Resolving pain medication-related GI trouble
What is NSAID?

NonSteroidal AntiInflammatory Drug

Numerous Side effects And Indispensable Drug
US mortality data in 1997

- 15th cause of death in USA
- Hospitalization: 100,000/ year and 10-20% of them die
단순 고혈압·당뇨병 환자에선 일차예방 겉해 아직 없어

박승우 성균관의대 교수·삼성서울병원 순환기내과

"아스피린은 동맥경화로 인한 심근경색증 또는 뇌졸중을 억제하거나 'Framingham Risk Score'로 계산한 10년 내 심혈관질환 발생 위험도가 10% 이상인 고위험군에서 심혈관질환의 예방효과가 입증되었다고 알려져 있다. 그러나 심혈관질환 병력이 없는 단순한 고혈압이나 당뇨병 환자에서 뇌졸중이나 심근경색증의 일차예방 목적으로 사용하는 것에 대해서는 아직 일치된 견해가 없다.

저용량의 아스피린이라 할지라도 출혈을 일으킬 위험성이 있기 때문에 아스피린 복용으로 위장관 출혈과 같은 합병증이 일어날 수 있다. 따라서 확실한 증가가 없이 무력하고 정기적으로 아스피린을 사용하기는 곤란하다.

2006년 미국심장협회 가이드라인에서는 심혈관질환 사망 발생의 10년 위험이 10~10% 사이인 중증도 위험군 환자에서도 저용량 아스피린을 투여하도록 권고하고 있다. 그렇지만, 2007년 발표된 유럽심장협회의 가이드라인은 혈압조절이 잘 될 경우, 심혈관사망의 10년 위험이 10% 이상인 경우 아스피린 복용을 고려하도록 권고하고 있다.

2009년 U.S. Preventive Services Task Force는 일차예방을 위한 아스피린의 사용과 관련한 권고안을 개정했다. 위장관출혈의 잠재적인 부작용보다 심혈관 및 뇌혈관질환 예방에 대한 이득이 더 크다고 생각되는 경우 45~79세의 남성과 55~79세의 여성에게 아스피린 사용을 권장하고 있으나, 그보다 나이가 적은 성인에게는 권장하지 않았다. 또 고령의 환자에서는 유의적인 태도를 보이고 있다.

최근 'JPAD (Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes)'와 POPADAD (Prevention of Progression of Arterial Disease and Diabetess)' 연구에 의하면, 당뇨병 환자에서 아스피린의 심혈관질환 예방효과가 저명하지 않은 것으로 나타나 추후 당뇨병 환자에서 일차예방 목적으로 아스피린의 사용 여부는 좀 더 자료가 모일 때까 지 기다려봐야 할 것으로 생각된다."
A double-edged sword
위장관 손상 기전

성균관대학교 내과 이준행
PG dependent pathway

Cyclooxygenase pathway

- COX-1 (physiologic)
  - Prostaglandins, thromboxane (stomach, intestine, kidney, platelets)
    - Mucosal protection, renal blood flow and haemostasis

Lipoxygenase pathway

- COX-2 (inducible)
  - Prostaglandins (inflammatory sites, macrophages, synovocytes)
    - Inflammation pain and fever
- Leukotrienes (inflammatory sites)
  - Inflammation
PG independent pathway

• **Ion trapping hypothesis**
  
  – NSAIDs remains unionized and diffusible in acid gastric juice, but on entering mucosal cell, it ionized and becomes indiffusible.
  
  – ‘Ion trapping’ in gastric mucosal cell enhances gastric toxicity
Small bowel injury: enteropathy

**NSAIDs**

Uncoupling of mitochondrial oxidative phosphorylation

Increased intestinal permeability

Invasion of luminal aggressive factors such as bile, hydro-/proteolytic enzyme, bacteria

Inflammation

Ulcer, perforation, strictures, bleeding

상부위장관 손상

성균관대학교 내과 이준행
Dyspepsia is so common

- *Dyspepsia: at least 10% - 20*
- Within a six-month period of treatment, 5% - 15% of patients with rheumatoid arthritis discontinue NSAID therapy due to dyspepsia.
급성 복통 - 아스피린 2일 복용 후
 만성 복통 - 강직성 척추염

Ankylosing spondylitis on NSAID
Endoscopically determined ulcer $\geq 3$ mm
- in patients with osteoarthritis
There is no plateau.

MUCOSA Trial\(^1\)

VIGOR Trial\(^2\)

NSAIDs (n=4439)

Naproxen (n=4029)

2. FDA Arthritis Advisory Committee; February 8, 2001; Gaithersburg.
출혈 (F/72)
- on aspirin + clopidogrel
Aspirin-induced bleeding (F/72 with melena)
PCI 후 aspirin, ticagrelor → 3주 후 출혈 → PPI add. 다시 약을 쓸래 2주 후 재출혈

PCI 3주 후 첫 출혈
2주 후 재출혈
Predictive and Protective Factors Associated With Upper Gastrointestinal Bleeding After Percutaneous Coronary Intervention: A Case-Control Study


1Department of Gastroenterology and Hepatology and 2Department of Cardiology, Royal Perth Hospital, Perth, Western Australia; 3School of Population Health, Faculty of Medicine and Dentistry, University of Western Australia, Perth, Western Australia; 4Department of Cardiology, Royal Perth Hospital, Perth, Western Australia; 5Department of Gastroenterology and Hepatology, Royal Perth Hospital, and School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia

BACKGROUND: Hemorrhagic complications of acute coronary syndromes and percutaneous coronary intervention (PCI) are associated with increased mortality. Upper gastrointestinal (UGI) bleeding after PCI is a potential target for preventative strategies.

RESULTS

A total of 5,673 patients had PCI between 1998 and 2005, of whom 70 (1.2% [95% CI 0.1–1.6%]) developed a UGI hemorrhage within 30 days. Sixty-five of these patients underwent endoscopy at the same institution, while two died prior to endoscopy. Three patients who were readmitted to peripheral hospitals for endoscopy with a diagnosis of UGI bleeding were alive at 6 months but were not included in the case-control analysis as we were unable to obtain sufficient clinical detail from their subsequent admission. Data on the 67 cases and 201 matched controls were otherwise complete.
Peptic ulcer with complication occurs in more than 1% for the first year - CLASS study (Celecoxib Long-term Arthritis Safety Study)

Silverstein FE. JAMA 2000;284:1247-55
Most patients are asymptomatic.

* Bleeding, perforation, and gastric outlet obstruction

- **Without Symptoms**
  - N = 141
  - Without Symptoms: 81%
  - With Symptoms: 19%

- **With Symptoms**
  - N = 1,921
  - Without Symptoms: 58%
  - With Symptoms: 42%


NSAID 십이지장 궤양 ⇒ 협착 ⇒ 수술
Multiple joint pain으로 NSAIDs를 반년 이상 복용하다가 갑작스런 복통 (M/58)

수술장: Stomach LB AW 0.5cm sized ulcer perforation 있으며 그 주변으로 inflammatory change로 stomach wall fibrosis, edema 심함.
Risk factors for ulcer complications induced by NSAIDs

- Prior complicated ulcer
- Use of multiple NSAIDs (including aspirin)
- High-dose of NSAIDs
- Anticoagulant therapy
- Prior uncomplicated ulcer
- Age > 70 years
- H. pylori infection
- Glucocorticoid therapy
There is no safe NSAID.

<table>
<thead>
<tr>
<th>Individual NSAID</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use</td>
<td>Reference</td>
</tr>
<tr>
<td>Celecoxib</td>
<td>1.0 (0.4 to 2.1)</td>
</tr>
<tr>
<td>Aceclofenac</td>
<td>2.6 (1.5 to 4.6)</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>3.1 (2.3 to 4.2)</td>
</tr>
<tr>
<td>Ibuprofen</td>
<td>4.1 (3.1 to 5.3)</td>
</tr>
<tr>
<td>Naproxen</td>
<td>7.3 (4.7 to 11.4)</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>8.6 (2.5 to 29.2)</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>9.0 (3.9 to 20.7)</td>
</tr>
<tr>
<td>Meloxicam</td>
<td>9.8 (4.0 to 23.8)</td>
</tr>
<tr>
<td>Ketorolac</td>
<td>14.4 (5.2 to 39.9)</td>
</tr>
</tbody>
</table>
# Risk of complications in the elderly

<table>
<thead>
<tr>
<th>Age</th>
<th>Case N=1,457</th>
<th>Control N=10,000</th>
<th>RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>25-49</td>
<td>374</td>
<td>5561</td>
<td>1.6</td>
</tr>
<tr>
<td>50-59</td>
<td>250</td>
<td>1740</td>
<td>1.6</td>
</tr>
<tr>
<td>60-69</td>
<td>376</td>
<td>1630</td>
<td>3.1</td>
</tr>
<tr>
<td>70-80</td>
<td>457</td>
<td>1069</td>
<td>5.6</td>
</tr>
</tbody>
</table>

* Aging is one of the most important risk factors for everything in medicine.

Rodriguez LAG. Lancet 1994;343:769
High dose is more dangerous. However, lower dose is not safe.

Table 5  Relative risk and 95% confidence interval of UGIB according to timing, dose and duration of aspirin

<table>
<thead>
<tr>
<th>Aspirin use</th>
<th>Cases (n = 2777)</th>
<th>Controls (n = 5532)</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Adjusted condition RR (95% CI)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-use</td>
<td>1941</td>
<td>4674</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>Current (0-7 days)</td>
<td>746</td>
<td>524</td>
<td>3.5 (3.1 to 4.0)</td>
<td>5.3 (4.5 to 6.3)</td>
</tr>
<tr>
<td>Past (8 days and more)</td>
<td>90</td>
<td>334</td>
<td>0.6 (0.5 to 0.8)</td>
<td>0.7 (0.6 to 1.0)</td>
</tr>
<tr>
<td>Aspirin dose</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-use</td>
<td>1941</td>
<td>4674</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>100 mg</td>
<td>132</td>
<td>185</td>
<td>1.8 (1.4 to 2.2)</td>
<td>2.7 (2.0 to 3.6)</td>
</tr>
<tr>
<td>200 mg</td>
<td>126</td>
<td>122</td>
<td>2.5 (2.0 to 3.3)</td>
<td>3.8 (2.7 to 5.2)</td>
</tr>
<tr>
<td>300 mg</td>
<td>114</td>
<td>74</td>
<td>3.8 (2.8 to 5.1)</td>
<td>6.1 (4.3 to 8.7)</td>
</tr>
<tr>
<td>500 mg</td>
<td>259</td>
<td>112</td>
<td>5.6 (4.4 to 7.0)</td>
<td>7.5 (5.7 to 9.9)</td>
</tr>
<tr>
<td>1 g</td>
<td>76</td>
<td>24</td>
<td>7.6 (4.8 to 12.4)</td>
<td>10.4 (6.1 to 17.8)</td>
</tr>
<tr>
<td>&gt;1 g</td>
<td>39</td>
<td>7</td>
<td>13.3 (5.9 to 29.8)</td>
<td>21.2 (8.7 to 51.9)</td>
</tr>
<tr>
<td>Aspirin duration</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-use</td>
<td>1941</td>
<td>4674</td>
<td>Reference</td>
<td>Reference</td>
</tr>
<tr>
<td>1-30 days</td>
<td>300</td>
<td>88</td>
<td>8.2 (6.4 to 10.4)</td>
<td>10.2 (7.7 to 13.5)</td>
</tr>
<tr>
<td>31-90 days</td>
<td>32</td>
<td>10</td>
<td>7.9 (3.9 to 16.1)</td>
<td>15.8 (6.8 to 36.8)</td>
</tr>
<tr>
<td>91-365 days</td>
<td>103</td>
<td>67</td>
<td>3.8 (2.8 to 5.2)</td>
<td>7.4 (5.0 to 11.1)</td>
</tr>
<tr>
<td>&gt;1 year</td>
<td>311</td>
<td>359</td>
<td>2.1 (1.8 to 2.5)</td>
<td>3.1 (2.5 to 3.8)</td>
</tr>
</tbody>
</table>

*Adjusted for age, sex, calendar semester, ulcer history, nitrates, anticoagulants, antiplatelets, acid-suppressing drugs, NSAID and coxib use.
UGIB, upper gastrointestinal bleeding.
Concomitant use of other medications
- *With tNSAIDs, warfarin is the worst.*

- Relative risk compared with those of nonusers of both types of drugs
  - tNSAID + aspirin: 4.9
  - tNSAID + steroid: 4.3
  - tNSAID + warfarin: **12.5**
H. pylori - an important factor

Naïve NSAID user or long-term user?

- Patients initiating chronic treatment with NSAID should be tested for *H. pylori* infection. Those who test positive should be offered eradication therapy.

- The benefit of testing and treating *H. pylori* in a patient already taking an NSAID remains unclear.
*H. pylori* in patients who are already receiving NSAID

- Eradication of *H. pylori* is not recommended for prevention of ulcers in patients who are already being treated with NSAIDs.
- **PPI therapy** provides a more effective ulcer risk reduction strategy than *H. pylori* eradication in patients on chronic NSAIDs.
There is a cumulative effect.

GI risk factors in Korean OA patients

<table>
<thead>
<tr>
<th>GI risk factors</th>
<th>Percent of cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Need for long-term NSAID use</td>
<td>79</td>
</tr>
<tr>
<td>Age over 65 yr</td>
<td>54</td>
</tr>
<tr>
<td>Comorbid disease (cardiovascular, renal, liver, diabetes, hypertension)</td>
<td>46</td>
</tr>
<tr>
<td>High dose of NSAID use</td>
<td>43</td>
</tr>
<tr>
<td>History of GI symptom</td>
<td>36</td>
</tr>
<tr>
<td>Aspirin use</td>
<td>15</td>
</tr>
<tr>
<td>Heavy smoking habit</td>
<td>14</td>
</tr>
<tr>
<td>Heavy drinking habit</td>
<td>13</td>
</tr>
<tr>
<td>History of steroid use</td>
<td>8</td>
</tr>
<tr>
<td>Currently poor health status</td>
<td>8</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>6</td>
</tr>
<tr>
<td>Previous hospitalization history due to GI events</td>
<td>6</td>
</tr>
<tr>
<td>Selective serotonin reuptake inhibitor (SSRI) use</td>
<td>4</td>
</tr>
<tr>
<td><em>Helicobacter pylori</em> infection</td>
<td>4</td>
</tr>
<tr>
<td>Anticoagulant use</td>
<td>2</td>
</tr>
</tbody>
</table>
NSAIDs 관련 상부위장관 손상 예방
- 위험도에 따른 접근

성균관대학교 내과 이준행
위험도에 따른 접근

GI risk

CV risk

NSAID

H. pylori

Ulcer
Esomeprazole vs famotidine
- Prevention of UGI bleeding in ACS of AMI

The study was terminated, and the patients were prescribed open-label PPI for their safety.
Cumulative rate of ulcer development
- Venous study

Scheiman et al. Am J Gastroenterol 2006;101:701-710
PPI + COX-2 – the best method for upper GI tract complication prevention

Chan. Lancet 2007;369:1621-1626
The Relative Efficacies of Gastroprotective Strategies in Chronic Users of Nonsteroidal Anti-inflammatory Drugs

LAURA E. TARGOWNIK,* S COLLEEN J. METGE,† S STELLA LEUNG,* S and DANIEL G. CHATEAU‡

*Section of Gastroenterology, Division of Internal Medicine, †Department of Pharmacy, and ‡Manitoba Centre for Health Policy, Department of Community Health Sciences, Faculty of Medicine, University of Manitoba, Winnipeg, Manitoba, Canada

• We used the Manitoba Population Health Research Data Repository to perform a population-based matched case-control analysis

Table 4. ORs and P Values for Comparisons Between Gastroprotective Strategies for Upper GI Complications Secondary to Peptic Ulcer Disease

<table>
<thead>
<tr>
<th>comparator</th>
<th>OR (95% CI)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>nsNSAID + low-dose misoprostol (0.61)</td>
<td>0.81 (0.48–1.38)</td>
<td>.20</td>
</tr>
<tr>
<td>nsNSAID + PPI (0.50)</td>
<td>0.74 (0.55–1.00)</td>
<td>.50</td>
</tr>
<tr>
<td>COX-2 inhibitor alone (0.46)</td>
<td>0.46 (0.18–1.21)</td>
<td>.17</td>
</tr>
<tr>
<td>nsNSAID + PPI + low-dose misoprostol (0.29)</td>
<td>0.49 (0.25–0.82)</td>
<td>.0084</td>
</tr>
<tr>
<td>COX-2 inhibitor + PPI (0.23)</td>
<td>0.50 (0.34–0.73)</td>
<td>.001</td>
</tr>
</tbody>
</table>

NOTE. ORs for relative risk reduction versus nsNSAID users alone shown in parentheses.
* Differences are statistically significant.
Utilization of protective strategies by presence of GI risk factors

1 Risk Factor
- Coxib alone: 2.5%
- Protective strategy (PS): 10.8%
- No gastroprotection: 0.1%
- Total: 86.6%

More Risk Factors
- Coxib alone: 4.0%
- Protective strategy (PS): 14.7%
- No gastroprotection: 0.2%
- Total: 81.2%

Legend:
- Yellow: Coxib alone
- Green: Protective strategy (PS)
- Orange: PS + Coxib
- Teal: No gastroprotection

Sturkenboom. Rheumatology 2003;42(S3):22-31
• Dyspepsia: change of the medication, dose reduction, empirical treatment with H$_2$RA or PPI
• *H. pylori* infection: eradication treatment in patients with risk factor(s)
• Active ulcer (NSAID discontinued): H$_2$RA or PPI
• Active ulcer (NSAID continued): PPI
• **Prophylactic therapy**: misoprostol, PPI, COX-2 selective agent
Risk assessment in NSAID user

<table>
<thead>
<tr>
<th>High risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. History of a previously complicated ulcer, especially recent</td>
</tr>
<tr>
<td>2. Multiple (&gt;2) risk factors</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Moderate risk (1–2 risk factors)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Age &gt;65 years</td>
</tr>
<tr>
<td>2. High dose NSAID therapy</td>
</tr>
<tr>
<td>3. A previous history of uncomplicated ulcer</td>
</tr>
<tr>
<td>4. Concurrent use of aspirin (including low dose) corticosteroids or anticoagulants</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. No risk factors</td>
</tr>
</tbody>
</table>
Algorithm for NSAID gastropathy

NSAID

Chronic NSAID user

HP(-/+)

Ulcer (-)

Low risk

Ulcer (+)

High risk

Coxib+PPI

HP eradication (?)

HP eradication (+)

NSAID 중단

PPI

Low risk

High risk

No prevention

Coxib+PPI

HP eradication (+)

Moderate risk

High risk

HP eradication +/- PPI

Naive NSAID user

HP(-/+) ulcer(-)

HP (+)

Low risk

High risk

CV(-/+)

Low risk

High risk

CV(-/+)

No prevention

Coxib+PPI

HP eradication (+/- PPI

자료 제공: 이혁
Moderate risk

- Ulcer history (-)
  - NSAID + PPI or Coxib
  - CV(+) NSAID (Naproxen) + PPI

- Ulcer history (+)
  - Coxib + PPI
  - HP eradication (?)

Moderate risk

- Ulcer history (-)
  - NSAID + PPI or Coxib
  - CV(+) NSAID (Naproxen) + PPI

- Ulcer history (+)
  - Coxib + PPI
CASE 1

• 76YO Male
• No cardiovascular disease
• Starting of ibuprofen d/t RA
• Recent EGD: \textit{HP} positive

♦ Next management?
  – \textit{HP} eradication
  – NSAID +/- PPI
Algorithm for NSAID gastropathy

NSAID

Chronic NSAID user

Ulcer (-)

HP (-/+)

Low risk

No prevention

Coxib+PPI HP eradication (?)

High risk

CV (-/+)

Naive NSAID user

Ulcer (+)

HP (-)

Low risk

No prevention

Coxib+PPI

High risk

CV (-/+)

HP (+)

HP eradication +/- PPI

Moderate risk

High risk

Self-generated object
CASE 2

- 52YO Female
- History of gastric ulcer
- Recent stroke with aspirin
- Long-term use of aceclofenac d/t OA
- Recent EGD: *HP* negative

♠ Next management?
  - NSAID (Naproxen) + PPI
Algorithm for NSAID gastropathy

**NSAID**

**Chronic NSAID user**
- HP(-/+)
  - Ulcer (-)
    - Low risk
    - CV(-/+)
    - No prevention
    - Coxib+PPI
    - HP eradication (?)
  - Ulcer (+)
    - High risk
    - Coxib+PPI
    - HP eradication (?)

**Naive NSAID user**
- ulcer(-)
  - HP(-)
    - Low risk
    - CV(-/+)
    - No prevention
    - Coxib+PPI
    - HP eradication (?)
  - HP (+)
    - High risk
    - HP eradication +/- PPI
    - Moderate risk
    - High risk

자료 제공: 이혁
<table>
<thead>
<tr>
<th>Ulcer history (-)</th>
<th>Ulcer history (+)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NSAID + PPI or Coxib</td>
<td>Coxib + PPI HP eradication (?)</td>
</tr>
<tr>
<td>CV(+) NSAID (Naproxen) + PPI</td>
<td>CV(+) NSAID (Naproxen) + PPI</td>
</tr>
</tbody>
</table>

자료 제공: 이혁
CASE 3

- 48YO Female
- No cardiovascular disease
- Long-term use of coxib d/t OA
- Recent EGD: ulcer scar with *HP* positive

♠ Next management?
  - Coxib + PPI
  - *HP* eradication
Algorithm for NSAID gastropathy

NSAID

Chronic NSAID user

- HP(-/+) → Ulcer (-)
  - Low risk
  - CV(-/+)
  - No prevention
  - Coxib+PPI
  - HP eradication (?)

- HP(-/+) → Ulcer (+)
  - High risk
  - CV(-/+)
  - NSAID 중단
  - PPI

Naive NSAID user

- ulcer(-) → HP (-)
  - Low risk
  - No prevention
  - Coxib+PPI

- ulcer(-) → HP (+)
  - High risk
  - CV(-/+)
  - HP eradication
  - +/- PPI
  - Moderate risk
  - High risk

자료 제공: 이혁
NSAID + PPI or Coxib

Moderate risk

Ulcer history (-)
NSAID + PPI or Coxib

Ulcer history (+)
Coxib + PPI
HP eradication (?)

CV(+)
NSAID (Naproxen) + PPI

자료 제공: 이혁
Celecoxib alone 만으로는 부족할 수 있다.
- 궤양 출혈 병력이 있는 환자에서 celecoxib 사용하고 melena
요약: 위험도에 따른 접근

• NSAIDs 처음 사용자에서 *H. pylori* 감염 여부를 확인하여 제균치료를 한다. 저위험환자에서도 치료할 수 있다.
• NSAIDs 장기 사용자에서는 *Hp* 제균치료보다 PPI 사용이 효과적이다. 그러나 제균치료는 해 볼 수 있다.
• ‘nsNSAID + PPI’ 전략은 celecoxib로 바꾸는 것과 유사하다. 더 강한 예방은 celecoxib + PPI 이다.
• CV 위험인자가 있으면 naproxen을 우선적으로 사용한다.
하부위장관 손상

성균관대학교 내과 이준행
NSAID enteropathy may be subtle

<table>
<thead>
<tr>
<th>Sub-clinical damage</th>
<th>Clinical damage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increased in mucosal permeability</td>
<td>• Anemia</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>• <strong>Bleeding/ Perforation</strong></td>
</tr>
<tr>
<td>Fecal occult blood loss</td>
<td>• <strong>Exacerbation of underlying disease</strong></td>
</tr>
<tr>
<td>Ileal dysfunction</td>
<td>• <strong>Diverticulitis</strong></td>
</tr>
<tr>
<td>Malabsorption</td>
<td>• Strictures</td>
</tr>
<tr>
<td></td>
<td>• Ulcerations</td>
</tr>
<tr>
<td></td>
<td>• Colitis</td>
</tr>
<tr>
<td></td>
<td>• Chronic inflammatory bowel disease</td>
</tr>
<tr>
<td></td>
<td>• Angiodysplastic lesions</td>
</tr>
</tbody>
</table>
Upper GI Complications are decreasing. Lower GI complications are increasing.
Aspirin-related jejunal ulcer bleeding
NSAIDs-induced enteropathy
NSAID-induced colopathy
Spectrum of NSAID-related *large bowel* diseases

- Ulcers: usually, right-sided. bleeding, perforation
- Strictures: diaphragm-like and broad-based
- Colitis:
  - diarrhea with/without bleeding
  - eosinophilic, collagenous, pseudomembranous, nonspecific
  - especially, mefenamic acid and flufenamic acid
- Anorectal inflammation, ulceration, stricture
- NSAIDs may exacerbate preexisting lesions, including diverticulitis, reactivation of inflammatory bowel diseases, and intestinal bleeding from angiodysplastic lesions.
Prevention of lower NSAID enteropathy

- **No therapies** specifically designed or approved for the prevention of NSAID-induced enteropathy

  - Selective NSAID (?)
    - Co-therapy
    - Misoprostol
  - Mucoprotective drugs (Rebamipide)
  - Antimicrobials
  - Probiotics
  - Phosphatidylcholine-associated NSAID
  - Nitric oxide-releasing NSAID
  - Hydrogen sulphide-releasing NSAID
PPI may increase small bowel injury

\[ P = .04 \]

\[ P = .11 \]

\[ P = .003 \]

Subject with small bowel injury (%)

COX-2 SI  COX-2 + PPI

Jejum  Ileum

임상에서 주의해야 할 점

Jun Haeng Lee, M.D. Samsung Medical Center, Seoul
Aspirin-associated ulcer로 PPI 장기복용 권하였으나 PPI 끊고 aspirin 쓰면서 재출혈
Concurrent NSAID, PPI use tapers over long term

BY DENISE NAPOLI
IMNG Medical News

Among chronic nonsteroidal anti-inflammatory drug patients at high risk for gastrointestinal bleeding, only two-thirds continue to be prescribed a proton pump inhibitor after 2 years.

Moreover, patients whose PPI prescriptions were discontinued were significantly more likely to experience a GI adverse event, compared with patients who had continuous NSAID and PPI coprescription, wrote Dr. Isabelle Le Ray and colleagues. The report was published in the May issue of Clinical Gastroenterology and Hepatology.

Dr. Le Ray, of the Centre Hospitalier Universitaire de Dijon, France, and colleagues looked at records from the Longitudinal Patient Database, which collects data from a representative sample of 1,200 general practitioners in France.

Specifically, Dr. Le Ray focused on high-risk patients within the database who received a ten-year probability of still having an active PPI prescription fell to 0.77 (95% confidence interval, 0.75-0.79).

By 2 years, that likelihood fell to 0.68 (95% CI, 0.66-0.70).

The authors then looked at the presence of GI adverse events in this cohort. They found that 379 patients experienced an event, with patients who were not persistently prescribed a PPI at significantly higher risk, compared with patients whose PPI prescriptions never lapsed (odds ratio, 1.45; 95% CI, 1.06-2.09, P = .02).

"Absolute risk reduction associated with a continuous prescription of PPI with NSAIDs in at-risk patients, was 3.2%," wrote the authors.

According to the researchers, factors associated with discontinuing a PPI included change from a given NSAID to a COX-2 inhibitor (multivariate hazard ratio for PPI discontinuation, 2.50; 95% CI, 1.91-3.28), despite the fact that "international guidelines recommend coprescription of a PPI for at-risk patients, even when using a COX-2 selective.

Factors increasing the risk for upper GI complications in NSAID users include older age (greater than 60-75 years); prior upper GI complications or symptomatic ulcers; and concurrent use of aspirin, other antithrombotics, or corticosteroids. If patients cannot be switched to a non-NSAID analgesic, strategies recommended to decrease GI risk include PPI (or misoprostol), cotherapy or substitution of a COX-2 selective NSAID. Patients at very high risk (e.g., recent ulcer bleeding) should receive a COX-2 selective NSAID plus PPI (or misoprostol).

However, multiple observational studies demonstrate that most NSAID users with GI risk factors do not receive protective therapy. Importantly, adherence to a PPI more than 80% of the time is associated with significantly fewer upper GI clinical events than adherence less than 80% and less than 20% of the time.

The study by Le Ray et al. looks at a group of NSAID users in whom a decision to provide a PPI prescription has been made. Co-therapy was stopped in patients who experienced a GI adverse event, but reduced the risk in high-risk patients. This approach may be useful in improving GI safety, despite the challenges of maintaining adherence.

Dr. Laine
NSAID ulcer 환자에게 드리는 말씀

혹시 다음에 다른 이유로 아스피린이나 소염진통제를 드실 일이 있으시면 목 의사를에게 “과거에 소염진통제 먹고 위궤양 생겼던 적이 있다”고 말씀해 주세요. 그러면 소염제와 함께 궤양 약을 처방받게 되실 것입니다. 재발을 막기 위해서 중요하니까 잊지 마세요.
Management of rheumatoid arthritis
- a multidisciplinary approach
집으로 가져가는 메세지

- NSAIDs 처음 사용자에서 *H. pylori* 감염 여부를 확인하여 제균치료를 한다. 저위험환자에서도 치료할 수 있다.

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