many assumptions, misoprostol prophylaxis generates a net saving to the NHS or a small net cost. The items that lead to a net cost above £3 over 3 months are the use of the higher dose (800 µg/day), assuming that the ambulatory care actually given by GPs is much lower than that reported and restricting the definition of ulcers to those lesions greater than 0.5 cm. These larger ulcers might have a lower undetected rate than the 30% used in the

base case; at 15% the net cost would be 25% less and at 0% it would be halved.

Discussion

Given the increased pressures on health service expenditure, it is important to demonstrate that medical treatments give good value for money. In the White Paper, *Working for Patients*,³⁵ the government has launched a number of initiatives to encourage a more efficient use of health care resources. It is proposed that Regional Health Authorities will give Family Practitioner Commit-

Table IV Costs of patient management in different settings: cost of misoprostol in addition to those costs

<i>Letters A-D refer to Table I Roman numerals I-V to Figure 1</i>	<i>Scotland £</i>	<i>England (WMRHA) £</i>
<i>A Initial symptoms</i>		
Antacid & GP care	16.45	20.24
<i>B Persistent symptoms</i>		
Diagnostic investigations and further GP care	66.79	84.91
<i>C Gastric ulcer</i>		
Biopsy, follow-up investigations, further GP care and H ₂ blocker	231.79	203.98
<i>D Negative investigations</i>		
Confirmatory endoscopy (some cases), further GP care	29.65	31.12
I Ambulatory ulcer care (A + B + C)	315.03	309.13
<i>Co-diagnosis arthritis (including A + B)</i>		
II Medical care	1308.37	1787.17
III Surgical care	1527.04	1642.45
<i>Over 60 age group (including A + B)</i>		
II Medical Care	1021.78	1090.10
III Surgical Care	1448.84	1546.12
<i>Weighted averages (no ulcer group)</i>		
IV Branch on misoprostol A, A + B + D	41.38*	50.23*
V Branch without misoprostol A, A + B + D	42.68**	51.80**

*The weighted average is formed by the cost of the patients on misoprostol with persistent symptoms, less the relevant ulcer rate – $(300 - 56) \times (A + B + D)$, and the cost and proportion of patients not investigated – $700 \times (A)$, divided by $(300 - 56 + 700)$. **For patients not on misoprostol the figures are the sum of $(430 - 217) \times (A + B + D)$ and $(570) \times (A)$, divided by 783.

Table V Balance of costs and savings; expected saving (cost) with misoprostol

	<i>Scotland</i>	<i>England (WMRHA)</i>
<i>Base case (400 µg/day, undetected ulcer rate 30%)</i>	6.1	8.4
Undetected ulcer rate 15%	11.1	12.7
No undetected ulcers	16.2	17.1
Ulcers over 0.5 cm	(9.9)	(7.5)
Higher dose (800 µg/day)	(25.0)	(22.7)
Hospitalization rate – 5.81%	6.9	9.5
– 1.86%	0.2	0.5
No ulcer cases – all have initial investigations	(6.4)	(6.7)
Savings in direct hospital costs only	(0.6)	0.1
Half endoscopy costs	(1.3)	2.5
Less intensive ambulatory care:-		
GP visits, investigations and out-patient attendances		
Reduced by 25% from base case	(0.1)	2.3
Reduced by 50% from base case	(6.2)	(3.7)

tees budgets for drug spending and that general practitioners will receive indicative budgets for their prescribing costs. Therefore, it will be increasingly important to demonstrate that prescribing certain proprietary brands of medicine is justified,

particularly when, as in the case of misoprostol, a drug may be used prophylactically to moderate the adverse effects of another.

This study has shown that in many cases the savings in health care resources from the pro-

phylactic use of misoprostol in patients on NSAIDs with abdominal pain outweigh the costs. Of course the real savings are not the financial amounts themselves, but the scarce health service resources in the ambulatory and hospital care sectors that are freed for the care of other patients. Financial savings may accrue in the longer term, however, if bed capacity can be reduced, or if general practitioners can cope with longer patient lists.

The impact of varying the key assumptions has been explored by sensitivity analysis. For example, the average costs of ambulatory care in the no ulcer group depend upon the proportion with transient symptoms. We have used 70% (misoprostol) and 57% (no prophylaxis) as in the controlled clinical trial.¹¹ However, if conservatively all patients are assumed to have persistent symptoms and to be investigated the expected cost increases to £162 and there is a net cost of £6.40 in Scotland with misoprostol.

Intention to treat ulcer rates from the clinical trial were used, as they are more relevant to clinical practice and include the effect of non-compliance. However, prescribing in general practice may lead to a lower compliance than implicit in these rates. An additional tree was added to account for non-compliant patients (Figure 1) all groups of whom were conservatively assumed to receive no clinical benefit, and receive only half the relevant amount of misoprostol. Sensitivity analysis shows that if compliance were 20% worse, the expected savings would fall by around £5 in Scotland. The intention to treat results were similar to those obtained using the evaluable cohort ulcer rates and a 15% non-compliance rate.

The savings from prophylaxis would also be lower if the costs of hospitalization were reduced. However, the hospitalization rate for ulcer is difficult to estimate from available UK data and we used 5.34% which, given an ulcer rate of 21.7%, is equivalent to 11.6 admissions for 1,000 cases over 3 months or per 250 patient years. A recent prospective study on rheumatoid arthritis cases in the USA³⁶ gives a figure for the over 60s of 3.75 per 250 patient years and a population-based study of NSAID users in Scotland, 12.6 for the 60–79 age group.¹⁰ The equivalent hospitalization rate would be 5.81% which slightly increases expected savings. These data¹⁰ were then adjusted for severity by standardizing to the proportion (48%) of admissions with perforation and haemorrhage found in the Glasgow study. This indicates that a hospitalization rate of 1.86% would be more appropriate, which balances the cost and benefit of misoprostol. In addition, not all hospital costs may be

avoided if fewer ulcer cases are admitted. If it is assumed that only direct ulcer treatment costs are saved (i.e. 'hotel' costs are still incurred) then a balance is obtained again. The analysis is sensitive to endoscopy costs – the effect of halving these is shown in Table V. New data can be incorporated in the analysis when they become available.

The savings from prophylaxis also depend crucially on the extent to which general practitioners will investigate patients with persistent symptoms. The results of the GP surveys in Glasgow and Birmingham were reassuringly similar, but both may reflect an ideal management which, in practice, might be less intensive. Therefore the ambulatory care components, except for drug costs, were reduced to 75% of the level assumed in the base case, eliminating the savings from prophylaxis in Scotland, and leaving a small net saving in WMRHA. Reduction to 50% led to net costs.

This economic evaluation does not consider the wider benefits of prophylaxis to the patient, for example the ability to maintain control of painful arthritis by continuing treatment on an existing effective NSAID. In addition, hospitalization for ulcer has a significant case fatality rate (6% in Scotland, 9% in England), and routine data sources apparently underestimate the proportion of cases with arthritis – perhaps due to the frequent omission of the locomotor system from medical clerking.³⁷

This study has not been extended to calculate cost-effectiveness in terms of cost per life-year saved, owing to the great uncertainty involved in extrapolating from a 3 month clinical trial, neither is it certain that the increased risks associated with NSAID use persist as they may decline after an initial period.³⁸ The increasing quest for economic efficiency in health care means that the non-financial economic benefits should not be overlooked.

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