Examining the risks for NSAID-induced gastropathy

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ABSTRACT: The medical literature describing the gastrointestinal risks associated with chronic nonsteroidal anti-inflammatory drug (NSAID) therapy is increasing rapidly. In spite of this, clinicians remain uncertain about how to translate this information into clinical practice. Clinical decisions regarding the management of adverse reactions to medications have two components. The first involves risk to the patient, and the second an evaluation of available alternatives for managing that risk. Three research designs have been used to examine this association: ecological studies, case control studies and retrospective cohort studies. Although these designs do not provide the strongest evidence for causation, their results point toward the existence of a risk of serious gastrointestinal reactions of between 1.5 and 10 times greater for NSAID users than for nonusers. The wide variation in results is due to multiple factors, including different research designs, study populations and outcome measures. Several subgroups have been suggested to be at particularly high risk. Risk factors include advanced age, female sex, debilitating rheumatoid disease, previous gastrointestinal disease, ethanol abuse and smoking. Only in the elderly has there been adequate data to support this association. Although the data regarding females is compelling, this may be confounded by the documented increased NSAID use among females. Decision analysis is a useful tool for the quantitative examination of the costs and benefits of management alternatives available for dealing with these risks. Research is needed to identify accurately subgroups of NSAID users at high risk. Can J Gastroenterol 1990;4(3):108-112

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DESPITE THE RAPIDLY EXPANDING medical literature describing gastrointestinal risks associated with chronic nonsteroidal anti-inflammatory drug (NSAID) therapy, definitive recommendations for clinical practice are lacking. In order to make sound clinical decisions regarding the management of NSAID-induced gastrointestinal effects, the risk to the patient must first be defined; alternatives for reducing that risk should then be examined (Figure 1). This controversy will be reviewed using these two issues as guidelines.

Figure 1) Components of clinical decisions regarding NSAID-induced adverse gastrointestinal events
DEFINING THE RISKS

Defining the risks to the patient involves answering the following three questions. Do NSAID users run an increased risk of adverse gastrointestinal effects compared to nonusers? If so, what is the magnitude of this risk? Which types of NSAID users are at particularly high risk? Is there a risk? The most important evidence for establishing a cause-effect relationship is the strength of the research designs used to study that relationship (1). Randomized controlled trials provide the strongest evidence but are seldom ethical in studies of causation because they involve the random assignment of individuals to receive or not receive potentially harmful therapy. Well conducted, prospective cohort studies are the next best design because they minimize the effects of selection and measurement bias. Following in strength of design are retrospective cohorts, case control studies and ecological studies; these have been used to examine the association between NSAID use and gastropathy.

Ecological studies have associated the general rise in NSAID use in a population with the increased prevalence of gastric ulcer or its complications. Such studies have been conducted in the United States and the United Kingdom (2-7). Both countries have demonstrated a relationship between rising prescription rates for NSAIDs and increasing rates of ulcer

Figure 2) Design of cohort and case control studies
TABLE 1
Retrospective cohort studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study population</th>
<th>Outcome</th>
<th>Rate ratio (CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jick 1985</td>
<td>GHC &lt;65 years 1977-82</td>
<td>Hospitalization UGI bleed</td>
<td>1.05 (NA)</td>
</tr>
<tr>
<td>Beard 1987</td>
<td>GHC &gt;64 years 1977-83</td>
<td>Hospitalization UGI bleed</td>
<td>1.3 (-0.2, 3.4)</td>
</tr>
<tr>
<td>Jick 1987</td>
<td>GHC 1977-83</td>
<td>Hospitalization UGI bleed</td>
<td>1.2 (0.5, 2.8)</td>
</tr>
<tr>
<td>Carson 1987</td>
<td>COMPASS All members</td>
<td>UGI bleed</td>
<td>1.5 (1.2, 2.0)</td>
</tr>
<tr>
<td>Guess 1988</td>
<td>All members</td>
<td>Fatal UGI bleed or perforation</td>
<td>3.1 (0.1, 23.2)</td>
</tr>
<tr>
<td>Bloom 1989</td>
<td>Pennsylvania Medicaid 1984-85</td>
<td>GI bleeding</td>
<td>3.27 (1.40, 7.66)</td>
</tr>
</tbody>
</table>

TABLE 2
Case control studies

<table>
<thead>
<tr>
<th>Reference</th>
<th>Rate ratio (CI)</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>McIntosh 1985</td>
<td>6.4 (2.3, 18.0)</td>
<td>Chronic gastric ulcer</td>
</tr>
<tr>
<td>Collier 1985</td>
<td>2.3 (0.84, 6.33)</td>
<td>Admissions</td>
</tr>
<tr>
<td>Bartle 1986</td>
<td>4.3 (1.5, 12.2)</td>
<td>Admissions</td>
</tr>
<tr>
<td>Duggan 1986</td>
<td>5.0 (1.4, 26.9)</td>
<td>Outpatient gastric or duodenal ulcer</td>
</tr>
<tr>
<td>Somerville 1986</td>
<td>2.7 (1.7, 4.4)</td>
<td>Admissions</td>
</tr>
<tr>
<td>Armstrong 1987</td>
<td>13.7 (9.93, 18.06)</td>
<td>Death or emergency surgery, peptic ulcer</td>
</tr>
<tr>
<td>Henry 1987</td>
<td>4.2 (0.9, 25.6)</td>
<td>Fatal peptic ulcer complications</td>
</tr>
<tr>
<td>Jick 1987</td>
<td>1.2 (0.45, 3.5)</td>
<td>Admission peptic ulcer</td>
</tr>
<tr>
<td>Levy 1988</td>
<td>9.1 (2.7, 31)</td>
<td>Admission upper GI bleeding</td>
</tr>
<tr>
<td>Griffin 1988</td>
<td>4.6 (3.1, 7.2)</td>
<td>Fatal peptic ulcer complications</td>
</tr>
</tbody>
</table>

Rate ratio Odds ratios, CI Confidence intervals; GHC Group Health Cooperative, Puget Sound: COMPASS Computerized online pharmaceutical analysis and surveillance system; UGI Upper gastrointestinal.

Disease and its complications. Because both NSAID use and the development of ulcers were measured in the population rather than in individuals, it is possible that the NSAID users were not the ones who developed ulcers or ulcer complications. Ecological studies, therefore, cannot be regarded as strong evidence for cause and effect. Such studies, however, represent an important step in developing the hypothesis of causation.

Two other research designs have been used to examine the association between NSAIDs and gastropathy: retrospective cohort and case-control studies; Figure 2 illustrates the differences between these designs. The design of prospective cohort studies is included for comparison.

In a cohort study, a group of people (the cohort), all of whom are ulcer-free, is followed over time to determine which members (NSAID users or nonusers) develop ulcers or associated complications. In retrospective cohort studies, NSAID use is identified from past records contained in health insurance registries. Such data are collected for patient care purposes and therefore may not be of sufficient quality for rigorous research. Alternatively, in prospective cohort studies, the data are collected specifically for the purpose of the study and hence many biases are avoided, resulting in improved studies examining the risk of NSAID-induced gastropathy.

Case control studies retrospectively compare the frequency of NSAID use in people with and without gastropathy. If patients with gastropathy were found more likely to be NSAID users this would constitute some evidence for causation. Case control studies are susceptible to many more biases than cohort studies. For example, patients receiving NSAIDs are more likely to be investigated for the presence of an ulcer than those not receiving NSAIDs, leading to increased detection of ulcers in this group.

Tables 1 and 2 summarize the main study characteristics and relative risks for adverse gastrointestinal events from case control (8-17) and cohort studies (15,18-22). Eleven of the 16 studies reviewed show a statistically significant increased risk of gastric ulcer or its complications for NSAID users compared to nonusers. The considerable variability in the reported relative risks (from 1.05 to greater than 10) is largely due to differences in research design, study population (e.g., pre-paid group practice, elderly, medical) and outcome measures (e.g., fatal upper gastrointestinal bleed, gastrointestinal hospitalization, chronic gastric ulcer). The majority of studies point to a relative risk for gastrointestinal events two to five times greater for NSAID users than nonusers.

Overall, the evidence for a causal relationship between NSAIDs and serious gastrointestinal events is strong. Therefore, the answer to the first question is yes, there is a risk.

What is the magnitude of risk? The risks of gastrointestinal complications among NSAID users have been estimated from various sources. Prospectively collected data from a large
computerized registry indicated risk of gastrointestinal hospitalization as 1% per year for rheumatoid arthritis patients (23). The Food and Drug Administration has quoted a risk for serious gastrointestinal events of 2 to 4% per year among NSAID users (24). A recent overview and meta-analysis which combined the rates of gastrointestinal complications from over 100 NSAID clinical trials reported an overall complication rate of 2% (25). Estimated absolute risks of gastrointestinal complications from the six cohort studies reviewed vary from 0.02% to 0.5%. Overall, the reported risks vary from two in 1000 to four in 100. This variation is due to differences in the ascertainment of NSAID exposure and outcome assessment.

Who is particularly at risk? Studies which examine the types of patients at risk yield somewhat inconsistent findings due to the fact that most studies examining risk factors fail to control for other potential confounders. For example, the evidence of an excessive risk in elderly females may be confounded by the documented increased NSAID use in this group (6). Other risk factors, such as history of previous gastrointestinal disease, alcohol use, smoking and severe rheumatic disease require further study.

EXAMINING ALTERNATIVES FOR REDUCING RISKS

Having established the presence of a clinically important risk, the next step is to examine the alternatives for reducing this risk (Figure 1). Some simple approaches to risk reduction include using the minimal dose of NSAID which will control the symptoms, switching to non-NSAID analgesia whenever possible, and carefully monitoring elderly patients. The decision to prescribe prophylaxis is much more difficult because it involves not only potential benefits but also potential risks and additional cost. Clinical decision analysis is useful because it quantitatively incorporates such information into the clinical decision making process.

Using 'decision tree' methodology, the authors have designed a clinical model representing clinical management decisions for physicians faced with these patients. This model can also be adapted for cost-effectiveness analyses. Preliminary data indicate that determining the cost-effectiveness of prophylaxis with misoprostol, a synthetic prostaglandin analogue, hinges on a more accurate definition of the ulcer complication rate.

SUMMARY

In summary, most of the available literature supports the existence of a causal relationship between chronic NSAID use and the development of gastric ulcer and its subsequent complications. The magnitude of the risk can be estimated to be between two in 1000 and four in 100. Although several subgroups have been suggested to be at high risk, only in the elderly and perhaps in females have there been adequate data to support this association. Decision analysis is a useful tool for the quantitative examination of the management alternatives available for dealing with these risks. It also represents a model to study the cost-effectiveness of prophylactic therapy. Research is needed to define accurately the natural history of NSAID-induced gastrointestinal mucosal damage and particularly the ulcer complication rate, in both the general population and various subgroups. Preventive strategies can then be targeted to the high risk groups.

REFERENCES


