Pain therapeutics

Acetaminophen/NSAIDs
Acute pain
Osteoarthritis
Migraine
Acute Gout
Neuropathic pain

James McCormack, Pharm.D.
Professor
Faculty of Pharmaceutical Sciences, UBC

Common types of pain killers

1. Acetaminophen (Tylenol)
2. Anti-inflammatories
   NSAIDs (aspirin, ibuprofen (Motrin, Advil), naproxen, 15 others)
   NSAIDs COX –2's - celecoxib (Celebrex)
3. Narcotics - codeine, morphine
4. Combinations of the above
5. Steroids - prednisone

Acetaminophen for post-operative pain

"About half of participants treated with paracetamol at standard doses achieved at least 50% pain relief over four to six hours, compared with about 20% treated with placebo" CD004602

Acetaminophen for acute migraine headaches

"For all efficacy outcomes paracetamol was superior to placebo, with NNTs of 12, 5.2 and 5.0 for 2-hour pain-free and 1- and 2-hour headache relief, respectively, when medication was taken for moderate to severe pain. Nausea, photophobia and phonophobia were reduced more with paracetamol than with placebo at 2 hours (NNTs of 7 to 11); more individuals were free of any functional disability at 2 hours with paracetamol (NNT 10); and fewer participants needed rescue medication over 6 hours (NNT 6)." CD008040

NSAIDs vs acetaminophen for acute pain in children

336 children; ibuprofen, acetaminophen or codeine
Ibuprofen better than either (for pain score and attaining "adequate" pain relief.

68 children; ibuprofen or aceta+codiene
No difference in pain scores

336 children; ibuprofen vs acetaminophen+codeine

No difference in mean pain scores – Ibuprofen less functional limitation & adverse events

Pediatrics 2007;119:460-7
Acad Emerg Med 2009;16:711-6
Ann Emerg Med 2009;54:553-60

NSAIDs vs acetaminophen for osteoarthritis

"NSAIDs are superior to acetaminophen for improving knee and hip pain in people with OA"CD004257

Patient global assessment (dichotomous)
40% acetaminophen, NSAID 50%
pain scores about 25% better on average

No difference in tolerability but studies typically 6 weeks

Topical NSAIDS for chronic musculoskeletal pain

"Topical NSAIDs can provide good levels of pain relief; topical diclofenac solution is equivalent to that of oral NSAIDs in knee and hand osteoarthritis, but there is no evidence for other chronic painful conditions. Formulation can influence efficacy. The incidence of local adverse events is increased with topical NSAIDs, but gastrointestinal adverse events are reduced compared with oral NSAIDs" CD007400

Topical NSAIDs for acute pain

"Topical NSAIDs can provide good levels of pain relief, without the systemic adverse events associated with oral NSAIDs, when used to treat acute musculoskeletal conditions" CD007402

Systematic review - ibuprofen, piroxicam, salicylates, diclofenac, eltenac

Topical NSAIDs vs placebo

Chronic pain (2 weeks) - OA, tendinitis -13 trials -1983 patients

> 50% pain relief (week 1) - 74 vs 44% (placebo)

> 50% pain relief (week 2) - 92 vs 58% (placebo)

> 50% pain relief (week 4) - 55 vs 57% (placebo)

Topical NSAIDs were not statistically significantly different compared to oral NSAIDs except during the first week

BMJ 2004;329:324-6

Capsaicin (0.075%)

Musculoskeletal pain - 4 weeks

3 placebo controlled trials - 368 patients

> 50% pain relief - 38 vs 25% (placebo)

Local adverse effects - 49% vs 10%

BMJ 2004;328:991-4

Topical NSAID RX

Topical NSAID's—generic, available at your favorite compounding Pharmacy (Pennsaid is more $ and smells like garlic)

RX-

Diclofenac or ketoprofen,10% in Difusimax

Disp.-100gm

Rub on joint am and pm. No need to protect hands

Slide stolen with permission from Mike Allan

GI Risks of Using NSAIDs

1. 10-20% of patients develop abdominal pain, dyspepsia, nausea
2. Symptomatic upper GI ulcers occur in 1% of patients over 6 months (3-4% over 1 year?)

Risk of GI haemorrhage with long term use of aspirin: meta-analysis

24 trials

66,000 patients

No difference between low dose/high dose or modified release formulations

Other studies support this finding – Heart 2001;85:265-71, Am J Gastroenterol 2000;95:2218-24

	GI bleed (%)
Aspirin	2.5
Placebo	1.4
Relative risk inc	79
Absolute risk	1.1
Number needed to harm	263

BMJ 2000;321:1183-7

COX-2 versus other NSAIDs

1. Appear to be equally effective
2. No difference in overall adverse effects
3. No difference in kidney effects
4. No effects of COX-2 on platelets
5. Upset stomach symptoms
   1. 3 studies – no difference
   2. 1 showed a 2% absolute difference
   3. 1 showed a 10% absolute difference
6. Approximately a 10-25% absolute difference in endoscopically-proven ulcers

COX-2 versus other NSAIDs

Serious GI events differences

1. One publication showed a 0.5% difference over 12 months in serious gastrointestinal complications (1.8% on old NSAIDs, 1.3% on COX-2)
2. To prevent one symptomatic ulcer you need to treat 300 people with one of the new NSAIDs for 1 year
3. To prevent 1 upper GI bleed = 600 people
4. No difference in death from GI complications
5. Cardiovascular issues

Of 50 Patients With a GI Bleed on an NSAID

16% of patients reported being informed of adverse effects

4% of patients informed about what to do if adverse symptoms occur

36% (18) of the patients had stomach pain before the bleed and all but 2 of these patients continued taking the drug

Br J Clin Pharmacol 1996;42:253-6

NSAID Concerns

1. NSAIDs are a common cause of stomach and bowel disorders (stomach upset, ulcers to perforation and fatal gastrointestinal bleeding)
2. NSAIDs, along with alcohol, are likely the most common drugs to produce drug-induced high blood pressure
3. NSAIDs will, in some people, reverse some of the beneficial effects of drugs used in patients with heart failure and they can damage kidney function in susceptible individuals
4. Some NSAIDs can cause mental confusion, especially in the elderly
5. NSAIDs do not retard or prevent the progression of either rheumatoid or osteoarthritis

Acetaminophen Benefits

1. Acetaminophen as a pain killer has a number of advantages over the NSAIDs
2. Acetaminophen produces almost no adverse effects on the heart, blood vessels, stomach, or the kidney and therefore is safer in people with stomach ulcers, heart failure, and high blood pressure
3. While acetaminophen is effective for some/many people, some people will require an NSAID to obtain partial or complete pain control

Acetaminophen and Dosing

1. While acetaminophen can cause liver damage, it rarely occurs except in overdose
2. Single doses can range from 325mg to 1-1.5 grams (2-3 of the extra strength or 500 mg tablets) – can be repeated every 6-8 hours
3. Many people will find much lower doses (325 mg or one regular strength tablet) may work for either their acute or chronic pain
4. Maximum daily dose in people with normal liver function is 4 grams (8 pills of the extra strength or 500 mg tablets) per day (2 grams per day if one has liver disease or consumes moderate to large amounts of alcohol on a regular (daily) basis)

The "BEST" dose

1. People respond very differently to different pain killers and/or doses therefore, it is important that the dose be adjusted to the least amount, least often, which will control the pain
2. Virtually none of the NSAIDs, when dosed daily, have to be given more frequently than twice daily
3. People with osteoarthritis do not necessarily have constant or consistent pain, and therefore dosing of an NSAID on a regular basis may not be needed
4. Many people may do well by dosing the acetaminophen or an NSAID 1 hour prior to a known aggravating factor (e.g., prior to walking to the store, or at bedtime if pain disturbs sleep)
5. Consider treating osteoarthritis with regular doses of acetaminophen and use NSAIDs on an as needed basis

NSAIDs versus placebo in sports injuries

19 trials in total
- 11 trials: NSAID better
- 7 trials: no difference
- 1 trial: placebo better

Quality of trials in general was fairly low

NSAID versus acetaminophen+/- a narcotic in sports injuries

8 trials in total
- 5 trials: no difference (regularly dosed narcotics produced more side effects)
- 1 trial: naproxen less pain - no difference in tenderness, swelling or limitation of movement
- 1 trial: ibuprofen returned patients to sport faster (not designed to evaluate this parameter)
- 1 trial: diclofenac better on day 6 and 7

Quality of trials in general was fairly low

"There is growing support for using paracetamol, also known as acetaminophen, in some countries including the United States of America, as first-line treatment for musculoskeletal sprains and strains, because paracetamol may be just as effective an analgesic as NSAIDs, yet will not increase bleeding into the injury site or potentially impair healing"

Physiotherapy Theory and Practice 2011;27:482–91

BMJ

BMJ 2012;345:e4737 doi: 10.1136/bmj.e4737 (Published 18 July 2012)

SPORTS DRINKS

The truth about sports drinks

Sports drinks are increasingly regarded as an essential adjunct for anyone doing exercise, but the evidence for this view is lacking. **Deborah Cohen** investigates the links between the sports drinks industry and academia that have helped market the science of hydration

Deborah Cohen *investigations editor*

BMJ July 2012

The Evidence

"There is a striking lack of evidence to support the vast majority of sports-related products that make claims related to enhanced performance or recovery, including drinks, supplements and footwear"

BMJ Open 2012;2:e001702. doi:10.1136/

"A meta-analysis of data from cyclists in time trials concluded that relying on thirst to gauge the need for fluid replacement was the best strategy."

Br J Sports Med 2011;45:1149–1156. doi:10.1136/bjsm.2010.077966

Too much water?

"There have been 16 recorded deaths and 1600 people taken critically ill during competitive marathon running due to a drop in their serum sodium"