Are NSAIDs inferior to other analgesics?

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Introduction

"**Pain**" can be defined as an unpleasant sensory and emotional experience associated with true or potential tissue damage, or described in terms of such damage. Pain is always subjective.

According to the *Stedman's Medical Dictionary*, "**analgesia**": is a condition in which nociceptive stimuli are perceived but are not interpreted as pain. This is usually accompanied by sedation without loss of consciousness.[1]

An analgesic, therefore, is a compound capable of producing analgesia, i.e. one that relieves pain by altering perception of nociceptive stimuli without producing loss of consciousness. Analgesics mostly function as central nervous system depressants. Specific receptors play a role in this regard, namely mu-receptors.[1] Drugs acting on these receptors are classified as analgesics and include morphine, pethidine and codeine. They are also referred to as narcotic or opioid analgesics. Tramadol is only partly an opioid analgesic, i.e. ± 30%. The rest have a mono-aminergic function.

Non-steroidal anti-inflammatory (NSAIDs) are drugs with analgesic effects, but are not classified as narcotic analgesics. Their mechanism of action is totally different from that of the opioid narcotics.

Classification

NSAIDs may be used in the treatment of inflammation and pain in a wide variety of disorders. NSAIDs constitute a diverse group of chemicals, categorised according to their chemical structures, that share the same therapeutic properties.

A wide variety of NSAIDs are available:

- Salicylates: aspirin, methyl salicylate, diflunisal;
- Arylalkanoic acids: indomethacin, sulindac, diclofenac;
- 2-arylpropionic acids (profens): ibuprofen, ketoprofen, naproxen, ketorolac;
- N-arylanthranilic acids: mefenamic acid;
- Oxicams: lornoxicam, piroxicam, meloxicam;
- Sulphonanilides: nimesulide;
- Coxibs: celecoxib, valdecoxib, etoricoxib.
- Pharmacokinetics

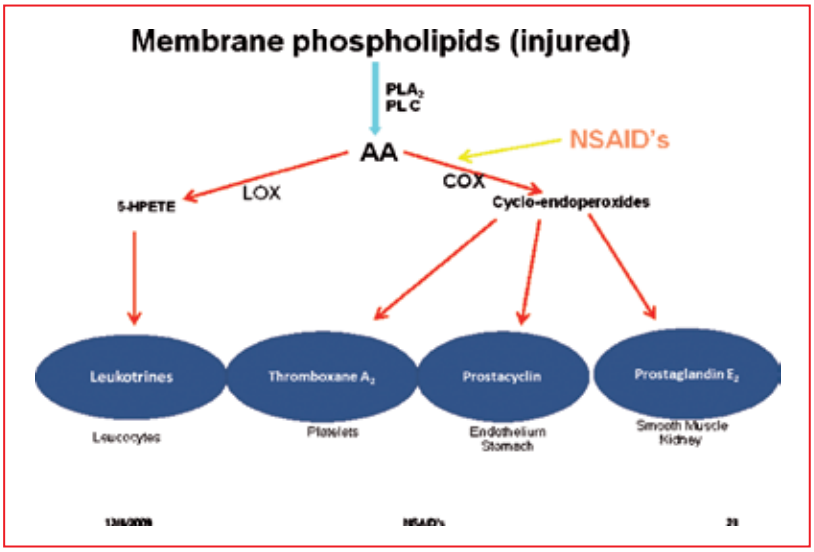
NSAIDs are weak acids, with a pKa of 3 – 5. They are highly bound to albumin, and are metabolised by the liver by either conjugation or oxidation. Excretion occurs primarily through the kidneys and, to a lesser extent, by the liver via the bile. The volume of distribution approximates plasma volume.

Mechanism of action

NSAIDs have analgesic, antipyretic and, in higher doses, anti-inflammatory effects. The term "non-steroidal" is used to distinguish these drugs from steroids, which have similar eicosanoid-inhibiting, anti-inflammatory actions. As analgesics, NSAIDs are unusual in that they are non-narcotic.

Most NSAIDs are non-selective inhibitors of the enzyme cyclo-oxygenase, inhibiting both the cyclo-oxygenase-1 (COX-1) and cyclo-oxygenase-2 (COX-2) iso-enzymes. Cyclo-oxygenase catalyses the formation of prostaglandins and thromboxane from arachidonic acid, which is derived from the action of phospholipase A_2 on the cellular phospholipid bilayer. Prostaglandins act as messenger molecules in the process of inflammation.

Figure 1: The COX-1 pathway



The COX-1 pathway is called the "constitutive pathway".The end product of each iso-enzyme has an effect on:

- Kidney function: production of prostaglandin E2, which controls normal glomerular filtration rate;
- Stomach protection: prostacyclin, which controls the formation of gastric mucous to protect the stomach lining against the effects of acid release;
- Platelet function: thromboxane A2, which is involved in the normal process of platelet adhesion;
- Other functions, for example, uterine function.
- The COX-2 pathway is called the "Induced pathway".

The purpose of administering NSAIDs is to challenge the COX-2 pathway and stop the inflammatory effects that occur with tissue damage. However, with the administration of traditional NSAIDs, the COX-1 pathway is also affected, resulting in the appearance of side-effects such as impaired renal function, gastric complaints, and bleeding tendencies.

Figure 2: The COX-2 pathway

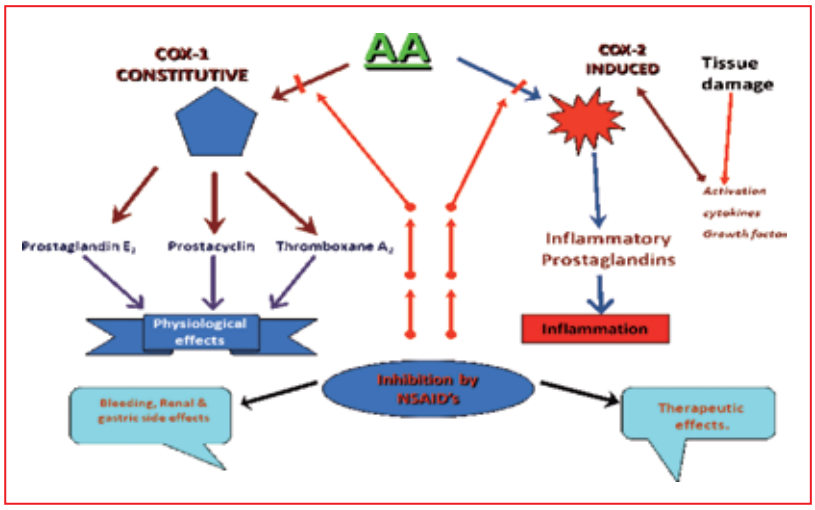
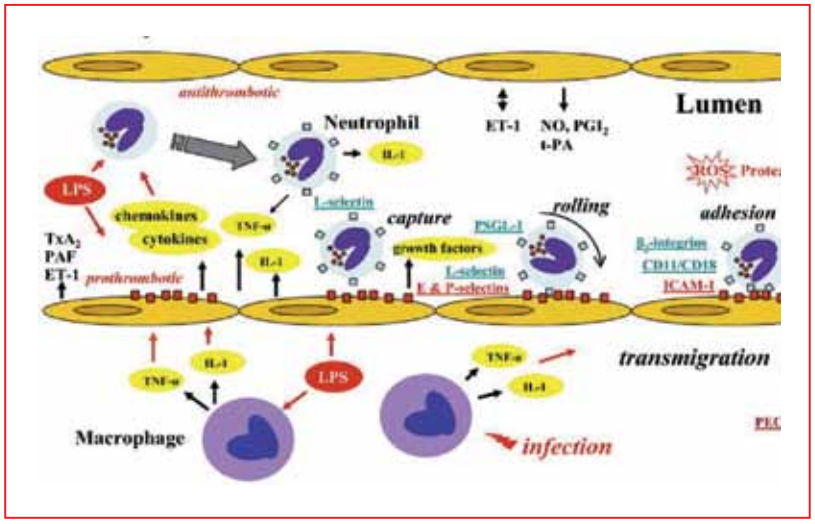


Figure 3: Inflammation is a complex process.



From: Orfanos, et al.[2,3]

The development of COX-2 specific inhibitors was aimed at preventing these side-effects, but whether this has been successful is still debatable. Post-launch data have indicated increased risk of cardiac and cerebrovascular events, due to an increased likelihood of clotting arising from a decreased production of prostaglandin around the platelets, resulting in diminished clotting factor release. Rofecoxib was subsequently withdrawn from the market due to this complication.

Originally, it was thought that administering NSAIDs would abolish pain by way of elimination of the inflammatory process. The inhibition of the COX-1 and COX-2 pathways was believed to be the only mechanism of action of the NSAIDs.

However, cumulative data indicate that NSAIDs also act on other targets to counteract pain. Their analgesic effects are not necessarily the consequence of their anti-inflammatory action.[4] Administration of NSAIDs reduces cutaneous and corneal pain induced by acidic pH in the absence of inflammation.

A recent study demonstrated that various NSAIDs also inhibit the activity of acid-sensing ion channels (ASICs) at therapeutic analgesic doses.[5] The ASICs are members of a sodium channel superfamily, and are activated by an increase in extracellular acidity (i.e. tissue acidosis).

ASICs are more sensitive to pH changes and, depending on the exact composition of the subunits, can detect an extracellular pH decrease from 7,4 to 7,0. A number of inflammatory mediators enhance ASIC activity and expression, and further implicate neuronal ASICs as key players in pain arising from tissue acidosis. Sensory neurons express both ASIC-1 and ASIC-3 subtypes, and both these subtypes have been implicated in nociception.[6]

This reduction in tissue pH occurs in acute and chronic pøºain conditions, including :

- Inflammation;
- Angina;
- Stroke;
- Ischaemic heart disease;
- Arthritis;
- Cancer; and
- Trauma.

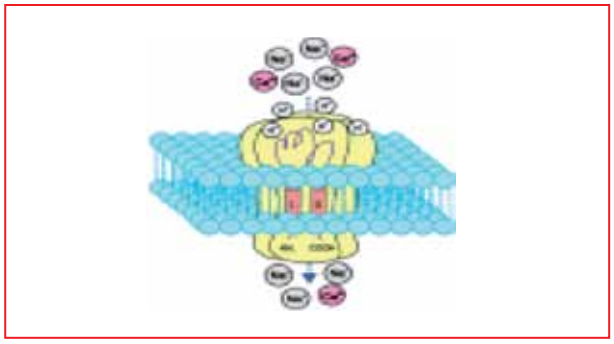
Tissue acidosis is associated with inflammation and is a significant source of pain. During inflammation, the extracellular pH values decrease (below pH=6), activating nociceptors by gating the ASICs. The ASICs are sodium channels belonging to the degenerin/ENaC super family. The most interesting, in the context of pain, is ASIC3, which is predominantly expressed in DRG neurons, making it a good candidate as a pain sensor.[7]

To date, six different isoforms of ASIC channels have been identified:[8]

- ASIC1a;
- ASIC1b;
- ASIC2a;
- ASIC2b;
- ASIC3; and
- ASIC4.

Of the six ASIC subunits, ASIC1 (1a/1b) and ASIC3 are widely distributed in the primary sensory neurons that detect and signal painful sensations to the brain, and thus are attractive targets for the treatment of pain. ASIC3 and ASIC1a are activated in an acidity range pH 7,0 – 6,0, which is seen in several acute and chronic pain conditions. Moreover, ASIC3 senses lactic acidosis created by anaerobic metabolism, and thus is considered an important component of the acid-sensing pain response in conditions such as cardiac and muscle ischaemia.

Figure 4: Proposed tetrameric structure of ASICs. Each channel is assembled by 4 identical or different subunits. Each subunit consists of two transmembrane domains (I and II), linked by large cysteine-rich extracellular domains with intracellular N- and C-.



From: Xiong et al[5]

In humans, ASIC3 contributes to hyperalgesia and allodynia in inflammation. ASIC3 is more widely distributed in humans than in mice, which may indicate a more extensive role in human nociception.

The sensitivity of ASICs to acidosis and their distribution in primary sensory neurons points to a significant role of these channels in acid nociception. However, despite the fact that the first ASIC was identified more than 10 years ago, the physiological and pathophysiological role of this channel family remains poorly understood. Some of the recent drug discoveries and ongoing development activities in laboratories point to ASICs as a relevant target for pain modulation.[9]

The manner in which these channels works seems to be an interaction with high-conductance Ca^{2+}- and voltage-activated K^+ (BK) channels.[10] The wide and varied expression patterns of ASICs, BK, and related K^+ channels suggest broad opportunities for this signalling system to alter neuronal function.

Ibuprofen and flurbiprofen, for example, inhibit ASIC1a. Aspirin and salicylate inhibit ASIC3-containing channels, whereas diclofenac inhibits the same channels with an IC_{50} of only 92 µM.[11]

The combined inhibition of NSAIDs on prostaglandin synthesis, ASIC currents, and ASIC expression make them ideal for the treatment of a large spectrum of pain conditions, particularly the pain caused by tissue inflammation. In the acute phase of tissue inflammation, for example, the rapid inhibition of ASIC currents by NSAIDs blocks the activation of pain-sensing neurons by inflammatory acidosis. Later,

Table I: Function of the ASICs

Name	Isoform	Alternative name	Expression pattern	Function
ASIC 1	ASIC 1a	BNaC2α	CNS SN	Synaptic plasticity, learning, memory
	Asic 1b	BNaC2ß	SN	Channel modulation?
ASIC 2	ASIC 2a	MDEG, BNaC1α	CNS SN (+) taste buds	Sour taste sensing, mechanosensation, brain tumour suppression
	ASIC 2b	MDEG2, BNaC1ß	CNS SN (+++) taste buds	Sour taste sensing
ASIC 3		DRASIC	SN	Pain modulation, ischaemic pain, mechanosensation
ASIC 4		SPASIC	CNS inner ear	Channel modulation?

SN = sensory neurons; CNS = central nervous system
Adapted from Bronstein Sitton[9]

the NSAIDs suppress the inflammation and pain via their effect on COX, limiting the production of prostaglandins. In the chronic phase, they may reduce the sensitisation to pain by combined inhibition of COX, ASIC currents, and ASIC expression.

Changes in pH have profound influence on the physiology of neurons, and in pathological conditions affect the outcome of neuronal injury.[12] Mild acidosis, for example, has been reported to reduce excitatory injury of neurons, most likely due to proton inhibition of NMDA channels.[13] Severe acidosis, on the other hand, induces neuronal injury. For decades, the entity or receptor that detects pH changes surrounding neurons and its signal transduction pathway remained elusive. The recent finding that a fall in pH activates a distinct class of cation channels, the ASICs, in peripheral sensory neurons and in the neurons of the central nervous system, dramatically changed the view of acid signalling and offered new pharmacological targets for neurological diseases.

Tissue acidosis, which is a dominant factor in inflammation, tumours and ischaemia, has an important contribution to pain and hyperalgesia. This is due to direct stimulation of the nociceptive sensory receptors by protons-gated depolarising currents. Actually, these receptors consist of a large number of ion channels that are sensitive to extracellular pH changes, i.e ASICs. ASIC channels are able to induce action potential triggering on sensory neurons after a moderate extracellular pH decrease. They undergo transcriptional induction and post-translational regulation during inflammation, and thus participate in the hypersensitisation of the nociceptive system in this pathophysiological condition.[14]

COX-independent direct inhibition of their activity by different NSAIDs has been shown to occur at therapeutic doses of these compounds, on native ASIC currents on sensory receptors, as well as on ASIC channels expressed in different systems.

NSAIDs have been found to prevent the inflammation-induced expression of acid-sensing ion channels. These two effects are thus proposed to play an important role in the analgesic effects of NSAIDs in addition to their well-known action through COX, and particularly in case of inflammation. The terms involving "ASIC" could be most advantageous, also indicating the tissue specificity (e.g. the dorsal root ASIC, DRASIC). However, it is still unclear whether H^+ are, in fact, natural ligands of these peculiar receptor channels.[15]

NSAIDs as analgesics

Oother mechanisms by which NSAIDs can produce analgesia is by the inhibition of inflammatory mediator release from neutrophils and a central neuromodulatory effect, probably mediated by NMDA receptors. Central NMDA receptors activate the nitric oxide system, which causes the release of prostaglandins.[16]

Nitric oxide (NO) is a soluble gas neurotransmitter and plays a role in gastric protection. It increases mucus and bicarbonate production, and decreases neutrophil adherence to the endothelium, both of which are key events in the pathogenesis of NSAID-induced gastropathy. Nitric oxide-releasing non-steroidal anti-inflammatory agents (NO-NSAIDs) have also been found to increase the anti-inflammatory effects of NSAIDs thus potentiating the analgesic effects of such drugs.[17,18]
NSAIDs have been the mainstay of pharmacological management of mild cancer pain, and as adjuvants for moderate to severe cancer pain and bone pain.

However, the most popular use of NSAID's currently is as an adjunct to opioid use. This approach decreases total opioid consumption and, hence, the unwanted adverse effects associated with opioid use. The opioid-sparing effect of NSAIDs has been shown in cancer pain literature as well as in other contexts such as acute postoperative pain. Potential limitations to this approach include the known ceiling effect on analgesic efficacy with increasing dose and adverse effects associated with long-term NSAID use.

Using NSAIDs in the context of balanced, or multimodal, analgesia is preferred, because the use of drugs from two or more analgesic classes will alter more than one nociceptive pathway, producing a synergistic effect. Combinations of analgesics also reduce the amount of each drug used, minimising the risk of side effects associated with each.

An example of multimodal analgesia would be preoperative administration of a parenteral NSAID and a parenteral opioid, followed by intra-operative use of an epidural opioid or intra-articular anaesthetic, and concluding with a local anaesthetic block of the wound with postoperative oral NSAID for extended analgesia following surgery. The combination of NSAID and morphine results in a 20 - 40% reduction in the use of opioids in the immediate post-operative period following medium and major surgery. Opioid and NSAIDs adverse effects are also minimised.[19]

Conclusion

To answer the question "are NSAIDs inferior to other analgesics?", there is an emphatic "no". NSAID's act as a class of their own. The mechanism of action is still being researched, with the end still not being in sight.

In specific situations, NSAIDs can be excellent analgesics on their own, or an excellent adjunct to opioid analgesia specifically in the postoperative setting.

Declaration

I have not received any financial compensation for this article.

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References are available from the author