Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis

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Abstract

***Objective*—To compare the relative risks of serious gastrointestinal complications reported with individual non-steroidal anti-inflammatory drugs.**

***Design*—Systematic review of controlled epidemiological studies that found a relation between use of the drugs and admission to hospital for haemorrhage or perforation.**

***Setting*—Hospital and community based case-control and cohort studies.**

***Main outcome measures*—(a) Estimated relative risks of gastrointestinal complications with use of individual drugs, exposure to ibuprofen being used as reference; (b) a ranking that best summarised the sequence of relative risks observed in the studies.**

***Results*—12 studies met the inclusion criteria. 11 provided comparative data on ibuprofen and other drugs. Ibuprofen ranked lowest or equal lowest for risk in 10 of the 11 studies. Pooled relative risks calculated with exposure to ibuprofen used as reference were all significantly greater than 1.0 (interval of point estimates 1.6 to 9.2). Overall, ibuprofen was associated with the lowest relative risk, followed by diclofenac. Azapropazone, tolmetin, ketoprofen, and piroxicam ranked highest for risk and indomethacin, naproxen, sulindac, and aspirin occupied intermediate positions. Higher doses of ibuprofen were associated with relative risks similar to those with naproxen and indomethacin.**

***Conclusions*—The low risk of serious gastrointestinal complications with ibuprofen seems to be attributable mainly to the low doses of the drug used in clinical practice. In higher doses ibuprofen is associated with a similar risk to other non-steroidal anti-inflammatory drugs. Use of low risk drugs in low dosage as first line treatment would substantially reduce the morbidity and mortality due to serious gastrointestinal toxicity from these drugs.**

Introduction

Interventions to reduce the morbidity and mortality from upper gastrointestinal disease caused by the widespread use of non-steroidal anti-inflammatory drugs include educational methods aimed at reducing prescribing, coprescription of a mucosal protective drug such as misoprostol, and the use of paracetamol as an alternative analgesic.[1 2] Another approach is to prescribe a drug associated with a comparatively low risk of gastrointestinal toxicity and use more toxic compounds only in the event of a poor clinical response to the first line drug.[3 4] However, evaluation of the data on comparative risk is difficult. Published epidemiological studies have provided variable coverage of individual drugs, making them unsuitable for meta-analytical approaches that attempt to pool data across all studies.[3] Also, apparent differences in the risks of gastrointestinal complications could be due to factors such as variation in the doses used or differences in the age or susceptibilities of the recipients of the various drugs.

We used meta-analytical methods to explore the range of reported relative risks. We were interested in the extent to which differences between drugs could be explained by the doses used. Our main hypothesis was that ibuprofen in the doses used in practice is associated with a lower relative risk of major upper gastrointestinal complications than other members of the class.[3 4]

Methods

LITERATURE SEARCH

A search of Medline CD-ROM was conducted for 1985-94 inclusive. This was supplemented by a review of the bibliographies of previously published meta-analyses and reviews.[5 6] Authors of relevant studies were contacted and asked to update their published results. In addition, they were sent a list of studies and asked whether they knew of work that was not listed.

QUALITY ASSESSMENT

We identified controlled epidemiological studies that found a relation between the use of non-steroidal anti-inflammatory drugs in the community and the development of serious peptic ulcer complications necessitating admission to hospital.[3 7-18] Some studies did not provide data on the use of individual drugs or did not show the association with gastrointestinal damage. These studies were excluded from further consideration. The remaining studies were assessed by the following criteria: ascertainment and validation of study outcomes, selection and comparability of controls, ascertainment of exposure, and control or adjustment for potential confounders. Tables summarising the results of these assessments and a list of excluded studies, with reasons for their rejection, are available by writing direct to DH.

DATA EXTRACTION

Data were extracted by LL and DH, differences being resolved by consensus. We extracted both the adjusted relative risks when these were provided by authors and the raw data relating to the use of individual drugs by cases and controls. These tasks were completed after a workshop attended by representatives of some of the groups that had carried out relevant studies. At the workshop authors clarified certain points and provided further data from three published studies, a reanalysis and extension of a previous study, and data on one unpublished study.[7 10 14-17]

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STATISTICAL METHODS

In estimating pooled relative risks we included only studies that provided comparative data for ibuprofen and the other drugs of interest. Consequently, the numbers of studies that contributed to the analyses varied from drug to drug. We calculated for every study the estimated relative risk of gastrointestinal complications with each comparator drug, exposure to ibuprofen rather than non-use of a drug being taken as reference. The odds ratio was assumed to provide a valid estimate of the relative risk. This required reanalysis of raw data from the authors' tables. It was necessary for some authors to provide unpublished data to enable this analysis to be carried out.[7 10 14-17] These data did not include adjustments for potential confounders. The estimated relative risks were pooled across studies by using the random effects model of Der Simonian and Laird.[19]

FINDING A SUMMARY RANK OF RELATIVE RISKS WITH INDIVIDUAL DRUGS

We tried to find an order that best summarised the sequence of adjusted relative risks seen with the drugs that had been included in two or more studies. The main advantage of this approach was that it maintained the within study comparisons and implicitly compared each agent simultaneously with every other drug analysed in a particular study.

The method entailed comparing all possible orderings of the non-steroidal anti-inflammatory drugs with the actual rankings observed in the studies. (We use the term ordering to refer to any theoretically possible arrangement of the drugs with respect to risk of complications and the term ranking to refer to the arrangements of the drugs observed within the studies.) A score was assigned to each of the 12 factorial possible orderings of the 12 drugs that were included in two or more studies. The score was derived as follows. The ranking of drugs by their relative risks in each study was compared with a given ordering in a pairwise fashion, the arrangement of each pair of agents in the study ranking being compared with that of the corresponding pair in the ordering, and a partial score allocated. Hence for a study with n drugs there was a total of $n(n-1)/2$ partial scores.

Partial scores were defined to take values between −1.0 and 1.0. A score was negative if the arrangement of the comparison pair in the study ranking was the opposite of that in the ordering being considered and positive otherwise. As a measure of the difference in risk between the pair of drugs we calculated a P value by statistical testing of the difference in relative risk between the two drugs. The partial score was calculated as 1.0 minus the P value, so that when the P value was small the partial score was close to 1.0 (thus making a large relative contribution to the score). When the P value was large the partial score was close to zero. With a relation of this nature, small studies contributed little because partial scores were small owing to their large P values. The total score associated with a particular ordering was the sum of the partial scores across all 12 studies (see below). The ordering associated with the maximum score was defined as the "best."

ASSESSING DOSE EFFECTS WITH INDIVIDUAL DRUGS

To evaluate dose effects with individual drugs we pooled the adjusted relative risks in strata defined by the dosage cut points reported by the authors. Five studies contributed data to the analyses of ibuprofen and naproxen[3 10 14 15 18] and three to the analysis of indomethacin.[10 15 18] The daily dosage cut points for each drug varied from study to study as follows: ibuprofen 1200 mg,[3 14] 1500 mg,[15 18] and 2400 mg[10]; naproxen 500 mg,[3] 750 mg,[15 18] and 1000 mg[10 14]; and indomethacin 75 mg[15 18] and 100 mg.[10] Relative risks for doses below the cut points were assigned to the low dose stratum and those above the cut points assigned to the high dose stratum. Within strata relative risks were pooled by the random effects model.[19]

Results

We identified 12 studies that examined relative risks of gastrointestinal complications with a total of 14 non-steroidal anti-inflammatory drugs and satisfied our criteria for inclusion. Twelve drugs had been included in two or more studies and 11 studies provided comparative data on ibuprofen and other agents.[3 7-18] Two reports were unpublished at the time of writing: one was an update and reanalysis of a previously published paper; the other had been published only as an abstract.[15 17] Three other studies were updated by the authors at the investigators' workshop or in subsequent correspondence.[7 10 14] All but one paper described case-control studies; three of the 12 used linkage of administrative records and one used computerised medical records. Three studies that employed automated records included validation of original medical records to ensure that patients had experienced the outcomes of interest.[10 15 18] However, one early study relied entirely on recorded diagnoses.[9]

All of the ad hoc studies employed classic case finding techniques with diagnostic confirmation of case status and ascertainment of prior drug use by structured interview. Controls in these studies were recruited from the community or from the same hospitals as the cases. Time windows for exposure also varied across the studies (from one week to three months). The most common exposure period was one week.

Despite variations in design and conduct of the studies the overall results were closely similar. When the estimated overall relative risks of complications with the use of non-steroidal anti-inflammatory drugs were calculated they lay mainly in the interval 3.0-5.0. These results were consistent with the findings of other meta-analyses.[5 6] Full details of these studies, including tables of overall results and data on the influence of dose, duration of treatment, and age and sex of recipients, are available on request.

RELATIVE RISKS WITH INDIVIDUAL DRUGS

Figure 1 shows the point estimates for the relative risks of serious gastrointestinal complications with the individual drugs. There was a wide distribution of results but figure 1 suggests that true differences existed between the drugs.

Table 1 gives the pooled relative risks for individual agents calculated with exposure to ibuprofen as reference. The different numbers of studies that

Table 1—*Comparison of comparative toxicity of range of drugs with use of ibuprofen as reference for calculating relative risks*

Comparator	No of studies	Pooled relative risk	95% Confidence interval for pooled relative risk	P value (heterogeneity)
Ibuprofen	—	1.0†	—†	—†
Fenoprofen	2	1.6	1.0 to 2.5	0.310
Aspirin	6	1.6	1.3 to 2.0	0.685
Diclofenac	8	1.8	1.4 to 2.3	0.778
Sulindac	5	2.1	1.6 to 2.7	0.685
Diflunisal	2	2.2	1.2 to 4.1	0.351
Naproxen	10	2.2	1.7 to 2.9	0.131
Indomethacin	11	2.4	1.9 to 3.1	0.488
Tolmetin	2	3.0	1.8 to 4.9	0.298
Piroxicam	10	3.8	2.7 to 5.2	0.087
Ketoprofen	7	4.2	2.7 to 6.4	0.258
Azapropazone	2	9.2	4.0 to 21.0	0.832

† Reference category for calculating relative risk.

contributed to the analyses reflected their variable coverage of individual drugs. In each case the relative risk with exposure to the comparator compared with exposure to ibuprofen was significantly greater than 1.0. Table 1 shows that the comparator drugs were associated with a 1.6-fold to 9.2-fold increase in the risk of serious upper gastrointestinal complications compared with ibuprofen. These analyses included no adjustments for potential confounding factors as they were based on the authors' raw data.

Table 2 lists the rankings achieved by individual drugs in the 12 studies. Ibuprofen was associated with the lowest relative risk (highest rank) in nine studies and equal lowest relative risk in one study. Several other drugs showed considerable variation in ranking among studies.

Table 3 gives the summary statistics obtained with the ranking method. Drugs that appeared in two or more studies were included in the analysis to obtain a weighted summary order according to relative risk. Twelve orderings achieved equal highest score. Ibuprofen ranked lowest, followed by diclofenac; data for the other drugs are summarised in table 3. An idea of the stability of the position of each drug in the 12 top scoring orderings can be obtained by comparing its highest and lowest values. Values for fenoprofen seemed unstable, probably because it was included in only two studies. The positions of the remaining drugs seemed fairly stable, though data for diflunisal, tolmetin, and azapropazone must be treated with caution owing to the small numbers of contributing studies.

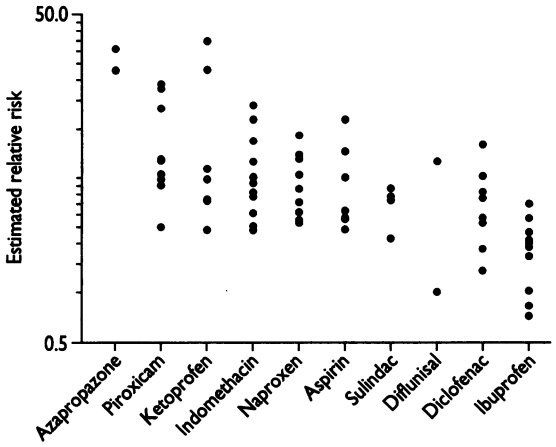

Fig 1—*Estimated relative risks of major gastrointestinal complications with individual non-steroidal anti-inflammatory drugs (calculated with non-use of non-steroidal anti-inflammatory drugs as reference)*

Table 3—*Results obtained with summary ranking method*

Comparator	Summary statistics obtained with ranking method†			
	Mean rank	SD	Minimum rank	Maximum rank
Ibuprofen	1.0	0	1	1
Diclofenac	2.3	0.5	2	3
Diflunisal	3.5	0.5	3	4
Fenoprofen	3.5	1.2	2	5
Aspirin	4.8	0.5	4	5
Sulindac	6.0	0	6	6
Naproxen	7.0	0	7	7
Indomethacin	8.0	0	8	8
Piroxicam	9.0	0	9	9
Ketoprofen	10.3	0.5	10	11
Tolmetin	11.0	0.9	10	12
Azapropazone	11.7	0.5	11	12

† Analysis based on 12 orderings that achieved equal highest score.

IMPORTANCE OF DOSE

Data on the distribution of relative risks according to dose of the individual drugs were available from five studies. Sample sizes were small, effectively limiting comparisons to the commonly used drugs. Extractable comparative data were available from the five studies relating to ibuprofen, naproxen, and indomethacin. By using the arbitrary dose stratifications chosen by the authors (see above) the following pooled relative risks were obtained: low dose—ibuprofen 1.6 (95% confidence interval 0.8 to 3.2), naproxen 3.7 (1.7 to 7.7), and indomethacin 3.0 (2.2 to 4.2); high dose—ibuprofen 4.2 (1.8 to 9.8), naproxen 6.0 (3.0 to 12.2), and indomethacin 7.0 (4.4 to 11.2).

Discussion

This meta-analysis suggests that ibuprofen, as used in clinical practice in seven countries, was associated with the lowest relative risk of severe gastrointestinal toxicity of the 12 non-steroidal anti-inflammatory drugs investigated in two or more studies. The differences seemed to be attributable to the fairly low dose of ibuprofen employed in clinical practice. We could find no evidence that the lower relative risk with ibuprofen was due to differences in the characteristics of the recipients of the

Table 2—*Within study rankings of drugs according to relative risks of major gastrointestinal complications*

Reference	Ibuprofen	Diclofenac	Diflunisal	Fenoprofen	Aspirin	Sulindac	Naproxen	Indomethacin	Piroxicam	Ketoprofen	Tolmetin	Azapropazone
Somerville *et al* (1986)[8]	1	—	—	—	3	—	2	4	5	—	—	—
Carson *et al* (1987)[9]	1.5	—	—	1.5	—	6	4	3	—	—	5	—
Laporte *et al* (1991)[11]	—	4	—	—	3	—	2	1	5	—	—	—
Griffin *et al* (1991)[10]	1	—	—	4.5	—	3	4.5	2	6	—	8	—
Nobili *et al* (1992)[13]	2.5	4	—	—	6	—	2.5	5	1	—	—	—
Savage *et al* (1993)[12]	1	4	—	—	3	5	6	8	7	2	—	—
Kaufman *et al* (1993)[14]	1	2	—	—	4	—	5	3	6	7	—	—
Henry *et al* (1993)[7]	1	3	2	—	5	4	7	6	9	8	—	—
Garcia Rodriguez and Jick (1994)[18]	1	3	—	—	—	—	2	5	6	4	—	7
Langman *et al* (1994)[3]	1	3	—	—	2	—	4	5	6	7	—	8
Abenhaim and Moride[17]	1	2	—	—	—	—	4	3	6	5	—	—
Perez Gutthann *et al* (1994)[15]	1	3	8	—	—	4	3	6	5	7	—	—
No of studies	11	9	2	2	7	5	12	12	11	7	2	2

Key messages

- Gastrointestinal complications of treatment with non-steroidal anti-inflammatory drugs are a major cause of morbidity and mortality
- Because there are no important differences in efficacy, choice of first line treatment with these drugs should be based on their relative toxicity
- Meta-analysis of the available epidemiological studies shows wide differences between individual drugs in the risk of inducing gastrointestinal bleeding and ulcer perforation
- Of the drugs in common use, ibuprofen and diclofenac rank low in toxicity whereas azapropazone, ketoprofen, and piroxicam rank high
- Some of the differences between drugs may be explained by dose, and the advantage of "low risk" drugs may be lost once their dose is increased

different drugs that might have led to altered susceptibility to their gastrointestinal effects (data not shown).

Langman *et al* highlighted the possible advantages of ibuprofen. They concluded that meta-analysis was difficult because comparable datasets could not be extracted from the available studies.[3] Our analytical approach restricted analyses to studies that had collected data relevant to the comparisons of interest. Our conclusions about the apparent advantage of ibuprofen were unchanged whether our analyses were based on pooling of unadjusted relative risks calculated from the raw data (ibuprofen being used as reference) or an alternative approach in which we tried to find an order that best summarised the rankings (by adjusted relative risk) seen in the individual studies. The summary ranking procedure has the advantage that it compares each drug with every other. Of the commonly used agents, ibuprofen and diclofenac ranked lowest by relative risk, ketoprofen and piroxicam ranked highest, and aspirin, sulindac, naproxen, and indomethacin held the middle rankings. Diflunisal, fenoprofen, and tolmetin were not included in enough studies for confident conclusions to be drawn about their relative toxicities. Azapropazone was included in two studies, both from the United Kingdom, but the relative risk estimates were so high that there must be doubt about its suitability for routine use.

IMPORTANCE OF DOSE

Five studies provided data on relative risk stratified by the dose of individual drugs consumed before the index day.[3 10 14 15 18] Pooling of these studies yielded positive dose-response relations for ibuprofen, naproxen, and indomethacin. Confidence intervals for the pooled relative risks with low doses of these drugs overlapped, as did the values for higher doses. The most likely explanation for the low overall relative risk seen with ibuprofen in the main analyses is that in practice it is used in comparatively lower doses than the other drugs reviewed. It should not be assumed that the apparent advantage of ibuprofen persists when doses are increased beyond 1600 mg daily. The evidence reviewed indicates that it does not.

Arguably if the low risk seen with ibuprofen (and diclofenac) is attributable simply to dose, then this does not represent a true advantage. However, the risks recorded in these studies were associated with the doses of ibuprofen and diclofenac actually used in populations around the world. It is likely that these doses were associated with clinical benefit.

Clinical and regulatory decisions have to be made on the basis of the data reviewed here. Though there have been calls for the withdrawal of piroxicam,[20] we do not support this approach. There is considerable variability in the clinical responses to different agents, and withdrawal of particular agents may deny treatment to patients in whom the benefits outweigh the risks. Our preference is to inform doctors and the public of the apparent advantages and disadvantages of the various non-steroidal anti-inflammatory drugs and to encourage use of the lowest effective doses of drugs that seem to be associated with a comparatively low risk. Progression to higher doses or switching to drugs that are associated with higher risks should occur only when the clinical situation requires it and after consideration of the benefits and risks to the patient concerned. On the basis of the data reviewed, use of regimens with comparatively low risks of gastrointestinal complications could result in substantial reductions in morbidity and mortality.

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