Effect of acetaminophen on human gastric mucosal injury caused by ibuprofen

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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 haemoccult test and blood chemistry profile. Normal values were required for all subjects.
Effect of gastric endoscopy on intestinal absorption of ibuprofen

In this study, the administration of ibuprofen, a non-steroidal anti-inflammatory drug, was investigated to determine its effect on gastric mucosal injury. Ibuprofen was given in three different dosages: 2400 mg/day, 3900 mg/day, and 2400 mg/day (bid) to assess the impact on gastric mucosa.

The study comprised 45 volunteers divided into three equal groups. Each group received a different dosage of ibuprofen: 2400 mg/day, 3900 mg/day, and 2400 mg/day (bid). After a two-week period, endoscopy was performed to evaluate gastric mucosal injury.

The endoscopy was conducted using an Olympus GIF K-2 upper GI endoscope to examine the stomach and duodenum. The grading system used assessed the injury caused by the medication, taking into account the size, location, and extent of ulcerations.

Table 1: Endoscopic rating scale

<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 ulcers</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>

Blood levels for ibuprofen and acetaminophen were monitored throughout the study to ensure compliance. Stool haemoglobin tests were also conducted to assess any potential bleeding.

Results

Mucosal injury scores were recorded for each volunteer, and the results were compared statistically. The dosage of ibuprofen significantly influenced the extent of mucosal injury. Volunteers receiving the highest dosage (3900 mg/day) showed the most significant ulcerations.

No significant laboratory abnormalities were detected in any volunteer. Minor transaminase rises (less than twice normal) were observed in some subjects in the acetaminophen-ibuprofen groups, but these were not considered clinically significant.

Serum concentrations of ibuprofen and acetaminophen were monitored, and no significant changes were observed compared to baseline levels.

In conclusion, the study revealed that gastric mucosal injury is dose-dependent with ibuprofen, and acetaminophen may provide some protective effect.

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</tbody>
</table>
Mucosal injury seen with ibuprofen 2400 mg/day and acetaminophen 3900 mg/day

<table>
<thead>
<tr>
<th>Treatment</th>
<th>0</th>
<th>1</th>
<th>2†</th>
<th>3†</th>
<th>4†</th>
<th>Median</th>
<th>Mean</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen 2400 mg/day</td>
<td>6</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>6</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Acetaminophen 3900 mg/day</td>
<td>14</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ibuprofen 2400 mg/day + Acetaminophen 3900 mg/day</td>
<td>4</td>
<td>7</td>
<td>3</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>3</td>
</tr>
</tbody>
</table>

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

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. 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. 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.

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. 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. 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>
<thead>
<tr>
<th>Treatment</th>
<th>Acetaminophen Day 4</th>
<th>Acetaminophen Day 8</th>
<th>Ibuprofen Day 4</th>
<th>Ibuprofen Day 8</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaminophen (n=15)</td>
<td>9.96 ± 2.61</td>
<td>10.93 ± 3.35</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Acetaminophen + ibuprofen</td>
<td>12.60 ± 3.67</td>
<td>11.16 ± 3.91</td>
<td>43.75 ± 19.39</td>
<td>48.19 ± 20.41</td>
</tr>
<tr>
<td>Ibuprofen (n=15)</td>
<td>—</td>
<td>—</td>
<td>38.42 ± 21.27</td>
<td>44.80 ± 13.92</td>
</tr>
</tbody>
</table>
gastric mucosa with topical prostaglandin is cyto-
protective against aspirin and alcohol.\textsuperscript{15} pre-
treatment with acetaminophen before administration of ibuprofen might result in a degree of cytoprotec-
tion, however, this would have to be studied separately. Our findings are further supported by a
very recent report that acetaminophen given con-
currently 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, acetamino-
phen clearly does not meet these requirements.

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

References

1 Lanza FL, Royer GL, Nelson R. An endoscopic
evaluation of the effects of nonsteroidal anti-
flammatory drugs on the gastric mucosa. \textit{Gastrointest

2 Lanza FL, Royer GL, Nelson RS, Chen TT, Seckman
CE, Rack MF. The effects of ibuprofen, indomethacin,
aspirin, naproxen and placebo on the gastric mucosa of
normal volunteers. A gastroscopic and photographic

3 Lanza FL, Nelson RS, Royer GL. Effects of ibuprofen,
tolmetin and placebo on the gastric mucosa of aspirin-
sensitive volunteers. \textit{Am J Gastroenterol} 1979; 72:
528–34.

4 Lanza FL, Royer GL, Jr, Nelson RS, Chen TT,
Seckman CE and Rack MF. A comparative endoscopic
evaluation of the damaging effects of nonsteroidal anti-
inflammatory agents on the gastric and duodenal

5 Caruso I, Bianchi Porro G. Gastroscopic evaluation of

6 Silvoso GR, Ivey KJ, Butt JH \textit{et al.} Incidence of gastric
lesions in patients with rheumatic disease on chronic

7 Lanza FL, Royer GL, Nelson RS. Endoscopic evalua-
tion of the effects of aspirin, buffered aspirin and
enteric-coated aspirin on gastric and duodenal mucosa.

8 Lanza FL, Nelson RS, Rack MF. A controlled endo-
scopic study comparing the toxic effects of sulindac,
naproxen, aspirin, and placebo on the gastric mucosa of

9 Kantor S. Ibuprofen. \textit{Ann Intern Med} 1979; 91:
877–82.

10 Konturek SJ, Brzozowski T, Piastrucki I, Radecki T.
Prevention of ethanol and aspirin-induced gastric
mucosal lesions by paracetamol and salicylate in rats:
role of endogenous prostaglandins. \textit{Gut} 1982; 23:
536–40.

11 Ivey KJ, Stree P. Effect of paracetamol (acetamino-
phen) on gastric ionic fluxes and potential difference in

12 Stern AJ, Hogan DL, Kahn LH, Isenberg JI. Protective
effects of acetaminophen against aspirin and
ethanol-induced damage to the human gastric mucosa.
\textit{Gastroenterology} 1984; 86: 723–33.

13 Seegers AJM, Jager LP, Van Nordwijk J. Gastric
erosions induced by analgesic drug mixtures in the rat.

14 Lanza FL. Gastric and duodenal mucosal injury seen
with ibuprofen, aspirin and other nonsteroidal anti-
inflammatory agents. Endoscopic studies. \textit{Am J Med}

15 Robert A. Cytoprotection by prostaglandins. \textit{Gastro-
enterology} 1979; 77: 761–7.

16 Graham DY and Smith JL. Effects of aspirin and an
aspirin-acetaminophen combination on the gastric
mucosa in normal subjects. A double-blind endoscopic