Pharmacotherapy of Pain: Nonopioid Analgesics

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Defining Pain

“An unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage.”

International Association for the Study of Pain (IASP)
Classifications of Pain

- **Acute**
- **Chronic**

**Pathophysiology**

- **Nociceptive**
- **Neuropathic**

Nociceptive pain

- Noc, brakhot, merah
- תימוק

- **NSAID**
- אפיזיטים
- תוספים לאפיזיטים.
Nociceptive pain is an appropriate physiologic response to painful stimuli.


NOCICEPTIVE PAIN

<table>
<thead>
<tr>
<th>Features</th>
<th>Somatic</th>
<th>Visceral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant</td>
<td>Constant or crampy</td>
<td></td>
</tr>
<tr>
<td>Aching</td>
<td>Aching</td>
<td></td>
</tr>
<tr>
<td>Well localized</td>
<td>Poorly localized</td>
<td></td>
</tr>
<tr>
<td>Referred</td>
<td>Referred</td>
<td></td>
</tr>
</tbody>
</table>

Examples

- Bone metastases
- Pancreatic CA
- Liver tumor
- Bowel obstruction
## FEATURES OF NEUROPATHIC PAIN

<table>
<thead>
<tr>
<th>COMPONENT</th>
<th>DESCRIPTORS</th>
<th>MEDICATIONS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Steady</strong></td>
<td>Burning, Tingling, Constant, Aching, Squeezing, Itching</td>
<td>Gabapentin, Tricyclic antidepressants, Corticosteroids, Mexilitene</td>
</tr>
<tr>
<td><strong>Paroxysmal</strong></td>
<td>Stabbing, Shocklike, electric, Shooting</td>
<td>Gabapentin, Baclofen, Tegretol, Corticosteroids, Mexilitene</td>
</tr>
</tbody>
</table>
Examples of Nociceptive and Neuropathic Pain

Nociceptive
Caused by tissue damage
- Arthritis
- Mechanical low back pain
- Sports/trauma injuries
- Postoperative pain
Low back pain
Facet pain
Neck pain
Cancer pain

Mixed
Caused by combination of primary injury and secondary effects
Neuropathic
Caused by lesion or dysfunction in the nervous system
- Painful DPN
- MPS
- Neuropathic low back pain
- Trigeminal neuralgia
- Central poststroke pain
- Complex regional pain syndrome
- Distal HIV polyneuropathy

Mechanistic Approach to Pain Treatment

Brain
Descending inhibition
Peripheral sensitization
Terminal
PNS
Spinal cord
Central sensitization

The ideal drug
- No metabolites
- No protein binding
- No drug interaction
- No toxicity
- No side effect
- Simple dosing
- Easy titration
- Oral
- Once a day
- Price
- Non Selective NSAIDs - Paracetamol
- NSAIDs - Cox 2 selective: Etoricoxib, Celecoxib
- Topical analgesic agents - NSAIDs, Capsaicin, EMLA
- Tramadol
- Antiarrythmics
- Antidepressants
- Anticonvulsants
- Local anesthetics
- NMDA receptor antagonists

יריוולות ליב או ליפור במבוא על יד בטני
אנלוגיות אוריינטטית במקן עם אנओידים
"ceiling" effect
ourneyת לאופיואדרניאית
או י זקוק לפלסטר או טלה פיזית

The Pain Elevator:
WHO Method for Relief of Cancer Pain:
- ‘By the mouth’ i.e. oral
- ‘By the clock’ i.e. regular
- ‘By the ladder’ (next slide)
- Individualise treatment
- Pay attention to detail

Paracetamol (Acetaminophen)
- The most widely recommended nonopioid analgesic for mild-to-moderate acute and chronic pain states.
- Centrally mediated analgesia
- Has analgesic, antipyretic properties and minimal anti-inflammatory effects
- The ACR guidelines for the medical management of osteoarthritis recommend paracetamol as the preferred first-line therapy in patients with symptomatic osteoarthritis of the knee.

Acetaminophen
Advantages:
- Readily available OTC
- Safe
- Can be used with other drugs
- Inexpensive
- Optimal dose is 1,000 mg/dose NNT= 3.8 (3.4 - 4.4)
- The initial drug of choice at a dose of up to 4 g daily.
**Acetaminophen**

**Adverse Effects**

*Disadvantages:*
- Helpful for only mild pain
- Poor compliance with higher doses
- Hepatotoxicity, including progressive, irreversible hepatic failure, is the major side effect associated with overdose
- 50% to 75% dose reduction recommended in patients with renal/hepatic dysfunction or history of current alcohol abuse

**NSAIDs: Overview**

**Effects:**
- Anti-inflammatory
- Analgesic
- Antipyretic

**Interactions with NSAIDs include:**
- Anticoagulants
- ACE inhibitors
- Antihypertensives
- Lithium
- Diuretics

**Roles of COX-1 and COX-2 in Prostaglandin Synthesis**

[Diagram showing COX-1 and COX-2 activities and prostaglandin synthesis]
The Phospholipid Pathway

NSAID

Mechanism
- Inhibit both peripheral and central cyclooxygenase, reducing prostaglandin formation
- 3 isoforms of COX
  - COX-1: Constitutive, physiologic
  - COX-2: Inducible, inflammatory
  - COX-3: Central, blocked by acetaminophen

NSAID Therapy for Various Chronic Pain Syndromes

- Osteoarthritis and Rheumatoid Arthritis
- Low Back Pain
- Fibromyalgia
- Peripheral Neuropathy-Mixed Pain Syndromes
Adverse Events Associated with NSAID Therapy

- Gastrointestinal Events
- Cardiovascular Events
- Hepatotoxicity
- Nephrotoxicity
- Central Nervous System

Gastrointestinal Events

- Dyspeptic symptoms
- Gastric or duodenal ulceration

Factors Associated With NSAID GI-ulcer

- NSAID dose
- NSAID time of treatment
- Type of NSAID
- Age > 60 years
- Past history of GI ulcer
- Combination with steroids
- Combination with anti-coagulants
- H. Pylori present
Risk Factors for Gastrointestinal Events Associated With NSAID Therapy

Relative Risk for Ulcer With Different NSAID Treatments

<table>
<thead>
<tr>
<th>Generic Name</th>
<th>Relative risk for ulcer</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ibuprofen</td>
<td>1</td>
</tr>
<tr>
<td>Diclofenac</td>
<td>2.3</td>
</tr>
<tr>
<td>Aspirin</td>
<td>4.8</td>
</tr>
<tr>
<td>Sulindac</td>
<td>6</td>
</tr>
<tr>
<td>Naproxen</td>
<td>7</td>
</tr>
<tr>
<td>Indomethacin</td>
<td>8</td>
</tr>
<tr>
<td>Piroxicam</td>
<td>9</td>
</tr>
<tr>
<td>Ketoprofen</td>
<td>10</td>
</tr>
</tbody>
</table>

Who Needs Protection?
High Risk Groups

- Age >65
- Previous GI bleeding, DU
- Dyspepsia or symptoms of gastroesophageal reflux disease
- Corticosteroid use
- Heart disease

Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

- All NSAIDs, including COX-2 inhibitors, raise the risk of GI ulcers and bleeding when combined with ASA taken chronically for cardioprotection
- Patients at increased GI bleeding risk should go on a PPI
- PPIs such as lansoprazole and omeprazole are preferred over misoprostol, sucralfate, or histamine 2 (H2)-receptor antagonists for both the prevention and treatment of gastroduodenal lesions associated with ASA and other NSAIDs

Expert Consensus Document on Reducing the Gastrointestinal Risks of Antiplatelet Therapy and NSAID Use

- Patients with a history of ulcers should be evaluated and, as appropriate, treated for *Helicobacter pylori* infection before starting antiplatelet therapy.

*J Am Coll Cardiol, 2008; Circulation, 2008*
Nephrotoxicity

- Elevation of serum creatinine level
- Sodium and water retention, hyperkalemia
- Acute renal failure
- Nephrotic syndrome
- Acute tubular necrosis
- Interstitial nephritis
Hepatotoxicity

- The risks appear to be rare
- The rate of hospitalization due to NSAID-induced hepatotoxicity in this review was 2.7/100,000 patients
- In the first review, diclofenac and rofecoxib were associated with the highest rate of aminotransferase level elevations


Cardiovascular Events

- Peripheral edema, and hypertension
- Heart Failure exacerbation
- Increase MI, cardiac arrhythmia
- COX-2 inhibition can result in an increased risk for thrombosis due to increased activity of thromboxane A2 and reduced activity of prostacyclin

COX-2

SELECTIVE

- Reduces inflammation with less stomach irritation
- NS-NSAIDs are generally ineffective
- Only COX-2 inhibitors, such as celecoxib and rofecoxib, are selective for COX-2
- CELECOXIB & ROFECOXIB
- Reduces stomach irritation and ulcer formation, yet still effective in pain relief

The use of COX-2 inhibitors is more selective and can reduce the risk of gastrointestinal complications.
APPROVE trial (2004)

Evaluated the efficacy of VIOXX 25 mg in preventing recurrence of colorectal polyps.

There was an increased relative risk for heart attack and stroke in low-risk patients—an excess of 16 myocardial infarctions or strokes per 1000 patients, beginning after 18 months of treatment vs. placebo.

What percent of the NSAID prescriptions that you prescribe are traditional NSAIDs and what percent are COX-2 selective agents?

European Medicines Agency announces regulatory action on COX-2 inhibitors

- A contra-indication is introduced for all COX-2 inhibitors in patients with ischaemic heart disease or stroke
- A contra-indication is introduced for etoricoxib in patients with hypertension (high blood pressure) whose blood pressure is not under control
- A warning is introduced for prescriptions to exercise caution when prescribing COX-2 inhibitors for patients with risk factors for heart disease
- Given the association between cardiovascular risk and exposure to COX-2 inhibitors, doctors are advised to use the lowest effective dose for the shortest possible duration of treatment

Ref: EMEA/62757/2005
AHA Updates NSAID Advice for Heart Disease Patients

- In patients at increased risk for thrombotic events, low-dose aspirin plus a proton-pump inhibitor could be added

- COX inhibitors can lead to impaired renal perfusion, sodium retention, and increases in blood pressure, which may contribute to their adverse cardiovascular effects

February 28, 2007
"Nonselective" NSAIDs also differ with regard to COX selectivity. Diclofenac has greater COX-2 selectivity than ibuprofen, which in turn has greater COX-2 selectivity compared with naproxen.

Naproxen is probably the NSAID associated with the lowest risk for thrombosis.

The stepwise approach to pharmacologic therapy for musculoskeletal symptoms:
1. Acetaminophen, tramadol, narcotic analgesics (short-term)
2. Nonacetylated salicylates
3. Non-COX-2 selective NSAIDs
4. NSAIDs with some COX-2 activity
5. COX-2 selective NSAIDs
Topical Treatments

Topical NSAID

- widely used, OTC preparations
- effective for both acute and chronic pain conditions
- NNT = 3-5
- systemic side effects were rare

"Topical NSAIDs may be a useful alternative to oral NSAIDs"

BMJ. December 4, 2007
Capsaicin

- Particularly useful for neuropathy
- Topical agent from chili pepper for site-specific pain
- Interferes with reuptake of substance P
- At least 3 randomized, controlled trials show beneficial effect of capsaicin cream in the treatment of OA over 1-3 months
- Should be started at the lowest dose 0.025% every 6 hours

Topical Capsaicin

- Provides modest improvement in pain after 4- to 6-week use
- Opens calcium channel via the TRPV1 receptor; C-fibers die back and regrow in 6 to 7 weeks
- Has a high rate of burning sensations that are unacceptably severe
- New capsaicin 8% patch in development

Symptomatic Treatments

- Capsaicin not NSAIDs
- May be a treatment option
- Improvement in quality of life measured in office and at home
Other Topical Agents

EMLA
- a mixture of lidocaine and prilocaine
- for use in incidental pain, venous cannula insertion, pain after circumcision and another postoperative pain

5% Lidocaine Patch
- Excellent safety and tolerability
- Systemic absorption from the patch must be considered in patients receiving oral class 1 antiarrhythmic drugs
- Two studies involving the transdermal lidocaine 5% patch show that it may have a role in both musculoskeletal and neuropathic pain
- Only adverse effect is mild skin reactions, erythema or rash

Tramadol
- Centrally acting synthetic codeine analog
- Useful for moderate to moderately severe pain

Two mechanism of actions:
- weak interaction of tramadol with the μ-opioid receptor
- inhibiting the reuptake of norepinephrine and serotonin
Tramadol: Indications

- Fibromyalgia
- Chronic low back pain
- Degenerative Joint Disease
- Painful diabetic neuropathy
- Tramadol has shown effectiveness in number of acute pain situations as well.

Tramadol: Dosing and Adverse Effects

- The typical dosing for healthy adult is 50 to 100 mg every 8 to 12 hours as needed
- Totaling not more than 400 mg/d (300 mg/d in patients aged 74 years and older).
- The most common adverse effects (dose related and transient): nausea and vomiting (transient)
  - constipation
  - headache and drowsiness
  - very low risk of seizures

Clinical Experience with Tramadol

- Atypical opioid
- Not toxic to organs
- Efficacy at least as good as NSAIDS, Coxibs, Percocet
- Less opioid related side-effects than other opioids (sedation, GI)
Cautions with Tramadol

- Reduce dosage in renal failure
- Avoid Use with MAO inhibitors
- Advise patients of potential drug interactions with SSRIs/NRIs
- Advise patients of potential of lowering seizure threshold

Questions?