Prospective study of acute gastrointestinal bleeding attributable to anti-inflammatory drug ingestion in the Yorkshire region of the United Kingdom

C H Lim, R V Heatley

Objective: To assess the general use of all non-steroidal anti-inflammatory drugs (NSAID) and their relation to upper gastrointestinal bleeding in view of National Institute for Clinical Excellence guidelines published in July 2001 in the UK.

Methods: Cross sectional study on all patients who were referred for endoscopy for suspected upper gastrointestinal bleeding in six hospitals in Yorkshire region of the UK.

Results: One hundred and sixty three patients presented for endoscopy for suspected upper gastrointestinal bleeding, 43 patients were taking at least one ulcerogenic drug, and 120 were not. The mean age difference between these two groups was eight years (p<0.01). The absolute difference between the proportion of patients with peptic ulcer disease/erosion (PUD) in NSAID with/without aspirin group and no ulcerogenic drug group was 31% (p = 0.02). The difference between the proportion of PUD in cyclo-oxygenase 2 with/without aspirin group and no ulcerogenic drug group was 30% (p = 0.1). The overall 30 days mortality rate was 14.1%.

Conclusions: Elderly patients are being inappropriately prescribed conventional NSAIDs. NSAIDs with or without aspirin use are still associated with a significant risk of upper gastrointestinal bleeding in the era of cyclo-oxygenase 2 selective agents. Substitution with cyclo-oxygenase 2 selective NSAIDs is not without risk of upper gastrointestinal bleeding.
independent *t* test for continuous data and *χ²* test for categorical data.

**RESULTS**

**Study sample**

One hundred and thirty patients had upper gastrointestinal endoscopy for suspected upper gastrointestinal haemorrhage within the two month study period. One hundred and thirty three patients (82%) were from the three teaching hospitals. Forty three (26%) patients were taking at least one potential ulcerogenic drug at admission. Table 1 shows the patient characteristics. The overall mean age was 64.6 years with a male predominance of 63% (103/163). The mean age for patients who were taking ulcerogenic drugs was on average eight years older (95% CI 2.3 to 13.6 years) than those who were not. This difference was significant (*p* = 0.006) using independent *t* test.

**Outcome**

Table 2 shows the proportion for upper gastrointestinal haemorrhage in each drug cohort with the endoscopic diagnoses, history for peptic ulcer disease (PUD), and concomitant proton pump inhibitor use. The concomitant use of aspirin with NSAIDs or COX-2 selective NSAIDs were combined in the same cohort because the number involved was small (two in each cohort) and unlikely to influence the overall result. The absolute difference in proportion of PUD and peptic erosion for all NSAIDs and/or aspirin use compared with no ulcerogenic drug was 18%. This was statistically significant and the 95% confidence interval does suggest all NSAIDs are probably more harmful. Most patients who were taking ulcerogenic drugs were taking either aspirin or a non-selective NSAID. Non-selective NSAIDs were associated with a greater number of PUD and peptic erosion bleeds than aspirin alone. COX-2 selective NSAIDs were also associated with bleeding PUD but the number of patients presenting during our study period were less than those taking non-selective NSAIDs. Table 3 shows the endoscopic diagnoses for all suspected upper gastrointestinal haemorrhage. Thirty nine per cent of all suspected upper gastrointestinal haemorrhage was associated with PUD. The overall 30 day mortality rate was 14.1%.

The mean number of monthly packs of NSAID prescribed in the geographical regions studied during the study period was 44 683 compared with 11277 for COX-2 selective NSAIDs (4:1 ratio). The non-selective NSAIDs included were diclofenac, ibuprofen, naproxen, misoprostol, meloxicam, indometacin, mfenamic acid, piroxicam, etodolac, cymicine, nabumetone, cefoxacin, ketoprofen, tiaprofenic acid, flurbiprofen, fenbufen, benorilate, sulindac, tenoxicam, piroxicam, azapropazone, acemetacin, and fenoprofen. The COX-2 selective NSAIDs included were rofecoxib, celecoxib, etoricoxib, and parecoxib. Therefore, the apparent lower number of patients taking COX-2 selective NSAID presenting with suspected upper gastrointestinal haemorrhage may reflect the prescription data.

**DISCUSSION**

There has been a general decline in Britain for hospital admissions and mortality rate for PUD from the 1950s to 1980s. The converse trend is true for perforated peptic ulcer and the mortality from duodenal ulcer increased among older women from the 1970s to 1980s. The discovery of ever more effective therapeutic agents and the benefit of *Helicobacter pylori* eradication in relation to PUD has led to an expectation that the incidence of PUD is in decline. However, a recent study showed that the hospital admission rates in England for upper gastrointestinal haemorrhage have increased among older patients from 1989 to 1998. The result of our study with a mean admission age of 64.6 years is consistent with this trend. Despite NICE guidelines, we must assume from our data than many “high risk” patients may not be prescribed NSAID totally appropriately. Our findings, as they are seen in several hospitals, can probably be extrapolated throughout the UK but it would be interesting to know if NSAID and COX-2 selective NSAID prescribing varies significantly in different geographical regions. There are scarce published data showing the extent of COX-2 selective NSAID prescribing in the UK and the appropriateness of patient selection for anti-inflammatory drug use.

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**Table 1**

<table>
<thead>
<tr>
<th>Characteristics of gastrointestinal haemorrhage patients</th>
<th>Ulcerogenic drug</th>
<th>No ulcerogenic drug</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>43</td>
<td>120</td>
<td>163</td>
</tr>
<tr>
<td>Male:Female</td>
<td>26:17</td>
<td>77:43</td>
<td>103:60</td>
</tr>
<tr>
<td>Mean age (SD)</td>
<td>70.5 (15.2)</td>
<td>62.5 (17.8)</td>
<td>64.6 (17.4)</td>
</tr>
</tbody>
</table>

Mean difference in age is eight years, 95% CI 2.3 to 13.6 years, *p* = 0.006.

**Table 2**

<table>
<thead>
<tr>
<th>Proportion for upper gastrointestinal haemorrhage in each drug cohort</th>
<th>Suspected upper gastrointestinal haemorrhage</th>
<th>Peptic ulcer disease</th>
<th>Peptic erosion*</th>
<th>Absolute difference between proportion (95% CI)†</th>
<th>PUD history</th>
<th>Concomitant proton pump inhibitor</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID +/− aspirin</td>
<td>17</td>
<td>11</td>
<td>2</td>
<td>31% (6% to 56%)†</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>18</td>
<td>3</td>
<td>5</td>
<td>−1% (−26% to 24%)‡</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>COX-2 +/− aspirin</td>
<td>8</td>
<td>6</td>
<td>0</td>
<td>30% (−6% to 66%)§</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Sub-total</td>
<td>43</td>
<td>20†</td>
<td>7†</td>
<td>18% (1% to 35%)†</td>
<td>5</td>
<td>5 (11%)</td>
</tr>
<tr>
<td>No ulcer related drug</td>
<td>120</td>
<td>44†</td>
<td>10†</td>
<td>0%</td>
<td>N/A</td>
<td>15 (13%)</td>
</tr>
<tr>
<td>Total</td>
<td>163</td>
<td>64</td>
<td>17‡</td>
<td></td>
<td>N/A</td>
<td>20</td>
</tr>
</tbody>
</table>

*An erosion if the lesion is small (< 5 mm diameter) and shallow with no sign of scarring. †The difference between the proportion of peptic ulcer disease and peptic erosion in each drug cohort and control group (no ulcer related drug). §Five also had reflux oesophagitis. *p* = 0.02; ‡*p* = 0.92; †*p* = 0.10; ‡*p* = 0.05

**Table 3**

<table>
<thead>
<tr>
<th>Endoscopic diagnoses for all suspected upper gastrointestinal haemorrhage</th>
<th>Frequency</th>
<th>Percentage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal</td>
<td>24</td>
<td>14.7</td>
</tr>
<tr>
<td>Erosive disease</td>
<td>17</td>
<td>10.4</td>
</tr>
<tr>
<td>Mallory Weiss</td>
<td>9</td>
<td>5.5</td>
</tr>
<tr>
<td>Oesophagitis</td>
<td>15</td>
<td>9.2</td>
</tr>
<tr>
<td>Gastric ulcer</td>
<td>28</td>
<td>17.2</td>
</tr>
<tr>
<td>Duodenal ulcer</td>
<td>36</td>
<td>22.1</td>
</tr>
<tr>
<td>Varices</td>
<td>19</td>
<td>11.7</td>
</tr>
<tr>
<td>Others</td>
<td>15</td>
<td>9.2</td>
</tr>
<tr>
<td>Total</td>
<td>163</td>
<td>100.0</td>
</tr>
</tbody>
</table>
Our overall mortality rate was 14%, which is at the higher end of the expected rate but is comparable to UK national audit.10 This mortality rate reflects the sample selection of our patients being older people often with significant morbidity. Moreover, most deaths were as a result of unrelated complications in elderly patients with significant comorbidities.

This study shows the relation of ulcerogenic drugs to upper gastrointestinal haemorrhage in daily clinical practice at the current time in different hospital environments. It does not directly address the question of whether COX-2 selective NSAIDs are safer than NSAIDs as no direct comparisons were made. This has been shown by a number of randomised controlled trials.11-13 It does however show that NSAID, aspirin, or COX-2 selective NSAID is associated with more than a quarter of all patients with suspected significant gastrointestinal haemorrhage giving comparable figures to those determined by others.14 The association between COX-2 selective NSAIDs and peptic adverse event was not statistically significant possibly because of the small number of patients in this group. This suggests that despite NICE and Committee on Safety of Medicine guidance, the prescription pattern for NSAIDs has not greatly changed.6,15 We accept that our selection method will not include all patients with suspected upper gastrointestinal haemorrhage in particular those who were not referred for endoscopy. However, these patients are likely to be younger with little or no comorbidity and unlikely to suffer from any significant adverse outcome.

There is little work on following up whether guidelines influence clinical practice. In the case of NSAID prescribing in our geographical region it is clear that not all high risk patients are being treated appropriately. Further research is needed to identify these reasons if we are going to have an impact on reducing serious gastrointestinal complications of NSAIDs. It is also clear that it is not always entirely possible to predict those patients at highest risk of gastrointestinal bleeding on the basis of their history.

Our results suggest that NSAID use is still significantly associated with gastrointestinal haemorrhage in the era of COX-2 selective NSAIDs. This is in line with the latest reminder from Committee on Safety of Medicine on gastrointestinal toxicity of NSAIDs.15 Poor adoption of the NICE guideline is one issue that will need tackling if we are to change the trend of hospital admission rates for upper gastrointestinal haemorrhage. It is apparent that high risk patients remain at risk of upper gastrointestinal haemorrhage even if COX-2 selective NSAID drugs are prescribed and patients may need to be vigilant.

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Authors’ affiliations

C H Lim, Department of Gastroenterology, The General Infirmary at Leeds, UK

R V Heatley, Department of Gastroenterology, St James’s University Hospital, Leeds, UK

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REFERENCES


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