



연수강좌 | 소강당

# 통증 치료에서 약물 골라 쓰기

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## 증 례 66세 여성, 퇴행성 슬관절염

- 과거력
  - 58세 때, 심근경색
- 현병력
  - 복용약  
: ramipril, bisoprolol, dichlozide, & aspirin
  - 증상  
: 간헐적인 속 쓰림

## 통증의 정의

## 통증의 분류

- Acute pain
- Sub-acute pain
- Chronic pain
  - for 6 months or more
  - physical sensation and negative psychologic impact on QOL

## Pain conditions encountered by family physicians

Acute pain conditions	Chronic pain conditions
Musculoskeletal injury (eg, Sprain)	Musculoskeletal injury (eg, LBP)
Headaches (eg, TTH & Migraine)	Osteoarthritis (eg, Knee pain)
Renal pain	Fibromyalgia
Dysmenorrhea	Rheumatoid arthritis

## 통증의 평가

## 통증의 평가

- ☐ **Pain history**
  - Medical Hx ; co-morbidities
  - Specific Pain Hx ; intensity, affect, quality, & location
- ☐ **Physical examination**
  - General, Neurological, Musculoskeletal exam, *etc*
  - Assessment of psychological factors
- ☐ **Specific diagnostic tests**
  - QST, 'Poor man's sensory testing', CT or MRI, *etc*

## 통증의 평가 도구

### Uni-dimensional pain scales

- ☐ Verbal Rating Scale (VRS)
- ☐ Numeric Rating Scale (NRS)
- ☐ Visual Analog Scale (VAS)
- ☐ Graphic Scale

## 통증의 약물 치료

## Clinical Guidelines for the Treatment of Chronic Pain

- **Use of a pain scale**  
; evaluation of the patient's response to a therapy
- **An assessment of QOL & ADL**  
; incorporation into the clinical evaluation
- **Identification of psychiatric co-morbidity**  
; use of anti-depressants for non-pain indications

## 통증의 약물 치료

**Acetaminophen  
(Paracetamol)**



## Acetaminophen

Pros	Cons
<b>GI safety</b> ; up to 2 g/d <b>Synergism b/w AAP and NSAIDs</b> ; rarely at therapeutic doses <b>Synergistic analgesic effect</b> ; superior to either alone <b>Safely in doses up to 4 g/d</b> ; even by patients with stable liver disease	<b>Intrinsic hepatotoxin</b> ; rarely at therapeutic doses <b>Hepatotoxicity</b> ; with massive overdoses (> 150 mg/kg over 8 hr or less) ; with therapeutic doses in susceptible patients (eg, chronic alcoholics)

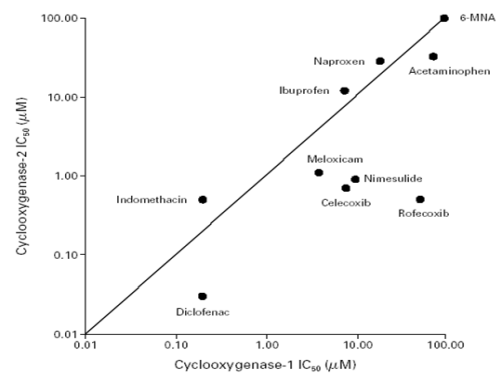
## 통증의 약물 치료

### tNSAIDs & Coxibs

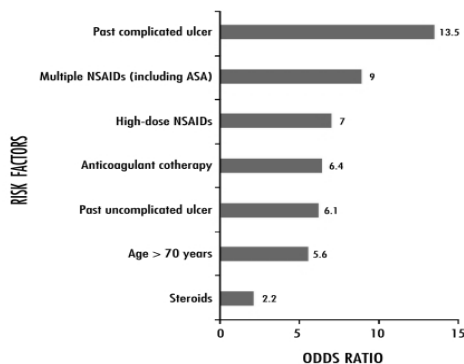
### tNSAIDs & Coxibs

- **COX-1**
  - PGs & TXA<sub>2</sub>
  - GI, Renal, & Vascular function
- **COX-2**
  - PGs
  - Inflammation, Pain, & Fever

### COX-1 vs COX-2



### Risk factors for NSAID-associated GI complications



### Dose-dependent risks for AAP & tNSAIDs for UGI bleeding

Variable	Daily dose (mg)	OR (95% CI)
AAP	< 2000	1.0 (0.5, 1.9)
	2,000 ~ 3,999	1.2 (0.8, 1.7)
	≥ 4,000	1.2 (1.0, 1.4)
Ibuprofen	< 1,200	1.1 (0.6, 2.0)
	1,200 ~ 1,799	1.8 (0.8, 3.7)
	≥ 1,800	4.6 (0.9, 22.3)
Diclofenac	< 75	2.2 (0.8, 5.8)
	75 ~ 149	3.2 (1.9, 5.5)
	≥ 150	12.2 (5.6, 26.7)
Piroxicam	≤ 10	9.0 (2.1, 39.2)
	11 ~ 20	12.0 (6.5, 22.1)
	≥ 21	79.0 (9.9, 931.8)

## Enzyme specificity & Tissue selectivity


Drug	$F_{\text{oral}}$ (%)	$T_{\text{max}}$ (h)	$T_{1/2}$	$V_d$ (l/kg)
Diclofenac				
Lumiracoxib				
Etoricoxib				
Celecoxib				
Chloroquine [23]	~90	~2	~50 days	>100
Non-specific COX-1 plus COX-2 inhibitors [22]				
Diclofenac	>50	1-6	1-2 h	~0.13
Ibuprofen	>90	1-6	1-2 h	~0.13
Naproxen	>90	1-6	10-15 h	~0.13
Piroxicam	>90	1-3	1-2 days	~0.13
Specific COX-2 inhibitors [1, 21, 22]				
Celecoxib	20-40	3-6	4-15 h	>1
Etoricoxib	>90	0.5-1	20-30 h	>1
Lumiracoxib	>90	1-2	2-4 h	0.13

## Practical implications in patients with Chronic Pain

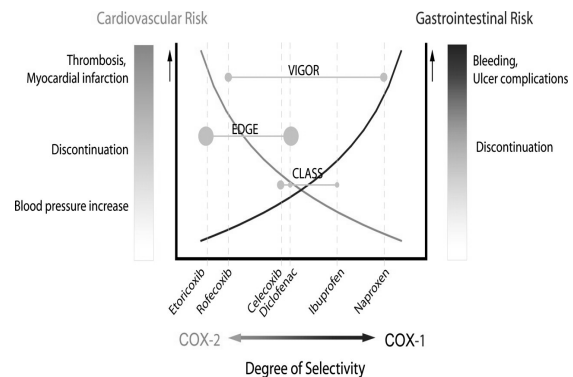
### Lowest doses & Long dosing intervals

- AAP; 1 g po bid
- Diclofenac; 75 mg po # 2~3
- Ibuprofen; 1,200 mg po # 2~3
- tNSAIDs + AAP
  - Ex) Ibuprofen 600 mg & AAP 1g po bid

## Comparison of effects of different Coxibs vs Placebo on Myocardial Infarction

COX 2 inhibitor	No of trials	Events/person years		Rate ratio COX 2 inhibitor: placebo
		Allocated COX 2 inhibitor	Allocated placebo	
<b>Myocardial infarction</b>				
Rofecoxib	37	54/6638	30/6415	
Celecoxib	41	44/8976	9/4953	
Etoricoxib	17	2/753	0/414	
Lumiracoxib	12	5/1375	2/584	
Valdecoxib	14	8/748	1/273	
Subtotal	121	113/18 490	42/12 639	
		(0.6%/year) (0.3%/year)		1.86 (1.33 to 2.59) P=0.0003
Heterogeneity between five drugs: $\chi^2=1.0$ , $df=4$ , $P=0.9$				

## Implication of the relative degrees of selectivity



## Diclofenac sodium (25, 50, 75 mg) Prescribing information

### Cardiovascular Risk

- NSAIDs may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS.)
- Voltaren® (diclofenac sodium enteric-coated tablets) is contraindicated for the treatment of perioperative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

### Gastrointestinal Risk

- NSAIDs cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).

## Celecoxib capsules Prescribing information

### Cardiovascular Risk

- CELEBREX may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. Patients with cardiovascular disease or risk factors for cardiovascular disease may be at greater risk. (See WARNINGS and CLINICAL TRIALS.)

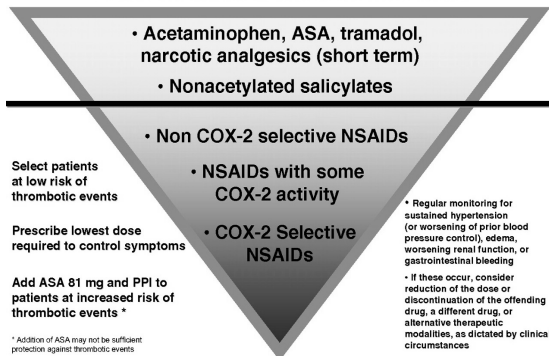
- CELEBREX is contraindicated for the treatment of peri-operative pain in the setting of coronary artery bypass graft (CABG) surgery (see WARNINGS).

### Gastrointestinal Risk

- NSAIDs, including CELEBREX, cause an increased risk of serious gastrointestinal adverse events including inflammation, bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal. These events can occur at any time during use and without warning symptoms. Elderly patients are at greater risk for serious gastrointestinal events (See WARNINGS).



## Stepped care for Musculoskeletal symptoms with known CV disease or RFs for IHD



## Therapeutic use of Coxibs

- Acute pain states
  - dental surgery
  - orthopedic surgery
  - primary dysmenorrhea
- Patients with OA or RA
  - at low risk of thrombotic events

## tNSAIDs & Coxibs

Pros	Cons
<b>Rare hepatotoxicity</b> ; 1~10/100,000 ; exception - ASA, Diclofenac, Sulindac ; Ibuprofen - in patients with hepatitis C	<b>Serious GI Cx</b> ; ulcers, bleeding, & perforation <b>Renal effects</b> ; edema, fluid retention, etc <b>Cardiovascular effects</b> ; BP ↑ ; risk of MI ↑ - the possible exception of Naproxen
<b>Coxibs</b> ; fewer GI Cx	

## 통증의 약물 치료

### Anti-depressants

## Common neuropathic pain syndromes

Peripheral neuropathic pain	Central neuropathic pain
Complex regional pain syndrome	Multiple sclerosis
HIV sensory neuropathy	Myelopathies
Infection	Parkinson's disease
<b>Metabolic disorders</b>	Post-stroke pain
Alcohol & other toxins	
Diabetic neuropathy	
Nutritional deficiencies	
Nerve compression or entrapment	
Postherpetic neuralgia	
Trigeminal neuralgia	

## Common side effects of TCAs

Medication	Sedation	Hypotension, Anticholinergic	Cardiac	Seizure	Wt gain
Amitriptyline	+++	+++	+++	++	++
Clomipramine	++	+++	+++	+++	+
Desipramine	-/+	+	++	+	+
Nortriptyline	+	+	++	+	+

## Anti-depressants

Pros	Cons
<b>Non-neuropathic pain relief effects</b> ; fibromyalgia, headache, LBP <b>Anxiolytic effects</b> ; with appetite stimulation, wt gain, sedation, or urinary retention ; TCAs & SNRIs - patients with depression, anxiety, or insomnia	<b>Anti-cholinergic effects of TCAs</b> ; dry mouth, constipation, blurred vision, cognitive changes, and sexual dysfunction ; <b>orthostatic hypotension &amp; cardiovascular side effects</b> <b>Caution of TCAs</b> ; the elderly, patients with BPH, glaucoma, cardiac disease, etc <b>Serotonergic AEs of SNRIs</b> ; A/N/V, withdrawal symptoms

## 통증의 약물 치료

### Anti-epileptics

## Used in chronic pain syndromes

### □ Carbamazepine

- 200 mg/d ; 200 mg/wk ↑; up to 1,200 mg/d
- Trigeminal neuralgia; drug of choice
- Severe adverse effects
  - Agranulocytosis, aplastic anemia, Steven-Johnson syndrome, hepatotoxicity

## Used in chronic pain syndromes

Gabapentin	Pregabalin
100 ~ 300 mg po hs ; ↑ by 100 mg every 3 d ; up to 600 ~ 1,200 mg tid	150 mg po hs (DPN) 300 mg bid (PHN) 450 mg/d (Fibromyalgia)
Dizziness, somnolence, peripheral edema, ataxia, infection	Dizziness, somnolence, peripheral edema, wt gain, vertigo

## 통증의 약물 치료

### Opioids

## Maxims for Using Analgesics

### 'by Mouth'

Use the simplest route where possible

### 'by the Ladder'

Move on to stronger analgesics if pain not controlled  
There is no upper limit to opioid dosage

### 'by the Clock'

Don't use prn orders

**Prevent pain rather than treat pain !**  
**No single drug is the perfect analgesic !**



## Efficacy of opioids for chronic pain

- ☐ Initial relief for chronic pain conditions
- ☐ High discontinuation rate d/t side effects
- ☐ (?) As a treatment of chronic non-cancer pain
  - potential for tolerance & opioid-induced hyperalgesia
  - concerns about misuse/abuse & opioid dependence
- ☐ Long-term pain control with functional improvement
  - weak evidence for morphine & trans-dermal fentanyl

## Side effects of opioid usage

Most common	Common	Less common
Constipation	Sedation	Delayed gastric emptying
Nausea	Dizziness	Hyperalgesia
	Vomiting	Immunologic dysfunction
	Physical dependence	Hormonal dysfunction
	Tolerance	Muscle rigidity
	Respiratory depression	Myoclonus

## Codeine

- half potency of morphine
- half-life; 2.5 ~ 3 hr
- 'metabolized by CYP2D6'
  - ☐ Inhibitors; bupropion, celecoxib, cimetidine
  - ☐ Inducers; dexamethasone, rifampin
- 'paradoxically more emetic at low dose'

## Drug Interaction of CYP2C/2D

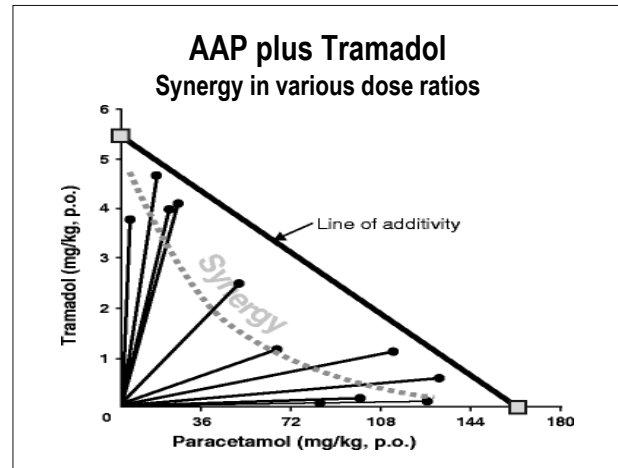
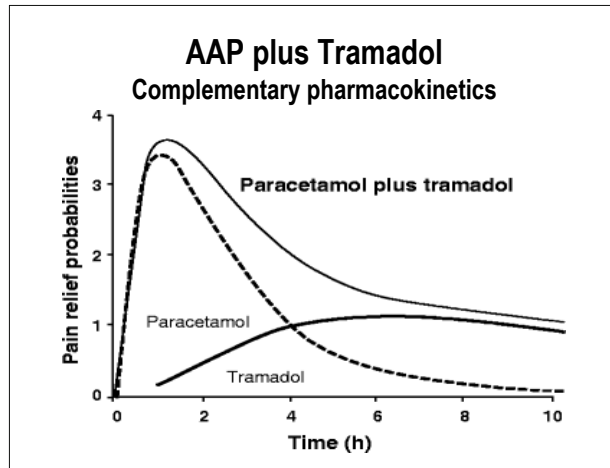
Isoenzymes	Drugs metabolized	Drugs: examples
CYP2D6	tricyclic antidepressants antipsychotics + SSRI β-blocker antiarrhythmic drugs 5-HT <sub>2</sub> antagonists antiemetics analgesics amphetamine warfarin phenytoin	amitriptyline, clomipramine, desipramine, imipramine haloperidol, fluoxetine, paroxetine metoprolol, timolol, propranolol mexiletine, flecainide, ajmaline, propafenone ondansetron, tropisetron metoclopramide
CYP2C9	nonsteroidal antiinflammatory drugs oral antidiabetics angiotensin II blockers proton pump inhibitors antiepileptics	codeine, tramadol, oxycodone, dextromethorphan ecstasy  ibuprofen, diclofenac, naproxen, meloxicam, celecoxib tolbutamide, glipizide losartan, irbesartan omeprazole, pantoprazole diazepam, phenytoin
CYP2C19		

## Tramadol

- 4-phenyl-piperidine analogue of codeine
- equal potency of codeine
- 50 mg tid, 100 mg bid, 150 / 200 mg qd
- most common side effects; HA & Nausea
- safe, well-tolerated, & suitable alternatives

## Comparative receptor affinities for opioids showing unique properties of Tramadol

	μ-opioid Rcp (μM)	NA Rcp (μM)	5-HT Rcp (μM)
Morphine	0.3	Inactive	Inactive
Oxycodone	9	Inactive	Inactive
Hydrocodone	10	Inactive	Inactive
Codeine	200	Inactive	Inactive
Dextromethorphan	1,300	20	200
Tramadol	2,100	1,000	800
Imipramine	3,700	20	7



- Ultracet : AAP 325 mg + Tramadol 37.5 mg
  - 1 tab po bid → tid
  - U-cet 1 tab & AAP-ER 650 mg po bid
- Ultracet-semi : AAP 162.5 mg + Tramadol 18.75 mg
  - 1 tab po q 8 hr → q 6 hr
  - U-semi 1 tab & AAP 500 mg po q 6~8 hr
- Ultracet-ER : AAP-ER 650 mg + Tramadol 75 mg
  - 1 tab po qd → bid (Max. 2 tab po bid)
  - U-ER 1 tab & U-cet 1 tab po bid
  - U-ER 1 tab & AAP 325 or 500 mg po bid

## 요점 정리

- 안전하고 효과적인 약물 선택
  - 적은 용량과 긴 간격
- Acetaminophen
  - Synergistic with NSAIDs & Tramadol
- COX-1 selective
  - Gastrointestinal risk
- COX-2 selective
  - Cardiovascular risk

- Enzyme specificity & Tissue selectivity
  - 예 : ibuprofen, diclofenac
- Neuropathic pain
  - 적절한 TCAs &/or Anti-epileptics 선택
- TCAs & Anti-epileptics
  - 충분한 증량으로 효과 평가
- Opioids
  - by mouth, by the ladder, by the clock !





## 증 례

### 66세 여성, 퇴행성 슬관절염

- DMOADs
  - ☐ Diacerhein
  - ☐ Avocado soya
  - ☐ Glucosamine sulfate or chondroitin sulfate
- AAP 1 g po bid로 시작
- Tramadol 추가와 증량 고려
- 저용량 tNSAIDs 추가 고려