

Endoscopic comparison of gastroduodenal injury with over-the-counter doses of new fast-dissolving ibuprofen and paracetamol formulations: a randomized, placebo-controlled, 4-way crossover clinical trial

Frank L Lanza¹
Agron Collaku²
Dongzhou J Liu³

¹Department of Gastroenterology,
Houston Institute for Clinical
Research, Houston, TX, USA;

²Biostatistics Department,
GlaxoSmithKline Consumer
Healthcare, Parsippany, NJ, USA;

³Global Clinical Development,
GlaxoSmithKline, Collegeville, PA,
USA

Background: While gastrointestinal (GI) effects of standard ibuprofen and N-acetyl-p-aminophenol (APAP) have been reported, upper GI injury following treatment with fast-dissolving (FD) formulations of these analgesics has not been investigated. We evaluated upper GI effects of over-the-counter doses of 2 FD ibuprofen products and 1 FD-APAP product.

Methods: In a randomized, placebo-controlled, endoscopist-blinded, 4-way crossover study, 28 healthy subjects received FD ibuprofen 2×200 mg liquid capsules 3 times daily (TID), ibuprofen 2×200 mg tablets TID, FD-APAP 2×500 mg tablets 4 times daily (QID), and placebo 2×500 mg tablets QID for 7 days. The primary end point was gastric mucosal damage assessed by endoscopy using the Lanza scale: 0=normal stomach or proximal duodenum, 1=mucosal hemorrhages only, 2=1 or 2 erosions, 3=numerous (3–10) erosions, and 4=large number of erosions (>10) or ulcer. Secondary end points included duodenal mucosal damage (Lanza scale); gastroduodenal mucosal injury, classified as present (gastric and/or duodenal endoscopy score ≥2) or absent (gastric and/or duodenal endoscopy score <2); and number of hemorrhages, erosions, and ulcers counted separately in the stomach and duodenum.

Results: Significantly greater gastric mucosal injury was observed after treatment with both ibuprofen products vs FD-APAP ($p<0.0001$ and $p=0.0095$, respectively). FD-APAP showed no difference from placebo ($p=0.4794$). The odds of having an incidence of gastroduodenal mucosal injury were over 6 times greater from FD ibuprofen liquid capsule treatment (odds ratio [OR]=6.19, 95% confidence interval [CI]: 1.60, 23.97) and over 3 times greater from ibuprofen tablet treatment (OR=3.19, 95% CI: 0.8, 12.74) vs FD-APAP.

Conclusion: Treatment with 2 ibuprofen products was associated with significant gastric mucosal injury. Of the 4 treatments studied, FD ibuprofen liquid capsules had the highest risk of incidence of gastroduodenal mucosal injury. Treatment with FD-APAP did not induce any clinically or statistically significant gastroduodenal mucosal injury.

Keywords: gastric mucosal damage, APAP, NSAIDs, erosions, hemorrhages, ulcer

Correspondence: Dongzhou J Liu
Global Clinical Development,
GlaxoSmithKline, 1250 South
Collegeville Rd, Collegeville, PA 19426,
USA
Email jeffery.d.liu@gsk.com

Introduction

Ibuprofen and paracetamol are common analgesics/antipyretics available as over-the-counter (OTC) drugs and have been extensively used for treatment of fever and pain in various conditions including musculoskeletal and arthritic disorders. Ibuprofen products are nonsteroidal anti-inflammatory drugs (NSAIDs) that strongly inhibit

the peripheral cyclooxygenase (COX) enzyme isoforms 1 and 2. Inhibition of COX-1 slows the regeneration of the gastric mucosa, which is associated with well-characterized gastrointestinal (GI) toxicity of most NSAIDs.^{1–8} Both systemic mechanisms, via nonselective prostaglandin inhibition and local and direct mucosal effects, have been implicated in the pathogenesis of injury.^{1–4} Numerous endoscopic studies indicate damage of the gastric mucosa and have shown differences in the degree of GI damage produced by different NSAIDs.^{5–8} In addition, older age, history of GI illness, concomitant corticosteroid use, and increasing NSAID dose are associated with an increased risk of NSAID-related GI damage. There is evidence suggesting that even OTC doses of NSAIDs are associated with GI hemorrhage and erosive lesions.^{9,10} Patients on long-term NSAID treatment, even if asymptomatic, may reveal damage including mucosal hemorrhage, ulceration, and perforation of the GI lining.⁵

N-acetyl-p-aminophenol (APAP) acts primarily in the central nervous system,¹¹ and therefore carries little risk of adverse GI effects related to prostaglandin deficiency in the periphery. Endoscopic examinations in previous studies have revealed that standard APAP does not carry the risk of GI toxicity.^{3,6} Studies comparing APAP and ibuprofen directly show that ibuprofen can produce GI damage following 7–10 days of treatment at approved maximum OTC doses.^{1–3,6}

Pharmacokinetic studies have shown that both fast-dissolving (FD) ibuprofen (Advil Liqui-Gels[®]; Pfizer Consumer Healthcare, Madison, NJ, USA) and FD-APAP tablets (Panadol Advance[®]; GlaxoSmithKline Consumer Healthcare, Weybridge, UK) exhibit rapid absorption properties, evidenced by higher maximum plasma concentrations (C_{max}) and shorter times to reach maximum concentration (T_{max}) when compared to respective standard ibuprofen and APAP products.^{12,13}

The GI effects of these OTC doses of FD analgesics have not been reported. This study was conducted to compare the effects of 7-day treatment with OTC doses of FD ibuprofen 2×200 mg liquid capsules 3 times daily (TID), ibuprofen 2×200 mg tablets TID (Advil[®]; Wyeth Consumer Healthcare), FD-APAP 2×500 mg tablets 4 times daily (QID), and placebo on both gastric and duodenal mucosa examined endoscopically in healthy volunteers.

Methods

Study population

A total of 27 healthy subjects between ages 18 and 60 years were enrolled in this study. All subjects were required to undergo a complete medical history and physical examination, clinical laboratory tests (including a pregnancy test if

the subject was a woman of childbearing potential), and an endoscopy demonstrating normal upper GI mucosa (ie, grade 0 on the mucosal injury scale) before receiving the first dose of each study medication. Key exclusion criteria were evidence of current/active or history of GI disease, renal disease, pulmonary edema, cardiomyopathy, liver disease, or hematologic disease. Participants were excluded if they were using or had a history of using antacids, H₂ receptor antagonists, proton pump inhibitors, or misoprostol more than twice a month or had taken any drug known to induce or inhibit hepatic drug metabolism within 1 month before the screening; had any contraindication to NSAIDs, FD-APAP, or midazolam; or had a gastric mucosal damage (GMD) score of ≥1 (endoscopic findings of hemorrhage, erosion, or ulcer) or a positive fecal occult blood test at the time of initiation of study. Pregnant or lactating women were excluded.

Study design

This was a randomized, placebo-controlled, single-blind (endoscopist-/assessor-blinded), single-center, 4-way crossover clinical trial (ClinicalTrials.gov NCT01822665; retrospectively registered on March 28, 2013). It was conducted at Houston Institute for Clinical Research (Houston, TX, USA) from 21 February (first subject first visit) to 12 July 2012 (last subject last visit). Treatments in this study were FD ibuprofen 2×200 mg liquid capsules TID, ibuprofen 2×200 mg tablets TID, FD-APAP 2×500 mg tablets QID, and placebo 2×500 mg tablets QID. Subjects who satisfied inclusion and exclusion criteria were assigned to a random treatment sequence. Randomization was done according to a computer-generated schedule created in SAS v.9.2 (SAS Institute, Cary, NC, USA). Each sequence involved in a random order the 4 treatments in the study. On the first day of treatment, a baseline gastroduodenal endoscopic examination was done in the morning and doses of study medication were then taken over the remainder of the day. On the following 6 days, medication was taken TID for ibuprofen treatments and QID for FD-APAP and placebo treatments. Subjects received the last dose of each treatment in the morning, followed by endoscopic examination 2–6 hours later. The first 3 treatment sessions were followed by a 2-week washout period, and the last treatment session had a follow-up phase of 5–14 days. Adverse events (AEs), use of concomitant medications, and pill counts were verified.

Mucosal injury scoring system

Endoscopic examinations were performed by a gastroenterologist blinded to the study treatments. All examinations

were recorded on digital video disc. Endoscopic observations of stomach mucosa and of the proximal duodenum mucosa were graded separately using the following 5-point Lanza scale: 0=normal stomach or proximal duodenum, 1=mucosal hemorrhages only, 2=1 or 2 erosions, 3=numerous (3–10) areas of erosion, and 4=large number of erosions (>10) or ulcer. The gastroenterologist enumerated mucosal hemorrhages, erosions, and ulcers for the stomach and the duodenum separately. Erosion was defined as a lesion producing a definite discontinuance in the mucosa but having no depth. Ulcer was defined as any lesion of unequivocal depth at least 3 mm in diameter.

End points

The primary end point was GMD measured by the endoscopy score in the Lanza scale. Duodenal mucosal damage (DMD) was a secondary end point also measured using the Lanza scale. Other secondary end points included incidence of gastric and/or duodenal mucosal injury (IGDMI), classified as present (gastric and/or duodenal endoscopy score ≥ 2) or absent (gastric and/or duodenal endoscopy score < 2); number of hemorrhages, erosions, and ulcers counted separately in stomach and duodenum; and positive fecal occult blood test. Safety end points included the incidence of AEs.

Statistical methods

Sample size was based on previous endoscopic studies,⁶ assuming a mean score of GMD of 0.25 for FD-APAP tablets, similar to the score observed for standard APAP. A mean GMD score of 1.1 was used for FD ibuprofen liquid capsules, assuming its effect to be 25% lower than that of naproxen.⁷ Based on these assumptions and estimates of standard deviation (SD) for FD-APAP tablets and FD ibuprofen liquid capsules of 0.53 and 0.9, respectively, a sample size of 23 subjects would provide 90% power to show a significant difference ($p \leq 0.01$) between these 2 treatments. A dropout rate of 20% for randomized subjects was considered.

All analyses were performed on the intent-to-treat (ITT) population, which included all randomized subjects who received at least 1 study dosing treatment (completed 1 full period of the study) and had at least 1 post-baseline endoscopic examination. GMD was analyzed based on a linear mixed effects model using Proc Mixed of SAS v.9.2 (SAS Institute). Period and treatment were included in the model as fixed effects, while subjects were a random effect. Difference between least square means of gastric endoscopy scores was tested at a 5% significance level ($p \leq 0.05$). DMD was analyzed the same way as GMD. IGDMI was analyzed as a binary

response (presence/no presence) based on logistic regression. The model included treatment as a factor and period as a covariate. Odds ratios (ORs) and 95% confidence intervals (CIs) for treatment comparisons were calculated. Gastric and duodenal lesion counts were summarized by frequency distribution for number of subjects per treatment group within each of 3 categories of lesions: hemorrhages, erosions, and ulcer. A chi-square test was performed to compare frequency distribution among treatment groups. Safety assessments included monitoring for AEs and measurement of changes in clinical laboratory values, vital signs, and physical examinations. AEs were summarized descriptively.

The protocol was approved by Western Institutional Review Board (Olympia, WA, USA), and the study was conducted in accordance with the ethical principles of the Declaration of Helsinki and the International Council for Harmonisation guideline for good clinical practice. Written informed consent was obtained from participants prior to initiation of the study.

Results

Subject disposition/demographics

A total of 28 subjects were randomized, 27 of whom were evaluable for the ITT population. A total of 8 subjects did not complete the study (3 due to AEs and 5 for other reasons). The number of subjects per treatment group was 27 for FD-APAP tablets, 23 for FD ibuprofen liquid capsules, and 22 each for the ibuprofen tablets and placebo groups. Average age of the study population was 38.1 years (range: 18–58 years), with a mean body mass index of 24.8 kg/m² (range: 18.6–29.9 kg/m²). The ratio of men to women was 25% to 75% (Table 1).

Gastric mucosal damage

Results of analysis for GMD are shown in Table 2 and Figure 1. GMD from treatment with FD ibuprofen liquid

Table 1 Demographic characteristics

Characteristics	Total ^a
Sex, n (%)	
Male	7 (25)
Female	21 (75)
Race, n (%)	
Asian	1 (3.6)
Black or African American	8 (25.6)
White	19 (67.9)
Age, mean (min–max) (years)	38.1 (18–58)
Body mass index, mean (min–max) (kg/m ²)	24.8 (18.6–29.9)

Note: ^aDemographic characteristics are based on total number of randomized subjects.

Table 2 Posttreatment gastric and duodenal endoscopy scores

Treatment	Endoscopy score, n (%) ^a					Mean (SD)	p-value
	0	1	2	3	4		
Gastric							
Ibuprofen liquid capsules	8 (34.8)	4 (17.4)	4 (17.4)	6 (26.1)	1 (4.3)	1.48 (1.34)	<0.0001 ^b ; 0.1429 ^c ; <0.0001 ^d
Ibuprofen tablets	12 (54.5)	2 (9.1)	4 (18.2)	3 (13.6)	1 (4.5)	1.05 (1.33)	0.0095 ^b ; 0.0020 ^d
FD-APAP	21 (77.8)	3 (11.1)	3 (11.1)	0	0	0.33 (0.68)	0.4794 ^d
Placebo	19 (86.4)	3 (13.6)	0	0	0	0.14 (0.35)	
Duodenal							
Ibuprofen liquid capsules	21 (91.3)	0	0	2 (8.7)	0	0.26 (0.86)	0.6497 ^b ; 0.8903 ^c ; 0.2227 ^d
Ibuprofen tablets	20 (91.0)	0	1 (4.5)	1 (4.5)	0	0.23 (0.75)	0.7591 ^b ; 0.2855 ^d
FD-APAP	26 (96.3)	0	0	0	1 (3.7)	0.15 (0.77)	0.4126 ^d
Placebo						0	

Notes: ^aLanza score based on 5 categories: 0=normal stomach or proximal duodenum, 1=mucosal hemorrhages only, 2=1 or 2 erosions, 3=numerous (3–10) areas of erosion, and 4=large number of erosions (>10) or ulcer. ^bComparison with FD-APAP. ^cComparison with ibuprofen tablets. ^dComparison with placebo.

Abbreviations: FD-APAP, fast-dissolving N-acetyl-p-aminophenol; SD, standard deviation.

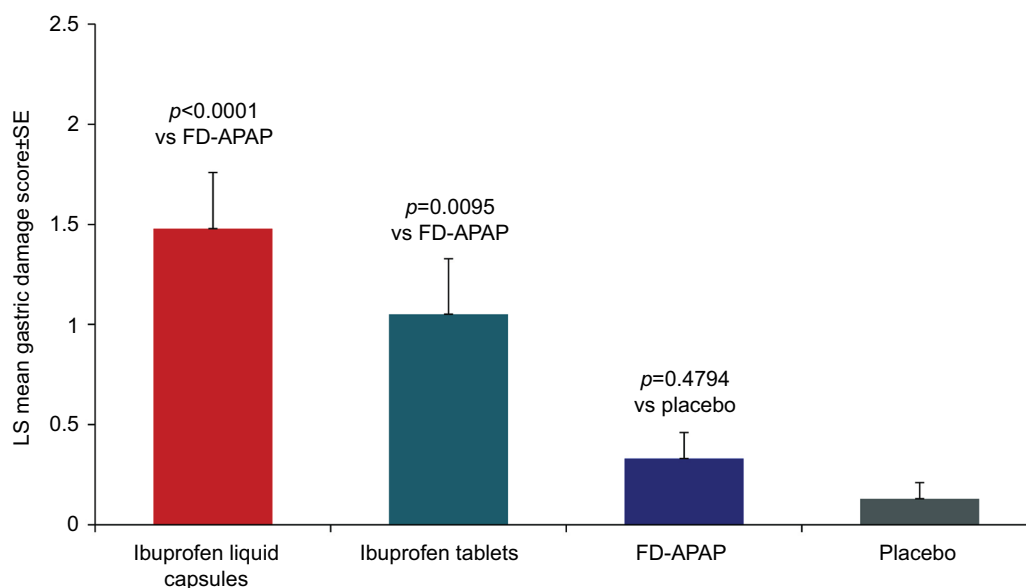


Figure 1 Gastric mucosal damage. Mean gastric mucosal damage score based on Lanza scale: 0=normal stomach or proximal duodenum, 1=mucosal hemorrhages only, 2=1 or 2 erosions, 3=numerous (3–10) areas of erosion, and 4=large number of erosions (>10) or ulcer. p-values of independent samples t-test for differences between LS means. **Abbreviations:** FD-APAP, fast-dissolving N-acetyl-p-aminophenol; LS, least squares; SE, standard error.

capsules was significantly greater than that from FD-APAP tablets ($p < 0.0001$). Mean (SD) GMD from treatment with FD ibuprofen liquid capsules was 1.48 (1.34), while mean (SD) for FD-APAP tablets was significantly smaller ($p < 0.0001$) at 0.33 (0.68). About 78% of subjects did not have any GMD (score=0) following treatment with FD-APAP tablets, while the proportion of subjects with this score was 35% following treatment with FD ibuprofen liquid capsules. Following treatment with FD ibuprofen liquid capsules, more than 30% of subjects had clinically significant GMD: 26% had a score of 3 (numerous areas of erosion, 3–10) and 4% had a score of 4 (ulcer). Following treatment with FD-APAP tablets, subjects had GMD scores ≤ 2 and as a consequence did not

have any clinically significant GMD. Mean GMD following treatment with ibuprofen tablets was also significantly greater than with FD-APAP tablets ($p = 0.0095$). There was no significant difference in GMD between FD-APAP tablets and placebo ($p = 0.4794$). Both ibuprofen treatments had significantly greater effect on GMD than placebo ($p < 0.0001$ and $p = 0.0020$, respectively). Mean GMD from treatment with FD ibuprofen liquid capsules was 41% greater than that from ibuprofen tablets (1.48 vs 1.05); however, this difference was not significant ($p = 0.1429$).

Erosions were the main effect contributing to gastric mucosal injury. These injuries were present in 48% and 36% of subjects following treatment with FD ibuprofen liquid

capsules and ibuprofen tablets, respectively (Table 3). These proportions were significantly greater than those observed with FD-APAP tablets ($p=0.0040$ and 0.0351 , respectively) and placebo ($p=0.0001$ and 0.0014 , respectively). With regard to other types of injuries (eg, hemorrhages and ulcer), there were no significant differences among the 4 treatments.

Duodenal mucosal damage

There were no significant differences among treatments for DMD (Table 2). All treatments had a very low DMD score: 0.15, 0.26, and 0.23 for FD-APAP tablets, FD ibuprofen liquid capsules, and ibuprofen tablets, respectively, and 0 for placebo. Over 90% of subjects in each treatment group did not have any DMD. There were 2 subjects treated with FD ibuprofen liquid capsules and 1 subject treated with ibuprofen tablets who had numerous erosions (3–10, score of 3) and 1 treated with FD-APAP tablets with mild ulcer (score of 4).

Table 3 Gastric and duodenal lesion counts

Treatment	N (%)		
	Hemorrhage	Erosion	Ulcer
Gastric^a			
Ibuprofen liquid capsules	8 (34.8)	11 (47.8) ^b	0
Ibuprofen tablets	5 (22.7)	8 (36.4) ^c	1 (4.5)
FD-APAP	4 (14.8)	3 (11.1)	0
Placebo	3 (13.6)	0	0
Duodenal^d			
Ibuprofen liquid capsules	0	2 (8.7)	0
Ibuprofen tablets	0	2 (9.1)	0
FD-APAP	0	0	1 (3.7)
Placebo	0	0	0

Notes: ^aComparisons of proportions of hemorrhage and erosion between treatments were performed using a 2×2 chi-square test. A chi-square test could not be performed for comparisons of proportions of ulcer because only 1 subject in the ibuprofen tablet group had an ulcer. ^bProportion of subjects with erosion following treatment with ibuprofen liquid capsules was significantly higher vs FD-APAP tablets ($p=0.004$) and placebo ($p=0.0002$). ^cProportion of subjects with erosion following treatment with ibuprofen tablets was significantly higher vs FD-APAP tablets ($p=0.0351$) and placebo ($p=0.0018$). ^dA chi-square test could not be performed for categories of duodenal hemorrhage (no patients showing hemorrhage) and ulcer (only 1 subject in the FD-APAP group).

Abbreviation: FD-APAP, fast-dissolving N-acetyl-p-aminophenol.

Table 4 Incidence of gastric and/or duodenal mucosal injury

Treatment	IGDMI=1 (score ≥2) ^a , n (%)	IGDMI=0 (score <2) ^a , n (%)	OR (95% CI) ^b	p-value ^c
Ibuprofen liquid capsules	11 (47.8)	12 (52.2)	6.19 (1.60, 23.97) ^d	0.0084
Ibuprofen tablets	8 (36.4)	14 (63.6)	3.19 (0.8, 12.74) ^e	0.0999
FD-APAP	4 (14.8)	23 (85.2)	1.94 (0.5, 7.65) ^f	0.1567
Placebo ^g	0	22 (100)		

Notes: ^aIncidence was present when endoscopy score for gastric and/or duodenal mucosal damage was ≥2 and absent when endoscopy score was <2. ^bOR and 95% CI from logistic regression model with treatment as factor and period as covariate. ^cp-value associated with chi-square testing of OR. ^dOR comparison between ibuprofen liquid capsules and FD-APAP. ^eOR comparison between ibuprofen tablets and FD-APAP. ^fOR comparison between ibuprofen liquid capsules and ibuprofen tablets. ^gPlacebo was not included in treatment comparisons because it had zero counts of IGDMI.

Abbreviations: CI, confidence interval; FD-APAP, fast-dissolving N-acetyl-p-aminophenol; IGDMI, incidence of gastric and/or duodenal mucosal injury; OR, odds ratio.

Incidence of gastroduodenal mucosal injury

There was a significantly higher effect of FD ibuprofen liquid capsules over that of FD-APAP tablets for the proportion of subjects with gastroduodenal injury (Table 4). The odds of having IGDMI were more than 6 times greater following treatment with FD ibuprofen liquid capsules compared with FD-APAP tablets (OR=6.19, 95% CI: 1.60, 23.97). The odds of IGDMI following treatment with ibuprofen tablets were more than 3 times greater than following treatment with FD-APAP tablets (OR=3.19, 95% CI: 0.8, 12.74); however, this effect was not significant ($p=0.0999$). There were no significant differences between FD ibuprofen liquid capsules and ibuprofen tablets (OR=1.94, 95% CI: 0.5, 7.65; $p=0.1567$). Placebo was not included in any of the treatment comparisons because it had zero counts of IGDMI. None of the participants showed positive result for fecal occult blood test.

Acute safety and tolerability of treatments

Similar rates of nonendoscopic-related AEs were observed between treatment groups. A total of 16 AEs were reported by 10 subjects: 4 AEs with FD-APAP tablets, 7 AEs with FD ibuprofen liquid capsules, 4 AEs with ibuprofen tablets, and 1 AE with placebo (Table 5). GI disorders were the most frequently reported AEs. There was 1 nontreatment-related serious AE, an invasive breast ductal carcinoma. This subject was discontinued from the study. Two other subjects were also withdrawn from the study due to AEs, 1 with mild gastric erosions and 1 with a mild duodenal ulcer. All AEs were resolved by the end of the study.

Following treatment with FD-APAP tablets, 1 subject had elevated liver enzyme levels of alanine aminotransferase (ALT) greater than 3 times the upper limit of normal (ULN) and levels of aspartate aminotransferase (AST) greater than 2 times the ULN. Another subject had slightly

Table 5 Treatment-emergent adverse events

Adverse event term	FD-APAP tablets	Ibuprofen liquid capsules	Ibuprofen tablets	Placebo
Total	3 (3)	5 (7)	4 (4)	1 (1)
Abdominal pain	0	3 (3)	1 (1)	0
Diarrhea	1 (1)	0	1 (1)	0
Dyspepsia	0	0	1 (1)	1 (1)
Arthralgia	0	1 (1)	0	0
Back pain	0	1 (1)	0	0
Chest pain	0	1 (1)	0	0
Flatulence	0	1 (1)	0	0
Gastritis erosive	1 (1)	0	0	0
Nausea	0	0	1 (1)	0
Somnolence	1 (1)	0	0	0

Note: Data are presented as number of subjects (number of events).

Abbreviation: FD-APAP, fast-dissolving N-acetyl-p-aminophenol.

higher-than-normal enzyme levels (ALT $<3 \times$ ULN and AST $<2 \times$ ULN). These 2 subjects were discontinued from the study, and their liver enzymes returned to normal by the end of the study. Three other subjects had slight elevations of liver enzyme levels ($<2 \times$ ULN), but these levels returned to the normal range during the washout period and all 3 subjects continued into the next period and completed the study.

Discussion

Results of this study showed that FD ibuprofen liquid capsules and ibuprofen tablets produce significantly greater damages to the gastric mucosa compared with FD-APAP tablets and placebo. The degree of damage observed from treatment with ibuprofen products, especially with FD ibuprofen liquid capsules, is notably greater in this study than previously observed for OTC doses of regular ibuprofen. In an endoscopic clinical trial following 7 days of treatment with regular ibuprofen, a mean GMD of 0.46 was reported.¹⁴ In our study, mean GMD from FD ibuprofen liquid capsules was 1.48. Although a direct comparison between results of our study and historical data cannot be made, these historical data can be used as a reference because of the similarity of clinical trial designs in both studies.

Clinical implications of the findings on GMD should be interpreted cautiously given the uncertain correlation between clinical symptoms and endoscopic findings.^{15–17} However, a recent analysis by Moore using Institute of Medicine criteria for biomarkers concluded that endoscopic ulcers are indeed a valid biomarker of NSAID-induced serious upper GI harm.¹⁸ In addition, the increase we observed in the degree of GMD may be of clinical significance. Following FD ibuprofen liquid capsule treatment, more than 30% of subjects developed grade 3 or 4 gastric mucosal injury, which involves numerous or widespread areas of erosions. A grade of 3 or

4 is considered severe damage, and is widely recognized to be clinically significant.^{6,14,19} Erosions were the main factor contributing to GMD caused by ibuprofen products. These injuries were present in 48% and 36% of subjects during treatment with FD ibuprofen liquid capsules and ibuprofen tablets, respectively. When treated with ibuprofen tablets, 18% of subjects developed clinically significant GMD. None of the subjects had this gastric damage when treated with FD-APAP tablets. Endoscopic scores observed for FD-APAP tablets were similar to those observed for placebo.

DMD was low for all study treatments. NSAID-induced DMD is usually less severe and less frequent than GMD;⁶ this was confirmed in the present study as well. However, when subjects were treated with FD ibuprofen liquid capsules, they were 6 times more likely to have an incidence of GMD or DMD compared with FD-APAP tablet treatment. It seems that the risk for gastroduodenal injury, caused primarily by GMD, is further increased by duodenal damage. Gastroduodenal endoscopic scores observed for FD-APAP tablets were similar to those observed for placebo. These findings are consistent with previous studies showing no significant gastroduodenal effects with FD-APAP.^{6,14}

NSAIDs and FD-APAP are routinely prescribed and are the most widely used OTC medications for treatment of pain/fever associated with various disease conditions.^{20,21} One of the major clinical concerns commonly encountered with frequent use of ibuprofen products is the increased risk of GI side effects that may have deleterious consequences.²² Prostaglandin inhibition is thought to play a role in the pathogenesis of these effects, and ibuprofen liquid capsules have been associated with a 50% reduction in prostaglandin synthesis.¹⁰ The GI safety profile of FD-APAP could be attributed to its nonacidic structure, unlike acidic NSAIDs that accumulate in the gastric epithelial cells, and also to its

weak inhibitory action on COX-1.²³ FD-APAP shows similarity to selective COX-2 inhibitors (celecoxib and etoricoxib), which have better GI tolerability compared with nonselective NSAIDs (eg, ibuprofen, ketoprofen, and naproxen) due to their COX-1-sparing mechanistic properties.

Both the ibuprofen and FD-APAP products used in this study have established FD properties which influence a faster absorption compared with respective standard products, as demonstrated by higher C_{max} and T_{max} .^{13,14} The endoscopic effects of these FD OTC analgesics have not previously been investigated. Findings from this study suggest that while FD-APAP tablets have similar GI tolerability as previously observed for standard APAP, FD ibuprofen (and particularly ibuprofen liquid capsules) causes significantly greater gastroduodenal damage that may be of clinical significance.

Treatment for 1 week with FD-APAP 2×500 mg tablets QID appeared to be associated with elevated liver function testing (LFT) enzymes in some subjects. Among the 5 subjects having elevated LFT, only 1 had both ALT and AST levels greater than 3× ULN. All enzyme elevations returned to normal after stopping treatment or after the washout period between treatments. Elevations in LFT have been previously observed in healthy adults receiving FD-APAP.²⁴ However, the evidence indicates that raised levels of liver enzymes associated with the maximum recommended dose of FD-APAP are short-lived, not associated with any signs or symptoms of liver damage, and not clinically significant.^{25,26} The enzyme levels observed in the present study are within the ranges, frequencies, and patterns previously reported and appear to follow a similar time course.^{25,26}

Although gastric ulcers and erosions have previously been reported with standard NSAID formulations,^{5–7,10,15} this is the first publication to look endoscopically at the GI effects of FD formulations of OTC analgesics. As noted earlier, the degree of GMD we observed with FD ibuprofen was greater than that previously reported with standard ibuprofen formulations. Also, from direct comparisons in this study we observed a 41% higher GMD score with FD ibuprofen compared with standard ibuprofen, although it did not achieve statistical significance, suggesting that further investigation may be warranted to directly compare the effects of different formulations of NSAIDs on gastric safety. This study also evaluated GMD with an FD-APAP formulation. Results in that regard provided reassurance of the gastric safety of FD-APAP and indicate that the risk of elevated liver enzyme levels with the FD formulation of APAP is similar to that previously reported with standard APAP formulations.^{25,26}

as well as with sustained-release paracetamol.²⁷ A previous study of paracetamol sodium bicarbonate, which is absorbed more quickly than standard paracetamol, found it to be well tolerated with no AEs that were considered treatment related; this study did not include endoscopic assessments of mucosal damage or routine liver enzyme monitoring, but no serious AEs were reported.²⁸

This study is limited by the duration of exposure, as subjects were treated for 7 days. Longer-term studies examining gastroduodenal endoscopic effects along with LFT levels may be required to assess the complete safety profile of FD ibuprofen and FD-APAP products. This may be of particular interest for their chronic use in treatment of musculoskeletal and arthritis disorders.

Another limitation of the study is that subjects were healthy volunteers of relatively younger age (mean age of 38 years). Increased risk of GMD from NSAIDs is associated with age and history of GI illness.⁹ Therefore, use of an older population may have captured a broader range of potential gastroduodenal damage.

Gastroduodenal injuries observed in this study, and in particular for FD ibuprofen, are the result of treatment with a full daily dose for a period of 7 consecutive days. These results may not apply to shorter durations of use or episodic use typical of acute pain episodes. For such uses, the choice of treatment product should be made primarily on the expected therapeutic effect of the product in the management of pain in a particular group of subjects, as gastroduodenal injuries are expected to be minimal with short-term or sporadic use.

Long-term use of FD ibuprofen, particularly ibuprofen liquid capsules, may have clinically significant effects on gastric mucosal injury. FD capsules are associated with faster absorption of ibuprofen,¹³ which is useful in potentially providing faster pain relief. However, their chronic use for at least 7 days as observed in this study appears to cause more GI injury than regular ibuprofen tablets. Use of FD-APAP tablets for treatment of musculoskeletal and arthritis disorders may represent an alternative with significantly fewer GI effects. This may have significant implications for analgesic treatment choice, especially for patients with chronic pain disorders.

Conclusion

This study suggests that treatment with FD ibuprofen products was associated with significantly more gastric mucosal injury than FD-APAP tablets, while the GI effects of FD-APAP tablets were no different from placebo when used as directed for OTC dosing after 7 days of treatment.

Acknowledgments

This trial was conducted with financial support from GlaxoSmithKline Consumer Healthcare, Warren, NJ. Editorial support was provided by Diane Sloan, PharmD, and Jim Wood of Peloton Advantage, LLC, Parsippany, NJ, and was funded by GlaxoSmithKline Consumer Healthcare.

Author contributions

A Collaku worked with the principal investigator for the design and conduct of the study. FL Lanza contributed to introduction, methods, results, and discussion, and is the guarantor of this article. A Collaku analyzed the data and contributed to methods, results, and discussion. DJ Liu contributed to introduction, results, and discussion. All the authors approved the final version of this manuscript. All authors were involved in the analysis and/or interpretation of data, drafting and revising the manuscript, and agree to be accountable for all aspects of the work.

Disclosure

FL Lanza is an employee of Houston Institute for Clinical Research, Houston, TX, and was contracted by GlaxoSmithKline Consumer Healthcare with respect of the work undertaken in this research. He has no financial interest in GlaxoSmithKline Consumer Healthcare and served as principal investigator for this study on a contract basis. A Collaku is a former employee of GlaxoSmithKline Consumer Healthcare. DJ Liu is an employee of GlaxoSmithKline Consumer Healthcare. The authors report no other conflicts of interest in this work.

References

1. Takeuchi K. Pathogenesis of NSAID-induced gastric damage: importance of cyclooxygenase inhibition and gastric hypermotility. *World J Gastroenterol.* 2012;18(18):2147–2160.
2. Colucci R, Antonioli L, Bernardini N, et al. Nonsteroidal anti-inflammatory drug-activated gene-1 plays a role in the impairing effects of cyclooxygenase inhibitors on gastric ulcer healing. *J Pharmacol Exp Ther.* 2012;342(1):140–149.
3. Blot WJ, McLaughlin JK. Over the counter non-steroidal anti-inflammatory drugs and risk of gastrointestinal bleeding. *J Epidemiol Biostat.* 2000;5(2):137–142.
4. Lanza FL, Rack MF, Simon TJ, et al. Specific inhibition of cyclooxygenase-2 with MK-0966 is associated with less gastroduodenal damage than either aspirin or ibuprofen. *Aliment Pharmacol Ther.* 1999;13(6):761–767.
5. Lanza FL, Marathi UK, Anand BS, Lichtenberger LM. Clinical trial: comparison of ibuprofen-phosphatidylcholine and ibuprofen on the gastrointestinal safety and analgesic efficacy in osteoarthritis patients. *Aliment Pharmacol Ther.* 2008;28(4):431–442.
6. Lanza FL, Codispoti JR, Nelson EB. An endoscopic comparison of gastroduodenal injury with over-the-counter doses of ketoprofen and FD-APAP. *Am J Gastroenterol.* 1998;93:1051–1054.
7. Bjarnason I, Macpherson A, Rotman H, Schupp J, Hayllar J. A randomized, double-blind, crossover comparative endoscopy study on the gastroduodenal tolerability of a highly specific cyclooxygenase-2 inhibitor, florusilide, and naproxen. *Scand J Gastroenterol.* 1997;32(2):126–130.
8. Bjarnason I. Ibuprofen and gastrointestinal safety: a dose-duration-dependent phenomenon. *J R Soc Med.* 2007;100(Suppl 48):11–14.
9. Wilcox CM, Shalek KA, Cotsonis G. Striking prevalence of over-the-counter nonsteroidal anti-inflammatory drug use in patients with upper gastrointestinal hemorrhage. *Arch Intern Med.* 1994;154(1):42–46.
10. Hawkey C, Burnett I, Gold MS, et al. Endoscopic evaluation of the gastroduodenal tolerance of short-term analgesic treatment with 25 mg diclofenac-K liquid capsules. *Aliment Pharmacol Ther.* 2012;35(7):819–827.
11. Smith HS. Potential analgesic mechanisms of acetaminophen. *Pain Physician.* 2009;12(1):269–280.
12. Wilson CG, Clarke CP, Starkey YY, Clarke GD. Comparison of a novel fast-dissolving acetaminophen tablet formulation (FD-APAP) and standard acetaminophen tablets using gamma scintigraphy and pharmacokinetic studies. *Drug Dev Ind Pharm.* 2011;37(7):747–753.
13. Ceppi Monti NC, Gazzaniga A, Gianesello V, Stroppolo F, Lodola E. Activity and pharmacokinetics of a new oral dosage form of soluble ibuprofen. *Arzneimittelforschung.* 1992;42(4):556–559.
14. Lanza FL. Endoscopic studies of gastric and duodenal injury after the use of ibuprofen, aspirin and other nonsteroidal anti-inflammatory agents. *Am J Med.* 1984;77(1A):19–24.
15. Larkai EN, Smith JL, Lidsky MD, Graham DY. Gastroduodenal mucosa and dyspeptic symptoms in arthritic patients during chronic nonsteroidal anti-inflammatory drug use. *Am J Gastroenterol.* 1987;82(11):1153–1158.
16. Yeomans ND, Lanans AI, Talley NJ, et al. Prevalence and incidence of gastroduodenal ulcers during treatment with vascular protective doses of aspirin. *Aliment Pharmacol Ther.* 2005;22(9):795–801.
17. Armstrong CP, Blower AL. Non-steroidal anti-inflammatory drugs and life threatening complications of peptic ulceration. *Gut.* 1987;28(5):527–532.
18. Andrew Moore R. Endoscopic ulcers as a surrogate marker of NSAID-induced mucosal damage. *Arthritis Res Ther.* 2013;15(Suppl 3):S4.
19. Lanza FL, Robinson MG, Isenberg JI, Basulk PM, Karlin DA. Effect of enprostil on the gastroduodenal mucosa of healthy volunteers. *Aliment Pharmacol Ther.* 1990;4(6):601–613.
20. Willett LR, Carson JL, Strom BL. Epidemiology of gastrointestinal damage associated with nonsteroidal anti-inflammatory drugs. *Drug Saf.* 1994;10(2):170–181.
21. Graham GG, Davies MJ, Day RO, Mohamudally A, Scott KF. The modern pharmacology of FD-APAP: therapeutic actions, mechanism of action, metabolism, toxicity and recent pharmacological findings. *Inflammopharmacology.* 2013;21(3):201–232.
22. Wallace JL. Prostaglandins, NSAIDs and gastric mucosal protection: why doesn't the stomach digest itself? *Physiol Rev.* 2008;88(4):1547–1565.
23. Nowak JZ, Jozwiak-Bebenista M. FD-APAP phenomenon: unprecedented worldwide popularity vs. toxic effects. *Military Pharm Med.* 2013;4:1–16.
24. Dart RC, Kuffner EK, Rumack BH. Treatment of pain or fever with paracetamol (acetaminophen) in the alcoholic patient: a systematic review. *Am J Ther.* 2000;7(2):123–134.
25. Heard K. Asymptomatic alanine aminotransferase elevations with therapeutic doses of acetaminophen. *Clin Toxicol (Phila).* 2011;49(2):90–93.
26. Kuffner EK, Temple AR, Cooper KM, Baggish JS, Parenti DL. Retrospective analysis of transient elevations in alanine aminotransferase during long-term treatment with acetaminophen in osteoarthritis clinical trials. *Curr Med Res Opin.* 2006;22(11):2137–2148.
27. Liu DJ, Collaku A. Bioequivalence and safety of twice-daily sustained-release paracetamol (acetaminophen) compared with 3- and 4-times-daily paracetamol: a repeat-dose, crossover pharmacokinetic study in healthy volunteers. *Clin Pharmacol Drug Dev.* 2018;7(1):77–86.
28. Burnett I, Schachtel B, Sanner K, Bey M, Grattan T, Littlejohn S. Onset of analgesia of a paracetamol tablet containing sodium bicarbonate: a double-blind, placebo-controlled study in adult patients with acute sore throat. *Clin Ther.* 2006;28(9):1273–1278.

Clinical and Experimental Gastroenterology

Dovepress

Publish your work in this journal

Clinical and Experimental Gastroenterology is an international, peer-reviewed, open access, online journal publishing original research, reports, editorials, reviews and commentaries on all aspects of gastroenterology in the clinic and laboratory. This journal is included on PubMed. The manuscript management system is completely online

and includes a very quick and fair peer-review system, which is all easy to use. Visit <http://www.dovepress.com/testimonials.php> to read real quotes from published authors.

Submit your manuscript here: <https://www.dovepress.com/clinical-and-experimental-gastroenterology-journal>