Omeprazole led to greater remission rate than misoprostol for ulcers associated with non-steroidal anti-inflammatory drugs


Question
In patients with gastroduodenal ulcers associated with long term non-steroidal anti-inflammatory drug (NSAID) use, is omeprazole more effective than misoprostol for promoting and maintaining healing?

Design
6 month randomised, double blind, controlled trial.

Setting
93 clinical centres in 14 countries.

Patients
935 patients who were 18–85 years of age; had conditions that required continuous treatment with at least a minimal dose of oral or rectal NSAIDs; and had ulcers > 3 mm in diameter in stomach, duodenum, or both, or >10 gastric or duodenal erosions. Exclusion criteria were reflux esophagitis, clinically important upper gastrointestinal bleeding, pyloric stenosis, history of gastric surgery, or gastrointestinal disorders that could impair drug absorption. Follow up was 99% (mean age 58 y, 63% women).

Intervention
Patients were allocated to omeprazole, 20 mg once/day (n=308) or twice/day (n=315), or misoprostol, 200 µg 4 times/day (n=298). Patients whose ulcers were considered healed were allocated to 1 of 3 maintenance treatments: omeprazole, 20 mg/day (n=274); misoprostol, 200 µg twice/day (n=296); or placebo (n=155).

Main outcome measures
Predefined treatment success at 8 weeks and maintenance of remission at 6 months.

Main results
Treatment success at 8 weeks did not differ between each omeprazole group and the misoprostol group (table). At 6 months, more patients were in remission in the omeprazole group, 20 mg (59% v 48%, p=0.001) or placebo (p<0.001) groups. Misoprostol led to more adverse events than did omeprazole, 20 mg (59% v 48%, p=0.007) or 40 mg (59% v 46%, p=0.002).

Conclusions
In patients who used long term non-steroidal anti-inflammatory drugs, omeprazole (20 or 40 mg/day) was as effective as misoprostol (800 µg/day) for healing ulcers. Omeprazole (20 mg/day) was better at maintaining remission than misoprostol (400 µg/day). Misoprostol caused more adverse events during treatment.

*p values calculated from data in article.

Source of funding: Astra Hässle, Sweden.

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**NS** = not significant; **RBI** = proportional increase in rates of good outcomes between groups; **NNT** = number of patients who must receive omeprazole to achieve 1 additional good outcome.

Note: the material presented in the table was not in the original article on which the commentary is based.

Commentary
Managing upper gastrointestinal disease associated with the use of non-steroidal anti-inflammatory drugs (NSAIDs) continues to present major problems for clinicians. Do the recent studies by Hawkey et al and Yeomans et al provide definitive recommendations?

The first, in 935 patients, compared omeprazole 20 or 40 mg daily with misoprostol 200 mcg four times daily for 8 weeks in healing gastric or duodenal ulcers or erosions detected endoscopically in NSAID takers, with re-randomisation of 732 successes after healing to omeprazole 20 mg, or misoprostol 200 mcg daily, or placebo for 6 months. On an intent-to-treat basis overall healing rates were: omeprazole 20 mg 75%, 40 mg 75%, and misoprostol 71% (confidence intervals (CI) not given, differences not significant). In the maintenance phase omeprazole recipients fared significantly better than misoprostol or placebo recipients (61%, 48%, and 27% respectively). Adverse effects were more common in the healing phase on misoprostol, mainly because of diarrhoea, abdominal pain and flatulence, with 16.9% dropping out compared with 9.9% and 10.6% dropping out on the two omeprazole regimens.
Omeprazole was more effective for healing and preventing relapse of ulcers associated with long term NSAID use


Question
In patients with gastroduodenal ulcers and erosions associated with long term nonsteroidal anti-inflammatory drug (NSAID) use, is omeprazole more effective than ranitidine for healing and preventing relapse?

Design
6 month randomised, double blind, controlled trial.

Setting
73 clinical centres in 15 countries.

Patients
541 patients who were 18–85 years of age, had conditions requiring continuous treatment with NSAIDs above specified therapeutic doses with ≤10 mg/day of prednisolone, and had ulcers ≥3 mm in diameter or >10 erosions in the stomach or duodenum. Exclusion criteria were neck instability, erosive or ulcerative esophagitis, pyloric stenosis, major active gastrointestinal bleeding, or disorders that could modify the absorption of study drugs. Follow up was 99% (mean age 56 y, 67% women) for the healing phase and 98% (mean age 56 y, 69% women) for the maintenance phase.

Intervention
Patients were allocated to omeprazole, 20 mg/day (n=174) or 40 mg/day (n=187), or ranitidine, 50 mg twice/day (n=174), for 4–8 weeks. Patients whose ulcers were considered healed were allocated to 1 of 2 maintenance treatments: omeprazole, 20 mg/day (n=210), or ranitidine, 150 mg twice/day (n=213).

Main outcome measures
Predefined treatment success at 8 weeks and maintenance of remission at 6 months.

Main results
More patients in each omeprazole group than in the ranitidine group had treatment success at 8 weeks (p<0.001 for both comparisons) (table). More patients in the omeprazole group than in the ranitidine group achieved remission at 6 months (p=0.004) (table). Adverse events did not differ among groups for the healing phase (30% and 38% for omeprazole, 20 mg and 40 mg, and 40% for ranitidine) or maintenance phase (64% for omeprazole and 58% for ranitidine).

Conclusions
In patients with ulcers associated with long term non-steroidal, anti-inflammatory drug use, omeprazole was more effective than ranitidine for healing and maintaining remission. Adverse event rates were high in all groups.

Source of funding: Astra Hässle Mölndal, Sweden.

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Omeprazole (OM) v ranitidine for ulcers associated with long term non-steroidal anti-inflammatory drug use*

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>OM 20 mg/day</th>
<th>OM 40 mg/day</th>
<th>Ranitidine 300 mg/day</th>
<th>RBI (95% CI)</th>
<th>NNT (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Healing at 8 weeks</td>
<td>80%</td>
<td>63%</td>
<td>27% (12 to 46)</td>
<td>6 (4 to 13)</td>
<td></td>
</tr>
<tr>
<td>Healing at 8 weeks</td>
<td>79%</td>
<td>63%</td>
<td>25% (10 to 44)</td>
<td>7 (4 to 16)</td>
<td></td>
</tr>
<tr>
<td>Remission at 6 months</td>
<td>72%</td>
<td>59%</td>
<td>22% (6 to 40)</td>
<td>8 (5 to 27)</td>
<td></td>
</tr>
</tbody>
</table>

*RBI = proportional increase in rates of good outcomes between groups; NNT = number of patients who must receive omeprazole to achieve 1 additional good outcome.

Note: the material presented in the table was not in the orginal article on which the commentary is based.

(commentary continued from page 744)

In the second study, 541 similar patients also received omeprazole 20 or 40 mg daily, or ranitidine 150 mg twice daily, for the same time and the 432 treatment successes were reassigned randomly to omeprazole 20 mg daily, or ranitidine 150 mg daily for 6 months. Healing rates were: omeprazole 20 mg 80%, 40 mg 79%, and ranitidine 63% (p<0.001 for both comparisons with ranitidine, CI not given). All treatments were generally well tolerated. Several issues must be examined before deciding whether the studies give clear guidance to clinicians: (a) Were the study designs robust? (b) Are differences detected likely to be real? (c) Can the conclusions be generalised?

Both studies were double blind and randomised. The authors do not describe the methods in detail, and we have to assume a double dummy technique, and for the first study it could even be a triple dummy technique because 20 mg and 40 mg omeprazole preparations differ. The point may matter because the more treatments given and the more often, then the greater the likelihood that patients will miss treatments. Non-compliance rates are not given and we must assume any were non-selective. There is also the possibility that where one treatment has particular adverse effects, like the diarrhoea and abdominal pain associated with the use of misoprostol, then investigators have a chance of guessing the true nature of the treatments in use. Endoscopies should, perhaps, have been carried out by individuals not responsible for supervising treatment.

The overall difference in success in healing for misoprostol versus omeprazole is marginal, and could be compatible with a small degree of superiority for either; confidence intervals would allow the reader to judge what that variation might be. Subgroup analyses are less dependable, and whether, as suggested, erosions really do better on misoprostol, or gastric ulcers on omeprazole is less certain. Other data suggest that omeprazole may do well in gastric ulceration compared with H₂ antagonists, but that is not the issue here. One problem that does not arise is skewing of results by dropouts, the rate being commendably low.

The maintenance data show clearly that no treatment gives a worse outcome than maintenance with misoprostol, which seemed less effective than omeprazole. Omeprazole also seemed superior to ranitidine. Interpretation has to take account of drug dosage. In the healing phases omeprazole was used in high and standard doses, and misoprostol and ranitidine at standard doses. It might be that gastrointestinal intolerance would limit or prevent a rise in
(commentary continued from page 745) the dose of misoprostol, but it is fair to ask if a reasonable comparison might have been between omeprazole 40 mg daily and ranitidine 300 mg twice daily. The same point can be made about the maintenance comparisons, where omeprazole was given in the standard dose used in the healing phase, whereas that of ranitidine was halved, and that of misoprostol reduced by three quarters. The dice seem loaded.

Generalisability—Strictly the results apply to patients on the particular NSAIDs who were prepared to be endoscoped. The authors point out that nearly half of the patients had moderate or severe symptoms. NSAID adverse effects on the upper gut have been shown to vary greatly with drug. In the same way, it is plausible that those adverse effects will be less likely on—for example, low dose ibuprofen than with high dose indomethacin or with piroxicam. Naproxen and diclofenac were commonly used NSAIDs in both studies, and indomethacin and ketoprofen each in one of them. However, that may reflect clinician preference ordinarily for these drugs. Naproxen and indomethacin have come out in the middle or higher reaches of gastrointestinal toxicity league tables, diclofenac in the lower reaches, with ketoprofen less certain in its placement.2,3

Conclusions—These are large, well-conducted studies. The authors suggest results are best applied in terms of risk factors of age, history (presumably of ulcer), type and dose of NSAID and the use of anticoagulants and corticosteroids. Unfortunately, no data are given from the trials to support these views. It would have seemed possible, for instance to factor out NSAID dosage in the results. The authors rightly point out that symptoms will be a poor guide, but what can the clinician do? The obvious options are to treat all on NSAIDs, say over the age of 60, to treatment selectively, and to endoscope takers and then decide. The first option will treat a significant number of people who do not need it at significant cost. (If there are 25 million NSAID prescriptions issued each year in the UK then the cost of additional therapy, unadjusted for benefits will be something like £500 million a year.) The third course implies an enormous endoscopic workload. If there are some 1.5 million takers currently in the 10 million aged 60 and over, then gastroenterologists could find a year’s endoscopic work absorbed, at the least. The pragmatic answer may be to treat selectively. Those selected might include those with previous ulcers, those taking corticosteroids, and those with significant symptoms (who will get endoscoped). On general principles there ought to be very few concurrent takers of anticoagulants and NSAIDs. Finally those receiving high doses of NSAIDs, particularly those near the top of the toxicity league, may merit prophylaxis. The advice of the Committee on Safety of Medicines of the UK given over 10 years ago still seems well placed—use simple analgesics first, then low doses of the least toxic NSAID (ibuprofen). Time will tell if COX selectivity makes the advice redundant.

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