[연수강좌]

일차진료에서 NSAIDS 사용의 최신 지견

유 빈

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근골격계 질환에서 NSAID 의 이용

- reduce pain
- decrease gelling phenomenon
- improve function
- reduce inflammation

- Background therapy in RA
- No evidence to slow the progression of RA

NSAID 의 사용

- 천 칠백만명 이상이 매일 사용 중(미국)
- 인구 노령화에 따른 근골격계 질환의 유병율 증가
- 그에 따른 NSAID 의 사용증가가 예상됨(CDC)

Aspirin was registered and marketed in March 1899

비스테로이드 항염제(NSAID)

1899년; 아스피린(acetylated salicylic acid)

1949년; phenylbutazone

1965년; indomethacine

Cox-2 specific(selective) inhibitors

celecoxib(12/98), rofecoxib(5/99)

현재 40 여종 이상

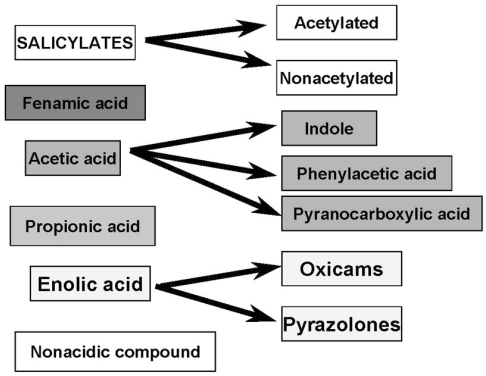
- NSAID의 분류
- NSAID의 기전
- NSAID의 부작용
- NSAID의 처방 시 유의점

NSAID의 분류

화학적구조; **8** 가지 혹은 그 이상

반감기; **long acting (qd, bid)**
short acting (tid, qid)

NSAID 의 구조적 분류



화학적구조 분류의 임상적 의미

1. 부작용의 공통성

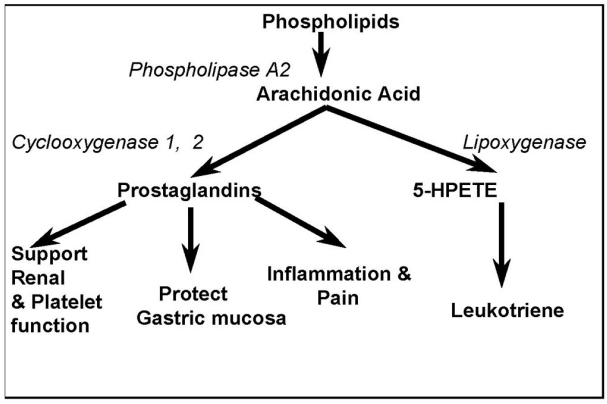
2. 한 부류의 효과가 없어 대체 처방 시**(controversial)**

NSAID 의 작용기전

1) Cyclooxygenase 억제

2) Nonprostaglandin-mediated

Cyclooxygenase/prostaglandin pathway



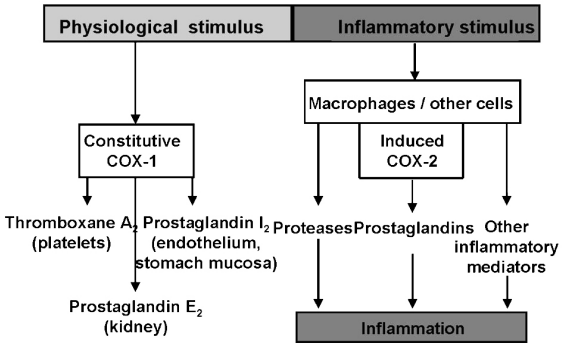
Discovery of Two Different isoforms of COX

- **COX-1 is a constitutive protein**
- **COX-2 is an inducible protein**
  - **COX-2 is not normally present in cells, but appears after exposure of the cell to inflammatory stimuli**

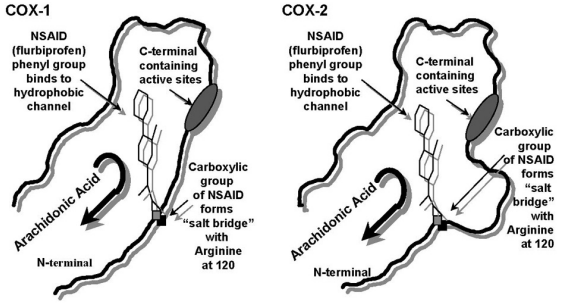
COX2 selective NSAIDs

Equal anti-inflammatory **effects**
Less GI toxicity

Actions of COX-1 and COX-2

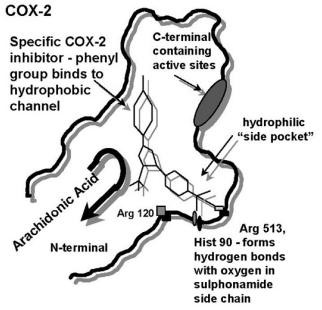


Classical NSAID: Non-specific Binding to COX-1 and COX-2



Kurumbail et al, Nature 1996; 384: 644-648

Specific COX-2 Inhibitor Binding to COX-2



Kurumbail et al, Nature 1996; 384: 644-648

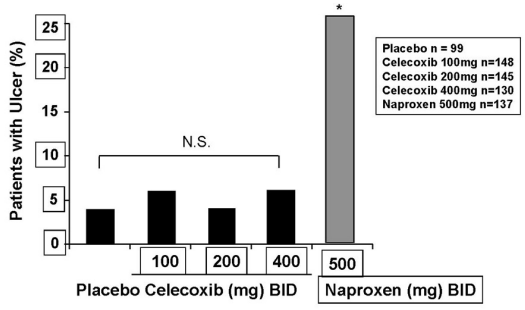
Classification of NSAID

Cox-1 preferential	Equipotent	Cox-2 preferential	Cox-2 specific
aspirin	nabumeton	meloxicam	celecoxib
ibuprofen	etodolac	nimesulide	rofecoxib
Ketoprofen	tenoxicam		
naproxen	fenclofenac		

Clinical Effects of Cox-2 Specific Inhibitors

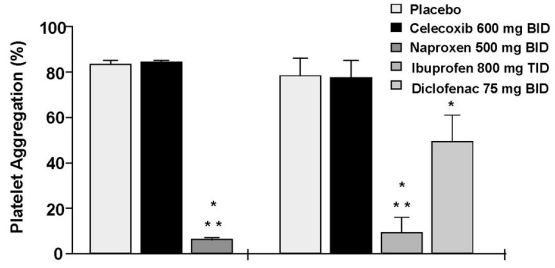
Similar to non-specific Cox inhibitors	Different from non-specific Cox-inhibitors
Anti-inflammatory	No anti-platelet effects !
Analgesic	Reduced erosion and ulceration !
Anti-pyretic	
Sodium excretion, blood pressure	

Incidence of Gastroduodenal Ulcers



Simon LS, JAMA 1999;24:1921-1927

No Effect on Platelet Aggregation



Journal of clinical pharmacology 2000; 40:124-32

Clinical Use of Specific Cox-2 Inhibitors

- **High risk for adverse GI events**
- **Perioperative**

Asthma
Renal insufficiency

NSAID 의 효과

Anti-inflammatory	↓ Prostaglandin
Analgesia	↓ Prostaglandin
Antipyresis	↓ CNS Prostaglandin
Antiplatelet;	↓ Thromboxane A2

Nonprostaglandin-mediated Mechanism

- uncouple oxidative phosphorylation
- inhibit lysosomal enzyme release
- inhibit complement activation
- suppress gene expression of COX mRNA (salicylate)

Clinical efficacy & toxicity of NSAID

Similar in population

Variable in individual

NSAID의 부작용

1) 위장관 부작용(esp. dyspepsia)

2) 신장계 부작용(often overlooked)

3) Skin reactions

4) CNS reactions

5) 기타

Committee on Safety of Medicines in the U.K

NSAID의 드문 부작용

- **Febrile reaction**- ibuprofen
- **Drug-induced lupus**- Phenylbutazone, ibuprofen
- **Vasculitis**- indomethacin, naproxen
- **Pericarditis, myocarditis**- phenylbutazone
- **Aplastic anemia**- most NSAIDs, but most significantly phenylbutazone

NSAID의 드문 부작용

- Thrombocytopenia- most NSAIDs
- Neutropenia- most NSAIDs
- Stomatitis- most NSAIDs
- Cutaneous effects(photosensitivity erythema multiform, urticaria, toxic epidermal necrolysis)- most NSAIDs, esp. Piroxicam

G-I toxicity of NSAIDs

- Dyspepsia, indigestion and vomiting
- Reflux
- Erosions
- Ulcers
- Hemorrhage and perforation
- Diarrhea

Peptic ulcer 환자 50%는 무증상 !

Risk factors for NSAID G-I toxicity

- **Old age**
- **History of peptic ulcer disease**
- **Higher dosage of NSAIDs**
- **History of abdominal pain of unclear etiology**
- **Concomitant corticosteroid use**

NSAID gastrotoxicity 예방대책

•Lowest possible dose of NSAID or use non-NSAID analgesic or nonacetylated salicylate

•Identify the high risk patient

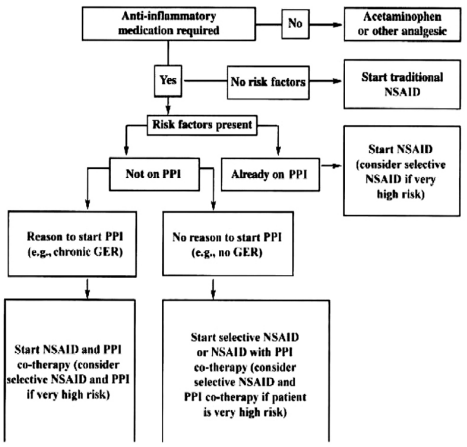
• Cox -2 specific inhibitor 사용----------> intolerable

⇩

misoprostol

⇩

H-2 blockers or omeprazol



H. pylori and NSAID G-I toxicity

No firm conclusion on the role of *H. pylori infection* in patients with NSAID-associated peptic ulcers

Aggravation of dyspeptic symptoms in NSAID users

H. pylori and NSAID G-I toxicity

1. Eradicate all peptic ulcer with/without NSAID

2. Omeprazole prophylaxis in NSAID user with ulcer associated with *H. pylori*

3. Eradication if *H.pylori* status is already known

(exacerbation of H. pylori-associated ulcer by NSAID ; Gut 1993) *But NO screening!*

Hepatotoxicity of NSAIDs

- Mild GOT/GPT elevation
- Severe hepatic failure 는 매우 드물다.
- Fatal hepatotoxicity in children (indomethacine)
- Cholestasis
- 대개 6개월 이내 나타남

Nephrotoxicity of NSAIDs

renal insufficiency
hypovolemic states

- acute renal failure < 1% / year
- sodium retention; esp in CHF
- hyperkalemia
- interstitial nephritis

Effect on Blood pressure of NSAID

평균 **5mmHg** 의 이완기 혈압상승

↓

Stroke risk 67%
CAD complication 15%

Risk for a hypersensitivity reaction to NSAIDs

nasal polyps
asthma
chronic urticaria

↓

acute bronchospasm &
shortness of breath

NSAID 선택은

Essentially Trial and Error process!

NSAID 선택에서 고려사항

환자의 경험	경험한 효과나 부작용
부작용	**NSAID** 특이 부작용
투여간격	가장 통증이 적은 간격
비용	값과 효능은 무관

환자의 경험
부작용
투여간격
비용
→ **NSAID** 선택

NSAID 선택 후 처방요령

1. 선택 후 **2**주간 효과관찰
2. 효과 없거나 부작용 시 교체
3. 부작용 위험군은 예방대책
4. 장기 투여시 부작용 감시
5. 가능한 한 중단이나 감량 고려

NSAID in Osteoarthritis

1. **Acetaminophen** as initial choice of oral Tx
2. **NSAID;** ibuprofen or salsalate

   try to avoid
   piroxicam, ketoprofen, indomethacin, meclofenamate

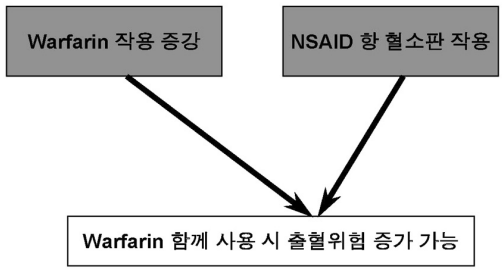
수술 전 NSAID 의 처방

COX-2 specific inhibitors

Aspirin: 수술 최소 **1**주전 중단

다른 **NSAID:** 반감기의 **4- 5**배 이전에 중단

NSAID의 약물 상호작용



2가지 이상 NSAID 의 병합 처방

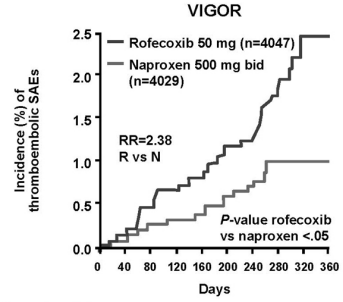
1. 부작용만 증강 시킴

2. 저용량 **Aspirin**과는 가능

맺음말

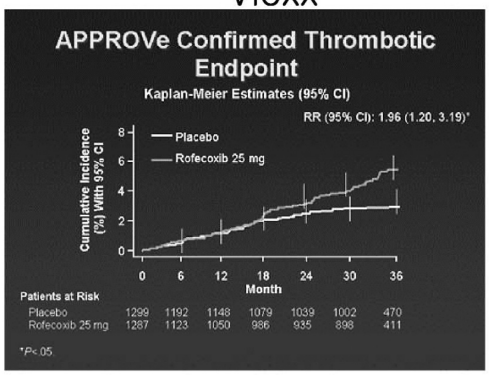
1. 환자 개인을 위해 가장 적절한 **NSAID** 정할 수 있다.
2. 부작용 감소를 위한 주의 필요

Serious Thromboembolic Cardiovascular Adverse Events in Vioxx Users from VIGOR study



SAEs=serious adverse effects.
Mukherjee D et al. *JAMA*. 2001;286:954-959.

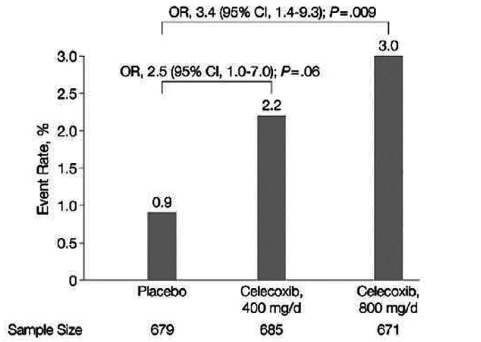
Adenoma Polyp Prevention on Vioxx



September 30, 2004

Rofecoxib was voluntarily withdrawn from the market due to increased cardiovascular risk versus placebo in the APPROVe trial, an adenomatous polyp prevention study

Event Rates of Cardiovascular Death, Myocardial Infarction, and Stroke in the Adenoma Prevention With Celecoxib (APC) Trial



Topol, E. J. JAMA 2005;293:366-368.

December 17, 2004

In the Celecoxib Adenomatous Polyp Cancer (APC) trial, a statistically significant increase in cardiovascular events was seen in patients taking 400 and 800 mg a day of celecoxib for an average of 33 months over patients taking placebo

- New
- Inconsistent
- Unexpected information

Recent 3 trials of celecoxib

Long-term trial	Objectives and Methods	Results (CV event)			
APC Trial (Adenoma Prevention with Celebrex)	• To determine the efficacy and safety of celecoxib versus placebo in preventing the occurrence of newly detected colorectal adenomas in subjects at increased risk for colorectal carcinoma. • Placebo (n=679), celecoxib 200 mg BID (n=685), or celecoxib 400 mg BID (n=671) • Average duration of treatment : 33 months	Placebo	1	7 cases	1.0%
		Celebrex 400 mg	2.3	16 cases	2.3%
		Celebrex 800 mg	3.4	23 cases	3.4%
PreSAP Trial (Prevention of Spontaneous Adenomatous Polyp)	•Identical design to APC trial; except in the comparator groups, celecoxib 400mg QD (n=933)compared to placebo (n=628)	• No significant difference between placebo and Celebrex (Placebo: 1.8%, Celebrex 1.7%) • Relative risk of Celebrex compared to placebo: 1.0.			
ADAPT (Alzheimer's Disease Anti-inflammatory Prevention Trial)	• To test the efficacy of long-term use of a non specific NSAID (naproxen 220mg bid) or specific COX-2 inhibitor (celecoxib 200mg bid) for the prevention of Alzheimer's Disease (AD).	• Celebrex 400mg: No significant difference with placebo Naproxen 440mg: 50% increased risk than placebo			

FDA Regulatory actions – April. 7

- Label change
  - **Boxed warnings of potential CV & GI risk for all COX-2 pain relievers and all NSAIDs**
  - **Revise labeling to include more information on the CV & GI risks as well as a warning about potential skin reactions for all OTC NSAIDs**