Effect of acetaminophen on human gastric mucosal injury caused by ibuprofen

F L LANZA, G L ROYER, R S NELSON, M F RACK, C E SECKMAN AND J H SCHWARTZ

From the Baylor College of Medicine, Division of Gastroenterology, Houston, Texas and the Upjohn Company Research Laboratories, Kalamazoo, Michigan, USA

SUMMARY  Acetaminophen has been proposed as an agent which protects the gastric mucosa against damage induced by aspirin and other non-steroidal anti-inflammatory agents. In order to evaluate this proposal further, 45 normal human volunteers were divided into three groups (n=15); group one received ibuprofen 2400 mg daily (600 mg qid); group two received acetaminophen 3900 mg daily (975 mg qid) and group three received both drugs at the same dosages. There was no significant difference in the mucosal injury scores noted at endoscopy between the ibuprofen and the ibuprofen-acetaminophen group. The acetaminophen group had virtually no observed mucosal injury and this was statistically significant in comparison with the other groups (p<0.01). We conclude that contrary to previously reported studies using single doses of aspirin, acetaminophen failed to decrease the mucosal injury seen with ibuprofen when given for a period of seven days in combination with acetaminophen.

Non-steroidal anti-inflammatory agents (NSAIDs) are the most widely prescribed class of drugs in the world today. Many NSAIDs including aspirin, have been shown endoscopically to produce significant degrees of gastric and duodenal mucosal injury.1-8 This damage is presumably because of diminished mucosal prostaglandin synthesis secondary to inhibition of cyclooxygenase pathways by these drugs. Ibuprofen, available in the United Kingdom since 1967, and in the United States since 1974 has been the most widely prescribed and extensively studied of the NSAIDs.9 Like other NSAIDs, ibuprofen has been associated with mucosal injury. The extent of that injury with ibuprofen, however, has been shown to be less than that associated with aspirin,1 2 tolmetin,3 4 indomethacin,4 phenylbutazone,1 or naproxen.2 4

Recent studies have shown that acetaminophen does not cause any significant degree of gastric mucosal injury, nor does it affect prostaglandin synthesis.10 11 Animal as well as human studies have also recently suggested that treatment with acetaminophen may exert a protective effect against the mucosal damage commonly seen with aspirin and alcohol.10 12 13 Logic would suggest, therefore, that a safer regimen in which NSAIDs are recommended – that is, in which mucosal damage is to be avoided, would be a combination of ibuprofen, one of the least damaging of the NSAIDs and acetaminophen for its protective effect. This study was designed to determine whether or not acetaminophen, given concurrently with ibuprofen, produced a protective effect against the mucosal injury seen with ibuprofen.

Methods

SUBJECTS
Forty five volunteers in good health participated in this phase of the study. All subjects were free from any history of gastrointestinal disease and allergy or hypersensitivity to aspirin or other NSAIDs. The volunteers, 16 women, 29 men, ranged in age from 19 to 46 years (mean 24 years).

This study was approved by the appropriate Institutional Review Committee for Studies Involving Human Subjects on 18 November, 1983. Each volunteer was carefully screened during the week before the study and received a thorough physical examination, complete blood count, urinalysis, prothrombin and partial thromboplastin times, stool haemocult test and blood chemistry profile. Normal values were required for all subjects...
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to continue in the study. On day 1 and before the administration of any medication, upper gastrointestinal endoscopy was carried out, at which time gastric juice was aspirated for pH determination. A normal upper gastrointestinal mucosa and a pH of 3-0 or lower were required for the subjects to remain in the study. For two weeks before the initiation of the study and during the period of drug administration volunteers were allowed to eat a normal diet; however, they were instructed to refrain from the use of alcohol and all medication.

The 45 volunteers were randomly divided into three equal groups. One group received ibuprofen, 2400 mg/day (600 mg qid). The second group received 3900 mg/day (975 mg qid) of acetaminophen. The third group received both drugs simultaneously at the dosages noted above. All medication was given after meals and at bedtime with a snack. After seven days of medication and two hours after the morning dose, all volunteers underwent upper gastrointestinal endoscopy and photography with an Olympus GIF K-2 upper GI endoscope. The stomach and duodenum were carefully examined and photographed in a proximal to distal manner in order to eliminate any error which might result from a misinterpretation of artefacts caused by passage of the instrument ('scope tracks'). The gastric and duodenal mucosa were graded according to the scale shown in Table 1. The same endoscopist carried out all the examinations. Endoscopic photographs were reviewed and graded in a similar blinded manner at a later date by a gastroenterologist unaware of the treatment groups and skilled in the interpretation of endoscopic photographs and who also used this grading system.

Volunteers were not informed as to which dosage they received; however, medications were obtained from standard pharmaceutical sources. The endoscopist was completely unaware of which medications or dosages the volunteers received. No conversation was allowed between the endoscopist and the volunteers, and medication had been disbursed by a study secretary who was not in the endoscopy room at the time of grading. As the results of the study depended on the objective observation of mucosal changes in the stomach and as no subjective data were required from the volunteers themselves, it was felt that the blind technique used in this phase of the study was adequate to protect the integrity of the results.

Blood levels for ibuprofen and acetaminophen were obtained at the midpoint and end of the study in order to insure compliance. Stool haemoccult tests were also done during these visits. At the conclusion of the study another complete laboratory evaluation was obtained on each volunteer.

Statistical analysis for the comparison of treatment groups was carried out by a one-way analysis of variance.

Results

Mucosal injury scores seen in the volunteers are indicated in Table 2. There is no significant difference between mean and median scores within any group. Volunteers taking acetaminophen alone had virtually no mucosal injury either in the stomach or duodenum. Volunteers taking ibuprofen 2400 mg/day or ibuprofen at that dosage level combined with acetaminophen 3900 mg/day had virtually identical degrees of gastric and duodenal mucosal injury.

Three subjects developed acute ulcer during the course of the study. These were all graded as 4+ and were of a size and depth to be considered significant if encountered in clinical practice. Subject no 19, a 30 year old woman developed a 1-0 cm lesser curvature antral ulcer along with scattered duodenal erosions. She had received the combination of ibuprofen and acetaminophen. Subject no 14, a 23 year old woman developed a small, 0-5 cm deep antral ulcer along with scattered duodenal erosions. She had received ibuprofen alone. Subject no 8, a 28 year old man developed a 0-7 cm duodenal ulcer and also had scattered submucosal haemorrhages throughout the stomach. He also had received only ibuprofen.

No significant laboratory abnormalities were detected in any volunteers. Minor transaminase rises (less than twice normal) were noted in some subjects in the acetaminophen and acetaminophen-ibuprofen groups, however, subsequent testing two weeks after the completion of the study revealed reversion to normal in all cases. No transaminase rise was noted in subjects taking ibuprofen alone. No positive haemoccult reactions were recorded during the course of the study and there were no decreases in haemoglobin levels suggestive of significant bleeding.

Serum concentrations of ibuprofen and acetaminophen

Table 1

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Normal</td>
</tr>
<tr>
<td>1</td>
<td>One submucosal haemorrhage or superficial ulceration.</td>
</tr>
<tr>
<td>2</td>
<td>More than one submucosal haemorrhage or superficial ulceration but not numerous or widespread.</td>
</tr>
<tr>
<td>3</td>
<td>Numerous areas with submucosal haemorrhages or superficial ulcerations.</td>
</tr>
<tr>
<td>4</td>
<td>Widespread involvement of the stomach with submucosal haemorrhage or superficial ulceration. Invasive ulcer of any size.</td>
</tr>
</tbody>
</table>
Table 2  Mucosal injury seen with ibuprofen 2400 mg/day and acetaminophen 3900 mg/day

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Mucosal Injury Score</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 +G +D G D G D G D G D</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ibu 2400 mg/day</td>
<td>6 12 1 0 6 2 1 0 1 1</td>
<td>2.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ac 3900 mg/day†‡</td>
<td>14 15 0 0 1 0 0 0 0 0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>Ibu 2400 mg/day + Ac 3900 mg/day</td>
<td>4 7 3 2 4 6 3 0 1 0</td>
<td>2.0</td>
<td>1.0</td>
</tr>
</tbody>
</table>

*G=Gastric mucosal injury score.
†D=Duodenal mucosal injury score.
‡Diffs significantly from other groups (p<0.01).
Ibu=Ibuprofen.
Ac=Acetaminophen.

Phen were consistent in all cases with good compliance by the subjects (Table 3). The photographic review and grading revealed close correlation with the endoscopic scores and that these were tabulated no significant difference in their means or medians and those observed at endoscopy were noted.

**Discussion**

Recent experiments in animals have shown that pretreatment with acetaminophen protects the gastric mucosa against damage induced by acidified aspirin and ethanol.10 13 Those studies were done in an acute model – that is, one in which test animals were killed after a single treatment. In a more recent study, human gastric mucosal protection against single doses of aspirin and alcohol is reported in subjects pretreated with acetaminophen.12

The data from our experiment, however, show no protective effect for acetaminophen in normal volunteers taking ibuprofen for seven days. It is shown rather conclusively that no difference exists in the degree of mucosal injury seen in volunteers taking 2400 mg ibuprofen daily and in those taking that same dosage of ibuprofen combined with acetaminophen 3900 mg/daily. It is interesting to note that three of the 30 subjects (10%) who took ibuprofen, one in the combination group and two in the ibuprofen only group, developed ulcer. Subjects taking acetaminophen alone showed virtually no mucosal injury which is consistent with previous reports in subjects taking this drug.10 11 In human volunteers, the degree of duodenal injury is less than that seen in the stomach. This has been noted previously in similar studies with ibuprofen, aspirin, and other NSAIDs.4 7 14 The degree of gastric and duodenal mucosal injury seen in this study is consistent with that reported for ibuprofen at this anti-inflammatory dosage level and is less than that noted with corresponding doses of the stronger prostaglandin inhibitors such as indomethacin, tolmetin, and naproxen.4 8 14

It has been suggested that the cytoprotection seen with acetaminophen in acute models is caused either by stimulation of prostaglandin synthesis or by inhibition of its degradation.12 This is supported by the demonstration that in the case of aspirin the protective effect of acetaminophen is abolished by indomethacin, a strong prostaglandin inhibitor.12 It would seem that, in this experiment, ibuprofen acts in a manner similar to indomethacin when given concurrently with acetaminophen – that is, the degree of enhancement of prostaglandin synthesis afforded by acetaminophen is outweighed by the inhibition of that process caused by ibuprofen.

As it has been shown that pretreatment of the

Table 3  Blood levels for ibuprofen and acetaminophen

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Acetaminophen</th>
<th>Ibuprofen</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Day 4</td>
<td>SD</td>
</tr>
<tr>
<td>Acetaminophen (n=15)</td>
<td>9.96 ± 2.61</td>
<td></td>
</tr>
<tr>
<td>Acetaminophen + ibuprofen</td>
<td>12.60 ± 3.67</td>
<td></td>
</tr>
<tr>
<td>Ibuprofen (n=15)</td>
<td>—</td>
<td></td>
</tr>
</tbody>
</table>
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Gastric mucosa with topical prostaglandin is cytoprotective against aspirin and alcohol.\textsuperscript{15} Pretreatment with acetaminophen before administration of ibuprofen might result in a degree of cytoprotection, however, this would have to be studied separately. Our findings are further supported by a very recent report that acetaminophen given concurrently with aspirin in normal human volunteers also fails to provide a cytoprotective effect.\textsuperscript{16} From a clinical standpoint, an ideal cytoprotective agent would have to be one which could be given concurrently with the offending agent or one which needs to be administered only once or twice daily. When ibuprofen is the offending agent, acetaminophen clearly does not meet these requirements.

This report was supported by a grant from The Upjohn Company, Kalamazoo, Michigan, USA.

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