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Gastrointestinal Tolerability of Ibuprofen Compared with Paracetamol and Aspirin at Over-the-counter Doses

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This multicentre, randomized, investigator-blinded, parallel-group study compared the gastrointestinal (GI) tolerability of ibuprofen, paracetamol and aspirin at over-the-counter doses for common pain indications. Patients (of whom 8633 were evaluable) took either ibuprofen up to 1200 mg daily, or paracetamol or aspirin, each up to 3000 mg daily, for 1 – 7 days. The main outcome was the proportion of patients with GI adverse events. There were significantly more patients who suffered GI adverse events, principally abdominal pain, dyspepsia, nausea and diarrhoea, with aspirin (18.5%) than with ibuprofen (11.5%), but the difference between ibuprofen and paracetamol (13.1%) was not significant. Significantly more of those patients with a history of non-ulcer GI disease (*n* = 371) developed GI adverse events than did those with no such history; the incidence of GI adverse events in both groups was lowest with ibuprofen. More women than men experienced GI adverse events (15.5% versus 12.8%). The higher incidence of GI adverse events with aspirin was evident from the first day of treatment. In conclusion, the GI tolerability of ibuprofen, at over-the-counter doses of up to 1200 mg daily for up to 7 days, was at least as good as that of paracetamol and significantly better than that of aspirin.

KEY WORDS: ASPIRIN; IBUPROFEN; PARACETAMOL; ANALGESICS; GASTROINTESTINAL TOLERABILITY

Introduction

Although the incidences of adverse events with ibuprofen, paracetamol and aspirin have been assessed in case–control studies and meta-analyses, they had not, until recently, been compared directly in short-term use in patients requiring treatment for common pain conditions. In the Paracetamol, Aspirin and Ibuprofen New Tolerability (PAIN) Study, a large-scale, randomized, investigator-blinded study, the overall tolerability of ibuprofen was shown to be equivalent to that of paracetamol and significantly better than that of aspirin ($P < 0.001$).[1]

This paper reports new data on the relative gastrointestinal (GI) tolerability of these three analgesics at over-the-counter (OTC) doses.

Patients and methods

PROCEDURE

The study methods have been described previously.[1] In this multicentre, randomized, investigator-blinded, parallel-group study, 8633 evaluable patients (of both sexes, aged 18 – 75 years) received 200 mg ibuprofen or 500 mg paracetamol or 500 mg aspirin tablets, up to six tablets per day (the recommended doses in France at that time) for at least 1 day and up to 7 days. Patients recorded the nature and severity of all adverse events on diary cards. The GI adverse events were analysed and are presented below.

OUTCOME MEASURES

The primary outcome measure was the percentage of patients with at least one GI adverse event (Coding Symbols for Thesaurus of Adverse Reaction Terms [COSTART][2] digestive system event and abdominal pain [usually classified as 'body as a whole'] combined). The percentages of patients with at least one GI adverse event were then categorized according to:

(i) COSTART digestive system term;
(ii) Severity of event (severe, moderate or mild);
(iii) GI disease history;
(iv) Gender.

The appearance of GI adverse events by time and by dose of study medication was also reported.

STATISTICAL ANALYSIS

For the analysis of GI adverse events, ibuprofen was compared with aspirin and with paracetamol, using two-sided χ^2 tests. The significance level for both comparisons was set at 0.035, using Dunnett's correction[3] to account for multiple comparisons and achieve an overall 5% significance level. Kaplan–Meier estimates of the percentage of patients experiencing GI adverse events, by day of treatment and by the number of tablets of study medication taken, were calculated for the three treatments, and differences assessed by log-rank tests.

Results

Of the 8633 evaluable patients, 1923 (22.3%) had at least one adverse event, and the majority of patients with adverse events (1241 of 1923, 64.5%) had GI adverse events. At least one GI adverse event was experienced by 11.5%, 13.1% and 18.5% of patients treated with ibuprofen, paracetamol and aspirin, respectively. Overall, the difference in favour of ibuprofen was highly significant ($P < 0.0001$) compared with aspirin, but there was no significant difference between ibuprofen and paracetamol. The most common GI adverse events were abdominal pain, dyspepsia, nausea and diarrhoea.

Significantly fewer patients receiving ibuprofen reported abdominal pain and dyspepsia compared with aspirin ($P < 0.0001$ for both events; Table 1). There were significantly more reports of dyspepsia and diarrhoea in patients receiving paracetamol compared with ibuprofen (both $P < 0.015$). There were no significant differences between treatments in the rates of nausea (Table 1).

Comparison between treatments for severe, moderate and mild categories of GI adverse events showed, in each category, significantly higher rates ($P = 0.0006$, $P < 0.0001$ and $P = 0.0002$, respectively) in the aspirin than in the ibuprofen group (Table 2). Only for moderate events was there a significantly higher rate with paracetamol than with ibuprofen ($P = 0.0065$; Table 2). There were no serious GI adverse events.

Patients with a history of peptic ulcer were excluded from the study, in accordance

TABLE 1:
Total and most frequent gastrointestinal (GI) adverse events, categorized according to Coding Symbols for Thesaurus of Adverse Reaction Terms (COSTART),[2] in patients using ibuprofen, paracetamol or aspirin at over-the-counter doses

Adverse event	No. of patients (%)			*P*-value (ibuprofen versus paracetamol)[a]	*P*-value (ibuprofen versus aspirin)[a]
	Ibuprofen (*n* = 2869)	Paracetamol (*n* = 2874)	Aspirin (*n* = 2890)		
Total GI adverse events	330 (11.5)	377 (13.1)	534 (18.5)	NS	< 0.0001
Abdominal pain	174 (6.1)	200 (7.0)	326 (11.3)	NS	< 0.0001
Dyspepsia	82 (2.9)	117 (4.1)	183 (6.3)	< 0.015	< 0.0001
Nausea	94 (3.3)	88 (3.1)	123 (4.3)	NS	NS
Diarrhoea	37 (1.3)	62 (2.2)	53 (1.8)	< 0.015	NS

NS, not significant.
[a]These comparisons used a significance level of 0.035. *P*-values are from two-sided χ^2 tests.

TABLE 2:
Gastrointestinal adverse events, categorized according to severity, in patients using ibuprofen, paracetamol or aspirin at over-the-counter doses

Event severity[a]	No. of patients (%)			*P*-value (ibuprofen versus paracetamol)[b]	*P*-value (ibuprofen versus aspirin)[b]
	Ibuprofen	Paracetamol	Aspirin		
Severe	42 (1.5)	44 (1.5)	80 (2.8)	NS	0.0006
Moderate	126 (4.4)	172 (6.0)	239 (8.3)	0.0065	< 0.0001
Mild	191 (6.7)	199 (6.9)	270 (9.3)	NS	0.0002

NS, not significant.
[a]Some patients experienced more than one adverse event.
[b]These comparisons used a significance level of 0.035. *P*-values are from two-sided χ^2 tests.

with the product labelling. There were 371 patients with a history of other GI disease, most commonly hiatus hernia, gastro-oesophageal reflux, colitis, gastritis, constipation and stomach pain. Overall, compared with those with no GI history (n = 8262), those with such a history were more likely to have GI adverse events (22.1% versus 14.0%; $P < 0.001$). The differences within each treatment group were also significant (all $P < 0.035$; Table 3); ibuprofen was associated with the lowest incidence of GI adverse events in those with a GI history, although the only significant difference between treatments was a lower incidence of GI adverse events in patients with no previous GI history in the ibuprofen group compared with the aspirin group.

Significantly more women (15.5%) than men (12.8%) experienced GI adverse events ($P < 0.001$). Ibuprofen produced a significantly lower incidence of GI adverse events than aspirin ($P < 0.0001$; Table 3) in patients of each gender.

Compared with the other two treatments, the higher incidence of GI adverse events with aspirin was evident from the first dose on day 1, and this incidence continued to increase throughout the treatment period (Fig. 1). By day 7, the Kaplan–Meier

TABLE 3:
Gastrointestinal (GI) adverse events in subgroups of patients using ibuprofen, paracetamol or aspirin at over-the-counter doses

Variable	No. of patients (%)			*P*-value (ibuprofen versus paracetamol)[a]	*P*-value (ibuprofen versus aspirin)[a]
	Ibuprofen	Paracetamol	Aspirin		
History of GI disease					
Yes	21 (17.6)	25 (22.5)	36 (25.5)	NS	NS
No	309 (11.2)	352 (12.7)	498 (18.1)	NS	< 0.0001
Gender					
Male	126 (10.6)	134 (11.1)	203 (16.7)	NS	< 0.0001
Female	204 (12.2)	243 (14.6)	331 (19.8)	NS	< 0.0001

NS, not significant.
[a]These comparisons used a significance level of 0.035. *P*-values are from two-sided χ^2 tests.

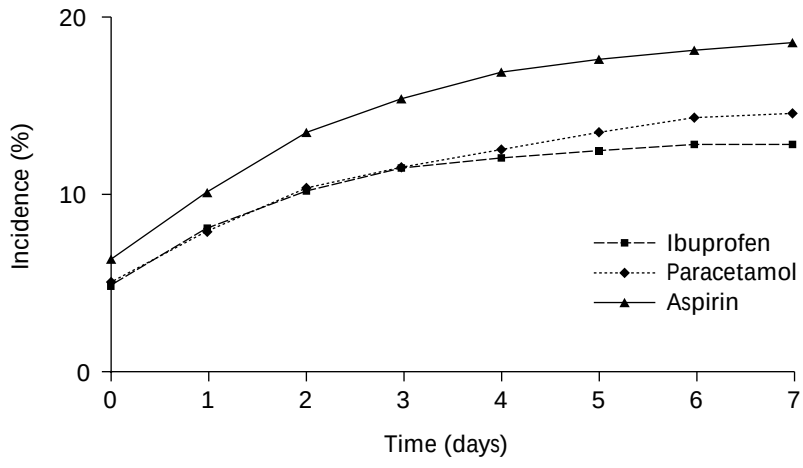

FIGURE 1: Estimated time to first event in patients affected by gastrointestinal adverse events during treatment with ibuprofen, paracetamol or aspirin at over-the-counter doses

estimates for patients experiencing a GI adverse event were 12.0%, 13.9% and 19.6% for ibuprofen, paracetamol and aspirin, respectively. Ibuprofen was associated with fewer GI adverse events than aspirin ($P < 0.0001$) and paracetamol, but in the latter case the difference was not significant. There were similar differences in the frequency of GI adverse events when plotted against the number of tablets taken (Fig. 2), and the higher incidence with aspirin was observed after the first dose.

Discussion

The results of this large-scale, direct comparison of short-term analgesic use at OTC doses show that the GI tolerability of

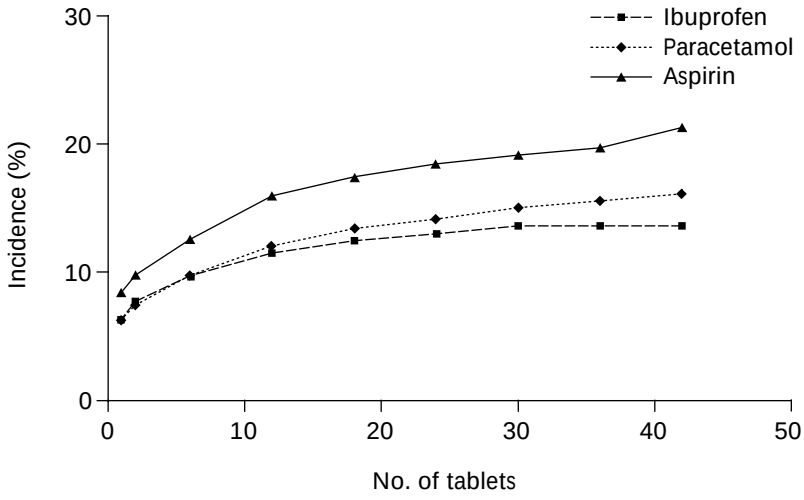

FIGURE 2: Estimated number of tablets to first event in patients affected by gastrointestinal adverse events during treatment with ibuprofen, paracetamol or aspirin at over-the-counter doses

ibuprofen is at least as good as that of paracetamol and significantly better than that of aspirin. There were no serious GI adverse events.

Patients with a history of non-ulcer GI disease experienced more GI adverse events than other patients, but in this group also, ibuprofen was associated with the lowest incidence of such events. The significantly higher incidence of GI adverse events with aspirin was observed as early as after the first dose.

In the only other large-scale comparative safety study of ibuprofen, in febrile children, low-dose, short-term treatment with ibuprofen was also shown to be well tolerated relative to paracetamol. The risk of hospitalization for GI bleeding, renal failure or anaphylaxis was not significantly different with ibuprofen compared with paracetamol.[4]

A recent double-blind, placebo-controlled study of the GI effects of ibuprofen 1200 mg daily for 10 days in healthy volunteers found that placebo-treated and ibuprofen-treated subjects had similar incidences of GI adverse events, and there were no significant differences between the treatments for the principal GI effects – dyspepsia, abdominal pain and nausea.[5]

The results from these safety studies are consistent with those from endoscopy, case–control and therapeutic studies, and meta-analyses, which demonstrate that the GI tolerability profile of ibuprofen (≤ 1200 mg daily) is better than that of other non-steroidal anti-inflammatory drugs (NSAIDs), including aspirin, and similar to that of paracetamol, which is generally regarded as being associated with a low incidence of GI ulceration and bleeding,[6] and placebo.

Endoscopy studies of the effect of ibuprofen 1200 mg daily on the gastric and duodenal mucosa showed that ibuprofen, like placebo, produced minimal mucosal injury, whereas aspirin caused substantial mucosal damage.[7]

A review of comparative upper-GI toxicity concluded that in doses of ≤ 1600 mg daily, ibuprofen has been associated with lower toxicity than other NSAIDs.[8] Epidemiological

studies have ranked ibuprofen lowest among many prescription NSAIDs in causing GI bleeding or peptic ulcer;[9,10] the risk was particularly low at doses < 1500 mg daily.[9]

A study of elderly patients admitted to hospital with upper-GI bleeding showed that, of the seven most commonly taken NSAIDs, ibuprofen was associated with the lowest risk of ulcer complication.[11] There was a significant association of ulcer complications with aspirin use, but not with paracetamol use. An epidemiological study of patients hospitalized with a first episode of upper-GI bleeding found that ibuprofen use did not significantly increase the relative risk of gastric or duodenal bleeding and carried a lower risk than aspirin.[12]

A meta-analysis of serious peptic ulcer complications in controlled epidemiological studies showed that ibuprofen (< 1600 mg daily) had the lowest or equal lowest risk, compared with other NSAIDs, in 10 of 11 studies. It was concluded that the use of low-risk drugs, such as ibuprofen, in low doses (< 1600 mg), as first-line treatment, would substantially reduce the risk of serious GI toxicity. Aspirin was associated with a 1.6-fold increase in the risk of serious GI complications compared with ibuprofen.[13] Even at the low doses used in cardiovascular prevention, aspirin increases the risk of GI bleeding.[14,15]

The good tolerability of ibuprofen is particularly evident at the low doses approved for OTC use (≤ 1200 mg daily). The OTC status of ibuprofen reflects its impressive safety record at OTC doses, especially compared with aspirin.[16]

In a therapeutic study in osteoarthritis, the incidence of GI adverse events with ibuprofen 1200 mg daily was similar to that with paracetamol 4000 mg daily during 4 weeks' treatment, a period longer than the recommended OTC usage, which is up to 5 days.[17]

Numerous reviews and meta-analyses reach the same conclusions as the individual studies cited above. A meta-analysis of 12 studies concluded that low doses of ibuprofen (< 1500 mg) have a safer GI profile than higher doses.[18,19]

A meta-analysis of published studies of paracetamol and ibuprofen (up to 4000 mg daily of paracetamol and 1200 mg daily of ibuprofen for < 7 days) found no apparent differences between the two drugs with respect to either overall or GI adverse events.[20]

Among the findings of a review that included 19 double-blind studies of single or multiple doses of 200 mg or 400 mg ibuprofen, placebo and naproxen sodium was the conclusion that there was no significant difference between ibuprofen and placebo for nausea, vomiting and diarrhoea.[21]

A meta-analysis of 15 single-dose studies of ibuprofen, paracetamol and placebo found a similar frequency of GI adverse events in the three groups.[22] A further meta-analysis of eight studies of ibuprofen, 800 – 1200 mg daily for 1 – 10 days, likewise indicated a similar frequency of GI adverse events with ibuprofen and placebo, nor were there significant differences in the incidence of dyspepsia, nausea and abdominal pain.[23]

A review of the quality of adverse event reporting in studies of 400 mg ibuprofen compared with placebo (20 studies) and of 1000 mg paracetamol compared with placebo (30 studies) in post-operative pain, which included an assessment of the individual events, nausea and vomiting, indicated that there was no significant difference between either of the active treatments and placebo.[24]

The data thus indicate that ibuprofen, at low doses, in short-term use for OTC indications, has a GI safety profile superior to that of aspirin and similar to that of paracetamol and placebo. The risk of GI complications is small and is minimized by

the product being contraindicated for patients with existing, or a history of, peptic ulceration. Serious GI adverse events are very rare with low-dose ibuprofen and are dose-related, the majority being associated with prescription doses which are higher and are taken for longer periods for conditions such as rheumatoid arthritis. The adverse event rates associated with the use of ibuprofen by such patients do not reflect the experience of patients using short-term OTC doses.[25,26]

Conclusion

This large-scale study, directly comparing the three most frequently used analgesics in patients taking low doses for short-term use for OTC indications, shows that the GI tolerability of ibuprofen is at least as good as that of paracetamol and is significantly better than that of aspirin. These findings are consistent with the results of previous smaller studies and of meta-analyses. The significant difference in GI adverse events with aspirin, compared with ibuprofen or paracetamol, was evident from the first day of treatment, and this difference continued to increase throughout the treatment period.

In patients with a history of GI disease, ibuprofen appears to be superior to aspirin, and similar to paracetamol in its GI tolerability, though the differences were not statistically significant.

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