NSAIDs
DARE TO COMPARE

July 1997 v

TheRxFiles

Produced by *the Community Drug Utilization Program, a Saskatoon District Health/St. Paul's Hospital program funded by Saskatchewan Health. For more information check our website www.sdh.sk.ca/RxFiles or, contact Loren Regier C/O Pharmacy Department, Saskatoon City Hospital, 701 Queen St. Saskatoon, SK S7K 0M7, Ph (306)655-8506, Fax (306)655-8804; Email regierl@sdh.sk.ca*

We have come a long way from the days of willow bark. Today salicylates and non-steroidal anti-inflammatory drugs (NSAIDs) comprise one of the largest and most commonly prescribed groups of drugs worldwide.[1] In Saskatchewan, over 20 different agents are available, accounting for more than 300,000 prescriptions and over $7 million in sales each year (Saskatchewan Health-Drug Plan data 1996). Despite the wide selection, NSAIDs are more alike than different. Although they do differ in chemical structure, pharmacokinetics, and to some degree pharmacodynamics, they share similar mechanisms of action, efficacy, and adverse effects.

Highlights

- All NSAIDs have similar efficacy and side effect profiles
- In low risk patients, **Ibuprofen** and **naproxen** may be *first choice* agents because they are effective, well tolerated and inexpensive
- **Acetaminophen** is the recommended first line agent for osteoarthritis
- **Misoprostol** is the only approved agent for prophylaxis of NSAID-induced ulcers and is recommended in high risk patients <u>if</u> NSAIDS cannot be avoided.

EFFICACY

NSAIDs work by inhibiting cyclooxygenase (COX) and subsequent prostaglandin synthesis as well as by other less understood mechanisms. In comparative studies between NSAIDs, no clinically significant differences in efficacy have been shown.[2] Wide variability in patients' response may be due to differences in pain threshold, disease severity, cyclooxygenase configuration, and other factors. Since there is no method of predicting who will respond to which NSAID, initial selection is empiric. About 60% of patients will respond to a specific NSAID; non-responders are just as likely to respond to an alternate agent particularly if it is from a different chemical class.[3]

Onset of analgesia occurs rapidly with all NSAIDs, usually within one hour. In recent years, more expensive, "fast-acting" formulations of some NSAIDs have been introduced. They are more quickly absorbed, and have a more "immediate" onset. While this may be advantageous in some highly acute situations, the benefit beyond the initial dose and in treatment of chronic pain is doubtful. In addition, anti-inflammatory activity often requires a week or more to become established. For this reason, an adequate trial of 1-2 weeks should be allowed before increasing the dose or changing to another NSAID. Combining NSAIDs is not recommended as it has no additive analgesic effect and increases risk of toxicity.[4]

Ketorolac (Toradol®) is sometimes mistaken for an analgesic superior to the NSAIDs since it is often compared with the opiates. In reality, its analgesia is similar to ibuprofen and its anti-inflammatory effects are poor compared with other NSAIDs.[5] Its only advantage is that it is available in injectable form which can be used in situations where oral NSAIDs are excluded (eg. acute post-op period).

ADVERSE EFFECTS

NSAIDs cause a variety of side effects including nausea, diarrhea, constipation, dizziness, headache, confusion, edema, rash, and pruritis. They can also cause more serious toxicities such as gastro-intestinal (GI) ulceration/bleeding, hematologic disturbances, bronchospasm, angioedema, renal dysfunction, and hepatotoxicity. Many of these are related to NSAID inhibition of prostaglandin synthesis other than at the desired site of action.

Non-acetylated salicylates are weak inhibitors of prostaglandin synthesis and are less apt to cause adverse allergic, gastric, renal, or antiplatelet effects. Reported differences in toxicity between NSAIDs must be interpreted in light of different utilization patterns and interpatient variability.[6]

Gastrointestinal side effects are most common. The propionic acid derivatives such as ibuprofen and naproxen are generally better tolerated than other NSAIDs. Enteric coated (EC) products may reduce complaints of stomach upset but do not appear to reduce the incidence of GI ulceration. Injectable ketorolac, suppository formulations, and pro-drugs which are activated after absorption from the GI tract also do not eliminate the problem of gastric mucosal damage.[7] Development of more selective COX-2 inhibitors such as nabumetone and etodolac that preferentially inhibit cyclooxygenase at sites of inflammation rather than in the internal organs may hold some promise. However, long-term studies are lacking to validate claims of reduced GI toxicity.

Upper GI complications may be more closely related to dose and duration of therapy than to any specific agent.[8] Since risk is greatest at the high end of dosing ranges and during the first 3-6 months, doses and duration should be minimized as much as therapeutically possible.

NSAIDs should be avoided in patients at high risk for GI complications (Tables 1,2). However if their use cannot be avoided, addition of a prophylactic agent to reduce ulceration is recommended. **Misoprostol** is the only agent approved for the prevention of NSAID induced ulcers. Misoprostol has been shown to significantly reduce the incidence of both gastric and duodenal ulcers in NSAID users.[9] Although misoprostol may cause GI side effects such as diarrhea, a gradual dosage titration may help to improve patient tolerance and compliance. A combination of misoprostol and ibuprofen was found to cause a lower incidence of endoscopic ulcers than the selective COX-2 agent, nabumetone.[10] H2 blockers (eg. ranitidine), omeprazole, and sucralfate are not indicated for the prevention of NSAID induced gastric ulcers.

Renal failure may result when NSAIDs are used in patients whose kidney perfusion is dependent on local prostaglandin production. Sulindac was thought to have a "renal sparing" effect but it appears to be only marginally safer and cannot be prescribed without risk.[11] The COX-2 inhibitors may prove to be less toxic but supporting data is lacking. NSAIDs should be avoided in those at high risk of nephrotoxicity (Table 3).

A recent review of NSAID utilization patterns in Saskatchewan revealed that a significant number of patients have concomitant prescriptions for H2 blockers, ACE inhibitors, diuretics, and multiple NSAIDs .[12] This raises the concern that high risk patients may be receiving inappropriate therapy.

COST

The most notable difference among NSAIDs is cost. Prescription prices vary considerably, ranging from less than $10 a month for ibuprofen to more than $100 for high dose etodolac. The cost of treating NSAID-related complications has additional impact on the health care system. Treatment of GI problems alone is estimated to add over 40% to the cost of arthritis care.[13] Newer, more expensive agents do not guarantee safer, more effective treatment, and in the majority of cases do not offer significant advantages over previously available NSAIDs. Ibuprofen and naproxen are recommended as first line agents as they are effective, inexpensive, and generally well-tolerated in low risk individuals.

PRESCRIBING CONSIDERATIONS

- Consider non-pharmacologic treament (eg. physiotherapy, weight loss, hot/cold therapy)
- Consider using acetaminophen before NSAIDs in osteoarthritis (eg. acetaminophen in doses of up to 4 g/day is highly effective, well tolerated, and safer than NSAIDS in osteoarthritis, and should be considered the drug of choice)[14]
- Try less expensive agents first (eg. ibuprofen, naproxen) when an NSAID is indicated
- Use the lowest effective dose and as short a duration as possible without compromising care
- Allow 1-2 weeks before increasing dose or changing agents
- Avoid combinations of NSAIDs
- Avoid NSAIDs if possible in patients at high risk of GI or renal complications

We wish to acknowledge those who have assisted in the development and review of this newsletter: Dr. Z. Tymchak (FM), Dr. P. Peloso (Rheum.), Dr. J. Richardson (Pharm.), and the CDUP Advisory Committee.

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The Rx Files: NSAIDS - Dare to Compare
Supplementary Charts

Table 1

Risk Groups for NSAID Induced Ulcers*[15]
• Age: >65 years
Previous GI History:
Recent Peptic Ulcer Disease
Previous GI Bleed
Coexisting Significant Disease
Cardiovascular
Hepatic or Renal Impairment
Concomitant Therapy with:
Corticosteroids (eg. prednisone)
Anticoagulants (eg. warfarin)
ASA (including low doses)

***** Any two risk factors constitutes a high risk individual (risk of serious bleeding >1% per year)

Table 2

Prevention of NSAID Induced Ulcers in High Risk Individuals[15]
Avoid NSAIDs if Possible & Use Alternatives:
• Acetaminophen (Max 4g/day)
• Physiotherapy
• Intra-articular Corticosteroid Injections
If NSAIDs must be used:
Use Lowest Effective Dose
Limit Duration of Use where possible
Add **Misoprostol** (Cytotec®) for Cytoprotection
100µg po daily cc x3 days then
100µg po BID cc x3 days then
200µg po BID cc thereafter
(gradual dose titration recommended to promote tolerance of side effects)
Reassess need for NSAID regularly
Monitor for GI complications
(especially over first 3 months)

Table 3

Risk Groups for Nephrotoxicity
• Age: >65
• Previous Renal InsufficiencyHypertension
• Hepatic Cirrhosis
• CHF
• Atherosclerotic Disease
• Concurrent Diuretic or ACE Inhibitor Use

Table 4

Misoprostol / NSAID Regimens: Cost Comparisons	
Misoprostol 200µg po BID	$40
Misoprostol 200 µg po BID + Ibuprofen 400mg po TID-QID	$52-$54
Misoprostol 200 µg po BID + Naproxen 250-375mg po BID	$57-$65
Misoprostol 200µg po BID + Diclofenac 50mg po BID-TID	$61-$73
Arthrotec® 1 tablet po BID-TID (tablet=diclofenac 50mg / misoprostol 200µg)	$48-$68
Arthrotec 75® 1 tablet po BID (tablet=diclofenac 75mg / misoprostol 200µg)	$61

Based on cost to patient for a 30 day prescription.

Comparison Chart: NSAIDS & Other Analgesics Prepared by: Loren Regier, Sharon Downey - ***The RxFiles***, **AUG/2000**

Class / Agent		Comments / Products	Usual Dosage Range	Max /day	Cost x30 days [#] (comparative dose)	
Salicylates						
ASA-Plain **ASA-Enteric Coated**	ASPIRIN® ENTROPHEN®	**OTC**; 650mg supp; 80,325mg tab; 81,325,650,975mg EC tab; irreversible platelet inhibition	325-650mg q4-6h 325-975mg QID	4g	650mg po QID	**$11**
Diflunisal	DOLOBID®	250,500mg tab	250-500mg BID	1.5g	250mg po BID	$37
Non-acetylated Salicylates - less adverse GI reactions, less cross-allergy in NSAID (& CSI?) allergic patients; available, but not commonly used						
Salsalate	DISALCID® ✘	500,750mg tab	1000mg TID	3g	1500mg po BID	$54
Choline Mg Trisalicylate	TRILISATE® ✘	500mg tab	1-1.5g BID	3g	1000mg po BID	$36
Indole Acetic Acids						
Indomethacin	INDOCID®	25,50mg cap; 50,100mg supp	25-50mg TID	200mg	25mg po TID	$17
Sulindac	CLINORIL®	150,200mg tab; PD	150-200mg BID	400mg	150mg po BID	$34
Tolmetin	TOLECTIN®	200,600mg tab; 400mg cap	200-600mg TID-QID	2g	400mg po TID	$53
Phenylacetic Acids						
Diclofenac ###	VOLTAREN®	25,50mg EC tab; 50,100mg supp; 75,100mg SR tab	25-50mg BID-TID	200mg	50mg po TID	$22
Diclofenac+Misoprostol	ARTHROTEC-50® ARTHROTEC-75®	(50mg + 200µg) tab (75mg + 200µg) tab	1 tab BID-TID 1 tab OD-BID	200mg/ 800µg	One tab po BID One tab po BID	**$47** $61
Pyrolizine Carboxylic Acids						
Ketorolac	TORADOL® ✘	##; 10mg tab; 30mg injectable IM formulation available	10mg po q6h x7d max 10-30mg **IM** q4-6h	40mg 120mg	10mg po QID ##	$67 ##
Pyranocarboxylic Acids						
Etodolac	ULTRADOL®	~COX-2 selective; 200,300mg cap	200-600mg BID	1.2g	300mg po BID	$50
Propionic Acids						
Fenoprofen	NALFON®	300mg cap; 600mg tab	300-600mg TID-QID	3.2g	600mg po TID	$63
Flurbiprofen	ANSAID®	50, 100mg tab	50-100mg TID-QID	300mg	100mg po BID	$32
Ibuprofen	MOTRIN®	**OTC:** 200mg tab; 100mg/5ml **susp**.; Rx. 300,400,600mg tab	200-800mg TID-QID	3.2g	400mg po QID	**$13**
Ketoprofen	ORUDIS®	50,100mg EC; 200mg SR tab 50mg cap; 50,100mg supp	25-100mg TID-QID	300mg	50mg po TID	$25
Naproxen ###	NAPROSYN®	125,250,375,500mg; 750mg SR; 125mg/5ml **susp**; 500mg supp; (EC available non-formulary)	125-500mg BID	1.5g	375mg po BID	**$16**
Oxaprozin	DAYPRO® ✘	600mg caplet; long t1/2 (50h)	600-1800mg OD	1.8g	600mg po OD	$30
Tiaprofenic Acid	SURGAM®	200,300mg tab	200-300mg BID	600mg	200mg po BID	$32
Oxicams - long t1/2 (>50h)						
Piroxicam	FELDENE®	10,20mg cap & supp	10-20mg OD	20mg	20mg po OD	$33
Piroxicam-beta-cyclodextrin	BREXIDOL® ✘	20mg tab (may give 40mg x1 initially)	20mg OD x 7d max	20mg	20mg po OD ###	$97 ##
Tenoxicam	MOBIFLEX® ✘	20mg tab	20-40mg OD	40mg	20mg po OD	$51
Naphthylalkanones - long t1/2 (>24h)						
Nabumetone	RELAFEN®	~COX-2 selective; PD; 500mg tab	1-2g OD	2g	1g po OD	$43
Anthranilic Acids						
Floctafenine	IDARAC®	200,400mg tab	200-400mg TID-QID	1.2g	200mg po QID	$59
Mefenamic Acid	PONSTAN®	250mg cap; (initially 500mg x1)	250mg QID x 7d max	1.5g	250mg po QID ##	$37 ##
COX-2 Specific Inhibitors **(CSIs)** - similar efficacy to NSAIDs but less GI upset/ulceration & no effect on platelets; lack long-term/published data						
Celecoxib	CELEBREX®	100,200mg cap	100mg BID (OA) - 200mg BID (RA;**$97**)	400mg	100mg BID 200mg OD	**$52**
Rofecoxib	VIOXX®	12.5, 25mg tab; 12.5mg/ml susp; **methotrexate DI** if for acute pain: 50mg X1, then 25-50mg od (X 5d)	12.5-25mg OD (OA)	50mg	12.5mg OD 25mg OD	**$52**
Analgesics: Non-Anti-inflammatory - least GI risk; recommended as first-choice option in osteoarthritis; monitor LFTs in chronic use						
Acetaminophen	TYLENOL®	**OTC;** 325,500mg tab; 120, 325,650mg supp; syrup/elixir	325-1000mg TID-QID	4g	650mg po QID not anti-inflammatory	**$12**

= **EDS** = **E**xception **D**rug **S**tatus; ✘ Not currently approved for Provincial Formulary coverage in Saskatchewan; **NA** = not yet available; **PD** = Pro-drug; **OTC** = over the counter; **Rx** = by prescription; **OA** = osteoarthritis; **RA** rheumatoid arthritis; **susp** = suspension; **supp** = suppository; **DI** = drug interaction

Approximate retail cost to consumer based on applicable acquisition cost, markup, and dispensing fee. Lowest generic price used where available.
Cost comparison based on **lowest anti-inflammatory dose** (as per Micromedex). Lower doses of NSAIDs often effective for analgesia (except CSIs).

Monthly cost for ketorolac, mefenamic acid, & Brexidol® shown for comparison only; Recommended maximum length of oral treatment is **7 days.**

**Fast-acting formulations** available but non-formulary in SK (Anaprox® 275, 550mg tabs; Voltaren Rapide® 50mg tabs); slightly faster onset, but more expensive.

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