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Review

The risk of upper gastrointestinal complications associated with nonsteroidal anti-inflammatory drugs, glucocorticoids, acetaminophen, and combinations of these agents

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Abstract

Most anti-inflammatory drugs have been associated with an increased risk of serious upper gastrointestinal complications. Epidemiological studies have estimated the magnitude of the risk for specific anti-inflammatory drugs. The risk of upper gastrointestinal tract bleeding or perforation increases around twofold with use of oral steroids or low dose aspirin, and increases around fourfold with use of nonaspirin nonsteroidal anti-inflammatory drugs. Acetaminophen at daily doses of 2000 mg and higher has also been associated with an increased risk. Overall, the risk is dose dependent and is greater with more than one anti-inflammatory drug taken simultaneously. Hence, whenever possible, anti-inflammatory drugs should be given in monotherapy and at the lowest effective dose in order to reduce the risk of serious upper gastrointestinal complications.

Keywords: acetaminophen, corticosteroids, gastrointestinal haemorrhage, NSAIDs, observational study

Introduction

Most anti-inflammatory drugs have been associated with gastrointestinal side effects. Gastrointestinal mucosa damage can range from endoscopic lesions with no clinical manifestations to serious upper gastrointestinal complications (UGIC) that, in some instances, may be fatal. Because of their relatively low incidence, severe gastrointestinal events can only be effectively evaluated in large, post-marketing, observational studies. This document presents epidemiological evidence of the magnitude of the risk of upper gastrointestinal tract bleeding or perforation among users of anti-inflammatory drugs: oral steroids, aspirin, nonaspirin nonsteroidal anti-inflammatory drugs (NA-NSAIDs), and acetaminophen (paracetamol in Europe).

Two methods will be used to examine the interaction resulting from multiple use of anti-inflammatory drugs on the risk of UGIC: firstly, we shall review epidemiological findings published by other authors [1–10]; and, secondly, we shall summarize results published by our group [11–13]. These cited papers provide a more detailed description of the methodology.

Our data was based on a nested case–control study carried out in the UK General Practice Research Database (GPRD) for the period 1993–1998. The study population consisted of 958,397 persons aged 40–79 years who had been enrolled for at least 2 years, and who were free of cancer, esophageal varices, Mallory–Weiss

CI = confidence interval; GPRD = General Practice Research Database; NA-NSAID = nonaspirin nonsteroidal anti-inflammatory drug; RR = relative risk; UGIC = upper gastrointestinal complications.

disease, liver disease, coagulopathies and alcohol-related disorders at the start date. All members of the source population were followed-up until they met a case definition criterion or an exclusion criterion, or until they died. We identified patients with codes for UGIC and manually reviewed the demographic data and clinical information in the computerized patient profiles. We excluded subjects with any of the risk factors already mentioned in the 2 months after the date of case detection, and excluded subjects in whom the sources of the bleeding and perforation were the esophagus or lower gastrointestinal tract. A patient was considered to have UGIC when no exclusion criterion was found, the subject had not been hospitalized in the previous month, and the specific site of the bleeding and perforation was located in the stomach or duodenum. Control subjects were frequency matched by age and gender, with the same exclusion criteria for patients also being applied to the control subjects. The analysis included 2105 patients and 11,500 control subjects. We used unconditional logistic regression to compute estimates of relative risk (RR) and 95% confidence intervals (CI) of UGIC associated with current use of steroids, aspirin, NA-NSAIDs, and acetaminophen. All estimates of RR were adjusted for age, sex, calendar year, smoking, antecedents of upper gastrointestinal disorders, and concomitant medications (including anticoagulants, misoprostol, H_2-receptor antagonists, omeprazole and nitrates).

Steroids

The literature on the gastrointestinal safety of oral steroids is controversial. Results from early clinical trials were interpreted both as a dose-dependent increased risk of peptic ulcers in the groups treated with steroids [14], and as no difference between the steroid and placebo groups [15]. Results from epidemiological studies have been heterogeneous and were often based on small numbers (pooled RR estimate, 1.9; 95% CI, 1.5–2.4) [1–6].

Two percent of controls in the GPRD had used oral steroids in the past month. Prednisolone accounted for more than 85% of systemic steroid use. The risk of UGIC was 1.8 (95% CI, 1.3–2.4) times higher for users of steroids than for non-users. The risk tended to be greater for steroid doses equivalent to or above 30 mg prednisone than for lower doses, although this dose response was not statistically significant (Table 1) [11,12].

Aspirin

Epidemiological studies have reported risks of UGIC from one to 10 times higher among aspirin users, with an estimated pooled relative risk between 2 and 3 [16–18]. The risk associated with aspirin was dose dependent but was still present at low daily doses (300 mg) [7–10] or even at very low daily doses (75 mg) [9,10].

Table 1

Relative risk (RR) and 95% confidence interval (CI) of upper gastrointestinal complications associated with use of steroids, aspirin, nonaspirin nonsteroidal anti-inflammatory drugs (NA-NSAIDs), and acetaminophen

	Cases (n=2105)	Controls (n=11,500)	RR*	95% CI
Steroids†				
Non-use	1724	9824	Reference	
Current	90	196	1.8	1.3–2.4
Low–medium dose†	75	174	1.5	1.1–2.1
High dose	9	13	2.9	1.2–7.3
Aspirin				
Non-use	1696	10,157	Reference	
Current	287	837	2.1	1.8–2.5
75 mg	140	420	2.0	1.6–2.6
150 mg	90	248	2.2	1.7–2.9
≥300 mg‡	57	169	2.2	1.6–3.1
NA-NSAIDs				
Non-use	1468	9746	Reference	
Current	438	758	4.1	3.6–4.8
Low–medium dose§	92	290	2.4	1.9–3.2
High dose§	311	449	4.7	3.9–5.6
Acetaminophen				
Non-use	1494	9532	Reference	
Current	376	1069	1.3	1.1–1.5
<2 g	201	852	0.9	0.8–1.1
2 g	84	127	1.9	1.4–2.6
≥2 g	91	90	3.7	2.6–5.1

Data are for United Kingdom General Practice Research Database, 1993–1998. *Adjusted for age, sex, calendar year, ulcer history, smoking, and concomitant medication. These analyses include only current users versus non-users (no use in the past 180 days); data on recent past (between 30 and 180 days) users are not presented. †There were 15 subjects with missing values for oral steroid dose. The cut-off point was 30 mg prednisolone or equivalent. ‡There were only eight cases and nine controls who were taking doses greater than 300 mg. §These analyses include only users of a single NA-NSAID.

Seven percent of controls in our population had used aspirin in the past month. The adjusted RR of UGIC for low dose aspirin users was 2.0 (95% CI, 1.6–2.6), as compared with non-users. No clear dose effect was found within the range of 75–300 mg (Table 1) [13].

Nonaspirin NSAIDs

Intake of NA-NSAIDs as a group has been consistently associated with a four- to fivefold increase in UGIC [16–19]. The risk is clearly dose dependent. The esti-

mated pooled RRs in a recent meta-analysis were 3.0 (95% CI, 2.6–3.4) for low doses, 4.1 (95% CI, 3.6–4.5) for medium doses, and 6.9 (95% CI, 5.8–8.1) for high doses [19].

Seven percent of controls in our population had used NA-NSAIDs in the past week. We found a RR of 4.1 (95% CI, 3.6–4.8) for NA-NSAIDs studied as a therapeutic class. Users of low/medium daily doses had a RR of 2.4, whereas users of high daily doses had a fivefold increase in risk (Table 1) [11].

Acetaminophen

Epidemiological data on the association between acetaminophen use and UGIC are limited and inconsistent (pooled RR, 1.4; 95% CI, 1.0–2.0) [2,8,20–22]. However, two studies evaluated the effect of dose, and both reported an increased risk of UGIC associated with use of acetaminophen at high doses (ie anti-inflammatory doses) [8,23].

Nine percent of controls in the GPRD had used acetaminophen in the past month. Overall, use of acetaminophen was associated with a negligible elevated risk of UGIC (RR, 1.3; 95% CI, 1.1–1.5). We found an increased risk of UGIC among current users of acetaminophen at doses greater than 2 g (RR, 3.7; 95% CI, 2.6–5.1), whereas doses below 2 g did not carry an increased risk (Table 1).

Concomitant medication

The use of oral steroids has been found to reinforce the risk of UGIC associated with NA-NSAIDs [16,24]. The risk was shown to be more than 12 times higher for concomitant users of both steroids and NA-NSAIDs, compared with non-users of either drug [1,5]. Users of multiple NA-NSAIDs simultaneously had about 10 times increased risk of developing UGIC, compared with non-users [5,6,11]. The risk associated with simultaneous use of aspirin and NA-NSAIDs, in contrast, was only slightly higher than the sum of their individual risks [7]. Concomitant use of aspirin together with NA-NSAIDs at high dose, however, increased substantially the risk of UGIC [9].

The RR values in our population, compared with those of non-users of any anti-inflammatory drug, were 8.5 (95% CI, 3.9–18.9) for current users of steroids and NA-NSAIDs, 3.1 (95% CI, 1.2–8.1) for users of steroids and aspirin, and 4.8 (95% CI, 1.1–20.9) for users of steroids and high doses of acetaminophen (≥ 2 g) (the latter two estimates are based on a small number of exposed patients). The corresponding RR value for current users of aspirin and NA-NSAIDs was 8.2 (95% CI, 5.3–12.8), and that for current users of aspirin and high doses of acetaminophen was 3.3 (95% CI, 1.7–6.5). We found a substantial interaction between NA-NSAIDs and high dose acetaminophen; compared with non-users of either drugs, the RR for concurrent users of NA-NSAIDs and acetaminophen (≥ 2 g) was 16.6 (95% CI, 11.0–24.9). Concomitant users of three or four anti-inflammatory drugs (excluding low dose acetaminophen) presented a relative risk of 18.0 (95% CI, 9.0–36.1) compared with persons not exposed to any of the anti-inflammatory drugs (Table 2).

Table 2

Relative risk (RR) and 95% confidence interval (CI) of upper gastrointestinal complications associated with combined use of anti-inflammatory drugs

Anti-inflammatory drugs	Cases (*n*)	Controls (*n*)	RR*	95% CI
None†	852	6768	Reference	
Steroids alone	41	132	2.1	1.4–3.0
Aspirin alone	177	609	2.4	1.9–2.9
NA-NSAIDs alone	193	489	3.6	2.9–4.3
Acetaminophen (< 2 g)	96	565	1.1	0.9–1.4
Acetaminophen (≥ 2 g)	52	124	2.4	1.7–3.5
Steroids and aspirin	6	17	3.1	1.2–8.1
Steroids and NA-NSAIDs	14	13	8.5	3.9–18.9
Steroids and acetaminophen (< 2 g)	5	31	1.1	0.4–2.9
Steroids and acetaminophen (≥ 2 g)	4	5	4.8	1.1–20.9
Aspirin and NA-NSAIDs	40	50	8.2	5.3–12.8
Aspirin and acetaminophen (< 2 g)	16	94	1.3	0.7–2.3
Aspirin and acetaminophen (≥ 2 g)	14	32	3.3	1.7–6.5
NA-NSAIDs and acetaminophen (< 2 g)	61	134	4.1	3.0–5.7
NA-NSAIDs and acetaminophen (≥ 2 g)	80	41	16.6	11.0–24.9
Three or four anti-inflammatory drugs‡	27	13	18.0	9.0–36.1

Data are for United Kingdom General Practice Research Database, 1993–1998. NA-NSAIDs, Nonaspirin nonsteroidal anti-inflammatory drugs. *Adjusted for age, sex, calendar year, ulcer history, smoking, and concomitant medications. These analyses include only current users versus non-users (no use in the past 180 days); data on recent past (between 30 and 180 days) users are not presented. †Patients exposed to no drug (steroids, aspirin, NA-NSAIDs, and acetaminophen). Categories are mutually exclusive. ‡Acetaminophen at doses < 2 g not included in this category.

Conclusion

In summary, use of oral steroids, aspirin and acetaminophen at doses ≥ 2 g are each associated with around twofold

increased risk of upper gastrointestinal complications; NA-NSAIDs are associated with a close to fourfold increased risk. Dose is an important predictor of the risk of UGIC for all anti-inflammatory drugs. For instance, we found that acetaminophen was associated with an increased risk only when taken at daily doses ≥ 2 g. The use of NA-NSAIDs concomitantly with oral steroids, aspirin, or high doses of acetaminophen increases the risk of UGIC greater than eightfold.

The incidence of hospitalization for complicated peptic ulcer disease among non-users of anti-inflammatory drugs is approximately one case per 1000 persons per year in the general population [5,25,26]. The number of UGIC events per 1000 persons per year, based on epidemiological studies, would be two events among steroid users, two events among aspirin users, and between four and five events among NA-NSAID users. The incidence would be higher for users of high doses of any anti-inflammatory drugs and for patients taking more than one anti-inflammatory drug simultaneously. For example, the incidence would be around eight cases per 1000 users of steroids and NA-NSAIDs or per 1000 users of aspirin and NA-NSAIDs concomitantly per year. The absolute risk in the small subgroup of patients that take concomitantly three or four different anti-inflammatory drugs would augment close to 20 per 1000 users (2% per year).

In conclusion, whenever possible, any anti-inflammatory drug should be given in monotherapy and at the lowest effective dose in order to reduce the risk of UGIC.

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