Time course inhibition of gastric and platelet COX activity by acetylsalicylic acid in humans

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Feldman, Mark, Kenneth Shewmake, and Byron Cryer. Time course inhibition of gastric and platelet COX activity by acetylsalicylic acid in humans. Am J Physiol Gastrointest Liver Physiol 279: G1113–G1120, 2000.—Aspirin causes peptic ulcers predominately by reducing gastric mucosal cyclooxygenase (COX) activity and prostaglandin synthesis. Because aspirin circulates for only a few hours, we hypothesized that aspirin’s inhibitory effect on gastric COX activity must be prolonged. We performed a placebo-controlled experiment in healthy humans to determine the duration of inhibition of aspirin on gastric mucosal COX activity (PGE$_2$ and PGF$_{2a}$ synthesis rates). Recovery of gastric COX activity after stopping aspirin was slow and linear. Seventy-two hours after 325-mg aspirin, gastric COX activity was still reduced by 57% (P < 0.001). Duration of inhibition of gastric COX activity was estimated to be 7–8 days after 325-mg aspirin and 5 days after 81-mg aspirin. Recovery of gastric prostaglandin synthesis after 325-mg but not after 81-mg aspirin occurred at slower rates in subjects with Helicobacter pylori-associated gastritis than in those with normal histology. In conclusion, aspirin inhibits gastric COX activity for much longer than predicted from its pharmacokinetic profile, explaining why aspirin at widely spaced intervals is ulcerogenic.

ACETYLSALICYLIC ACID (ASA, aspirin) irreversibly acetylates a key serine moiety of platelet cyclooxygenase (COX)-1, reducing COX-1-derived synthesis of thromboxane (Tx) A$_2$, a potent platelet aggregator and vasoconstrictor (17). As a consequence, chronic administration of low doses of ASA protects against thrombotic occlusion of coronary arteries, cerebral arteries, and vascular grafts (11). The most serious side effect of chronic low-dose ASA therapy is gastric and/or duodenal ulcer formation, sometimes accompanied by life-threatening ulcer bleeding or perforation (11, 17, 25). Upper gastrointestinal (GI) mucosal damage results primarily from inhibition of GI mucosal COX activity by ASA, slowing synthesis of mucosa-protective PGs such as PGE$_2$ and PGF$_{2a}$ (5, 15), although other PG-independent mechanisms such as topical gastric injury may contribute to ulcer formation. Inhibition of COX-mediated PG production by the human upper GI mucosa, particularly by the gastric mucosa, has been demonstrated after doses of ASA as low as 10 or 30 mg/day (3, 15). Because these previous studies assessed gastric PG production only 1.5–3 h after ASA administration, the duration of ASA’s inhibitory effect on gastric COX activity is unknown.

ASA is rapidly metabolized to salicylate, and within 2 or 3 h little if any ASA can be detected in the blood (6, 8). Even though the salicylate metabolite of ASA can be detected in the blood for several hours, salicylate does not inhibit platelet COX-1 or gastric COX activity, reduce GI synthesis of mucosa-protective PGs, or cause upper GI mucosal injury (2, 5). Therefore, how administration of low doses of ASA at widely spaced intervals can cause gastric and duodenal ulcers (3, 22, 24) has remained a mystery. Perhaps a very brief period of PG synthesis suppression may be sufficient to predispose to ulcer formation or, alternatively, the inhibitory effect of ASA on GI PG synthesis might extend well beyond ASA’s short serum half-life. To test the latter possibility, we performed a placebo-controlled experiment in which we measured for 72 h the rate of recovery of gastric mucosal PGE$_2$ and PGF$_{2a}$ synthesis after exposure to ASA in healthy men and women. Measurements were made after participants had completed a 46-day treatment consisting of 81 mg of ASA every day or 325 mg of ASA every third day. Because asymptomatic Helicobacter pylori-associated gastric inflammation is common in healthy adults (9, 18) and may be associated with significantly enhanced mucosal PG synthesis in the gastric body (4), we also examined whether PG synthesis rates in placebo- and/or ASA-treated participants were affected by the presence of H. pylori-associated microscopic gastritis. We simultaneously evaluated the rate of recovery of platelet COX-1 activity after discontinuing ASA.

METHODS

Subjects and randomization. A human studies subcommittee of our medical center’s research committee approved this experiment. Informed, written consent was obtained from 32 healthy women and 29 healthy men between the ages of 18 and 61 yr (Table 1). None of the 61 participants had received ACE.

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aspirin, a nonaspirin nonsteroidal anti-inflammatory drug, or a gastric antisecretory drug for at least 14 days before beginning the experiment. None had a history of peptic ulcer, upper GI malignancy or surgery, or any chronic medical illness, and none was allergic to aspirin. We screened our study population for antibodies to *H. pylori* (FlexSure HP, SmithKline Diagnostics, Palo Alto, CA) so that approximately one-half of the subjects were seropositive for *H. pylori* and one-half were seronegative. Thus roughly equal numbers of participants with normal gastric histology or gastric inflammation were included.

Subjects participated in a randomized double-blind study and received an opaque capsule containing 81 mg of ASA to be taken daily (group A); an identical-appearing capsule containing 325 mg of ASA to be taken every third day, with an identical-appearing placebo capsule containing methyl cellulose to be taken on the other days (group B); or a placebo capsule to be taken daily (group C). Subjects were allocated to the three therapies in a 3:3:2 proportion for groups A (n = 23), B (n = 23), and C (n = 15), respectively. Pilot studies had demonstrated that 81 mg of ASA per day and 325 mg of ASA every third day produced similar antiplatelet effects. Medication was administered for 46 days to simulate long-term clinical use. This 1.5-mo duration of treatment with low-dose aspirin in volunteers has been found to be safe (3). Experimental measurements were made on day 46.

**Measurement of gastric COX activity (PG synthesis rates).** After an overnight fast, and 2 h after the last dose of ASA or placebo was taken on day 46, we obtained three fluoroscopy-guided mucosal biopsies from the gastric body through a modified nasogastric tube as previously described (1, 9). Subjects did not receive sedation for the gastric biopsies. We then removed the modified nasogastric tube and allowed the participants to drink two cans of Slim-Fast (Slim-Fast Foods, West Palm Beach, FL) over the next hour, but no other food was allowed for the next 6 h. Eight hours after the last dose of ASA or placebo, we reintubated each subject and obtained three additional biopsies from the gastric body. Intubation and fluoroscopy-guided biopsies were repeated after overnight fasts on the next three mornings (i.e., days 47, 48, and 49), 24, 48, and 72 h after the last dose of ASA or placebo.

The five sets of biopsies were assessed for gastric COX activity by measuring rates of ex vivo synthesis of PGE2 and PGF2α, the two major PGs produced by the human gastric mucosa (19). Freshly obtained gastric biopsies were placed in a preweighed incubation medium, reweighed, minced, and vortexed for 3 min to liberate arachidonic acid, allowing generation of PGE2 and PGF2α (2). The reaction was quenched by addition of 100 μg/ml indomethacin. Aliquots from in vitro incubations were mixed with [3H]PGE2 or PGF2α.

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**Table 1. Gender and age of study participants in the 3 treatment groups**

<table>
<thead>
<tr>
<th>Group</th>
<th>n</th>
<th>Gender (female/male)</th>
<th>Age, years</th>
</tr>
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<tbody>
<tr>
<td>81-mg ASA</td>
<td>23</td>
<td>12/11</td>
<td>18–61</td>
</tr>
<tr>
<td>325-mg ASA</td>
<td>23</td>
<td>12/11</td>
<td>21–54</td>
</tr>
<tr>
<td>Placebo</td>
<td>15</td>
<td>8/7</td>
<td>19–56</td>
</tr>
<tr>
<td>Total</td>
<td>61</td>
<td>32/29</td>
<td>18–61</td>
</tr>
</tbody>
</table>

Subjects received 81 mg of acetylsalicylic acid (ASA) daily (group A), 325 mg of ASA every 3rd day (group B), or placebo daily (group C).

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**Fig. 1. Mean (±SE) rate of gastric mucosal synthesis of PGE2 (A), PGF2α (B), or their sum (C) at various times after the last dose of a 46-day treatment with placebo (Pl, open bars), 325 mg of acetylsalicylic acid (ASA) every 3rd day (hatched bars), or 81 mg of ASA daily (solid bars) in 61 healthy volunteers. *P ≤ 0.003 for 325-mg ASA or 81-mg ASA vs. placebo; ‡P < 0.05 for 325-mg ASA vs. 81-mg ASA.**

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**Hours after Medication**

![Graph](http://example.com/graph.png)
H. pylori and with antisera to PGE<sub>2</sub> or PGF<sub>2α</sub> (Sigma Immunochemicals, St. Louis, MO). Antibodies were first reconstituted in 5 ml of bovine serum albumin buffer and then diluted 1:10 (for PGE<sub>2</sub> antibody) or 1:5 (for PGF<sub>2α</sub> antibody). After incubation, bound counts were determined by liquid scintillation. Standard curves using known amounts of PGE<sub>2</sub> or PGF<sub>2α</sub> were used to assay PG concentrations in study samples. Radioimmunoassay results were expressed as picograms of PGE<sub>2</sub> or PGF<sub>2α</sub> (or their sum) per milligram of tissue per minute.

**Gastric histology.** Two separate gastric biopsies were obtained on day 46 from the gastric body for microscopic examination by a GI pathologist. The pathologist was blinded to treatment group and H. pylori serology results. The gastric biopsies were stained with hematoxylin and eosin and classified microscopically as either normal (i.e., no inflammation present) or inflamed (i.e., gastritis present). When gastritis was present, it was almost invariably chronic and active (i.e., containing lymphocytes and neutrophils), associated with visible H. pylori organisms, and moderate or severe in intensity (9, 18).

**Measurement of platelet COX activity (platelet-derived serum TxB<sub>2</sub> concentrations).** Just before each set of gastric mucosal biopsies was obtained, a venous blood sample was collected and allowed to clot and serum was obtained by centrifugation. Serum was later radioimmunoassayed for platelet-derived serum TxB<sub>2</sub> concentration as previously described (2, 3, 6, 8, 15). Platelets use COX-1 to generate TxB<sub>2</sub> or PGF<sub>2α</sub>, or their sum) per milliliter of serum.

**Statistical analysis.** Data were entered into a Microsoft Excel spreadsheet and then imported into Systat version 8.0 for Windows (SPSS, Chicago, IL). Results for each treatment group were expressed as means ± SE. Differences in mean gastric PGE<sub>2</sub> or PGF<sub>2α</sub> synthesis rates (or their sum) or in platelet-derived serum TxB<sub>2</sub> concentrations among groups were tested for significance by analysis of variance. Pairwise differences were subjected to the Bonferroni post hoc test to determine significant differences. A general linear model of gastric PG synthesis inhibition (PGE<sub>2</sub>, PGF<sub>2α</sub>, or their sum) as a function of time after the last ASA dose was used. Differences in slopes of regression lines were compared by \( t \)-tests after pooling the SEs, according to the formula \( t = (\text{slope } 1 - \text{slope } 2)/\text{pooled SE} \). Two-tail probability \( (P) \) values < 0.05 were considered significant.

**RESULTS**

**Rate of recovery of gastric mucosal PG synthesis.** As shown in Fig. 1, gastric PGE<sub>2</sub> and PGF<sub>2α</sub> synthesis (and their sum) in placebo-treated participants were quite constant over the 72-h experiment. PGE<sub>2</sub> synthesis was approximately twofold greater than PGF<sub>2α</sub> synthesis.

Gastric mucosal PGE<sub>2</sub> and PGF<sub>2α</sub> synthesis 2 h after 325- or 81-mg ASA was much lower than after placebo \( (P < 0.001) \). Reductions in PGE<sub>2</sub> and PGF<sub>2α</sub> synthesis, relative to placebo, ranged from 86% to 93%.

By 24 h after ASA, there was only slight recovery of gastric PGE<sub>2</sub> and PGF<sub>2α</sub> synthesis, which remained reduced by 68–85% \( (P < 0.001; \text{Fig. 1}) \). Over the ensuing 2 days, there was continued but very slow recovery of gastric PG synthesis. For example, 72 h after 325-mg ASA, gastric PGE<sub>2</sub> and PGF<sub>2α</sub> synthesis were still reduced by 58% and 55%, respectively \( (P < 0.001) \).

Gastric mucosal PG (PGE<sub>2</sub> + PGF<sub>2α</sub>) synthesis 72 h after the last 81-mg ASA dose was reduced by 34% \( (P = 0.04) \); inhibition averaged 28% for PGE<sub>2</sub> alone (not significant) and 45% for PGF<sub>2α</sub> alone \( (P = 0.04) \) (Fig. 1). PGE<sub>2</sub> synthesis (and the sum of PGE<sub>2</sub> + PGF<sub>2α</sub> synthesis) had recovered to a significantly higher rate 72 h after 81-mg ASA than 72 h after 325-mg ASA (Fig. 1).

**Platelet-derived serum TxB<sub>2</sub> concentrations.** As shown in Fig. 2, mean platelet-derived serum TxB<sub>2</sub> concentrations were fairly constant (220–250 ng/ml) in subjects receiving placebo. After both 325- and 81-mg ASA, serum TxB<sub>2</sub> concentrations were sharply reduced throughout the 72-h experiment \( (P < 0.001 \text{ vs. placebo}) \). Serum TxB<sub>2</sub> levels 72 h (3 days) after ASA were still significantly reduced relative to placebo by 89% and 84% for 325 and 81 mg, respectively \( (P < 0.001) \).
Thus platelet COX-1 activity was inhibited to an even greater extent than gastric COX activity throughout the 72-h experiment (Fig. 3; days 0–3).

Regression analyses. Mean percent reductions of gastric PG (PGE$_2$ + PGF$_{2a}$) synthesis are plotted as a function of time after the last dose of 325- or 81-mg ASA in Fig. 4. Recovery of PG synthesis after either ASA dose was linear, with correlation coefficients for the linear regression equations exceeding 0.99 (Table 2; $P < 0.001$). Recovery of gastric PG synthesis was also dose related, with a significantly ($P < 0.001$) faster recovery (steeper slope) after the 81-mg dose (Fig. 4B; Table 2) than after the 325-mg dose (Fig. 4A; Table 2).

If the regression lines in Fig. 4 are extrapolated to no (0%) PG synthesis inhibition, an estimate of the total duration of inhibition of ASA on gastric PG synthesis...
Table 2. Linear regression analyses comparing role of ASA dose on PG recovery

<table>
<thead>
<tr>
<th></th>
<th>m</th>
<th>b, %</th>
<th>r</th>
<th>x-Intercept, hours (days)</th>
</tr>
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<tr>
<td>81-mg ASA</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGE₂ data</td>
<td>0.840</td>
<td>-89.7</td>
<td>0.995</td>
<td>106.8(4.5)</td>
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<td>PGF₂α data</td>
<td>0.591</td>
<td>-86.2</td>
<td>0.993</td>
<td>145.9(6.1)</td>
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<tr>
<td>Combined</td>
<td>0.751</td>
<td>-88.3</td>
<td>0.999</td>
<td>117.6(4.9)</td>
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<tr>
<td>325-mg ASA</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PGE₂ data</td>
<td>0.504</td>
<td>-94.3</td>
<td>0.994</td>
<td>187.2(7.8)</td>
</tr>
<tr>
<td>PGF₂α data</td>
<td>0.492</td>
<td>-89.1</td>
<td>0.992</td>
<td>181.2(7.5)</td>
</tr>
<tr>
<td>Combined</td>
<td>0.492</td>
<td>-92.2</td>
<td>0.993</td>
<td>187.3(7.8)</td>
</tr>
</tbody>
</table>

Data for either ASA dose regimen were fit to the regression equation \( I = mh + b \), where \( I \) is percent inhibition of gastric synthesis of PGE₂a, PGF₂α, or the 2 combined, with inhibition plotted as a negative percentage (e.g., 80% inhibition = -80%). \( m \) is slope of the best-fit regression line, \( h \) is time in hours after the final 81-mg or 325-mg ASA dose; \( b \) is \( I \) at time 0 (y-intercept), and \( r \) is correlation coefficient (all \( P < 0.001 \)). x-Intercepts were calculated by extrapolation and represent ASA’s duration of inhibitory effect on gastric PG synthesis in hours or days. *See Fig. 4B for regression line. †See Fig. 4A for regression line. ‡P < 0.001 vs. slope with 81-mg ASA (combined).

can be obtained. The duration of inhibition of 325-mg ASA on gastric PG (PGE₂ + PGF₂α) synthesis was estimated to be 7.8 days (Fig. 3B; Table 2). As shown in Table 2, similar estimates resulted when only PGE₂ data or only PGF₂α data were used (7.8 and 7.5 days, respectively). The duration of inhibition of 81 mg ASA on gastric PG (PGE₂ + PGF₂α) synthesis was likewise estimated to be 4.9 days (Fig. 3A; Table 2), and to be 4.5 or 6.1 days when only PGE₂ data or only PGF₂α data were used, respectively.

Role of gastritis in gastric mucosal PG synthesis. Twenty-nine of the sixty-one subjects had H. pylori-associated gastritis on gastric body biopsies, whereas the other thirty-two had normal gastric histology. As shown in Fig. 5, mean PG synthesis rates tended to be slightly higher in participants with gastritis, regardless of treatment group or the time after the last dose of medication at which measurements were made. The difference in mucosal PG synthesis between biopsies with normal histology vs. biopsies with gastritis was statistically significant at 8 h (\( P = 0.007 \)), and differences approached significance at other times (\( P = 0.07–0.28 \)).

As shown in Fig. 6B, the rate of recovery of gastric mucosal PG (PGE₂ + PGF₂α) synthesis was similar in subjects treated with 81-mg ASA, whether they had gastritis or not (\( P = 0.51 \) for comparison of slopes). The duration of inhibition with 81-mg ASA was estimated by extrapolation to be 4.8 days in subjects with normal histology and 5.2 days when gastritis was present (Table 3).

With the 325-mg ASA dose (Fig. 6A), the duration of inhibition of PG synthesis was significantly longer in subjects with gastritis (less steep slopes) than in subjects with normal histology (\( P = 0.003 \) for comparison of slopes). Duration of inhibition with 325-mg ASA was estimated to be 9.7 days in participants with gastritis and 6.4 days in participants with normal histology (Table 3).

**DISCUSSION**

ASA irreversibly acetylates a key serine residue of COX, blocking COX activity (17). As a consequence, production of prostanoids (PG, TxA₂) from arachidonic acid and from PGH₂ declines, and the physiological functions that the prostanoids subsume are impaired. COX activity returns to normal and the physiological actions of the prostanoid products of the COX reaction are restored only if COX is regenerated in cells or if new cells are produced.

The platelet is a unique cell in that it has no nucleus and thus cannot regenerate COX-1 to produce TxA₂ after its COX-1 activity has been irreversibly eliminated by ASA. Thus restoration of platelet COX-1 activity requires release of fresh platelets into the circulation from bone marrow megakaryocytes that have not been exposed to ASA. Because the life span of a platelet is 10 days, only 10% of platelets are replaced each day (17). Moreover, some of the newest platelets...
to appear in the circulation soon after ASA is discontinued undoubtedly are derived from megakaryocytes that had been exposed to ASA and whose COX-1 activity has been inactivated. Thus it requires 12–14 days for platelet COX-1 activity and platelet-derived serum TxB2 concentrations to return to normal after low-dose ASA is discontinued (Ref. 16; Fig. 3).

Because GI mucosal cells that produce COX are nucleated, they at least theoretically are capable of regenerating COX mRNA and protein, thus restoring COX activity and mucosal PG production after ASA has disappeared from the body. However, we found that the stomach recovered very slowly from the inhibitory effect of ASA on gastric COX activity. For example, 3 days after 325-mg ASA, gastric COX activity was still inhibited by nearly 60%. Recovery of gastric COX activity was linear with time, allowing us to estimate that it would require a week or more for gastric COX activity to return to normal after 325-mg ASA. Recovery of gastric COX activity was significantly faster after 81-mg than after 325-mg ASA. However, after 81-mg ASA was discontinued, complete recovery of gastric COX activity was still estimated to require 5 days. These data suggest that the regeneration of COX by the gastric mucosa is very slow.

The gastric surface epithelium has a turnover time of 3 days, and the turnover time for mucous neck cells and stem cells is 7 days (13). Our PG recovery data therefore suggest that recovery of gastric COX activity is, like the platelet, dependent on production of new cells rather than synthesis of new protein by extant cells. The somewhat faster recovery of gastric COX than platelet COX (Fig. 3) parallels the differences in gastric and platelet cell turnover rates.

ASA serum concentrations after oral dosing peak in 20–30 min and by 2–3 h after dosing are barely detectable by a sensitive chromatographic method (6, 8). ASA is rapidly converted to salicylate by tissue and plasma esterases. Once the acetyl group of ASA has been removed by these esterases, ASA can no longer acetylate COX. Salicylate, which can circulate for $12 \text{h}$ after a 325-mg ASA dose, does not inhibit gastric COX activity in vitro or in vivo (2, 5). Thus the inhibitory effect of ASA on gastric COX activity outlasts its life in the circulation by 40- to 60-fold.

The prolonged duration of effect of low-dose ASA on gastric COX activity helps explain the clinical observation that peptic ulcer formation and GI bleeding are increased significantly with low-dose ASA. In the Physician’s Health Study (22), for example, duodenal ulcer formation and melena occurred significantly more often in physicians receiving 325 mg of ASA every 48 h than in physicians receiving placebo. As shown by the 325-mg ASA data presented here, gastric PG synthesis is still reduced by $\sim65\%$ at 48 h (Figs. 1 and 3). Likewise, in the Swedish Aspirin Low-Dose Trial (SALT), there was more upper GI bleeding in patients receiving 75 mg of ASA per day than in those receiving placebo treatment (23). (In Europe 75 mg of ASA is the “baby-sized” dose, whereas in the US 81 mg of ASA is the “baby-sized” dose.) Gastric PG synthesis 24 h after 81-mg ASA is still reduced by 70% (Figs. 1 and 3).

It appears very unlikely from our data that an oral ASA dose regimen will be found that produces a prolonged platelet inhibition with little or no GI mucosal PG inhibition. In other words, GI toxicity may be an inevitable consequence of low-dose ASA therapy. Despite this inevitability, there may be a dose of ASA that has an optimal benefit-risk ratio. An 81-mg ASA dose was about as effective in inhibiting platelet COX-1 activity at 72 h as a 325-mg dose in the present study and in other studies (3, 15, 16). Moreover, gastric COX activity had nearly recovered by 72 h after the 81-mg ASA dose (Figs. 1 and 3), making an ASA dose of 81 mg

**Table 3.** Linear regression analyses comparing role of inflammation (gastritis) on PG synthesis recovery

<table>
<thead>
<tr>
<th>Dose</th>
<th>m</th>
<th>b, %</th>
<th>r</th>
<th>x-Intercept, hours (days)</th>
</tr>
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<tbody>
<tr>
<td>81-mg ASA</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No gastritis</td>
<td>0.760</td>
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<td>0.986</td>
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<td>Gastritis</td>
<td>0.717</td>
<td>-89.2</td>
<td>0.992</td>
<td>124.4 (5.2)</td>
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<td>325-mg ASA</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>No gastritis</td>
<td>0.609</td>
<td>-93.4</td>
<td>0.973</td>
<td>153.4 (6.4)</td>
</tr>
<tr>
<td>Gastritis</td>
<td>0.390</td>
<td>-90.7</td>
<td>0.988</td>
<td>232.6 (9.7)</td>
</tr>
</tbody>
</table>

Four sets of combined $\text{PGE}_2 + \text{PGF}_{2\alpha}$ data from Fig. 6 were fit to regression equations, as described in Table 2.

**Fig. 6.** Gastric mucosal PG ($\text{PGE}_2 + \text{PGF}_{2\alpha}$) synthesis inhibition (% relative to placebo) at various times after the last dose of 325-mg (A) or 81-mg (B) ASA in 32 subjects with normal gastric histology and in 29 subjects with *H. pylori*-associated gastritis. Lines represent best-fit linear regression equations. Slopes of lines and correlation coefficients are given in Table 3.
even low doses of ASA given every 24 or more) is associated with a reduced risk of colorectal adenomas and carcinoma (12). For this reason, we examined whether gastric PG synthesis, and responsiveness to ASA therapy, varied as a function of *H. pylori* gastritis. We found that gastric PG synthesis rates were slightly but consistently higher in *H. pylori*-infected subjects with chronic, active gastritis than in noninfected subjects with normal histology, presumably because of COX-2-mediated PG synthesis by inflammatory cells. ASA, which blocks both COX-1 and COX-2 (2), lowered gastric PG synthesis to approximately the same level in infected and noninfected participants. Moreover, PG synthesis recovery rates were significantly slower in participants with gastritis than in participants with normal histology after the 325-mg aspirin dose (Fig. 6 and Table 3). However, recovery rates were similar after 81-mg ASA. Whether the *P* value <0.05 with 325-mg ASA represents a type I error, the *P* value >0.05 with 81-mg ASA represents a type II error, or the apparent difference between the two aspirin doses was caused by differences in responses of volunteers assigned randomly to the two treatment groups is uncertain.

Upregulation of COX-2 may be an important step in colorectal adenoma and carcinoma formation, an effect that may be antagonized by low-dose ASA (12, 21). Oral ASA (325 mg) inhibits rectal COX activity when measured 2 h after administration (3). In light of the prolonged effect of ASA on gastric COX activity we observed in this study, one may speculate that inhibition of colorectal COX activity by low-dose ASA could also be prolonged. This speculation is supported by a recent study in which rectal mucosal PGE$_2$ and PGF$_{2\alpha}$ content was still slightly but significantly reduced 3 days after a 14-day course of ASA was discontinued in healthy men (21). A prolonged inhibitory effect of ASA on colorectal COX activity and on colorectal PG synthesis may explain why epidemiological studies have found that even infrequent ASA use (e.g., twice a week or more) is associated with a reduced risk of colorectal adenomas and carcinoma (12).

In summary, antiplatelet doses of ASA, such as those used to prevent or to treat cardiovascular diseases, likely inhibit gastric COX activity for 5–10 days after ASA exposure, even though ASA is metabolized to salicylate within a few hours. This markedly prolonged pharmacodynamic effect of ASA on the gastric mucosa is most likely caused by a slow turnover of COX (mainly COX-1) in the gastric mucosa that appears to parallel production of new epithelial cells. Our findings help explain how even low doses of ASA given every 24 or 48 h can be ulcerogenic in the upper GI tract (3, 22). Slow recovery of gastric COX activity after ASA therapy occurs both in the normal gastric mucosa and, perhaps to an even greater extent, in mucosa inflamed because of infection with *H. pylori*. Gastric mucosal prostaglandin depletion due to the inhibition of mucosal COX activity appears inevitable with antiplatelet (antiplatelet) doses of ASA.

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