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MAXAIR™
AUTOHALER™
(pirbuterol acetate inhalation aerosol) Bronchodilator Aerosol
For Inhalation Only
BRIEF SUMMARY

INDICATIONS AND USAGE: MAXAIR AUTOHALER is indicated for the prevention and reversal of bronchospasm in patients with reversible bronchospasm including asthma. It may be used with or without concurrent theophylline and/or steroid therapy.
CONTRAINDICATIONS: MAXAIR is contraindicated in patients with a history of hypersensitivity to any of its ingredients.
WARNINGS: As with other beta adrenergic aerosols, MAXAIR should not be used in excess. Controlled clinical studies and other clinical experience have shown that MAXAIR like other inhaled beta adrenergic agonists can produce a significant cardiovascular effect in some patients, as measured by pulse rate, blood pressure, symptoms, and/or ECG changes. As with other beta adrenergic aerosols, the potential for paradoxical bronchospasm (which can be life threatening) should be kept in mind. If it occurs, the preparation should be discontinued immediately and alternative therapy instituted.

Fatalities have been reported in association with excessive use of inhaled sympathomimetic drugs.

The contents of MAXAIR AUTOHALER are under pressure. Do not puncture. Do not use or store near heat or open flame. Exposure to temperature above 120°F may cause bursting. Never throw container into fire or incinerator. Keep out of reach of children.
PRECAUTIONS: General — Since pirbuterol is a sympathomimetic amine, it should be used with caution in patients with cardiovascular disorders, including ischemic heart disease, hypertension, or cardiac arrhythmias, in patients with hyperthyroidism or diabetes mellitus, and in patients who are unusually responsive to sympathomimetic amines or who have convulsive disorders. Significant changes in systolic and diastolic blood pressure could be expected to occur in some patients after use of any beta adrenergic aerosol bronchodilator.
Information for Patients — MAXAIR effects may last up to five hours or longer. It should not be used more often than recommended and the patient should not increase the number of inhalations or frequency of use without first asking the physician. If symptoms of asthma get worse, adverse reactions occur, or the patient does not respond to the usual dose, the patient should be instructed to contact the physician immediately. The patient should be advised to see the Illustrated Patient's Instructions for Use.

The Autohaler actuator should not be used with any other inhalation aerosol canister. In addition, canisters for use with MAXAIR AUTOHALER should not be utilized with any other actuator.
Drug Interactions — Other beta adrenergic aerosol bronchodilators should not be used concomitantly with MAXAIR because they may have additive effects. Beta adrenergic agonists should be administered with caution to patients being treated with monoamine oxidase inhibitors or tricyclic antidepressants, since the action of beta adrenergic agonists on the vascular system may be potentiated.
Carcinogenesis, Mutagenesis and Impairment of Fertility — Pirbuterol hydrochloride administered in the diet to rats for 24 months and to mice for 18 months was free of carcinogenic activity at doses corresponding to 200 times the maximum human inhalation dose. In addition, the intragastric intubation of the drug at doses corresponding to 6250 times the maximum recommended human daily inhalation dose resulted in no increase in tumors in a 12-month rat study. Studies with pirbuterol revealed no evidence of mutagenesis. Reproduction studies in rats revealed no evidence of impaired fertility.
Teratogenic Effects — Pregnancy Category C — Reproduction studies have been performed in rats and rabbits by the inhalation route at doses up to 12 times (rat) and 16 times (rabbit) the maximum human inhalation dose and have revealed no significant findings. Animal reproduction studies in rats at *oral doses* up to 300 mg/kg and in rabbits at oral doses up to 100 mg/kg have shown no adverse effect on reproductive behavior, fertility, litter size, peri- and postnatal viability or fetal development. In rabbits at the highest dose level given, 300 mg/kg, abortions and fetal mortality were observed. There are no adequate and well controlled studies in pregnant women and MAXAIR should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.
Nursing Mothers — It is not known whether MAXAIR is excreted in human milk. Therefore, MAXAIR should be used during nursing only if the potential benefit justifies the possible risk to the newborn.
Pediatric Use — MAXAIR AUTOHALER is not recommended for patients under the age of 12 years because of insufficient clinical data to establish safety and effectiveness.
ADVERSE REACTIONS: The following rates of adverse reactions to pirbuterol are based on single and multiple dose clinical trials involving 761 patients, 400 of whom received multiple doses (mean duration of treatment was 2.5 months and maximum was 19 months).

The following were the adverse reactions reported more frequently than 1 in 100 patients: **CNS:** nervousness (6.9%), tremor (6.0%), headache (2.0%), dizziness (1.2%). **Cardiovascular:** palpitations (1.7%), tachycardia (1.2%). **Respiratory:** cough (1.2%). **Gastrointestinal:** nausea (1.7%).

The following adverse reactions occurred less frequently than 1 in 100 patients and there may be a causal relationship with pirbuterol: **CNS:** depression, anxiety, confusion, insomnia, weakness, hyperkinesia, syncope. **Cardiovascular:** hypotension, skipped beats, chest pain. **Gastrointestinal:** dry mouth, glossitis, abdominal pain/cramps, anorexia, diarrhea, stomatitis, nausea and vomiting. **Ear, Nose and Throat:** smell/taste changes, sore throat. **Dermatological:** rash, pruritus. **Other:** numbness in extremities, alopecia, bruising, fatigue, edema, weight gain, flushing.

Other adverse reactions were reported with a frequency of less than 1 in 100 patients but a causal relationship between pirbuterol and the reaction could not be determined: migraine, productive cough, wheezing, and dermatitis.

The following rates of adverse reactions during three-month controlled clinical trials involving 310 patients are noted. The table does not include mild reactions.

PERCENT OF PATIENTS WITH MODERATE TO SEVERE ADVERSE REACTIONS

Reaction	Pirbuterol N = 157	Metaproterenol N = 153	Reaction	Pirbuterol N = 157	Metaproterenol N = 153
Central Nervous System			**Gastrointestinal**		
tremors	1.3%	3.3%	nausea	1.3%	2.0%
nervousness	4.5%	2.6%	diarrhea	1.3%	0.7%
headache	1.3%	2.0%	dry mouth	1.3%	1.3%
weakness	.0%	1.3%	vomiting	.0%	0.7%
drowsiness	.0%	0.7%	**Dermatological**		
dizziness	0.6%	.0%	skin reaction	.0%	0.7%
Cardiovascular			rash	.0%	1.3%
palpitations	1.3%	1.3%	**Other**		
tachycardia	1.3%	2.0%	bruising	0.6%	.0%
Respiratory			smell/taste change	0.6%	.0%
chest pain/tightness	1.3%	.0%	backache	.0%	0.7%
cough	.0%	0.7%	fatigue	.0%	0.7%
			hoarseness	.0%	0.7%
			nasal congestion	.0%	0.7%

OVERDOSAGE: The expected symptoms with overdosage are those of excessive beta-stimulation and/or any of the symptoms listed under adverse reactions, e.g., angina, hypertension or hypotension, arrhythmias, nervousness, headache, tremor, dry mouth, palpitation, nausea, dizziness, fatigue, malaise, and insomnia.

Treatment consists of discontinuation of pirbuterol together with appropriate symptomatic therapy.

The oral acute lethal dose in male and female rats and mice was greater than 2000 mg base/kg. The aerosol acute lethal dose was not determined.

Note: The indented statement below is required by the Federal government's Clean Air Act for all products containing or manufactured with chlorofluorocarbons (CFC's).

WARNING: Contains trichloromonofluoromethane and dichlorodifluoromethane, substances which harm public health and environment by destroying ozone in the upper atmosphere.

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CAUTION: Federal law prohibits dispensing without prescription.
Store between 15° and 30°C (59° to 86°F).
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Is Misoprostol Cost-effective in the Prevention of Nonsteroidal Anti-inflammatory Drug–Induced Gastropathy in Patients With Chronic Arthritis?

A Review of Conflicting Economic Evaluations

Gerold Stucki, MD; Magnus Johannesson, PhD; Matthew H. Liang, MD, MPH

Whether misoprostol, a synthetic prostaglandin E_1 analogue, should be routinely prescribed along with nonsteriodal anti-inflammatory drugs (NSAIDS) to prevent gastric damage is of great clinical importance and has profound cost implications. No consensus exists on whether misoprostol cotherapy results in a cost-saving, is cost-effective, or is costly. The different conclusions reached by five economic evaluations of misoprostol can be explained solely by the assumed absolute risk reduction of symptomatic ulcer, which was more than seven times greater in the studies that concluded that misoprostol was cost-effective than in a study that concluded misoprostol to be costly. Since no study has directly shown the effectiveness of misoprostol cotherapy in preventing clinically significant ulcer disease (ie, hemorrhage and preforation), it is impossible to judge which assumptions are most appropriate. The absence of firm data on the rate of NSAID-induced gastric ulcers reduced by misoprostol makes it impossible to conclude whether it is cost-effective in patients with chronic arthritis who use NSAIDS. *(Arch Intern Med. 1994;154:2020-2025)*

Concerns about the increase in health care expenditure have stimulated research on the costs and benefits of health care interventions. Misoprostol, a synthetic prostaglandin E_1 analogue, is the only drug approved by the Food and Drug Administration for the prevention of gastric damage from nonsteroidal anti-inflammatory drugs (NSAIDs). Nonsteroidal anti-inflammatory drugs are used by more than 8% of the US population,[1,2] and NSAID-associated gastropathy accounts for at least 2600 deaths and 20 000 hospitalizations each year. For rheumatoid arthritis, $200 million is spent each year for hospitalizations due to this complication.[3] Whether misoprostol should be prescribed routinely along with NSAIDs is therefore of great clinical importance and has profound cost implications.

The published economic evaluations of misoprostol are interpreted by Roth et al[4] as "the data has consistently demonstrated that it is cost-effective to coprescribe misoprostol" in high-risk patients, but others point out limitations of the studies,[5,6] warn against their uncritical extrapolation,[7] or question the assumptions of the evaluations.[8] This review evaluates the evidence on the cost-effectiveness of routine prescription of misoprostol to prevent NSAID-induced gastric ulcers in patients with arthritis conditions and outlines important areas for future research.

From the Department of Health Policy and Management, Harvard School of Public Health (Drs Stucki, Johannesson, and Liang), and the Departments of Medicine (Dr Liang) and Rheumatology/Immunology (Dr Liang) and Robert B. Brigham Multipurpose Arthritis and Musculoskeletal Disease Center (Drs Stucki and Liang), Brigham and Women's Hospital, Boston, Mass. Dr Johannesson is now with the Centre for Health Economics, Stockholm (Sweden) School of Economics.

REVIEW OF PUBLISHED ECONOMIC EVALUATIONS

Article Selection

Economic studies published in the English language in peer-reviewed journals were identified by a MEDLINE search up

to December 1993. Five studies were identified.[9-13]

General Comparison of Studies

Four studies carried out an analysis of the economic benefit of misoprostol in patients receiving NSAIDs for osteoarthritis[9-12] and one study for rheumatoid arthritis.[13] An American study[9] and a British study[10] were planned together to allow cross-national comparisons[14]; both studies were funded by the manufacturer of misoprostol. The studies by Edelson et al[13] and Gabriel et al[12] were not supported by industry and no information on research support was made available for the study by Jönsson and Haglund.[11]

All studies used the same analytic model and compared the costs and probability of developing a symptomatic gastric ulcer of NSAID use with and without routine misoprostol (**Table 1**) therapy. Of those who had development of a symptomatic gastric ulcer, some would be hospitalized. Of those hospitalized, a certain proportion would require an operation, and the rest would be treated medically.

In each study "symptomatic gastric ulcer" and "hospitalization" were defined somewhat differently. Symptomatic gastric ulcer was described as "ulcer,"[9-11] as "symptomatic ulcer" or "important gastrointestinal event,"[12] or "bleed."[13] Hospitalization was described as "hospitalization,"[9-11] defined as "serious bleed,"[12] or as "complicated ulcer."[13] Gabriel et al[12] were the only ones to factor in the costs of misoprostol-induced diarrhea, and Edelson et al[13] was the only study to include fatal bleeding.

Knill-Jones et al[10] performed a cost comparison to identify the least costly treatment alternative, while Hillman and Bloom[9] evaluated the price at which the two treatment alternatives would cost the same. The remaining three studies used symptomatic ulcer avoided as the measure of effectiveness and calculated the cost to prevent a symptomatic ulcer. In addition, Edelson et al[13] calculated the cost per life-year gained. No study considered the quality-of-life impact of NSAID-induced gastropathy or of significant side effects of misoprostol such as diarrhea.

All studies used the probability of an endoscopically detected gastric ulcer developing with misoprostol prophylaxis from a 3-month double-blind randomized trial by Graham et al[15] who studied the effect of misoprostol in 420 NSAID recipients with osteoarthritis *and* epigastric pain. Different from the other studies, Hillman and Bloom[9] and Jönsson and Haglund[11] did not use the published data based on intent to treat with a risk of 21.7% having an ulcer develop within a 3-month period of treatment under NSAID therapy vs 5.6% under NSAID and misoprostol therapy. Instead they used an "assessable cohort" approach, assuming a risk of 31.3% with NSAIDs vs 2% for patients receiving misoprostol cotherapy. Edelson et al[13] used only the relative risk reduction from the study by Graham et al[15] but used other data to calculate the absolute risk of "bleeding" over 1 year. The probabilities of a symptomatic ulcer developing among patients with endoscopic ulcer, compliance with misoprostol treatment, rate of hospitalization, and surgery were obtained from different data sources and varied among the studies.

The two American analyses[9,13] studied 800 μg of misoprostol daily, and the other three studied 400 μg. Edelson et al[13] used a time frame of 1 year, whereas the other study used 3 months. Jönsson and Haglund[11] included both health care costs and indirect costs (ie, those attributable to loss of productivity at work), whereas the other studies included only health care costs. The assessment of costs varied between the studies.

Table 1. Methodological Characteristics of Economic Evaluations of Misoprostol Prophylaxis for NSAID-Induced Gastric Ulcer in Patients With Arthritis Conditions*

	Hillman and Bloom[9]	Knill-Jones et al[10]	Jönsson and Haglund[11]	Edelson et al[13]	Gabriel et al[12]
Type of analysis	Cost analysis	Cost analysis	Cost-effectiveness	Cost-effectiveness	Cost-effectiveness
Perspective	Health care system	Health care system	Societal	Health care system	Health care system
Effectiveness measure	...	...	Symptomatic ulcer avoided	Years of life saved; bleed avoided	Gastrointestinal event avoided
Costs included	Direct costs	Direct costs	Direct and indirect costs	Direct costs	Direct costs
Estimation of hospitalization costs					
Price per unit of service	Charges	Accounting costs	Accounting costs of average hospitalization	Charges	Charges
Resource utilization	Epidemiologic study	Case review		Assumptions by the authors	Expert consensus
Estimation of ambulatory costs					
Price per unit of service	Charges	Accounting costs	Accounting costs	Charges	Charges
Resource utilization	Survey of internists	Survey of general practitioners	Assumptions by the authors	Assumptions by the authors	Expert consensus

**NSAID indicates nonsteroidal anti-inflammatory drug.*

Table 2. Risk Estimates Used in Five Economic Evaluations of Misoprostol Prophylaxis for NSAID-Induced Gastric Ulcer in Patients With Arthritic Conditions*

Study	Dose, μg (Price/d†)	Endoscopically Detected Ulcer Rate			Symptomatic Ulcer Rate		
		No Misoprostol, %	Misoprostol, %	Risk Difference, pu	No Misoprostol, %	Misoprostol, %	Risk Difference, pu
Hillman and Bloom[9]	800 ‡	31.3	2	29.3	18.8	1.2	17.6
Knill-Jones et al[10]	400 ($0.77)	21.7	5.6	16.1	15.2	3.9	11.27‡
Jönsson and Haglund[11]	400 ($0.93)	31.3	8.2	23.1	18.8	4.9	13.9
lower risk (sensitivity analysis)	400	5	1.31	3.69	3	0.79	2.21
Edelson et al[13]	800 ($2.34)	NA	NA	NA	2.5 (9.4 annual risk‖)	0.135 (0.54 annual risk‖)	2.3 (8.9 annual risk‖)
Gabriel et al[12]	400 ($1.48)	21.6	5.6	16	14	4.1	9.9‡

NSAID indicates nonsteroidal anti-inflammatory drug; pu, percentage units; NA, not applicable.

†Cost figures, adjusted for average currency exchange rate in year of publication in US dollars, based on 1987,[9] 1988,[10,11] 1989,[13] and 1990 prices.[12]

‡The cost of misoprostol was not provided. Breakthrough pricing was evaluated instead.

§Absolute risk reduction used for the base-case analyses. Conversion of Swedish, British, and Canadian currencies into US dollars based on exchange rates for corresponding years.[17]

*‖Annual risk reversed to 3-month risk (3-month risk=[−0.25*ln(1-annual risk)]).*

RESULTS

Hillman and Bloom[9] found that the cost of the two treatment alternatives would be the same at a price of $1.74 per day for misoprostol and concluded that misoprostol cotherapy is cost saving (**Table 2**). The result was sensitive to assumptions about rates of silent ulcer and compliance but was less sensitive to rates of hospitalization and surgery.

Knill-Jones et al[10] concluded that misoprostol is cost saving. The result was sensitive to the silent ulcer rate, the compliance rate, and the ambulatory costs but not to assumptions about the hospitalization rate from ulcer disease.

Jönsson and Haglund[11] concluded that misoprostol is cost saving in patients with osteoarthritis suffering from epigastric pain. Inclusion of indirect costs only marginally changed the result. The result was sensitive to assumptions about the price of misoprostol, the compliance rate, the cost of ambulatory care, the risk of ulcer, and the reduction of that risk. It was not sensitive to assumptions about the rates of hospitalization and surgery.

Edelson et al[13] showed that the prophylactic administration of misoprostol to patients with rheumatoid arthritis resulted in costs of $5300 per bleed avoided, $381 500 per fatal bleed avoided, and $95 600 per life-year gained. The cost per life-year gained was sensitive to assumptions about compliance, the risk of bleeding, the risk of serious bleeding, and the risk of fatal bleeding. No sensitivity analysis of the cost per bleed avoided was presented. Compared with other well-accepted prevention strategies such as pneumococcal vaccination of the elderly ($2200 per year of life saved, 1989 prices), both the cost per life-year gained and cost per bleed avoided of $5300 were judged high.

Gabriel et al[12] concluded that misoprostol is cost-effective and costs $625 per symptomatic gastric ulcer prevented. The results were sensitive to assumptions about the ulcer complication rate (hospitalization), the cost of ambulatory treatment, and the cost of misoprostol.

COMMENT

Reasons for the Different Conclusions

The results of five economic evaluations of misoprostol prophylaxis for NSAID-induced gastropathy range from cost saving[9-11] or cost-effective[12] to excessively costly.[13] These different conclusions could result from the use of different decision models, different probabilities, different target populations and treatment periods, and different cost estimates or computational errors.

A critical examination of the studies shows that the apparent differences in the results are not from differences in the decision-analytic model or computational errors but from the assumptions about the magnitude of the misoprostol effect. Four studies are based exclusively on the results of one randomized controlled trial evaluating the effect of misoprostol on the development of endoscopically detected ulcer in patients with osteoarthritis.[15] Edelson et al[13] combined the relative risk from this trial with an absolute ulcer risk obtained from epidemiologic studies. Since to our knowledge no study has directly shown the effectiveness of misoprostol cotherapy in preventing clinically significant ulcer disease such as hemorrhage and perforation, it is not possible to judge which assumptions are most appropriate. In Table 2, the absolute risk reduction of Edelson et al[13] is converted to a

Compliance-Adjusted Rate			
No Misoprostol, %	Misoprostol, %	Risk Difference, pu	Results†
11.3	0.72	10.58‡	Cost saving if drug costs <$1.74/d
NA	NA	NA	Cost saving
14.8	3.4	10.95‡	Cost saving
2.37	0.62	1.75	Net costs per symptomatic ulcer avoided ($3754)
1.5	0.08	1.4‡	Net costs per bleed avoided ($5300)
NA	NA	NA	Net costs per gastrointestinal event avoided ($625)

3-month risk figure[16] to allow a comparison with the other studies. After adjustment for silent ulcer rate and compliance, the absolute risk reduction of Edelson et al[13] is 1.4 percentage units (pu) whereas the other four studies use an absolute risk reduction of approximately 10 pu. The critical impact of this difference can be demonstrated comparing the result of Edelson et al[13] with that of Jönsson and Haglund.[11] When the latter authors varied the absolute risk reduction in a sensitivity analysis using approximately 1.75 pu instead of 10.95 pu, the net costs per symptomatic ulcer avoided were estimated to be $3754 (Table 2). This cost-effectiveness ratio is of similar magnitude to the $5300 reported by Edelson et al,[13] and both studies would have reached the conclusion that misoprostol cotherapy is a costly strategy for preventing NSAID gastropathy.

Differences in hospitalization rates used probably explain why Gabriel et al[12] showed net costs whereas Jönsson and Haglund[11] and Knill-Jones et al[10] documented cost savings even though the same drug dose and similar absolute ulcer risk reduction were used. Knill-Jones et al[10] used a hospitalization rate of 5.6% and Jönsson and Haglund[11] used a figure of 8.6% among patients with symptomatic ulcer, whereas the 0.3% reported by Gabriel et al[12] for patients younger than 60 years of age is considerably lower. Using sensitivity analysis, Gabriel et al[12]showed that a hospitalization rate of 1.2% among NSAID users (a figure corresponding to a conditional probability of hospitalization among ulcer users of 8.6%) would result in cost savings. This risk is, in fact, equivalent to the probability (8.6%) assumed by Jönsson and Haglund[11] and by Hillman and Bloom.[9]

Hillman and Bloom[9] examined 800 μg of misoprostol daily rather than 400 μg in the other three studies[10-12] and calculated an absolute risk reduction of approximately 10.6 pu—a value similar to the approximately 11 pu used by Knill-Jones et al[10] and Jönsson and Haglund.[11] The similar absolute risk reduction computed despite differences in the absolute risk for different doses of misoprostol results from different interpretation of the Graham et al[15] clinical trial. Knill-Jones et al[10] and Gabriel et al[12] used intent-to-treat data, whereas Hillman and Bloom[9] and Jönsson and Haglund[11] included only patients who completed misoprostol therapy (the assessable cohort). The latter yields a 31.3% risk of endoscopically detected ulcer without misoprostol and a 2% risk with 800 μg of misoprostol daily, as compared with 21.7% and 1.4% actually reported by Graham et al.[15] When the studies of Hillman and Bloom[9] and Jönsson and Haglund[11] are adjusted for compliance (assuming rates of 60% and 79%, respectively), similar absolute risk reduction results.

Different study conclusions may also be related to assumptions about the costs of misoprostol and ambulatory care. Estimates of ambulatory costs were similar and between $733 and $986 in four studies[9,11,12] (figures based on the average currency exchange rate in the year of analysis).[17] Ambulatory costs were lower in Britain ($561[10]), but since misoprostol costs were also lowest in Britain, this had no impact on the result. For the other studies, the different costs of misoprostol were mainly due to the different doses used. The effect of the higher dose in the study of Edelson et al[13] was small compared with the effect of assumptions about absolute risk reduction.

Critique of the Studies

Endoscopically observed gastric damage has been questioned as a clinically meaningful end point since progression to significant bleeding and frank gastric ulcer is not clear. The endoscopic ulcer risk from NSAID therapy varies between 5% and 25%.[18] The rate of 21.7% observed in the study of Graham et al[15] and used by four studies[9-12] is likely to be high. In recent studies by Verdickt et al[19] and Graham et al[20] on cotherapy of misoprostol with different NSAIDs, the absolute endoscopic gastric ulcer risk was 4%[19] and 9%[20] in the placebo group, which is considerably smaller than the one used in the economic evaluations. Using the correspondingly smaller

absolute risk reduction would have led to net costs for misoprostol in all studies.

The absolute gastric ulcer risk is critical to the result and differs between patient populations. Patients with osteoarthritis (the focus of four studies) are more likely to have development of an NSAID-induced gastropathy since they are generally elderly, a group shown to be at increased risk.[21] Patients with rheumatoid arthritis (the object of the study of Edelson et al[13]), however, may be at increased risk owing to their frequent steroid use in combination with NSAID therapy.[21] However, whether the two diseases themselves are associated with a different ulcer risk is unknown. Of more importance may be the NSAID utilization pattern. The cumulative risk in long-term for rheumatoid arthritis is likely to be higher than in short-term or intermittent users as in osteoarthritis. However, the cumulative effect from misoprostol prophylaxis is also dependent on the hazard function of gastropathy developing under NSAID therapy. Less cumulative effectiveness and a higher cost-effectiveness ratio are expected if the risk of NSAID-induced gastropathy decreases over time. A decreasing risk over time has been suggested by epidemiologic studies[2,22] and corresponds to the biologic phenomenon of "gastric adaptation."[23] Alternatively, the decreasing risk may be explained by subjects intolerant of NSAIDs stopping therapy early after starting NSAID therapy; the hazard function itself may well be stable over time. The last possibility is consistent with a constant hospitalization rate observed over years among patients with rheumatoid arthritis.[3] Better epidemiologic data on the hazard function, the risk of first users vs repeated users, and the absolute risk for patients with different conditions are therefore for more precise estimates and a more accurate economic evaluation. Finally, the scenarios studied should be clinically relevant and the four studies that model decision-making for osteoarthritis beg the question altogether of whether NSAIDs are necessary and for how long. Recent data show that analgesic therapy with acetaminophen is as effective as NSAIDs.[24,25] Even in the presence of an inflammatory component, prolonged dosing of NSAIDs may not be necessary.

The value judgment of whether the cost of prophylaxis per symptomatic ulcer prevented is acceptable cannot be deduced unless we know how much society is willing to spend to avoid an ulcer. The comparison of costs with "symptomatic ulcer prevented" used in the published economic evaluations is difficult to interpret since the burden of ulcer disease remains unquantified and important effects such as adverse events and death are omitted. It would therefore be preferable to express the effects in terms of quality-adjusted life-years,[26] healthy-years equivalents,[27] or willingness to pay.[28] Expressing the effects in terms of utilities or willingness to pay aggregates important health effects, including suffering from gastropathy, death, and adverse treatment effects into one single, common unit and permits meaningful comparisons with other health-care programs.

The most important component of cost that must be investigated further is ambulatory care, since the results of all five studies were sensitive with respect to these costs. It is critical to obtain actual ambulatory costs on the basis of observed utilization.

CONCLUSION

Concern about the clinical relevance of modeling 3-month NSAID usage in osteoarthritis and uncertainty about key assumptions in the studies published to date make it hazardous to draw conclusions about the cost-effectiveness of prophylactic misoprostol in NSAID users with arthritic conditions. Routine prophylactic use of misoprostol, a practice promulgated with the marketing of fixed combinations of misoprostol with NSAIDs available in Europe and Canada, is likely to be excessively costly for many patients at low risk of gastropathy. The evidence of cost-effectiveness is not strengthened by the publication of more studies based on the same uncertain assumptions. Instead, better effectiveness data on clinically relevant outcomes and evaluation methods that integrate all relevant health effects into one common, interpretable unit are needed before misoprostol is recommended on cost-effectiveness grounds.

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