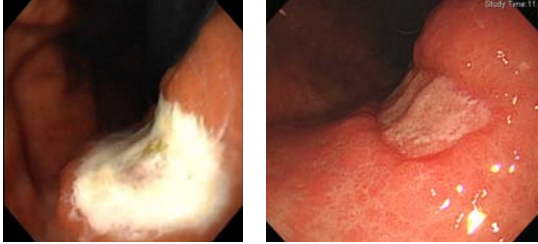


성균관대학교 Unique Origin Unique Future

NSAIDs 부작용

삼성서울병원 소화기내과 이준행

질병이 있는 경우 합병증의 위험을 감수하고 NSAID를 쓸 수 밖에 없다

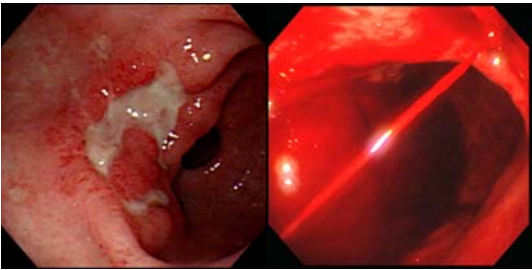


Ankylosing spondylitis on NSAID

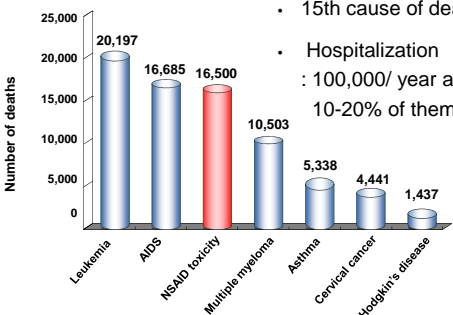
적응증과 무관하게 NSAID, 아스피린을 복용하는 환자 혹은 건강한 성인이 매우 많다



그러나, 적지 않은 위장관 부작용이 있다



US mortality data in 1997




Cause of Death	Number of Deaths
Leukemia	20,197
AIDS	16,685
NSAID toxicity	16,500
Multiple myeloma	10,503
Asthma	5,338
Cervical cancer	4,441
Hodgkin's disease	1,437

- 15th cause of death in USA
- Hospitalization : 100,000/ year and 10-20% of them die

Singh et al. J Rheumatol 1999

A double-edged sword



오늘 강의의 내용: NSAIDs 부작용

- 상부위장관 부작용 빈도와 위험인자
- 상부위장관 부작용 치료와 예방
- 하부위장관 부작용 비중이 증가하고 있다
- 하부위장관 부작용 예방법은 없는가?
- 대장부작용
- 기타

상부위장관 부작용 빈도와 위험인자

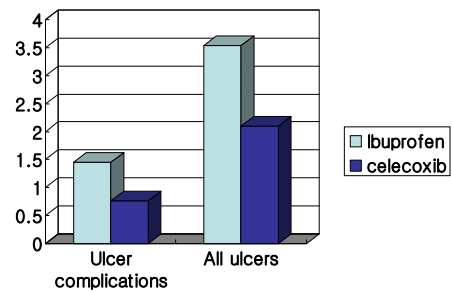
삼성서울병원 소화기내과 이준행

Dyspepsia는 매우 흔하다

- **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.

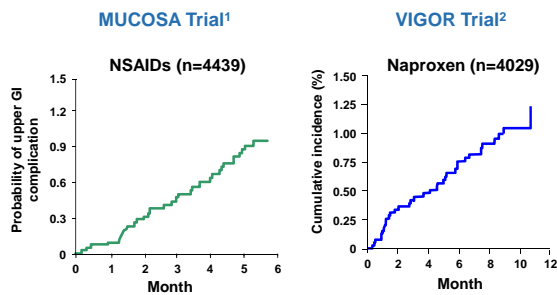
합병증을 동반한 소화성 궤양은 1년에 1% 이상 발생한다

- CLASS study (Celecoxib Long-term Arthritis Safety Study)



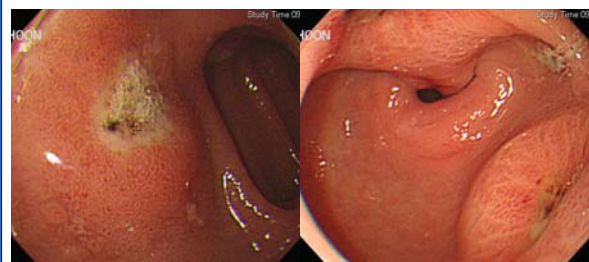
Silverstein FE. JAMA 2000;284:1247-55

합병증은 1주부터 지속적으로 발생한다



1. Silverstein FE et al. Ann Intern Med. 1995;123:241-249.
2. FDA Arthritis Advisory Committee; February 8, 2001; Gaithersburg, Md

NSAID 5일 후 복통. 7일째 검사



정도의 차이는 있으나 모든 약제가 위험하다

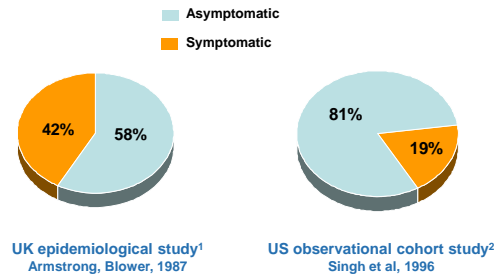
TABLE 2. Relative risk of ulcer bleeding according to type of NSAID^{2,3}

Nonuse	Reference
Celecoxib	1.0 (0.4-2.1)
Diclofenac	3.1 (2.3-4.2)
Ibuprofen	4.1 (3.1-5.3)
Naproxen	7.3 (4.7-11.4)
Lornoxicam	7.7 (2.4-24.4)
Ketoprofen	8.6 (2.5-29.2)
Indomethacin	9.0 (3.9-20.7)
Meloxicam	9.8 (4.0-23.8)
Piroxicam	12.6 (7.8-20.3)
Ketorolac	14.4 (5.2-39.9)

NSAID, nonsteroidal antiinflammatory drug.

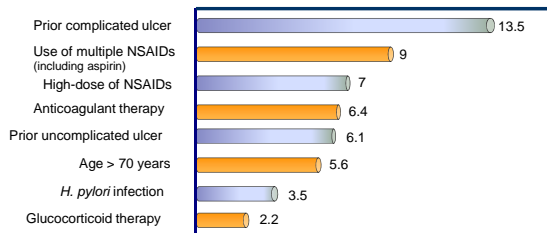
Lanas. Am J Med Sci 2009;338(2):96-106

NSAID 관련 위장관 합병증 환자의 대부분은 합병증 발생 이전에 증상이 없었다



Armstrong. Gut 1987;28:527-532; Singh. Arch Intern Med 1996;156:1530-1536.

NSAID 관련 궤양발생의 위험인자



Gabriel. Ann Intern Med 1991; Garcia Rodriguez. Lancet 1994; Silverstein. Ann Intern Med 1995

고령자에서 합병증의 위험성이 높다

Age	Case N=1,457	Control N=10,000	RR
25-49	374	5561	
50-59	250	1740	1.6
60-69	376	1630	3.1
70-80	457	1069	5.6

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

Rodriguez LAG. Lancet 1994;343:769

물론 고용량이 저용량보다 위험하지만 저용량에서도 위장관 합병증은 발생한다

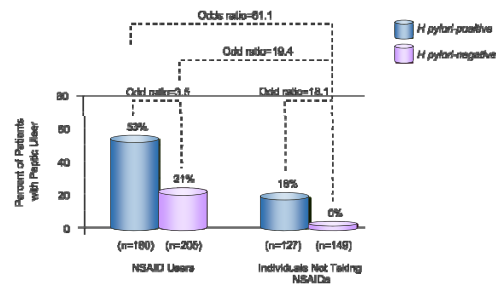
Table 5 Relative risk and 95% confidence interval of UGIB according to timing, dose and duration of aspirin

	Cases (n=2777)	Controls (n=5532)	Age-adjusted RR (95% CI)	Adjusted condition RR (95% CI)*
Aspirin use				
Non-use	1941	4674	Reference	Reference
Current (0-7 days)	746	524	3.5 (3.1 to 4.0)	5.3 (4.5 to 6.3)
Past (8 days and more)	90	334	0.6 (0.5 to 0.8)	0.7 (0.6 to 1.0)
Aspirin dose				
Non-use	1941	4674	Reference	Reference
100 mg	132	185	1.8 (1.4 to 2.2)	2.7 (2.0 to 3.6)
200 mg	196	122	2.5 (2.0 to 3.3)	3.8 (2.7 to 5.2)
300 mg	114	74	3.8 (2.8 to 5.1)	6.1 (4.3 to 8.7)
500 mg	299	112	5.8 (4.4 to 7.8)	7.5 (5.7 to 9.9)
1 g	76	24	7.6 (4.8 to 12.4)	10.4 (6.1 to 17.8)
>1 g	39	7	13.3 (5.9 to 29.8)	21.2 (8.7 to 51.9)
Aspirin duration				
Non-use	1941	4674	Reference	Reference
1-30 days	300	88	8.2 (6.4 to 10.4)	10.2 (7.7 to 13.5)
31-90 days	32	10	7.9 (3.9 to 16.1)	15.8 (6.8 to 36.8)
91-365 days	103	67	3.8 (2.8 to 5.2)	7.4 (5.0 to 11.1)
>1 year	311	399	2.1 (1.8 to 2.5)	3.1 (2.5 to 3.8)

*Adjusted for age, sex, calendar semester, ulcer history, nitrates, anticoagulants, antiplatelets, acid-suppressing drugs, NSAID and coxibs use
UGIB, upper gastrointestinal bleeding.

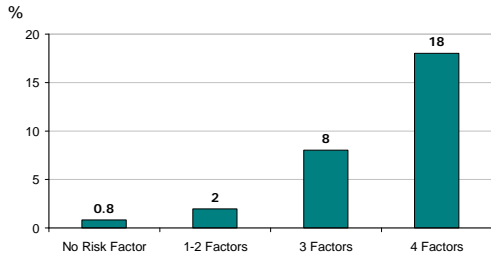
Lanas. Gut 2006;55:1731-1738

Hp (+)에서 NSAID 관련 궤양이 많다



Huang. Lancet 2002;359:14-22

위험인자가 다수면 궤양합병증도 많다



Silverstein FE. Ann Intern Med 1995;123:241-9

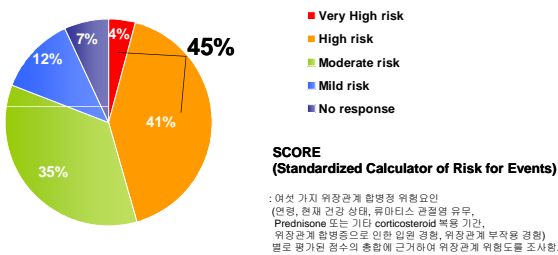
GI risk factors in Korean population taking NSAIDs
2008 GI risk assessment study



Base: 각 위험 요인 별로 위험군에 속한 cases, Unit: % *기존 문헌 review에 근거하여 정의된 위장관계 질환 위험 요인들
Data on file (GI risk assessment study, presented at 2008 fall congress of Korean Orthopaedic Association on Oct 16, 2008)

조사된 NSAIDs 복용 중인 20세 이상 환자 2명중 1명은 위장관계 합병증의 고위험군입니다.

SCORE* 계산식에 따른 위장관계 합병증의 위험도



SCORE (Standardized Calculator of Risk for Events)
: 여섯 가지 위장관계 합병증 위험요인 (연령, 현재 건강 상태, 류마티스 관절염 유무, Prednisone 또는 기타 corticosteroid 복용 기간, 위장관계 합병증으로 인한 입원 경험, 위장관계 부작용 경험) 별로 평가된 점수의 총합에 근거하여 위장관계 위험도를 조사함.

대상: 병원을 방문한, 현재 NSAIDs를 복용 중인 20세 이상의 성인 환자 (N=3,140)
Data on file (GI risk assessment study, presented at 2008 fall congress of Korean Orthopaedic Association on Oct 16, 2008)

상부위장관 부작용
치료와 예방

삼성서울병원 소화기내과 이준환

The Relative Efficacies of Gastroprotective Strategies in Chronic Users of Nonsteroidal Anti-inflammatory Drugs

LAURA E. TARGOWNIK,^{1,2} COLLEEN J. METGE,^{1,2} STELLA LEUNG,^{1,2} and DANIEL G. CHATEAU³
¹Section of Gastroenterology, Division of Internal Medicine, ²Department of Pharmacy, and ³Manitoba Centre for Health Policy, Department of Community 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

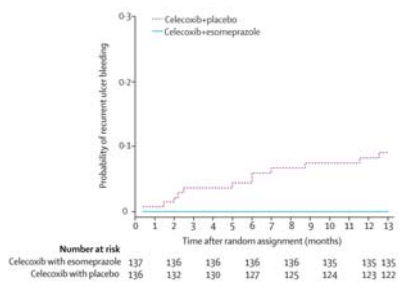
Table 4. ORs and P Values for Comparisons Between Gastroprotective Strategies for Upper GI Complications Secondary to Peptic Ulcer Disease

Comparison	OR (95% CI)	P Value
nsNSAID + low-dose misoprostol (0.61)	0.81 (0.48-1.38)	P > .20
nsNSAID + PPI (0.50)	0.74 (0.55-1.00)	P = .050
COX-2 inhibitor alone (0.46)	0.91 (0.55-1.50)	P > .20
nsNSAID + PPI + low-dose misoprostol (0.29)	0.48 (0.18-1.21)	P = .117
COX-2 inhibitor + PPI (0.23)	0.58 (0.21-1.60)	P > .20
nsNSAID + low-dose misoprostol	0.37 (0.23-0.57)	P < .001*
nsNSAID + PPI	0.49 (0.29-0.82)	P = .0084*
COX-2 inhibitor alone	0.63 (0.25-1.60)	P > .20
nsNSAID + PPI + COX-2 inhibitor + PPI	0.50 (0.34-0.73)	P < .001*
low-dose misoprostol	0.79 (0.29-2.09)	P > .20

NOTE. ORs for relative risk reduction versus nsNSAID users alone shown in parentheses.
*Differences are statistically significant.

Targownik. Gastroenterology 2008;134:937-944

COX-2를 쓰면서 PPI를 더하면
부작용이 더욱 감소한다



Chan. Lancet 2007;369:1621-1626

Risk groups and recommendations

	Low GI risk	High GI risk	Very high GI risk
Not on aspirin	nsNSAID	nsNSAID + PPI/misoprostol	Coxib + PPI/misoprostol
On aspirin	Naproxen	Naproxen + PPI/misoprostol	Avoid NSAIDs or coxibs if possible

Graham. Gastroenterology 2008;134:1240-1246

비스테로이드소염제 관련 소화성궤양의 예방과 치료 가이드라인

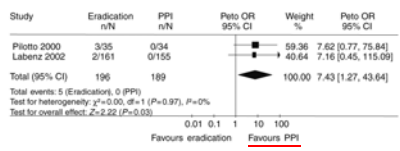
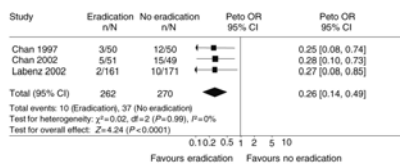
성균관대학교 의과대학 내과, 연세대학교 의과대학 내과학교실, 경북대학교 의과대학 내과학교실, 중앙대학교 의과대학 내과학교실, 고려대학교 의과대학 내과학교실

이준행 · 이용찬* · 전성우¹ · 김정욱¹ · 이상우¹ · 대한 *Helicobacter* 및 상부위장관 연구학회 · 대한소화기학회

- Dyspepsia: change of the medication, dose reduction, empirical treatment with H₂RA or PPI
- *H. pylori* infection: eradication treatment in patients with risk factor(s)
- Active ulcer (NSAID discontinued): H₂RA or PPI
- Active ulcer (NSAID continued): PPI
- Prophylactic therapy: misoprostol, PPI, COX-2 selective agent

Lee JH. Korean J Gastroenterol 2009;54:309-317

제균치료도 좋지만 PPI가 더 좋다



Vergara. Aliment Pharmacol Ther 2005;21:1411-1418

성균관대학교

Unique Origin Unique Future

하부위장관 부작용 비중이 증가하고 있다

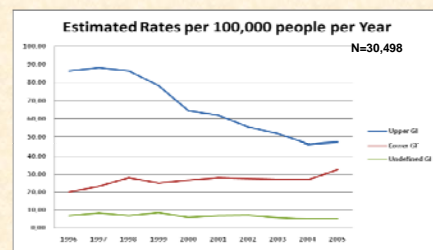
삼성서울병원 소화기내과 이준행

NSAID enteropathy

Sub-clinical damage Clinical damage

- | | |
|--|--|
| <ul style="list-style-type: none"> • Increased in mucosal permeability • Mucosal inflammation • Fecal occult blood loss • Ileal dysfunction • Malabsorption | <ul style="list-style-type: none"> • Anemia • Bleeding/ Perforation • Exacerbation of underlying disease • Diverticulitis • Strictures • Ulcerations • Colitis • Chronic inflammatory bowel disease • Angiodysplastic lesions |
|--|--|

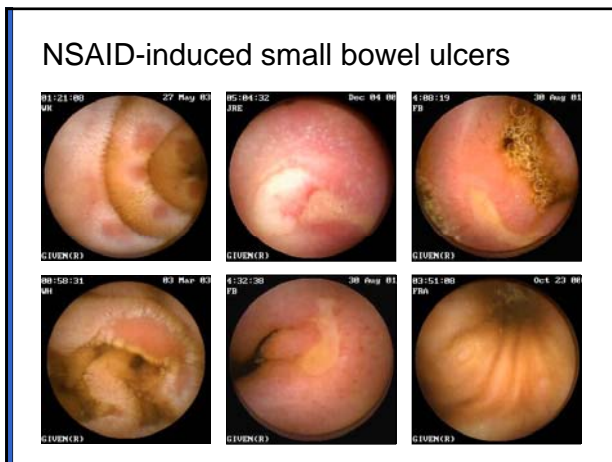
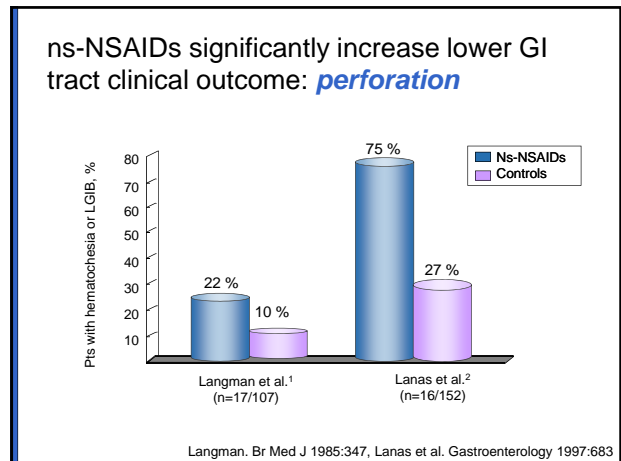
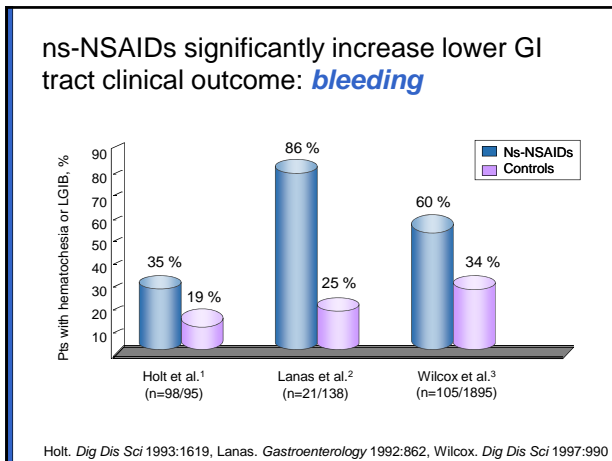
하부위장관 부작용 비중이 증가되었다



Over the last 10 years, there has been a decreasing trend in the rates of hospitalisations due to upper GI complications in contrast with an increasing trend of lower GI complications.

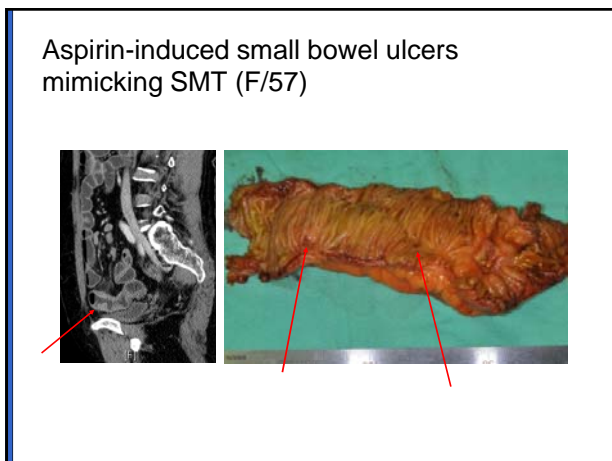
The clinical impact and severity of hospitalisations due to lower GI events were greater than those of upper GI events.

Lanas. Am J Med Sci 2009;338:96-106



Aspirin-induced small bowel ulcers mimicking SMT (F/57)

- 6년 전부터 1년에 2번 정도 혈변 간헐적으로 발생
- 당시 고통약 약에 아스피린 포함되어 있었음
- 최근 다량의 hematochezia 있어서 근처 병원에서 검사. 캡슐내시경에서 r/o small bowel SMT로 큰병원 권유받고 전원



성균관대학교 Unique Origin Unique Future

하부위장관 부작용 예방법은 없는가?

삼성서울병원 소화기내과 이준형

COX-2 selective agent는 permeability에 미치는 영향이 적다

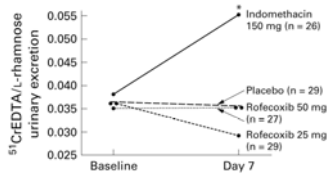
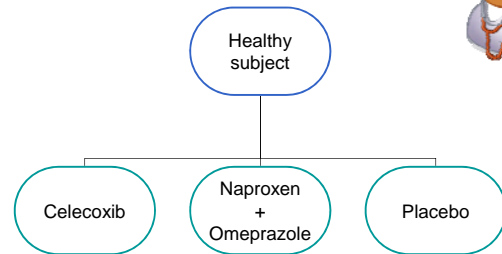


Figure 1 Five hour geometric mean urinary excretion ratios for ⁵¹CrEDTA/L-rhamnose at baseline and on day 7 for subjects who received placebo, rofecoxib 25 mg, rofecoxib 50 mg, and indomethacin 150 mg (per protocol analysis). Indomethacin 150 mg significantly increased the ⁵¹CrEDTA/L-rhamnose ratio compared with baseline values, whereas placebo, rofecoxib 25 mg, and rofecoxib 50 mg did not. *p<0.05 versus baseline values

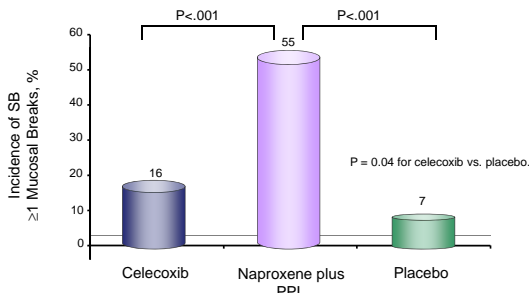
Sighorsson. Gut 2000;47:527-532

COX-2 selective agent는 캡슐내시경으로 관찰한 mucosal break가 적다



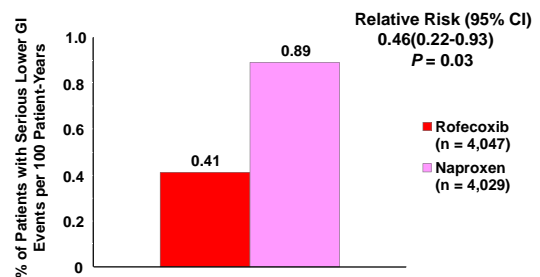
Goldstein. Clin Gastroenterol Hepatol 2005;3:133-41

COX-2 selective agent는 캡슐내시경으로 관찰한 mucosal break가 적다



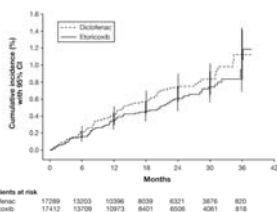
Goldstein. Clin Gastroenterol Hepatol 2005;3:133-41

COX-2 selective agent는 기존 연구의 이차분석에서 하부위장관 부작용이 적다



Laine. Gastroenterology 2003;124:288-292

But, there are some controversies



- In MEDAL study, there were no benefits of etoricoxib over diclofenac when looking at the incidence of lower GI complications.

Laine. Gastroenterology 2008;135:1517-1525
Lanas. Am J Med Sci 2009;338:96-106

대장 부작용 및 기타

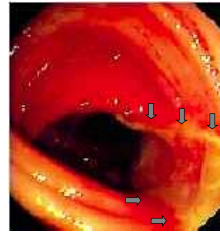
삼성서울병원 소화기내과 이준형

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.

Lanas. Am J Med Sci 2009;338:96-106

Colon ulcer associated with NSAID



54-year-old woman presented with severe iron deficiency anemia, cramping abdominal pain and watery diarrhea. During endoscopy, long, linear ulcers were found in the transverse colon near the right colonic flexure. Histologic examination of the biopsy specimens taken from this area was suggestive of ischemic type lesions as seen with chronic NSAID use.

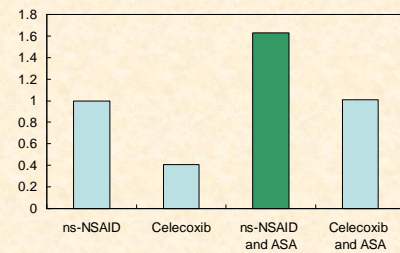
Celecoxib may be safely used in the setting of inflammatory bowel disease

- A total of 222 patients with *ulcerative colitis in remission* were randomized to receive oral celecoxib 200 mg or placebo twice daily for 14 days.
- Results: Three percent of patients in the celecoxib group experienced disease exacerbation through day 14, as compared with 4% in the placebo group (P = .719).
- Conclusion: *Therapy with celecoxib for up to 14 days* did not have a greater relapse rate than placebo in patients with ulcerative colitis in remission.

Sandborn. Clin Gastroenterol Hepatol 2006;4:203-11

Hospitalization for gastrointestinal bleeding associated with non-steroidal anti-inflammatory drugs among elderly patients using low-dose aspirin: a retrospective cohort study

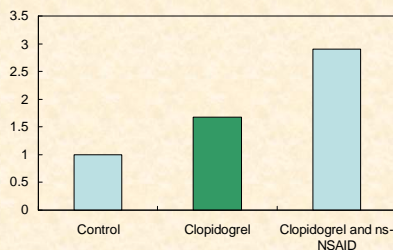
E. Rahme¹, M. Bardou², K. Dasgupta¹, Y. Toubouti¹, J. Ghosn¹ and A. N. Barkun^{1,3}



Rahme. Rheumatology 2007;46:265-272

Clopidogrel is safe?

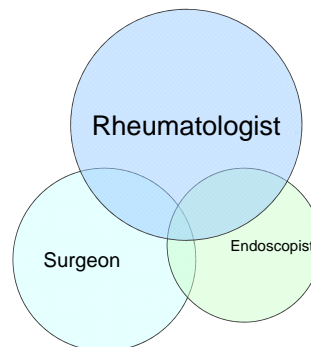
- Risk of gastrointestinal bleeding



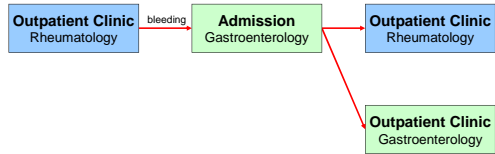
Jelaney. CMAJ 2007;177:347-51

Management of rheumatoid arthritis

- a multidisciplinary approach



Some issues regarding the management of the patients with bleeding complication



- Issue 1: Is the consultation to the Rheumatology mandatory during the admission? Do the rheumatologists want it? How can we give the related information to the doctors in other department?
- Issue 2: How long the patient should be followed in the Gastroenterology department? Life-long or just a few weeks...
- Issue 3: Who will give the preventive medicine to the patient?

결론

- NSAID/aspirin 사용자에서 적절한 예방책을 통하여 상부위장관 합병증을 매우 감소시킬 수 있다.
- 하부위장관 합병증의 비율이 증가하고 있으며 예방법에 대한 연구가 활발히 진행되고 있다.
- ns-NSAID와 aspirin의 병용은 금지되어 있다.
- Clopidogrel과 같은 항혈소판제도 위장관 합병증으로부터 자유롭지 못하다.

