Prophylaxis of NSAID associated gastroduodenal damage: A critical review of risk factors

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DJ LEDDIN. Prophylaxis of NSAID associated gastroduodenal damage: A critical review of risk factors. Can J Gastroenterol 1993;7(5):440-443. Nonsteroidal anti-inflammatory drugs (NSAIDs) are associated with a significant morbidity and mortality, not because they are particularly dangerous drugs but because they are so commonly prescribed. In epidemiologic terms the problem is characterized by a high level of the risk factor (NSAID use) rather than a high risk of complications. The risk in any individual patient depends on age, concomitant conditions and medications, dose of NSAID, and duration of treatment. There is no evidence that prophylactic therapy decreases the risk of clinically important events such as hemorrhage. Prophylactic therapy has been shown to prevent endoscopic signs of gastroduodenal damage and should be used in high risk patients pending proof of clinically relevant efficacy.

Key Words: *Bleeding, Nonsteroidal anti-inflammatory drugs (NSAIDs), Peptic ulceration, Perforation, Prophylaxis, Treatment*

Prophylaxie de la lésion gastroduodénale liée aux AINS: analyse critique des facteurs de risque

RÉSUMÉ: Les anti-inflammatoires non stéroïdiens (AINS) sont associés à un taux significatif de morbidité et de mortalité, non pas parce qu'ils sont particulièrement dangereux, mais parce qu'ils sont prescrits fréquemment. En termes d'épidémiologie, le problème est caractérisé par un degré élevé du facteur de risque (recours aux AINS) plutôt qu'à un degré élevé de complications. Le risque chez tout individu dépend de l'âge, des problèmes de santé et des médicaments concomitants, de la posologie d'AINS et de la durée du traitement. Rien ne prouve que le traitement prophylactique diminue le risque d'incidents cliniquement importants, comme l'hémorragie. Le traitement prophylactique s'est révélé efficace à prévenir les signes endoscopiques de lésions gastroduodénales et devrait être utilisé chez les patients à risque élevé, en attendant une preuve d'efficacité clinique pertinente.

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THE QUESTION OF PROPHYLACTIC treatment for nonsteroidal anti-inflammatory drug (NSAID) associated gastroduodenal damage is controversial. At present one could plausibly argue either that prophylactic therapy should always be used in the hope of preventing NSAID damage or, alternatively, that prophylaxis should never be used.

Proponents of the always viewpoint could argue that 10 million prescriptions are given for NSAIDs in Canada each year (1). Extrapolating from data from the United Kingdom and the United States, this likely results annually in over 1000 upper gastrointestinal (GI) bleeds, many more thousands of hospitalizations and a significant number of deaths (2-4). Since there is evidence that prophylactic treatment can decrease endoscopically visible gastroduodenal damage (5,6), then it is reasonable to assume that it will also prevent clinically important adverse events and it is therefore reasonable to use prophylaxis.

Proponents of the never viewpoint might counter that there is no hard evidence indicating that prophylactic therapy decreases the risk of clinically important events such as GI hemorrhage, hospitalization, ulcer perforation or death (7).

TABLE 1
Method of calculating the percentage risk of a serious gastrointestinal event in the next 12 months

Variable	Factor
Age (years)	x2
History of previous NSAID side effect	+50
Disability index (0-3) or ARA class-1	x10
NSAID dose as fraction of maximum recommended	x15
Current prednisone use	+40
Total score: Risk = (Score–100)/40	

Adapted from reference 13. ARA American Rheumatological Association; NSAID Nonsteroidal anti-inflammatory drug. Example: A 70-year-old with previous NSAID side effect, ARA class 2, on 100% of recommended NSAID dose and using prednisone will have a risk of (70x2) + (50) + ((2-1)x10) + (1x15) + (40) = 255. Risk = (255-100)/40 = 3.9% of major event in next year

TABLE 2
Measures to prevent NSAID complications

Avoid NSAIDs and consider alternative such as physiotherapy and acetaminophen
Use the lowest dose of NSAID possible
Use the shortest duration of treatment possible
Avoid combinations of NSAIDs
Use prophylactic therapy if:
elderly
serious concomitant disease
past history of peptic ulcer disease or NSAID side effect
concomitant use of corticosteroids or anticoagulants
alcohol abuse

NSAID Nonsteroidal anti-inflammatory drug

This review explores the background to the controversy surrounding the question of prophylactic therapy and suggests a strategy for prophylaxis based on current understanding of the problem.

WHAT IS THE PURPOSE OF PROPHYLAXIS?

When considering the literature on prophylaxis of NSAID associated gastroduodenal damage, it is important to keep the endpoint in mind. Prevention of an asymptomatic gastric erosion detected by endoscopy is clearly of less significance than the prevention of symptomatic hemorrhage or ulcer perforation. The literature on efficacy of agents used to prevent damage refers almost entirely to endpoints such as endoscopic detection of erosions and ulceration and not to endpoints such as hemorrhage, perforation, hospitalization or death (7). It is the lack of data on the prevention of clinically important events which has fuelled the controversy surrounding prophylactic therapy.

WHAT IS THE RISK OF CLINICALLY SIGNIFICANT NSAID COMPLICATIONS?

NSAID therapy increases the risk of symptomatic gastric ulceration fivefold, upper GI bleeding threefold, ulcer perforation sixfold, and death due to GI causes eightfold (8). There is some debate as to whether NSAIDs actually cause duodenal ulceration or simply exacerbate an underlying ulcer diathesis (9) but the relative risk may be increased by as much as threefold (8). Statement of relative risk alone is not sufficient to describe the extent of the problem. A significant increase in relative risk may not be very important if the absolute rate of the event is miniscule.

In the general population the annual rate of upper GI bleeding is about one in 2000 (10). If NSAIDs are associated with a fourfold increase in risk of bleeding, then the absolute risk of bleeding with NSAIDs can be estimated at one in 500 patients per year or one in 6000 patients receiving NSAIDs for one month.

The estimate calculated above is in approximate agreement with the observed incidence of bleeding. In 1987, Carson et al (11) examined the computerized Medicare records of patients in Michigan and Minnesota. In approximately 47,000 patients exposed to NSAIDs for one month, 155 upper GI bleeds occurred. In approximately 45,000 patients not exposed to NSAIDs 96 bleeds were seen.

The excess bleeding rate in the NSAID exposed group is low compared with hospital based studies (12). However, these data illustrate both the infrequency of the event which one is trying to prevent by prophylactic therapy (GI bleeding), and the necessity of identifying subgroups if prophylaxis is to be cost effective. It will be difficult to justify 47,000 prescriptions for prophylaxis in the hope of preventing 155 bleeds, when only about one-third of the bleeds can be truly ascribed to NSAID therapy.

The absolute rate of bleeding in the Carson study of 1.27 per 10,000 patient months, or one bleed in 7800 patients receiving NSAIDs for one month, agrees closely with that which can be calculated based on relative risk of NSAID use and the incidence of bleeding in the general population (8).

A risk of bleeding of one in 7800 does not seem very substantial. In epidemiological terms, therefore, the problem of NSAID-associated upper GI bleeding is characterized by a high prevalence of the risk factor (NSAID use) rather than a high risk of complications. However, in patients with rheumatoid arthritis receiving NSAIDs the risk of hospitalization for GI reasons (primarily GI bleeds) may be as high as 1.5% per year (13). The risk of death is about a 10th of that at 0.15% per year (13). Furthermore, NSAID therapy may be required for many years or even lifelong, resulting in a very significant cumulative risk. Therefore, it is clear that while the overall risk of bleeding from NSAIDs is small, the risk for certain subgroups may be very substantial.

WHO IS AT RISK OF NSAID COMPLICATIONS?

Patient characteristics: Risk has been best defined for the subgroup of patients with rheumatoid arthritis. In the American Rheumatological Association Medical Information System

(ARAMIS), study data has been collected on nearly 3000 patients for a total of nearly 10,000 patient-years (13). During that time 128 GI events (events requiring admission to hospital) occurred.

Age, level of disability, use of prednisone, a previous history of NSAID GI side-effect, and increasing NSAID dose were predictive of an adverse GI event (13). A scoring system was drawn up which allows calculation of risk in the following 12 months (Table 1).

Many of the risk factors identified in the ARAMIS study have been confirmed by other investigators. Whether age is an independent risk factor for the development of NSAID complications is controversial because not all studies have corrected for the increased use of NSAIDs in the elderly when assessing age related risk. The increasing risk of GI adverse events with age, which has been documented in most studies (13,14), may be compounded by another variable such as an increasing prevalence of *Helicobacter pylori* (15), decreasing bodyweight, or alterations in drug metabolism. There is, however, some biological evidence that the elderly might be more prone to complications of NSAIDs (16). It is not clear at which age prophylaxis based on age alone should be instituted or indeed whether age alone is a reasonable indication for prophylaxis.

The frail elderly patient may not only be more prone to NSAID complications but also may have a high mortality from GI bleeding if it occurs. Data on this subgroup are lacking but if we can extrapolate from the ARAMIS data (13) then degree of disability is an important determinant of risk.

A higher mortality from bleeding may also justify the use of prophylaxis in patients with serious organ system disease such as chronic obstructive pulmonary disease (COPD) and ischemic heart disease.

Prednisone alone is probably not associated with an increased risk of bleeding (17,18). The combination of NSAID and corticosteroids, however, significantly increases the risk of adverse events (14). Similarly the use of anticoagulants with NSAIDs clearly has the potential to convert an asymptomatic ulcer into a symptomatic hemorrhage. Such an interaction has been demonstrated for prednisone (18).

A past history of upper GI disease is associated with increased risk of complications (14) although curiously this has not always been found (19). The ARAMIS study found an association between risk of complications and a past history of H_2 receptor blockade (13). The proposed explanation was that a history of H_2 blocker use indicated a past history of peptic ulceration. The alternate explanation, that H_2 blockade in combination with NSAID may be more damaging than either agent alone, is not supported by several trials of H_2 blockers in the prophylaxis of NSAID associated ulceration.

The ARAMIS study did not find an association between alcohol use, or smoking, and an increased risk of NSAID complications (13). The elderly, however, do not tend to be major consumers of alcohol or tobacco, making interpretation of these data difficult. Smoking is associated with delayed ulcer healing and alcohol may cause gastric injury in the absence of NSAIDs. The combination of alcohol and NSAID is more injurious than either agent alone (20,21) but there is a lack of firm evidence of a clinically important association.

The risk of upper GI bleeding increases with both increasing duration of exposure to NSAIDs and increasing dose of NSAID (13,14,22). The risk is highest early in therapy and decreases thereafter, probably because compliance is greater early in treatment, patients who will bleed have been selected out, and mucosal adaptation may occur. Even low oral doses of NSAIDs are associated with an increased risk (9) as is the use of these drugs as suppositories.

PREVENTING NSAID COMPLICATIONS

Prescribing: NSAIDs should be avoided if possible, especially in the elderly. It is likely that many prescriptions are given for analgesic rather than anti-inflammatory effect. If analgesia is required then acetaminophen should be tried, since this drug is probably not associated with an increased risk of GI bleeding (8).

The lowest dose of NSAID and shortest treatment duration possible should be used.

Some NSAIDs may be less toxic than others but all carry an increased risk (23,24). Further information in this regard would be helpful.

Prophylaxis: Prophylaxis should be considered in the frail elderly patient who may be both at more risk of bleeding and less able to withstand a bleed.

A history of previous peptic ulcer disease, H_2 antagonist/antacid use, or NSAID adverse effect may point to underlying gastroduodenal pathology and these patients should be treated.

Patients with serious organ system disease such as COPD and cardiovascular disease should be considered for prophylactic therapy as should those on steroids or those taking anticoagulants.

There are no data showing that prophylaxis in these groups will significantly alter the history of NSAID associated complications. It is likely that studies currently underway in the US will resolve this question for at least some subgroups of the patient population.

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