© *Basic & Clinical Pharmacology & Toxicology* 2006, **98**, 297–303.
Printed in Denmark . All rights reserved

Pharmacology & Toxicology

ISSN 1742-7835

MiniReview

Upper Gastrointestinal Complications among Users of Paracetamol

Antonio González-Pérez and Luis A. García Rodríguez

Spanish Centre for Pharmacoepidemiological Research, Madrid, Spain

(Received June 7, 2005; Accepted September 8, 2005)

Abstract: Non-steroidal anti-inflammatory drugs (NSAIDs) have been associated with upper gastrointestinal complications such as bleeding or perforation. Paracetamol has been traditionally considered a safer alternative to NSAIDs. In a previous case-control study we found that paracetamol at high doses increased the risk of upper gastrointestinal complications. We proposed to review all studies addressing the association between paracetamol and upper gastrointestinal complications and placed our results in the context of existing literature. We conducted a nested case-control study using the United Kingdom General Practice Research Database during the period between April 1993 and October 1998. Then we performed a systematic review of the literature indexed in MEDLINE published between 1980 and 2004. We identified a total of twelve studies that assessed the association between paracetamol and upper gastrointestinal complications. We used a fixed effects model to calculate a summary estimate of these studies. In the nested case control study, use of paracetamol was associated with a small elevated risk of upper gastrointestinal complications (relative risk (RR), 1.3; 95% confidence interval (CI), 1.1–1.5). The RR was 3.6 (95% CI, 2.6–5.1) among paracetamol users of more than 2 g daily, whereas smaller doses did not increase the risk. Among the twelve studies identified in the systematic review, estimates ranged from 0.2 through 2.0 with a summary estimate of 1.3 (95% CI, 1.2–1.5). Our findings indicate that use of paracetamol at the doses most commonly used confer little or no increased risk of upper gastrointestinal complications. More data are needed to confirm or refute the suggestion that high-dose paracetamol is associated with an increased risk of upper gastrointestinal complications of the same magnitude as the one observed with traditional NSAIDs.

Non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for their analgesic, antiinflammatory and antipyretic effects. Both aspirin and non-aspirin NSAIDs have been associated with an upper gastrointestinal complication, bleeding or perforation (Gabriel *et al*. 1991; Bollini *et al*. 1992; Henry *et al*. 1996; Hernández-Díaz & García-Rodríguez 2000; García-Rodríguez *et al*. 2001). Strategies to reduce the gastrotoxicity associated with conventional NSAIDs include dose reduction (Henry *et al*. 1996; Hernández-Díaz & García-Rodríguez 2000), adding an acid-suppressing drug or misoprostol (Hawkey *et al*. 1998), switching to the new cyclooxygenase-2 specific inhibitors, or use of paracetamol (Smalley & Griffin 1996).

However, very few studies have reported estimates of relative risk of upper gastrointestinal complications for paracetamol (also known as acetaminophen). The widespread use of paracetamol advocates for more evidence-based information. We studied the association between paracetamol and the risk of upper gastrointestinal bleed/perforation in a population-based cohort of 958,397 persons in the United Kingdom between 1993 and 1998 (García-Rodríguez & Hernández-Díaz 2001). Our nested case-control analysis included 2,105 cases and 11,500 controls. Compared with non-users, users of paracetamol at doses less than 2 g daily did not present an increased risk of upper gastrointestinal complications. The adjusted relative risk (RR) for paracetamol at doses greater than 2 g was 3.6 (95% confidence interval (CI), 2.6–5.1). Nonetheless, the fact that paracetamol is widely available over-the-counter without prescription complicates a valid assessment of its effects in observational studies.

In this article we reviewed all other studies addressing the association between paracetamol and upper gastrointestinal complications and placed our results in the context of existing literature.

Nested case-control study

We conducted a nested case-control study using the United Kingdom General Practice Research Database during the period between April 1993 and October 1998. The study population comprised persons, 40–79 years of age, who had been enrolled at least 2 years with the general practitioner and who were free of cancer, oesophageal varices, Mallory-Weiss disease, liver disease, coagulopathies, and alcohol-re-

Author for correspondence: Luis A. García Rodríguez, Spanish Centre for Pharmacoepidemiological Research, C/Almirante 28 2°, 28004 Madrid, Spain (fax +34 91 531 2871, e-mail lagarcia@ceife.es).

lated disorders at start date. All study members were traced until they met a case definition criterion or one of the above-mentioned exclusion criteria, until they died, or until October 1998, whichever came first.

We identified patients with codes for upper gastrointestinal complications (defined as upper gastrointestinal bleeding, perforation, or melena) and manually reviewed the demographic data and clinical information in their computerized patient profiles. To validate the case status ascertained after review of the computerized information, we sent the general practitioners a questionnaire and a request to send all the information related to that event for a random sample of 100 patients. We received information for 99 patients, with only 1 patient not confirmed as a case of upper gastrointestinal complications. At the end, a total of 2,105 cases were identified. We randomly sampled 11,500 controls from the study population frequency-matched to cases by age and sex.

Exposure to paracetamol was categorized as "current", when the supply of the most recent prescription lasted until the index date or ended in the 30 days before the index date (close to 80% of current use lasted until the index date or ended in the week before the index date); "recent", when it ended 31–90 days before the index date; "past", when it ended 91–180 days before the index date; and "non-use", when there was no recorded use in the 6 months before the index date. We evaluated duration of use adding the periods of "consecutive" prescriptions, defined as an interval of less than 2 months between two prescriptions. Among current paracetamol users, we calculated the dose-response relation using the following five daily dose categories, in mg: ≤1,000; 1,001–1,999; 2,000; 2,001–3,999; and ≥4,000. The dose 2 g stands on its own because it was a commonly used daily dose.

The analysis included 2,105 cases and 11,500 controls. We used unconditional logistic regression to compute estimates of RR and 95% CIs of upper gastrointestinal complications associated with current use of each drug group of interest. We chose non-users of each respective drug group as the reference category. All estimates of RR were adjusted for age; sex; calendar year; smoking; antecedents of upper gastrointestinal disorders; and use of steroids, anticoagulants, non-aspirin NSAIDs, paracetamol, H_2 receptor antagonists, omeprazole, misoprostol, and aspirin. A more detailed description of this study is provided in the original report (García-Rodríguez & Hernández-Díaz 2001).

Systematic review

We conducted a MEDLINE search using the keywords "acetaminophen" or "paracetamol" combined with "gastrointestinal complications", "bleeding", "gastrointestinal haemorrhage", "gastrointestinal toxicity" or "peptic ulcer". The search was restricted to human studies on adults published between 1980 and 2004. We reviewed the abstracts of all the entries retrieved by this strategy plus the references of original articles and reviews related to paracetamol and upper gastrointestinal complications. To be included in the analysis, articles had to be case-control or cohort studies on paracetamol use and upper gastrointestinal compli-

Table 1.

Relative Risk (RR) and 95% Confidence Interval (95% CI) of upper gastrointestinal complications according to recency of acetaminophen exposure, dose, and duration, compared with non-use.

	Cases N	Controls N	Crude RR (95% CI)	Adjusted RR (95% CI)*
Paracetamol use				
Non-use (>180 days)	1494	9532	*Reference*	*Reference*
Current (0–30 days)	376	1069	2.2 (2.0–2.6)	1.3 (1.1–1.5)
Recent (31–90 days)	140	496	1.8 (1.5–2.2)	1.1 (0.9–1.4)
Past (91–180 days)	95	403	1.5 (1.2–1.9)	1.1 (0.8–1.4)
Paracetamol dose (mg)†				
Non-use	1494	9532	*Reference*	*Reference*
≤1000	142	610	1.5 (1.2–1.8)	1.0 (0.8–1.2)
1001–1999	59	242	1.6 (1.2–2.1)	0.8 (0.6–1.1)
2000	84	127	4.2 (3.2–5.6)	1.9 (1.4–2.6)
2001–3999	78	83	6.0 (4.4–8.2)	3.4 (2.4–4.8)
≥4000	13	7	11.8 (4.7–29.7)	6.5 (2.4–17.6)
Paracetamol duration†				
Non-use	1494	9532	*Reference*	*Reference*
Less than 3 months	140	382	2.3 (1.9–2.9)	1.4 (1.1–1.7)
≤2000 mg	120	376	2.0 (1.6–2.5)	1.2 (1.0–1.6)
>2000 mg	20	6	21.3 (8.5–53.0)	10.5 (3.8–28.9)
3 months and more	236	687	2.2 (1.9–2.6)	1.2 (1.0–1.5)
≤2000 mg	165	603	1.7 (1.5–2.1)	1.0 (0.8–1.2)
>2000 mg	71	84	5.4 (3.9–7.4)	3.2 (2.2–4.6)

* Adjusted for age, sex, calendar year, ulcer history, smoking, steroid, anticoagulant, gastroprotective drugs, non-aspirin non-steroidal anti-inflammatory drugs and aspirin use.

† The effect of daily dose and duration was analyzed among current users.

Source: García-Rodríguez & Hernández-Díaz (2001).

Table 2.

Characteristics and summary estimates of the studies.

Author (year)	Cases N	Design	Exposure definition	Variables controlled for by design/analysis	
Coggon *et al.* (1982)	277	Community-matched case-control	Any use in the prior week	Age, sex, steroids, warfarin, NSAIDs	1.9 (1.2–3.3)
Levy *et al.* (1988)	57	Hospital case-control	Regular use (≥4 days/week) in the prior week	Age, sex, date, smoking, alcohol, caffeine, peptic ulcer disease, cirrhosis, steroids, anticoagulants, H2 blockers education, geographic area, religion, myocardial infarction, stroke,	1.5 (0.4–6.1)
Faulkner *et al.* (1988)	230	Community-matched case-control	Any use in the prior week	Age, sex, NSAIDs	1.2 (0.8–2.0)
Laporte *et al.* (1991)	875	Hospital-matched case-control	Any use in the prior week	Age, sex, date, study site, smoking, alcohol, caffeine, peptic ulcer disease, cirrhosis, coagulopathy, NSAIDs, anti-ulcer drugs	1.5 (0.8–2.5)
Holvoet *et al.* (1991)	161	Hospital-matched case-control	Any use in the prior week	Age, sex, study site	1.4 (0.5–4.1)
Nobili *et al.* (1992)	441	Hospital-matched case-control	Any use in the prior week	Age, sex, date, study site, smoking, peptic ulcer disease, cirrhosis, coagulopathy, NSAIDs	0.20 (0.02–2.10)
Savage *et al.* (1993)	494	Hospital-matched case-control	Regular use (≥2/week) in the prior month	Age, sex, smoking, alcohol, prior bleeding disorders, NSAIDs, anticoagulants	1.94 (1.35–2.81)
Langman *et al.* (1994)	1144	Hospital- & community-matched case-control	Any use in the prior 3 months	Age, sex, study site, smoking, alcohol, peptic ulcer disease, dyspepsia, NSAIDs	1.1 (0.7–1.7)
Matikainen *et al.* (1996)	48	Hospital-matched case-control	Any use in the prior week	Age, sex, date, study site	1.08 (0.11–10.68)*
García-Rodríguez *et al.* (2001)	2105	Community case-control study	Any use in the prior month	Age, sex, date, smoking, peptic ulcer disease, NSAIDs, steroids, anticoagulants, anti-ulcer drugs	1.3 (1.1–1.5)
Lanas *et al.* (2003)	1122	Hospital & community case-control	Any use in the prior week	Age, sex, prior upper gastrointestinal complications, peptic ulcer disease, cardiovascular disease, cerebrovascular disease, NSAIDs, antisecretory drugs, nitrates	0.7 (0.4–1.2)
Gallerani *et al.* (2004)	940	Hospital case-control	Any use in the prior week	Age, sex, calendar year, smoking, alcohol, comorbidity index, NSAIDs, steroids, anticoagulants	1.95 (1.07–3.56)
				Pooled estimate (fixed effects)	1.3 (1.2–1.5)
				Pooled estimate (random effects)	1.4 (1.1–1.6)

* Point-estimate and confidence interval calculated using data from table 5 of the original manuscript.

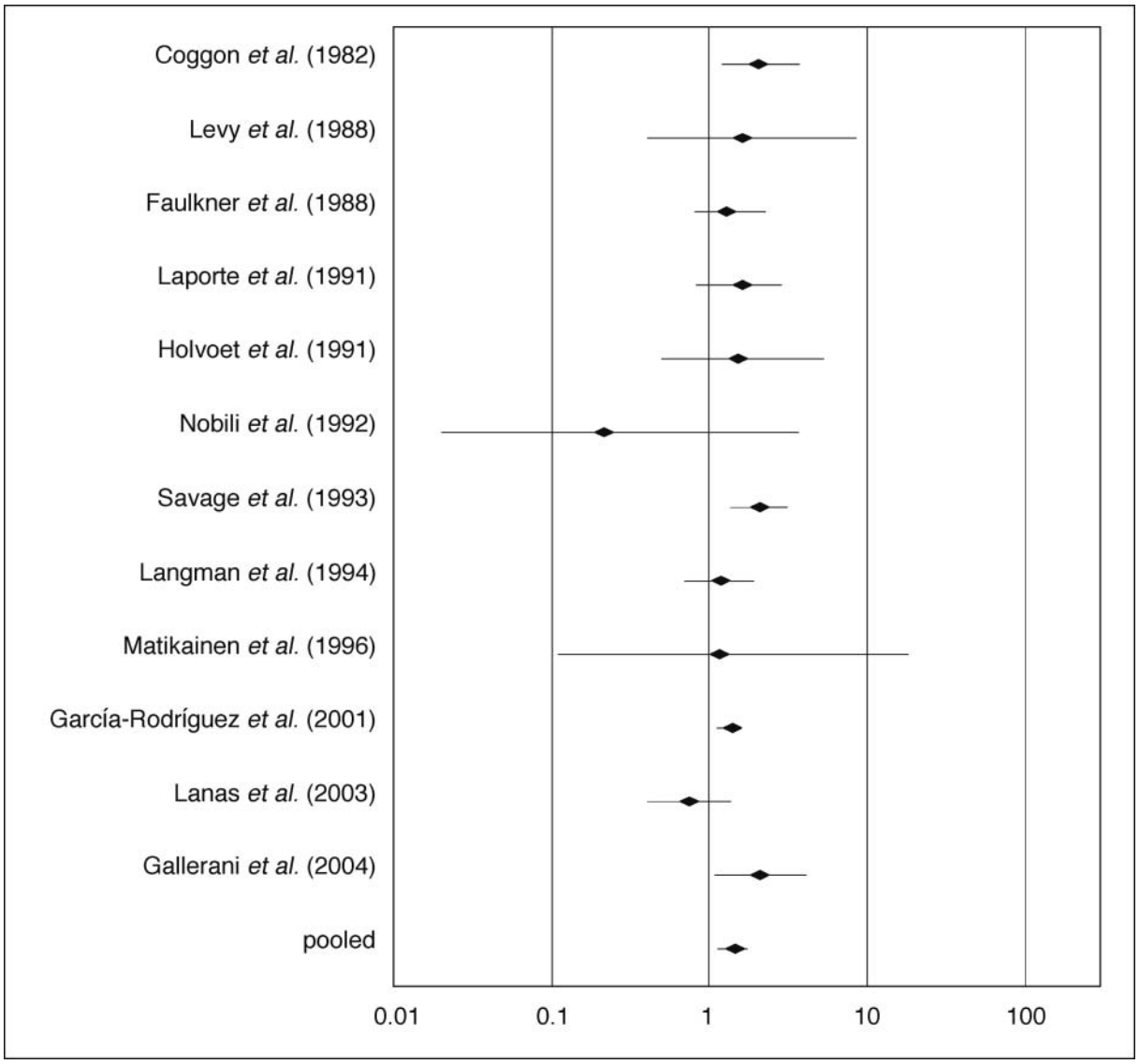

Fig. 1. Summary estimate of published studies.

cations and had to provide enough data to estimate a relative risk comparing paracetamol users with non-users. Studies that used uncomplicated peptic ulcer patients as controls were not included. Estimates published solely in letter, commentary or abstract forms were not considered. A total of ninety-two abstracts were reviewed to determine if they met the predefined inclusion criteria. We extracted the data from the selected publications using a standardized data extraction form. Decisions regarding inclusion of studies were reached by consensus. A total of twelve studies were finally included in the meta-analysis (Coggon *et al*. 1982; Faulkner *et al*. 1988; Levy *et al*. 1988; Holvoet *et al*. 1991; Laporte *et al*. 1991; Nobili *et al*. 1992; Savage *et al*. 1993; Langman *et al*. 1994; Matikainen & Kangas 1996; García-Rodríguez & Hernández-Díaz 2001; Lanas *et al*. 2003; Gallerani *et al*. 2004).

Adjusted relative risks (RR) estimated in the original articles were collected together with information on study methodology and objective quality-related characteristics. Variables assessed included: authors, year of publication, journal, geographic region, study years, source population, inclusion and exclusion criteria, source of cases, source of controls, outcome definition, source of exposure information, exposure definition, sample size, and attempt to control for confounding.

We calculated a summary RR and 95 percent CI, weighting study estimates by the inverse of the variance and estimating linear predictors for the log effect measure (DerSimonian & Laird 1986; Poole & Greenland 1999). In addition to the fixed effects estimate, we also calculated the corresponding random effects estimate, which gave similar results. The odds ratio from case-control studies was assumed to provide a valid estimate of the relative risk (Walker 1991). To determine whether it was appropriate to pool the individual results into one common summary measure, the heterogeneity in effects between studies was

analyzed using the DerSimonian and Laird's test statistic (Q) (Takkouche *et al*. 1999). We explored potential publication bias qualitatively using a "funnel plot" (Cooper & Hedges 1994). We performed an alternative analysis excluding our study that yielded similar results.

Nested case-control study

In our study, use of paracetamol was associated with a small elevated risk of upper gastrointestinal complications (RR, 1.3; 95% CI, 1.1–1.5). The RR was 3.6 (95% CI, 2.6–5.1) among paracetamol users of more than 2 g daily, whereas smaller doses did not increase the risk (table 1). When we restricted the analysis to individuals who never received a prescription for NSAIDs and who had no recorded antecedents of upper gastrointestinal disorders (including dyspepsia), the corresponding RR for paracetamol use at doses greater than 2 g was 5.7 (95% CI, 2.0–16.4). The dose-response increased risk among paracetamol users was independent of treatment duration. We compared the risk of upper gastrointestinal complications between paracetamol users with osteoarthritis, rheumatoid arthritis or pain-related disorders as indication, and found no important differences between indications. Compared with non-users of either any of these drugs, the RR for concurrent users of NSAIDs and paracetamol (2 g and more) was 13.2 (95% CI, 9.2–18.9).

Systematic review and meta-analysis

We found twelve published epidemiological studies including our study (Coggon *et al*. 1982; Faulkner *et al*. 1988; Levy *et al*. 1988; Holvoet *et al*. 1991; Laporte *et al*. 1991; Nobili *et al*. 1992; Savage *et al*. 1993; Langman *et al*. 1994; Matikaienen & Kangas 1996; García-Rodríguez & Hernández-Díaz 2001; Lanas *et al*. 2003; Gallerani *et al*. 2004) that included estimates of relative risk of upper gastrointestinal complications associated with any use of paracetamol (table 2). All studies shared a case control design. Most of them used hospital controls only (n=7), three studies used community controls and the other two studies used both hospital and community controls. Four studies were carried out in the UK, two in Spain, and two in Italy. The remaining were conducted in Belgium, Finland, New Zealand, and one international study had sites in the US, Canada, and Israel. Eleven studies ascertained drug exposure by means of an interview, as opposed to our study that ascertained drug exposure using computerized prescriptions recorded in the database. The most frequent exposure definition was any use in the prior week (eight studies). Other exposure definitions were regular use in the prior week, in the previous month and any use in the previous month or in the previous three months (table 2). The estimates ranged from 0.2 through 2.0 with a summary estimate of 1.3 (95% CI, 1.2–1.5) (fig. 1). The random effects model yielded similar results (table 2). Also, when we excluded our study from the pooled analysis, the summary estimate remained virtually the same (RR=1.4, 95%CI, 1.2–1.7). We did not detect significant heterogeneity between the pooled studies (P=0.12) nor did we appreciate evidence suggestive of publication bias in the funnel plot (fig. 2)

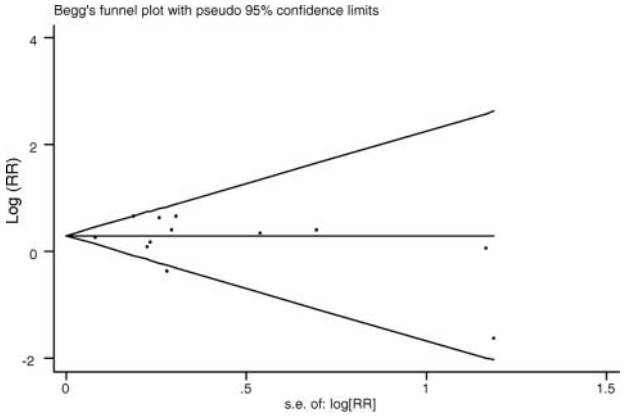

Fig. 2. Funnel plot.

Apart from our study, only two studies reported an estimate for risk of upper gastrointestinal complications associated with use of paracetamol at high doses. Coggon *et al*. (1982) found a RR of 2.4 associated to "heavy" paracetamol users (more than 20 tablets in the past week) compared to non-users, a little more than the overall ratio. Savage *et al*. (1993) found an increased risk of upper gastrointestinal complications associated with paracetamol at doses higher than 1000 mg/day (adjusted relative risk of 2.6).

The results from the pooled analysis suggest that paracetamol could be associated with a thirty percent increased risk of upper gastrointestinal complications. This small increased risk is fully compatible with our data. In fact exclusion of our study from the pooled analysis had a negligible effect on the summary estimate.

Unfortunately only few studies (a total of three) explored the association between daily dose of paracetamol and upper gastrointestinal complications. In our study, paracetamol was associated with an increased risk of upper gastrointestinal bleeding/perforation (RR=3.6) only when taken at daily doses above 2000 mg. Also, we found a substantial interaction when taking NSAIDs and high dose paracetamol (2 g or more) together. The other two studies also reported larger estimates among high-dose users than among medium-low dose users (Coggon *et al*. 1982; Savage *et al*. 1993).

Among those studies that did not meet the criteria to be included in the pooled analysis, a recent study reported a dose-response relation of paracetamol with gastrointestinal adverse events (Rahme *et al*. 2002). After adjustment for risk susceptibility, users of paracetamol at high doses (>3250 mg/day) had a similar risk of gastrointestinal adverse events as users of NSAIDs at high dose. In the same study, those using low doses of paracetamol (≤650 mg/day) had a reduced risk of gastrointestinal events compared to users of NSAIDs at high doses.

Other studies have investigated the association between paracetamol use and gastric ulcer. McIntosh *et al*. (1985) found that daily use of paracetamol during the year before was more than twice higher among cases than among controls. However this result was not statistically significant (RR=3.2; 95%CI, 0.0–110.0). In a second study, the same authors observed a relative risk of 1.2; 95%CI, (0.5–2.6) among daily users of paracetamol compared to non-users (McIntosh *et al*. 1988). Piper *et al*. (1981) observed a highly elevated risk of gastric ulcer among paracetamol "heavy" users (RR=24, P<0.001) and another study by Lanas *et al*. (1995) found that use of high doses of paracetamol (>1500 mg/day) was associated with refractory ulcers (defined as endoscopically proven ulcer that did not heal after at least 2 months of pharmacological treatment). Finally Imhof *et al*. (1997) compared exposure to paracetamol between patients with ulcer bleeding and patients with uncomplicated peptic ulcer. Paracetamol use was more common among those with ulcer bleeding (RR=3.20; 95%CI, 1.17–8.73).

Non-steroidal anti-inflammatory drugs inhibit the cyclooxygenase enzyme, responsible for the conversion of arachidonic acid to prostaglandins (Hawkey 1999). Two isoforms of this enzyme have been described: cyclooxygenase-1, with protective functions in the gastrointestinal mucosa and other tissues, and cyclooxygenase-2, with an inflammatory role. It has been suggested that NSAIDs exert their toxic effects mainly by inhibiting the cyclooxygenase-1. Paracetamol might also inhibit the formation of prostaglandins, thereby providing a mechanism for an ulcerogenic effect. *In vitro* analyses have shown that paracetamol is a weak non-selective inhibitor of both isoforms of cycloxygenase in human whole blood assays (Cryer & Feldman 1998). The increased risk associated with concomitant use of NSAIDs and high doses of paracetamol may be attributable in part to an augmentation of cycloxygenase inhibition, of the same type as the increased risk observed among users of high-dose NSAIDs or multiple NSAIDs (García-Rodríguez & Hernández-Díaz 2001).

Despite the biological plausibility of a gastrointestinal effect, paracetamol has been traditionally considered a safer alternative than NSAIDs for the pharmacological treatment of various osteoarticular conditions (Dajani 1998), as well as an analgesic and antipyretic drug (Smalley & Griffin 1996). This belief is based on clinical trials that 1) studied mainly doses lower than 2000 mg/day in healthy persons and 2) studied endoscopic gastroduodenal injuries (Hoftiezer *et al*. 1982; Lanza *et al*. 1998) which are poor predictors of major clinical gastrointestinal complications (Armstrong & Blower 1987), 3) studied acute effects after short-term use (Hoftiezer *et al*. 1982), 4) studied very few subjects (Hoftiezer *et al*. 1982). Endoscopic studies have shown that paracetamol produces some damage to gastric mucosa when given acutely, although minimal compared to aspirin (Ivey 1978).

A spurious association between paracetamol use and upper gastrointestinal complications may occur in observational studies due to preferential use of paracetamol when patients have a history of ulcer or dyspepsia, to the extent that practitioners believe that paracetamol is less gastrotoxic than NSAIDs. Although we adjusted for antecedents of upper gastrointestinal disorders (including dyspepsia), gastroprotective co-therapy, and several other factors associated with the risk of upper gastrointestinal complications, incomplete control of confounding can still be present. Nevertheless, two lines of evidence argue against this possibility: the clear dose-effect found (physicians would tend to prescribe low doses rather than higher doses to patients at greatest baseline risk of upper gastrointestinal complications) and the similar results found upon restriction of the analyses to persons without known major risk factors (i.e. with no prior upper gastrointestinal disorders and no NSAID use).

A common concern for all studies using computerized prescription data is the under-ascertainment of the over-the-counter drug use. Since paracetamol is widely available without prescription there is a certain degree of misclassification in the exposure variable. We could indirectly assess the magnitude of the misclassification using data from a study in the UK in a similar population, in which the authors interviewed patients to obtain information on all prescribed and self-administered paracetamol intake (Langman *et al*. 1994). They reported a prevalence of 20% in the previous three months in the control series whereas such prevalence was 14% in our study; 25% of their controls were older than 80 years, whereas in our study the upper age limit was 79 years. Since the use of drugs is higher among the elderly, it is apparent that no major under-recording of paracetamol was present in our data, after allowing for the different age distributions. We did a sensitivity analysis to quantify the impact of non-recorded drug use. With false negative probabilities beyond 30% (an estimate likely to be more extreme than the true one), the net impact of non-differential under-recorded use of paracetamol would have been a small underestimation of the excess risk. Moreover, although misclassification of exposures collected prospectively is usually close to non-differential among between cases and controls, we also examined the effects of differential misclassification. Even unrealistically high differential under-recording could not cancel the elevated risks of upper gastrointestinal complications found for high dose paracetamol. The small impact of missing over-the-counter antiinflammatory drug use has also been previously reported (Ulcickas-Yood *et al*. 2000).

In conclusion, our findings indicate that the use of paracetamol at the doses most commonly used confer little or no increased risk of upper gastrointestinal complications. More data are needed to confirm or refute the suggestion that high-dose paracetamol is associated with an increased risk of upper gastrointestinal complications of the same magnitude as the one observed with traditional NSAIDs.

Acknowledgements

We are in debt to Dr. Sonia Hernández-Díaz for her help in the preparation of the manuscript.

References

Armstrong, C. P. & A. Blower: Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut* 1987, **28**, 527–532.

Bollini, P., L. A. García Rodríguez, S. Pérez Gutthann & A. M. Walker: 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**, 1289–1295.

Coggon, D., M. J. Langman & D. Spiegelhalter: Aspirin, paracetamol, and haematemesis and melaena. *Gut* 1982, **23**, 340–344.

Cooper, H. & L. V. Hedges: *The handbook of research synthesis*. Russel Sage Foundation, New York, 1994.

Cryer, B. & M. Feldman: Cyclooxygenase-1 and cyclooxygenase-2 selectivity of widely used nonsteroidal anti-inflammatory drugs. *Amer. J. Med.* 1998, **104**, 413–421.

Dajani, E. Z: Gastrointestinal toxicity of over-the-counter analgesics. *Amer. J. Gastroenterol.* 1998, **93**, 1020–1022.

DerSimonian, R. & N. Laird: Meta-analysis in clinical trials. *Controll. Clin. Trials* 1986, **7**, 177–188.

Faulkner, G., P. Prichard, K. Somerville & M. J. S. Langman: Aspirin and bleeding peptic ulcers in the elderly. *Brit. Med. J.* 1988, **297**, 1311–1313.

Gabriel, S. E., L. Jaakkimainen & C. Bombardier: Risk for serious gastrointestinal complications related to use of nonsteroidal anti-inflammatory drugs. *Ann. Intern. Med.* 1991, **115**, 787–796.

Gallerani, M., M. Simonato, R. Manfredini, S. Volpato, G. B. Vigna & R. Fellin: Risk of hospitalization for upper gastrointestinal tract bleeding. *J. Clin. Epidemiol.* 2004, **57**, 103–110.

García-Rodríguez, L. A., S. Hernández-Díaz & F. J. De Abajo: Association between aspirin and upper gastrointestinal complications: Systematic review of epidemiologic studies. *Brit. J. Clin. Pharmacol.* 2001, **52**, 563–571.

García-Rodríguez, L. A. & S. Hernández-Díaz: Relative risk of upper gastrointestinal complications among users of acetaminophen and nonsteroidal anti-inflammatory drugs. *Epidemiology* 2001, **12**, 570–576.

Hawkey, C. J., J. A. Karrasch, L. Szczepanski, D. G. Walker, A. Barkun, A. J. Swannell & N. D. Yeomans: A comparison of omeprazole and misoprostol for treating and preventing ulcers associated with non-steroidal anti-inflammatory drugs. *New Engl. J. Med.* 1998, **338**, 727–734.

Hawkey, C. J.: COX-2 inhibitors. *Lancet* 1999, **353**, 307–314.

Henry, D., L. L. Lim, L. A. Garcia Rodriguez, S. Perez Gutthann, J. L. Carson, M. Griffin, R. Savage, R. Logan, Y. Moride, C. Hawkey, S. Hill & J. T. Fries: Variability in risk of gastrointestinal complications with individual non-steroidal anti-inflammatory drugs: results of a collaborative meta-analysis. *Brit. Med. J.* 1996, **312**, 1563–1566.

Hernández-Díaz, S. & L. A. García-Rodríguez: Overview of epidemiological studies published in the nineties on the association between non-steroidal anti-inflammatory drugs and upper gastrointestinal bleed/perforation. *Arch. Int. Med.* 2000, **160**, 2093–2099.

Hoftiezer, J., J. O'Laughkin & K. Ivey: Effects of 24 hours of aspirin, Bufferin, paracetamol and placebo on normal human gastroduodenal mucosa. *Gut* 1982, **23**, 692–697.

Holvoet, J., L. Terriere, W. Van Hee, L. Verbist, E. Fierens & M. Hautekeete: Relation of upper gastrointestinal bleeding to nonsteroidal anti-inflammatory drugs and aspirin: a case-control study. *Gut* 1991, **32**, 730–734.

Imhof, M., C. Ohmann, A. Hartwig, K. P. Thon, K. J. Hengels & H. D. Roher: Which peptic ulcers bleed? Results of a case-control study. *Scand. J. Gastroenterol.* 1997, **32**, 131–138.

Ivey, K. J., G. R. Silvoso & W. Krause: Effect of paracetamol on gastric mucosa. *Brit. Med. J.* 1978, **1**, 1586–1588.

Lanas, A., B. Remacha, F. Esteva & R. Sainz: Risk factors associated with refractory peptic ulcers. *Gastroenterology* 1995, **109**, 1124–1133.

Lanas, A., P. Serrano, E. Bajador, J. Fuentes & R. Sainz: Risk of upper gastrointestinal bleeding associated with non-aspirin cardiovascular drugs, analgesics and nonsteroidal anti-inflammatory drugs. *Eur. J. Gastroenterol. Hepatol.* 2003, **15**, 173–178.

Langman, M. J., J. Weil, P. Wainwright, D. H. Lawson, M. D. Rawlins, R. F. Logan, M. Murphy, M. P. Vessey & D. G. Colin-Jones: Risks of bleeding peptic ulcer associated with individual nonsteroidal anti-inflammatory drugs. *Lancet* 1994, **343**, 1075–1078.

Lanza, F. L., J. R. Codispoti & E. B. Nelson: An endoscopic comparison of gastroduodenal injury with over-the-counter doses of ketoprofen and acetaminophen. *Amer. J. Gastroenterol.* 1998, **93**, 1051–1054.

Laporte, J. R., X. Carné, X. Vidal, V. Moreno & J. Juan: Upper gastrointestinal bleeding in relation to previous use of analgesics and non-steroidal antiinflammatory drugs. *Lancet* 1991, **337**, 85–89.

Levy, M., D. R. Miller, D. W. Kaufman, V. Siskind, P. Schwingl, L. Rosenberg, B. Strom & S. Shapiro: Major upper gastrointestinal tract bleeding. Relation to the use of aspirin and other nonnarcotic analgesics. *Arch. Inter. Med.* 1988, **148**, 281–285.

Matikainen, M. & E. Kangas: Is there a relationship between the use of analgesics and non-steroidal anti-inflammatory drugs and acute upper gastrointestinal bleeding? A Finish case-control prospective study. *Scand. J. Gastroenterol.* 1996, **31**, 912–916.

McIntosh, J., K. Byth & D. W. Piper: Environmental factors in aetiology of chronic gastric ulcer: a case control study of exposure variables before the first symtoms. *Gut* 1985, **26**, 789–798.

McIntosh, J. H., C. S. Fung, G. Berry & D. W. Piper: Smoking, nonsteroidal anti-inflammatory drugs, and acetaminophen in gastric ulcer. A study of associations and of the effects of previous diagnosis on exposure patterns. *Amer. J. Epidemiol.* 1988, **128**, 761–770.

Nobili, A., P. Mosconi, M. G. Franzosi & G. Tognoni: Non-steroidal anti-inflammatory drugs and upper gastrointestinal bleeding, a post-marketing surveillance case-control study. *Pharmacoepidemiol. Drug Safety* 1992, **1**, 65–72.

Piper, D. W., J. H. McIntosh, D. E. Ariotti, B. H. Fenton & R. MacLennan: Analgesic ingestion and chronic peptic ulcer. *Gastroenterology* 1981, **80**, 427–432.

Poole, C. & S. Greenland: Random-effects meta-analyses are not always conservative. *Amer. J. Epidemiol.* 1999, **150**, 469–475.

Rahme, E., D. Pettitt & J. LeLorier: Determinants and sequelae associated with utilization of acetaminophen versus traditional nonsteroidal antiinflammatory drugs in an elderly population. *Arthritis Rheum.* 2002, **46**, 3046–3054.

Savage, R., P. Moller, C. Ballantyne & J. Wells: Variation in the risk of peptic ulcer complications with nonsteroidal antiinflammatory drug therapy. *Arthritis Rheum.* 1993, **36**, 84–90.

Smalley, W. E. & M. R. Griffin: The risk and costs of upper gastrointestinal disease attributable to NSAIDs. *Gastroenterology Clinics of North America* 1996, **25**, 373–396.

Takkouche, B., C. Cadarso-Suárez & D. Spiegelman: An evaluation of old and new tests of heterogeneity in meta-analysis in epidemiologic research. *Amer. J. Epidemiol.* 1999, **150**, 206–215.

Ulcickas-Yood, M., K. J. Rothman, C. C. Johnson, S. S. Jick, J. Lang, K. E. Wells & H. Jick: Using prescription claims data for drugs available over-the-counter (OTC). *Pharmacoepidemiol. Drug Safety* 2000, **9**, S37 (abstract).

Walker, A. M.: *Observation and inference. An introduction to the methods of epidemiology*. Epidemiology Resources Inc., Newton Lower Falls, 1991.