

Low-Dose Aspirin-Induced Ulceration Is Attenuated by Aspirin–Phosphatidylcholine: A Randomized Clinical Trial

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- OBJECTIVES:** Relative contributions of local and systemic mechanisms of upper gastrointestinal (GI) injury following aspirin are unknown. Studies suggest that aspirin's GI risk is age related and that gastroprotection may be needed at therapy initiation. We determined acute gastroduodenal erosion and ulceration following low-dose aspirin and aspirin–phosphatidylcholine complex (PL2200) in subjects at risk of aspirin ulcers.
- METHODS:** In a randomized, single blind, multicenter active-controlled study, we compared upper GI damage of aspirin and PL2200 in healthy subjects ($n=204$, ages 50–74 years) following 7 days of oral 325 mg once daily, immediate release aspirin or PL2200.
- RESULTS:** Overall, 42.2% of aspirin-treated subjects developed multiple erosions and/or ulcers, whereas 22.2% treated with PL2200 developed such damage ($P=0.0027$). Gastroduodenal ulcers were observed in 17.6% of aspirin-treated compared with 5.1% of subjects treated with PL2200 ($P=0.0069$).
- CONCLUSIONS:** Low-dose aspirin induced a surprisingly high incidence of acute gastroduodenal ulcers in at risk subjects, highlighting that aspirin's upper GI risk begins early and may require gastroprotection. Local mechanisms of GI protection are important as aspirin's preassociation with surface-active phospholipids significantly reduced mucosal damage. PL2200 may be an attractive alternative or complement to proton pump inhibitors in older patients who are at risk of aspirin-induced ulceration. Longer-term studies assessing clinical GI events are desirable to confirm the clinical GI safety profile of PL2200.

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INTRODUCTION

Low-dose aspirin (75–325 mg) is one of the most frequently used drugs for cardiovascular prophylaxis. However, 45% of patients with cardiovascular risk factors are not treated with antiplatelet agents because their risks of gastrointestinal (GI) bleeding outweigh vascular benefit (1,2), which may contribute to aspirin's under utilization (3). Daily low-dose aspirin frequently induces GI mucosal damage (40–50%) (4–6), ulcerogenic even in doses as low as 10 mg (7) and increases risks of GI bleeding (8). Aspirin's risk increases with age and is highest at therapy initiation (8,9). Therefore, cardiovascular patients are frequently discharged on low-dose aspirin and gastroprotective agents (10).

Although proton pump inhibitors (PPIs) are effective gastroprotective agents (11), they may not be optimal for reducing aspirin-induced GI toxicity when combined with clopidogrel, as decreased *ex vivo* antiplatelet efficacy has been observed; however, the clinical relevance of this observation is controversial (10,12). Although the chronic risks of PPIs appear to be few, their usage has been linked to an increased incidence of infection and skeletal fractures (13,14). Therefore, alternative approaches to gastroprotection for aspirin-based antiplatelet therapy may be useful and potentially complementary.

Davenport (15) originally suggested that aspirin-induced gastric damage is due to surface injury that alters the gastric barrier to acid. Surface-active phospholipids are important to the

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hydrophobic biophysical surface properties of the gastric barrier to acid (16–18). Within minutes of oral administration, aspirin associates with mucosal phospholipids, attenuates tissue surface hydrophobicity (19), increasing the corrosive effects of luminal acid. Clinical importance of aspirin's and other non-steroidal anti-inflammatory drugs' (NSAIDs') local effects is suggested by a reduction of gastroduodenal ulceration when co-administered with PPIs and H2RAs (11,20,21), presumably by decreasing the proton gradient and acid mucosal back diffusion. These observations suggest that local mechanisms of mucosal protection are important in prevention of aspirin-induced GI injury.

To decrease aspirin enabled acid damage, a novel oral drug delivery system creates a non-covalent complex of aspirin–phosphatidylcholine (PC), PL2200 (PLx Pharma, Houston, TX). In preclinical and pilot clinical studies, non-covalent association of aspirin and PC makes aspirin or other NSAIDs more lipophilic, facilitating transit across the GI mucosal layer and reducing gastric surface injury (22,23) with no loss in functional bioavailability. To determine the clinical relevance of these local effects of low-dose aspirin, we compared gastroduodenal ulcerogenic and erosive potential of PL2200 vs. immediate release aspirin in subjects with an age-associated risk for GI injury.

METHODS

Assessment of gastroduodenal erosion and ulceration

Study population. This phase II, randomized, single blind, active-controlled, multicenter study (NCT00872534) recruited 204 subjects with increased risk of NSAID-induced gastropathy by virtue of older age. Subjects were healthy volunteers, ages 50–75 years without active *Helicobacter pylori* infection or gastroduodenal erosions or ulcers, or ≥ 10 petechiae at baseline (**Table 1**).

Exclusion criteria included abnormal screening/baseline laboratory, or erosions or, ulceration during baseline endoscopy. Also excluded were active *H. pylori* infection (Mertek BreathTek UBT), history of GI complications, sensitivity to soy, aspirin containing

product within 4 weeks of baseline, an NSAID, salicylate or potassium within 3 weeks of baseline, antiplatelet agents, anticoagulants, antidepressants, antisecretory or gastroprotective agents within 2 weeks of baseline.

Study procedures. Subjects were randomized to immediate release aspirin or PL2200 at a 1:1 ratio and underwent a baseline endoscopy to evaluate their GI mucosa before study drug. Number of petechiae, erosions, and ulcers (those between 3 and 4 mm, and those ≥ 5 mm) were enumerated, and assigned a score based on the Mucosal Injury Scoring System (see below). Gastric and duodenal mucosae were evaluated separately. Each procedure was captured on a high-resolution DVD for subsequent central review and adjudication, as described below. Starting 1–7 days following baseline endoscopy, subjects meeting inclusion criteria took one 325 mg, immediate release aspirin tablet or one PL2200 capsule containing 325 mg aspirin once daily for 7 days at least 30 min before a meal. On Study Day 7, a second endoscopy was performed. Subjects received the last dose between 5:00 and 9:00 hours, followed by endoscopy 4–6 h later. Subjects diagnosed with an ulcer at second endoscopy were PPI treated for 30 days, endoscoped in a month verify healing. Adverse events (AEs), use of concomitant medications, and compliance were monitored throughout and pill counts were verified.

Mucosal injury scoring system. Endoscopic observations were scored using the following definitions. Petechiae were submucosal hemorrhages having no mucosal break. Erosions were definite mucosal discontinuities, without depth. Ulcers were mucosal breaks ≥ 3 mm in length with unequivocal depth. All lesions characterized as ulcers were assessed by video review of the mucosal lesion with the endoscope placed tangentially to the lesion and with unequivocal depth confirmed through video review of the lesion by an adjudication committee of experienced blinded gastroenterologists. Measurement of lesion size was aided by a 6 mm extended biopsy forceps placed adjacent to lesions.

A modified Lanza scoring system was used to assess mucosal injury as follows: Grade 0, no injury; Grade 1, 1–10 petechiae; Grade 2, > 10 petechiae or 1–5 erosions; Grade 3, 6–10 erosions; Grade 4, > 10 erosions and/or an ulcer. A gastroduodenal composite score was derived by adding the scores for the stomach and duodenum.

Central endoscopic review and adjudication. Endoscopic mucosal damage was scored by a blinded endoscopist at the study site and subsequently by a blinded central reviewer. All endoscopists were trained on procedural guidelines to minimize procedure-related trauma, and on mucosal lesion definitions for petechial, erosions, and ulcers. All baseline and post-treatment endoscopies were captured on high-resolution video to enable central review. When a significant discrepancy was noted between the scoring results of the site endoscopist and central reviewer, scores were adjudicated by a panel of three blinded endoscopists. Significant discrepancies were defined as a difference in lesion scoring between the site and central reviewer that

Table 1. Demographic characteristics

	PL2200 (N=100)	Aspirin (N=104)
<i>Age (years)</i>		
Mean	58.1	56.6
s.d.	6.35	6.00
(Min, max)	(50.0, 74.0)	(50.0, 73.0)
<i>Gender, N (%)</i>		
Male	56 (56.0)	60 (57.7)
Female	44 (44.0)	44 (42.3)
<i>BMI</i>		
Mean	26.9	27
(Min, max)	(20.2, 32.1)	(20.2, 32.3)
BMI, body mass index.		

could affect either subject eligibility due to baseline erosions and/or ulcers, or study end points.

Study end points. The primary end point was the incidence of subjects with gastroduodenal erosions or ulcers (>5 erosions, or 1 or more ulcers ≥ 3 mm) with PL2200 compared with aspirin. Secondary objectives were the incidence of subjects with ulcers ≥ 3 mm, mean number of duodenal erosions, gastric erosions, or erosions in the gastric antrum, body, and fundus. Safety end points were incidence of AEs, mean change from baseline in hematology, blood chemistry, and vital signs.

Sample size was based on previous endoscopic studies of 325 mg immediate release aspirin and previous experience with aspirin-dipalmitoylphosphatidylcholine complex (23), and used a historical weighted average incidence of 39.1% for gastroduodenal erosions and/or ulcers (24) induced by 300–325 mg of aspirin daily over 7–10 days and powered for a 60% reduction with PL2200 compared with immediate release aspirin's rate of 15.6% with 90% confidence in Fisher's exact two-sided test at a 0.05 level of significance. A discontinuation or ineligibility rate of 20% of randomized subjects was assumed.

Statistical analysis. The intent-to-treat population was all subjects randomized receiving at least one study drug dose and who underwent the day 7 endoscopy; this group was used for evaluation of GI injury. The following statistical methods were used: descriptive statistics, Fisher's exact test, Cochran-Mantel-Haenszel test, Breslow-Day test, *t*-test, and analysis of variance. Assumptions of normality and homogeneity of variance were tested using the Shapiro-Wilks test. If the distributional assumptions were violated, non-parametric techniques, such as Wilcoxon's rank-sum test and signed rank test, were employed. A *P* value of ≤ 0.05 was considered statistically significant for all two-sided tests.

The study was approved by the institutional review boards of all participating study sites, and informed consent was provided by all subjects.

RESULTS

Assessment of gastroduodenal injury

Subject disposition/demographics. Overall, 204 subjects were enrolled from six sites (56.9% male). Average age was 58.1 years in the PL2200 group and 56.6 years in the aspirin group (Table 1). Of the 204 randomized subjects, 3 subjects discontinued due to study withdrawal or being lost to follow-up (Figure 1). Eighteen subjects were deemed non-evaluable due to baseline erosions noted during adjudication. The impact of these 18 subjects on endoscopic observations was assessed with an intent-to-treat and evaluable group analysis.

Incidence of gastroduodenal erosions and ulcers. In the intent-to-treat population, subjects treated with PL2200 had a 47.4% lower risk (95% confidence interval, 17.38–77.19%) of developing multiple gastroduodenal erosions or an ulcer than subjects treated with immediate release aspirin for 7 days (Figure 2a). Forty-three

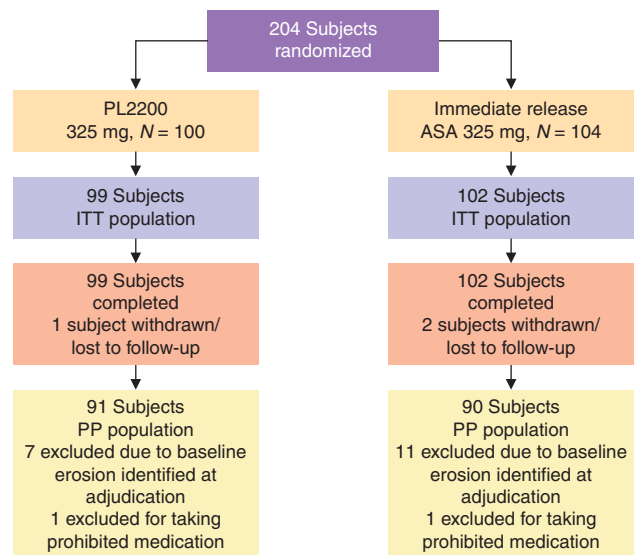


Figure 1. Summary of the endoscopic study. ASA, aspirin; PP, per protocol.

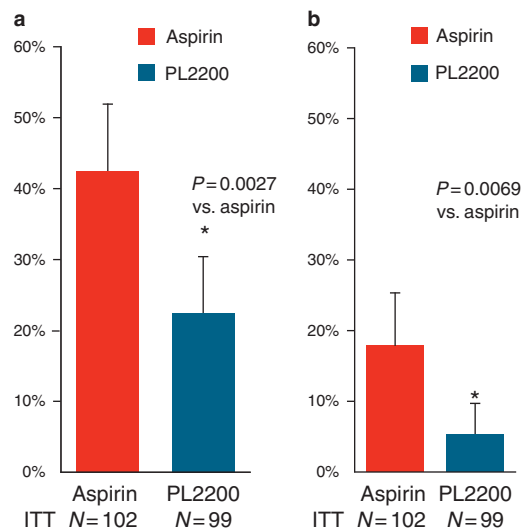


Figure 2. Gastroduodenal mucosal damage. (a) Percentage of subjects with erosions and/or ulcers. (b) Percentage of subjects with ulcers. *P* values are two-sided Fisher's exact tests. Bars, incidence \pm 95% confidence interval. ITT, intent-to-treat.

(42.2%) aspirin-treated subjects developed six or greater erosions or an ulcer, whereas 22 subjects (22.2%) treated with PL2200 developed such damage ($P=0.0027$, Fisher's exact test). Consistently, the PL2200-treated group had a lower mean number of gastric erosions of 2.26 vs. 3.83 in the aspirin group ($P=0.0009$). The vast majority of erosive damage to the gastroduodenal mucosa was in the antrum with a mean erosion number of 3.04 vs. 2.07 ($P=0.0095$) in the aspirin vs. PL2200 groups, respectively. Similar observations were made in the analysis of the per-protocol evaluable population.

Incidence of subjects developing gastroduodenal ulcers was lower in the PL2200 group (Figure 2b). In the intent-to-treat

population, PL2200 treatment had a 71% lower incidence of ulcers (95% confidence interval, 22.85–100%) than seen with aspirin at the day 7 endoscopy: Ulcers developed in 5 subjects (5.1%) in the PL2200 group and in 18 subjects (17.6%) in the aspirin group. This difference is statistically significant ($P=0.0069$, Fisher's exact test). These findings were also consistent with the per-protocol analysis, in which the ulcer incidence was 17.8% for aspirin and 5.5% for PL2200 ($P=0.0110$). All ulcers detected by endoscopy were asymptomatic and predominately in the stomach. Four gastric and two duodenal ulcers were found in the PL2200 group, and 12 gastric and 6 duodenal ulcers were found in the aspirin group. One subject in the PL2200 group developed both a gastric and duodenal ulcer. All subjects identified with an ulcer were treated with a PPI for 30 days and had endoscopic resolution of their ulcers.

Acute safety and tolerability of PL2200

Laboratory parameters, physical examination findings, and vital signs at baseline and post-treatment were similar and not clinically or statistically significantly different in out treatment groups in the safety population. There were no treatment-related discontinuations or serious AEs. Similar rates of non-ulcer-related AEs were observed between treatment groups ($P=0.4308$). No clinically or statistically significant differences in treatment-related AEs between groups were noted. The most frequently reported treatment-related AEs were nausea (5.0 vs. 2.9%, PL2200 vs. aspirin, $P=0.4918$); dyspepsia (4.0% PL2200 vs. 1.9% aspirin, $P=0.4383$); and heartburn (3.0% PL2200 vs. 1.0% aspirin, $P=0.3616$) and self-resolved by a median of 1–3 days.

DISCUSSION

This study suggests that non-covalent association of aspirin with PC in PL2200 confers improved GI safety as determined by endoscopy over a 7-day study period, in older subjects aged 50–75 years. In this study we found that aspirin induced a surprisingly high incidence of gastroduodenal ulceration in healthy subjects with an age-associated risk of GI bleeding. Such ulcerations were statistically significantly reduced by 7 days with PL2200.

In an independent study, we determined that PL2200 administered at an aspirin dose of 325 and 650 mg has equivalent bioavailability to the same immediate release aspirin used in this study in healthy subjects, based upon both pharmacokinetic analysis and antiplatelet efficacy (data not shown). Thus, the increased GI safety conferred by PL2200 is not at the cost of an attenuation in bioavailability or therapeutic efficacy. Our observation in this study that the non-covalent association of aspirin with PC is associated with reduced upper GI injury complements observations from a previous study of PC conjugated with a different NSAID, namely, ibuprofen (25). In that earlier study, PC-conjugated ibuprofen demonstrated improved GI safety in older osteoarthritis patients while having comparable bioavailability, pain relief, and reduction of inflammation as unmodified ibuprofen (25).

The relative contributions of local vs. systemic mechanisms of GI mucosal injury with aspirin have not yet been fully elucidated. The

observation from this study that PC's association with aspirin leads to a significant reduction in upper GI mucosal injury suggests that local GI mucosal mechanisms of injury have an important role in GI mucosal injury following administration of aspirin. Use of low-dose aspirin in cardiovascular disease is limited by its GI mucosal damage. In secondary prevention of cardiovascular disease, clopidogrel is commonly added to aspirin to further decrease risks of cardiovascular events. However, this combination has an elevated risk of major bleeding, predominately in the GI tract. Use of more potent antiplatelet agents, which have recently become clinically available, has been associated with increasing rates of GI bleeding (26,27). Clopidogrel has been thought to increase risk of aspirin-induced ulceration by delaying the healing of aspirin-induced GI mucosal breaks via inhibition of angiogenesis (28,29). Supporting the hypothesis that local mechanisms of GI mucosal injury are important is the observation that upper GI mucosal damage from the combination of aspirin plus clopidogrel is decreased by concomitant administration of omeprazole, which has the effect of decreasing the proton gradient across the GI mucosa (30). Esomeprazole (11) and famotidine (21) are also effective against low-dose aspirin-induced upper GI ulceration. As these agents also decrease the proton gradient across the GI mucosa, back diffusion of acid through a compromised mucosal barrier is likely an important component of aspirin-induced gastropathy.

GI mucosal integrity depends on a homeostatic balance between attack and repair. Luminal acid, pepsin, and bile acids compromise mucosal integrity. Bicarbonate, surface-active phospholipids, mucosal blood flow, intercellular tight junctions, and mucosal lesion healing require COX-derived prostaglandins (17,18,28). In addition to mucosal prostaglandin inhibition, aspirin associates with surface-active phospholipids that contribute to hydrophobic barrier properties, and consequently enables mucosal back diffusion of acid, resulting in erosions and ulceration (19).

Preassociation of aspirin with exogenous PC mitigates association of aspirin with native phospholipids in the GI barrier to acid, thereby reducing mucosal damage. In rodents and humans, aspirin-PC complex attenuated gastric hemorrhagic lesions and bleeding compared with unmodified aspirin, despite a significant reduction of protective prostaglandins in the gastric mucosa (16,23). Aspirin depletes mucosal prostaglandins for several days after discontinuation at doses from 81 to 325 mg in humans (29). Demonstration of lower ulcerogenesis with PL2200, presumably with prostaglandin inhibition, suggests that local effects of aspirin disrupt the gastric barrier to acid, and the degree of resulting injury may be more clinically relevant than previously appreciated. Because PL2200 targets a mechanism complementary to PPI by minimizing local disruption to the GI barrier, PL2200 could be an alternative or complement to PPIs as an effective strategy to reduce GI injury in high-risk patients.

The relative importance of local effects of aspirin have been confounded by the observations that enteric-coated aspirin may have lower mucosal injury, but does not confer a reduction in GI bleeding relative to immediate release aspirin. This apparent discrepancy may be due to ulcer definition used in previous assessments of enteric-coated aspirin-induced ulceration (superficial mucosal

breaks without depth). As this study used the contemporary definition of ulcer (mucosal breaks that penetrate the muscularis), the reduction in such damage with PL2200 further supports the importance of local injury.

The study is limited by the duration of exposure, as subjects were treated 7 days and relied on surrogate endoscopic ulcer end points as a proxy for GI bleeding. Longer-term studies examining clinical events are required to assess durability of PL2200's GI safety. However, the clinical importance of these observations over this acute period is supported by the observations that: (i) risk of an aspirin-induced GI bleeding begins at therapy initiation, with the greatest risk in the first 2 months, which persists (7); (ii) aspirin-induced endoscopic ulceration is related to the subsequent occurrence of a GI bleed (6); and (iii) tolerance to gastropathic effects of aspirin appears minimal as risk of bleeding persists over long-term use (31). Therefore, there is a clinical need to reduce aspirin-induced GI mucosal damage, particularly, in aspirin-naïve patients. Another limitation of our study is that medications were administered before meals, which may have exaggerated aspirin's ulcerogenic effect.

In the long term, low-dose aspirin users frequently experience GI side effects, which may lead to aspirin discontinuation. In patients taking antiplatelet therapy, discontinuation can markedly increase risks of secondary vascular events, particularly, in stent patients (32). Although this study did not specifically evaluate GI symptoms, no significant differences in dyspeptic symptoms were observed between PL2200 and aspirin. Compliance with guidelines for gastroprotection of at-risk subjects is poor (33). Therefore, a fixed dose combination of aspirin plus a cost-effective gastroprotective agent or an intrinsically safer aspirin formulation, such as PL2200, may increase compliance. In summary, this study suggests that local effects that disrupt the gastric barrier to acid are an important component of aspirin-induced gastropathy. PL2200 may be clinically useful by providing effective antiplatelet activity with improved upper GI safety, both alone and potentially in combination with other anti-platelet agents, in the management of patients requiring such therapy.

CONFLICT OF INTEREST

Guarantor of the article: Byron Cryer, MD.

Specific author contributions: PLx personnel (U.K.M. and L.M.L.) were involved with study design, worked with the principal investigators in design of both studies and contracted inVentiv Clinical Solutions to manage clinical operations, data management, statistical analysis, and worked with other authors in manuscript preparation, interpretation, and decision to publish the manuscript. All authors had complete access to all clinical data, and meaningfully contributed to the study design, execution or data interpretation.

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Potential competing interests: Byron Cryer has been a consultant to PLx Pharma, Astra Zeneca Pharmaceuticals, Cogentus Pharmaceuticals, Horizon Therapeutics, Nicox, Pozen, TAP Pharmaceuticals, as well as Advisory and Review Committees for Pfizer. Deepak Bhatt has been a research collaborator with Cogentus and PLx Pharma. Upendra Marathi is an employee and an equity holder in PLx Pharma Inc. Jing-fei Dong has no disclosures.

(a) *Study endoscopists:* Phil Miner, Michael Schwartz, Howard Schwartz, Larry Grier; (b) *clinical operations:* Mary Francis Rack (Houston Institute for Clinical Research), and Gwynne Mabie and Kara Turner (Ventive Clinical Solutions); (c) *statistical support:* John Mabie and Stacie Arrambide (inVentive Clinical Solutions). All authors, investigators, endoscopists, and PLx personnel were blinded until database lock for both studies. Study protocols and statistical analysis will be made available through written agreement with PLx Pharma Inc., Houston, TX, via Dr Marathi (marathi@plxpharma.com).

Study Highlights

WHAT IS CURRENT KNOWLEDGE

- ✓ Low-dose aspirin is a major cause of gastrointestinal (GI) tract injury and morbidity.
- ✓ The relative contributions to local and systemic mechanisms to the pathogenesis of upper GI injury following aspirin are poorly understood.

WHAT IS NEW HERE

- ✓ Upper GI tract injury was prospectively evaluated in healthy human subjects 50–75 years of age at risk for developing aspirin-induced GI damage using a non-covalent complex of aspirin-phosphatidylcholine, PL2200.
- ✓ PL2200 has equivalent antiplatelet efficacy to aspirin while reducing gastroduodenal ulcers by 70% when compared with aspirin.
- ✓ This study demonstrates that local mechanisms of GI protection are important as aspirin's preassociation with surface-active phospholipids significantly reduced mucosal damage.
- ✓ PL2200 may be an attractive strategy in at risk to reduce aspirin-induced GI injury.

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