SK+F

Painkiller BULLETIN

Nabumetone is more gastro-friendly NSAID than Aceclofenac

Osteoarthritis (OA) is the most prevalent musculoskeletal disorder and the most common form among various types of arthritis, affecting worldwide population. The prevalence of this condition increases with increasing age and functional disability due to pain in OA is one of the most common disabilities in the elderly population and accounts for approximately half of all chronic conditions in persons older than 65 years.

Aim and objectives: the present study was done 1) To compare the efficacy of nabumetone and aceclofenac in patients with moderate to severe osteoarthritis of the knee. 2) To compare the safety of nabumetone and aceclofenac in patients with moderate to severe osteoarthritis of the knee.

Materials and methods: This is a randomized, parallel group, open label, comparative clinical study. Informed consent was taken from 72 patients out of which 4 patients were excluded as they did not meet inclusion criteria. 68 patients were then randomized into 2 treatment groups. 34 patients were given nabumetone 1000 mg tablet once a day orally and the other 34 patients were given aceclofenac 100 mg twice a day orally. Patients were instructed not to take any other drugs during the study period and the duration of the treatment is 12 weeks. Evaluation of of efficacy was done based on pain at the knee joint assessed by Visual analogue scale (VAS) at 0 and at 12 weeks and safety assessment was done based on adverse effects caused by the individual drugs during the study period.

Results: The mean reduction in VAS is 3.55 with nabumetone while with aceclofenac it is 3.37.

Although the mean reduction in VAS is slightly more with nabumetone than with aceclofenac the result is statistically not significant. The overall incidence of adverse events with nabumetone and aceclofenac was 18.75% and 21.875% respectively. $P > 0.05$,. The incidence of GI side effects was more or less similar for nabumetone 12.5% (reported by 4 patients) when compared with aceclofenac 15.625% (reported by 5 patients). But withdrawal rates because of these GI events was higher with aceclofenac (9.375%) compared to nabumetone (3.125%). $P < 0.01$, the result is statistically highly significant.

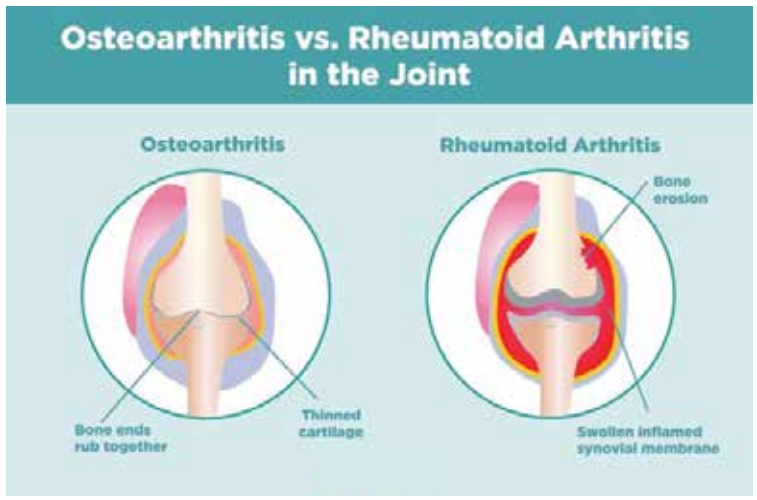
Conclusion: The efficacy and safety of nabumetone is similar to that of aceclofenac in patients with moderate to severe osteoarthritis of knee. However, Nabumetone is more gastro friendly NSAID than aceclofenac as the patient withdrawal rates are lesser for nabumetone than for aceclofenac.

Efficacy of Nabumetone versus Diclofenac, Ibuprofen, and Piroxicam in Osteoarthritis and Rheumatoid Arthritis

The efficacy of nabumetone was compared with that of diclofenac, ibuprofen, and piroxicam in patients with osteoarthritis (OA) or rheumatoid arthritis (RA) in a randomized, controlled, open-label, multicenter trial. Patients ≥18 years with clinical and radiographic evidence of OA or RA (functional class I, II, or III), who provided written informed consent, were eligible. To mimic real-life therapy, no washout phase preceded randomization. Eligible patients were assigned in a 3:1 ratio to receive nabumetone or a comparator NSAID for 12 weeks. Thus a total of 4,411 eligible patients were randomized to receive nabumetone (N = 3,315) or one of the comparator NSAIDs (N = 1,096). Initial daily doses were: nabumetone, 1,000 mg; diclofenac, 100 mg; ibuprofen, 1,200 mg; piroxicam, 10 mg. Dosage increases were permitted after a 2-week trial period.

All patients were evaluated at baseline, and at 4 and 12 weeks. Of all patients randomized, approximately 46% had RA and approximately 54% had OA. Demographic characteristics were similar for the nabumetone and comparator

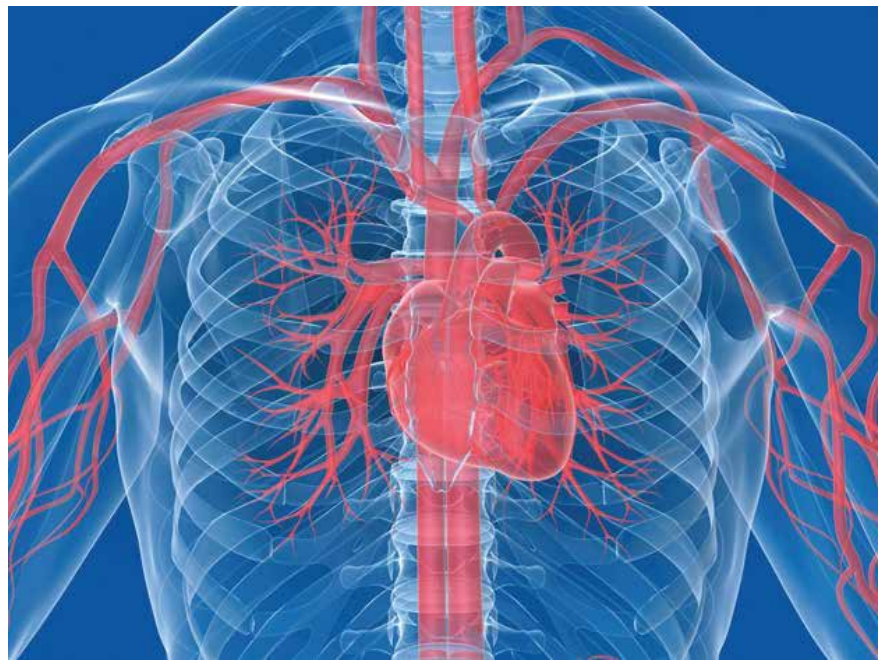
NSAID treatment groups. In OA, nabumetone was as effective as the comparator NSAIDs in the physician and patient global assessments of disease activity, in improving the Activities and Lifestyle Index, and in decreasing the degree of pain. Nabumetone was significantly ($p \leq 0.02$) more effective than the comparator NSAIDs in RA patients for the global assessments of disease activity, pain relief, and improving the Activities and Lifestyle Index, primarily due to the poor response in the ibuprofen and piroxicam treatment groups. Furthermore, fewer nabumetone-treated RA patients (8.8%) withdrew for lack of efficacy than those treated with diclofenac (10.3%), piroxicam (13.5%), or ibuprofen (13.2%).



In conclusion, in a large, randomized, open-label trial that mimicked real-life therapy, nabumetone was as effective as diclofenac, piroxicam, and ibuprofen for the treatment of patients with OA. However, in RA, nabumetone was significantly more effective than the comparator NSAIDs, and fewer patients were withdrawn because of lack of efficacy.
(https://www.sciencedirect.com/science/article/abs/pii/00029343939039)

Present evidence suggests that Naproxen is the safest NSAID and might be preferred in patients prone to CVS events

Nonsteroidal anti-inflammatory drugs (NSAIDs) are in use since 1960. They are non specific cyclooxygenase (COX) enzyme inhibitors. Later, specific COX-2 inhibitors were introduced starting with rofecoxib. NSAIDs and COX-2 inhibitors are common drugs used in the management of mild-to-moderate pain. Although these drugs provide good pain relief, they should be used with caution due to cardiovascular (CVS) side effects associated with its use. Although paracetamol and aspirin are nonopioids recommended by the WHO as the first-line agents for managing cancer pain and non cancer chronic pain, NSAIDs are mostly used instead of aspirin. Of all NSAIDs currently in use, naproxen seems to have a safe CVS profile.



COX-1 and COX-2 enzymes are essential for homeostasis. COX-1 protects gastric mucosa from acid and generates thromboxane A2 (TXA2) by activating platelets in response to injury. Factors precipitating CVS events such as platelet aggregation, vasoconstriction, and increase in vascular and cardiac remodeling are mediated by COX-1 via TXA2. This means that selective COX-1 inhibition will inhibit TXA2 production, thereby preventing adverse CVS events. COX-2 activation leads to prostanoid production due to the release of inflammatory mediators.
Endothelial cells express COX-1 and COX-2, whereas platelet aggregation is mediated by COX-1 only. NSAIDs are classified as nonselective or selective depending on the COX inhibition caused by their use. The COX-2 inhibitors preferentially inhibit COX-2 enzyme with a very minimal COX-1 inhibition. They do not have any antiplatelet effects due to negligible COX-1 effect. Although COX-2 inhibitors protect gastrointestinal (GI) mucosa, the non-COX- 1 effects lead to thrombotic events which made them notorious. Among all the nonselective NSAIDs, naproxen has increased selectivity for COX-1 and negligible COX-2 inhibition. This differential selectivity of naproxen is the reason for CVS safety. Naproxen has a long half-life owing to which it strongly inhibits platelet aggregation reversibly by inhibiting COX-1. When compared to other NSAIDs, sodium retention with the use of naproxen is less as a result of which increase in systolic blood pressure is less. Like any other NSAIDs, naproxen also reduces renal blood flow due to prostaglandin inhibition. Therefore, the drug should be avoided in acute and chronic renal failure and in predisposing situations.

In 2004, rofecoxib was banned due to serious adverse CVS events associated with its use. Later, celecoxib was introduced and showed promise due to less CVS events associated with its use. The Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen trial showed noninferiority of moderate doses of celecoxib when compared with naproxen or ibuprofen, with regard to the CVS outcome with celecoxib treatment, resulting in lower rates of GI and renal adverse events. Still, naproxen has an edge over celecoxib due to its mechanism of action which is different from other NSAIDs such as ibuprofen and diclofenac. The present evidence suggests that naproxen is the safest NSAID and might be preferred over celecoxib in patients prone to CVS events.
(https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6388596/)

Naproxen plus acid blocking drug shows promise in preventing Bladder Cancer

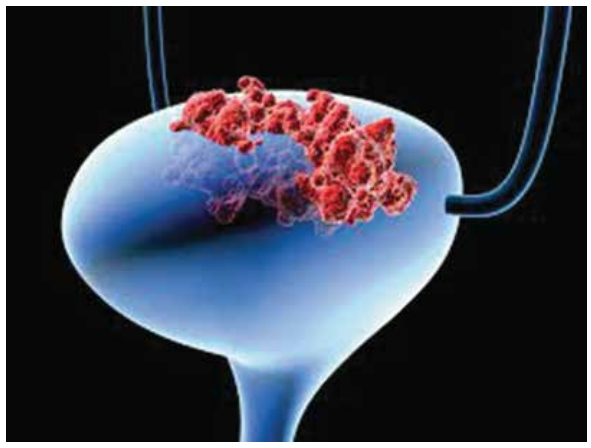
The anti-inflammatory class of drugs NSAIDs have shown great promise in preventing cancers including colon, esophagus and skin. However, they can increase the risks of heart attacks, ulcers and rare but potentially life-threatening bleeds.

A new study suggests there may be ways to reduce these dangerous side effects.

Collaborators from the University of Michigan, the National Cancer Institute and the University of Alabama looked at naproxen, which is known to have a lower cardiovascular risk than other NSAIDs. Naproxen, like most NSAIDs and aspirin, does increase the risk for gastric ulcers or bleeding. Here, the researchers used the proton pump inhibitor omeprazole, a commonly used acid inhibitor, in combination with naproxen and tested its effects on cancer prevention in a rat model of bladder cancer.

They found that naproxen reduced the incidence of bladder cancer by 75 percent in rats. Omeprazole by itself did not affect the development of cancer but it also did not interfere with the effect of naproxen at preventing tumors.

The rats who received naproxen alone or naproxen with omeprazole developed cancer at similarly low rates, while all rats receiving omeprazole alone or no treatment developed bladder cancer.
Clinical data in humans has previously shown combining omeprazole plus naproxen reduced gastric toxicity roughly 70 percent.



The authors also found that intermittent dosing with naproxen (three weeks on the drugs, followed by three weeks off) was highly effective and likely to reduce gastric toxicity. However, it does not have the clear clinical data supporting reduced gastric toxicity associated with naproxen and omeprazole.

"Our study shows that naproxen works just as well with a proton pump inhibitor as without. This provides proof of principle that this could be a valuable cancer prevention strategy and one hopes it can advance quickly to a clinical trial for those at high risk of colon, esophageal, squamous cell skin cancer or potentially other cancers," says lead study author Ronald A. Lubet, Ph.D., a scientist with the Chemo-preventive Agent Development Research Group at the National Cancer Institute.

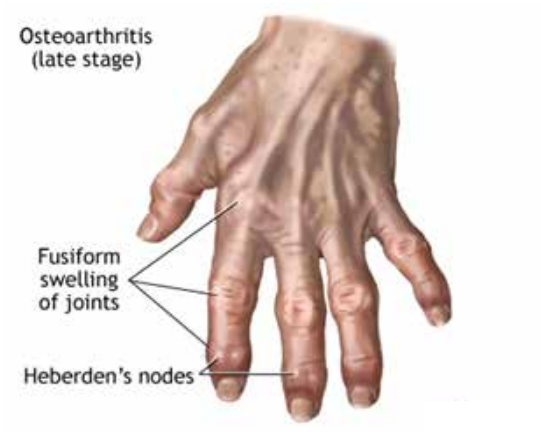
"The ability to reduce the gastric effects of NSAIDs adds another element to ongoing discussions of whether the NSAID aspirin might be applicable to prevention studies in a more general population, since the gastric toxicity of even low-dose aspirin has been considered a hurdle," he adds.

The current study is published in the American Association for Cancer Research journal Cancer Prevention Research.

"Naproxen is a great candidate for chemoprevention. It comes with a risk of gastrointestinal side effects, but if you can mitigate that with a co-prescription, it's possibly an ideal chemoprevention drug," says study author James Scheiman, M.D., professor of gastroenterology at the University of Michigan Medical School. Scheiman has studied the use of NSAIDs in chemoprevention and has co-authored guidelines on the gastrointestinal risks of aspirin and NSAIDs.
(https://medicalxpress.com/news/2015-03-naproxen-acid-blocking-drug-bladder.html)

Gastrointestinal safety of Etoricoxib in Osteoarthritis and Rheumatoid Arthritis

To ascertain if etoricoxib increases the risk of gastrointestinal adverse events (GAEs) compared with placebo, diclofenac, and naproxen in the treatment of patients with osteoarthritis (OA) or rheumatoid arthritis (RA).



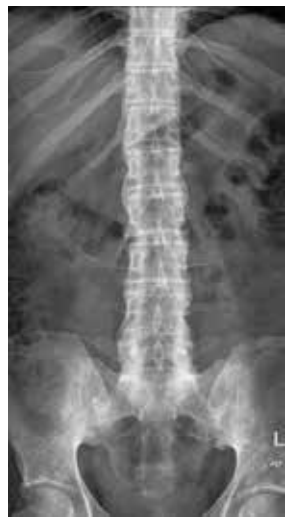
We found nine randomized clinical trials (RCTs) that included information on gastrointestinal safety during follow-up time. Among them, five RCTs compared etoricoxib with placebo, four RCTs compared etoricoxib with diclofenac, and three RCTs compared etoricoxib with naproxen. Etoricoxib did not increase the risk of GAEs compared with placebo. Compared with diclofenac and naproxen, etoricoxib reduced the GAE risk (RR, 0.67; 95% CI, 0.59–0.76; p < 0.00001; 0.59; 0.48–0.72; < 0.00001) during follow-up time.

In patients with OA or RA, etoricoxib did not increase the GAE risk compared with placebo, but reduced the GAE risk effectively compared with diclofenac and naproxen during follow-up time.

To access the full article visit :
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5761870/

Etoricoxib is the most cost-effective initial NSAID treatment for AS patients

To evaluate the cost effectiveness of etoricoxib (90 mg/day) relative to celecoxib (200 or 400 mg/day), and the non-selective NSAIDs naproxen (1000 mg/day) and diclofenac (150 mg/day) in the initial treatment of ankylosing spondylitis (AS) from the UK NHS perspective.



A Bayesian cost-effectiveness model was developed to estimate the costs and benefits associated with initiating AS treatment with etoricoxib, celecoxib, diclofenac or naproxen. Efficacy, safety and medical resource and cost data were obtained from the literature. The obtained efficacy estimates were synthesized with a mixed treatment comparison meta-analysis. Treatment benefit and degree of disease activity, as reflected with Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) scores, were related to QALYs and AS-specific costs (related to BASDAI).

Other cost outcomes related to drug acquisition, and gastrointestinal and cardiovascular safety. Uncertainty in the source data was translated into uncertainty in cost-effectiveness estimates and therefore decision uncertainty. Costs and outcomes were discounted at 3.5% per annum. There was a >98% probability that treatment with etoricoxib results in greater QALYs than the other interventions. Over a 30-year time horizon, starting AS treatment with etoricoxib was associated with about 0.4 more QALYs than the other interventions. At 2 years there was a 77% probability that etoricoxib had the lowest cost. This increased to >99% at 30 years. Etoricoxib is expected to save 13 620 UK pounds (year 2007 values) relative to celecoxib (200/400 mg), 9957 UK pounds relative to diclofenac and 9863 UK pounds relative to naproxen. For a willingness-to-pay ceiling ratio of 20 000 UK pounds per QALY, there was a >97% probability that etoricoxib was the most cost-effective treatment. Additional analysis with different assumptions, including celecoxib 200 mg, and ignoring cost-offsets associated with improvements in disease activity, supported these findings. This economic evaluation suggests that, from the UK NHS perspective, etoricoxib is the most cost-effective initial NSAID treatment for AS patients.

Commonly used NSAIDs and their risk of Gastrointestinal Bleeding and Perforation

Drug	Daily adult dose	Doses/ day	Idiosyncratic side-effects, comments
Low risk			
Celecoxib	100–200 mg	1–2	Both are Selective COX-2 inhibitor
Etoricoxib	60–120 mg	1	
Medium risk			
Ibuprofen	1600–2400 mg	3–4	Gastrointestinal adverse effects more likely than with COX-2 inhibitors, even with PPI therapy
Naproxen	500–1000 mg	1–2	
Diclofenac	75–150 mg	2–3	
High risk			
Indometacin	50–200 mg	3–4	High incidence of dyspepsia and CNS side-effects
Ketoprofen	100–200 mg	2–4	
Piroxicam	20–30 mg	1–2	Restricted use in those > 60 years

(Reference : Davidson's principles and practice of medicine 24th Edition Table 24.30 Page 1003)

Dos & Don'ts In prescribing NSAIDs:

Dos:

- Use the lowest dose for the shortest time possible to control symptoms.
- Allow 2–3 weeks to assess efficacy. If response is inadequate, consider a trial of another NSAID.
- Co-prescribe a proton pump inhibitor for patients with risk factors for gastrointestinal adverse effects.

Don'ts:

Avoid NSAIDs in patients on warfarin.

- Never prescribe more than one NSAID at a time.
- Avoid in patients with vascular disease.(Reference: Davidson's principles and practice of medicine 24th Edition Table 24.32 Page 1003)

Safest, most effective medications for Spine-Related Pain in older adults?

Some medications are safer and more effective than others for treating spine-related pain in older patients, a new comprehensive literature review suggests.

Investigators assessed the evidence for medications used for this indication in older adults by reviewing 138 double-blind, placebo-controlled trials.

Among their key findings and recommendations: acetaminophen has a favorable safety profile for spine-related pain but nonsteroidal anti-inflammatory drugs (NSAIDs) have greater efficacy.

However, NSAIDs should be used in lower doses in the short term, with gastrointestinal precaution, the researchers note.

Corticosteroids have the least evidence for treating nonspecific back pain, they add.

"Most older people experience neck or low back pain at some point, bothersome enough to see their doctor," co-investigator Michael Perloff, MD, PhD, Department of Neurology, Boston University School of Medicine, Massachusetts, said in a news release.

"Our findings provide a helpful medication guide for physicians to use for spine pain in an older population that can have a complex medical history," Perloff added.

The results were published online June 27 in Drugs and Aging.

Recommendations, Warnings

With the graying of the US population, spine-related pain is increasingly common, the investigators note.

Medications play an important role in pain management, but their use has limitations in the elderly, owing to reduced liver and renal function, comorbid medical problems, and polypharmacy.

Other key findings from the literature review include that although the nerve pain medications gabapentin and pregabalin may cause dizziness or difficulty walking, they also have some demonstrated benefit for neck and back nerve pain, such as sciatica, in older adults.

These agents should be used in lower doses with smaller dose adjustments, the researchers note.

They caution that the muscle relaxants carisoprodol, chlorzoxazone, cyclobenzaprine, metaxalone, methocarbamol, and orphenadrine should be avoided in older adults because of their association with risk for sedation and falls.

Rational Therapeutic Choices

"Medications used at the correct dose, for the correct diagnosis, adjusting for preexisting medical problems can result in better use of treatments for spine pain," co-investigator Jonathan Fu, MD, also with the Department of Neurology, Boston University School of Medicine, said in the release.
"Rational therapeutic choices should be targeted to spine pain diagnosis, such as NSAIDs and acetaminophen for arthritic and myofascial-based complaints, gabapentinoids or duloxetine for neuropathic and radicular symptoms, antispastic agents for myofascial-based pain, and combination therapy for mixed etiologies," the investigators write.
They also emphasize that medications should be coupled with physical therapy and exercise programs, as well as treatment of the underlying degenerative disease process and medical illness - while keeping in mind the need for possible interventions and/or corrective surgery.
(Source: https://www.medscape.com/viewarticle/976859)

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