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...
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, nonaspirin nonsteroidal anti-inflammatory drugs (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, H₂-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 prednisolone 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     |
| ≥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).

**Conclusion**

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

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**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      | 6788         | 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       | 32           | 3.3 | 1.7–6.5 |
| 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.
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.

References
1. Piper JM, Ray WA, Daugherty JR, Griffin MR: Corticosteroid use and peptic ulcer disease: role of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991, 114:735–740.
2. Holvoet J, Terriere L, Van Hee W, Verbist L, Fierens E, Hautekeete M: Relation of upper gastrointestinal bleeding to nonsteroidal anti-inflammatory drugs and aspirin: a case–control study. Gut 1991, 32:730–734.
3. Keating J: Anti-inflammatory drugs and emergency surgery for peptic ulcers in the Waikato. NZ Med J 1992, 105:127–129.
4. Hallas J, Lauritsen J, Dalsgard Villadsen H, Frenge Gram L: Nonsteroidal anti-inflammatory drugs and upper gastrointestinal bleeding, identifying high-risk groups by excess risk estimates. Scand J Gastroenterol 1995, 30:438–444.
5. Pérez-Gutthann S, García Rodríguez LA, Raiford DS: Individual nonsteroidal anti-inflammatory drugs and other risk factors for upper gastrointestinal bleeding and perforation. Epidemiology 1997, 8:18–24.
6. García Rodríguez LA, Cattaruzzi C, Troncon MG, Agostinis L: Risk of hospitalization for upper gastrointestinal tract bleeding associated with ketorolac, other nonsteroidal anti-inflammatory drugs, calcium antagonists, and other antihypertensive drugs. Arch Intern Med 1998, 158:33–39.
7. Henry D, Dobson A, Truner C: Variability in the risk of major gastrointestinal complications from nonaspirin nonsteroidal anti-inflammatory drugs. Gastroenterology 1993, 105:1078–1088.
8. Savage R, Møller P, Ballantyne C, Wells J: Variation in the risk of peptic ulcer complications with nonsteroidal anti-inflammatory drug therapy. Arthritis Rheum 1993; 36:84–90.
9. Weil J, Colin-Jones D, Langman M, Lawson D, Logan R, Murphy M, Rawlins M, Vessey M, Warnwright P: Prophylactic aspirin and risk of peptic ulcer bleeding. Br Med J 1995, 310:927–930.
10. Kelly JP, Kaufman DW, Jugelom JM, Sheehan JE, Koff RS, Shapiro S: Risk of aspirin-associated major upper gastrointestinal bleeding with enteric-coated or buffered product. Lancet 1996, 348:1414–1418.
11. García Rodríguez LA, Jick H: Risk of upper gastrointestinal bleeding and perforation associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994, 343:769–772.
12. Hernández-Díaz S, García-Rodríguez L: Steroids and risk of upper gastrointestinal bleeding/perforation. Am J Epidemiol 2000, in press.
13. De Abajo FJ, García Rodríguez LA: Risk of upper gastrointestinal bleeding and perforation associated with low-dose aspirin as plain and enteric-coated formulations [abstract]. Pharma-gastrointestinal Drug Safety 2000, 8:S174.
14. Messer J, Reitman D, Sacks HS, Smith H, Chalmers TC: Association of adenocorticosteroid therapy and peptic-ulcer disease. N Engl J Med 1983, 309:21–24.
15. Conn H, Poyntard T: Corticosteroids and peptic ulcer: meta-analysis of adverse events during steroid therapy. J Intern Med 1994, 236:619–632.
16. Gabriel SE, Jaakkimainen L, Bombardier C: Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. Ann Intern Med 1991, 115:787–796.
17. Bollini M, Weil J, Warnwright P, Pérez-Gutthann S, Walker AM: The impact of research quality and study design on epidemiologic estimates of the effect of nonsteroidal anti-inflammatory drugs on upper gastrointestinal tract disease. Arch Intern Med 1992, 152:1289–1296.
18. Henry D, Lim LL, García Rodríguez LA, Perez Gutthann S, Carson JL, Griffin M, Savage R, Logan R, Moride Y, Hawkey C, Hill S, Fries JT: Variability in risk of gastrointestinal complications with individual nonsteroidal anti-inflammatory drugs: results of a collaborative meta-analysis. Br Med J 1996, 312:1563–1566.
19. Hernández-Díaz S, García-Rodríguez LA: Overview of epidemiological studies published in the nineties on the association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding/perforation. Arch Intern Med 2000, 160:2093–2099.
20. Laporte J-R, Carné X, Vidal X, Moreno V, Juan J: Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal anti-inflammatory drugs. Lancet 1991, 337:37–40.
21. Nobili A, Mosconi P, Franzosi MG, Tognoni G: Non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding, a post-marketing surveillance case–control study. Pharma-coepidemiol Drug Safety 1992, 1:65–72.
22. Langman M, Weil J, Warnwright P, Lawson DH, Rawlins MD, Logan RF, Murphy M, Vessey MP, Colin-Jones D: Risks of bleeding peptic ulcer associated with individual non-steroidal anti-inflammatory drugs. Lancet 1994, 343:1075–1078.
23. Rahme E, Pettitt D, LeLorier J: Dose–response curves with time dependent exposure: the case of acetaminophen gastrointestinal side effects [abstract]. Pharamacoepidemiol Drug Safety 2000, 9:S104.
24. Hansen JM, Hallas J, M LJ, Bytzer P: Non-steroidal anti-inflammatory drugs and ulcer complications: a risk factor analysis for clinical decision-making. Scand J Gastroenterol 1996, 31:126–130.
25. Garcia Rodriguez LA, Walker AM, Pérez Gutthann S: Non-steroidal anti-inflammatory drugs and gastrointestinal hospitalizations in Saskatchewan: a cohort study. Epidemiology 1992, 2:337–342.
26. Lanza LL, Walker AM, Bortnichack EA, Dreyer NA: Peptic ulcer and gastrointestinal hemorrhage associated with non-steroidal anti-inflammatory drug use in patients younger than 65 years. A large health maintenance organization cohort study. Arch Intern Med 1995, 155:1371–1377.

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