The Efficacy of Nonsteroidal Anti-inflammatory Drugs for Acute Pain

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Introduction

The modern science of drug testing began to mature in the 1960s, when scientific methodology developed the capability to provide demonstrable safety and efficacy data on new drugs, such as those used for the pharmacotherapy of pain. In subsequent decades, standardized models have been developed that constitute a key component of a sophisticated methodology permitting the objective investigation of analgesics.

Various major models of acute pain are now accepted as important areas of investigation for clinical trials. The postoperative pain model is among the most important and has been explored in clinical trials in a wide range of surgeries, such as postorthopedic, postgeneral, and postgynecologic surgery.

The oral surgery model, which focuses on the extraction of impacted third molars, is important because it is associated with several distinct advantages of experimental approach. Major advantages include the following: the patients in whom the evaluation of pain management is studied are young and healthy, and they can be rapidly enrolled; the degree of interpatient variation is less than is characteristic of other pain models; and these patients are generally naive of previous pain experiences.

Dysmenorrhea provides another important model for pain management because this self-repeating condition is suitable to investigation by means of crossover design. More than one treatment may be administered to each patient over the course of several months. Such an experimental strategy addresses interpatient variations through the study design itself.

Analgesic research methodology has been enhanced since the 1960s through the use of categorical and visual analog scales. These scales are tools that permit the standardization of pain scores, thus a rationalization of the results of analgesic trials. Decades of scientific study have shown that they provide the best indication available for the evaluation of the efficacy of analgesics. One frequently used categorical scale is a four-point measure of pain intensity (0 = no pain, 1 = mild pain, 2 = moderate pain, 3 = severe pain) and a five-point measure of relief (0 = no relief, 1 = a little relief, 2 = some relief, 3 = a lot of relief, 4 = complete relief). Visual analogue scales are also used to measure pain. The validity and reliability of both categorical and visual analogue scales have been confirmed in numerous trials, although the visual analogue scale appears to be slightly more sensitive for the measurement of both acute and chronic pain.1

Additional advances in the study of nonsteroidal anti-inflammatory drugs (NSAIDs) used to treat acute pain include methods to approach the definition of differing characteristics that affect the relative efficacy of various analgesics. For example, a variety of variables have been employed to ascertain how the benefits conferred by a drug with a rapid onset, but a short duration of action differentiate from the benefits conferred by another drug with a longer onset, and an extended duration. Results of clinical studies are analyzed so that data are produced that measure, for example, the sum of pain intensity differences (the difference between baseline pain compared to subsequent pain assessments summed over time) and the total pain relief achieved over time. In addition, a measurement of the percentage of patients requiring rescue analgesia in placebo-controlled studies, after one or more hours, has become an important endpoint for clinical analgesic trials. Furthermore, patients' global assessment of a drug, ie, how they feel about it overall, can be an important measure of the clinical effectiveness of an analgesic. The quantitative measurement of the safety and tolerability of pain medications has also been developed.

Analgesic Properties of NSAIDs — Mechanism of Action

NSAIDs are known to have analgesic and anti-inflammatory effects albeit sometimes at different doses, depending on the particular drug. Initially, the analgesic effect was thought to be peripheral in nature by modulating the response of the nociceptor. More recent data have suggested a dual action, both peripheral and central.2-4

Peripheral Mechanism

With cellular damage, there is release of products of both the cyclooxygenase and lipooxygenase pathways resulting in prostaglandins and leukotrienes. Prostaglandins sensitize afferent neurons (nociceptors) to noxious stimuli such as chemical, heat, and mechanical pressure.5,6 Prostaglandins and leukotrienes probably do not activate the nociceptors directly, but work through activation of cyclic adenosine monophosphate (cAMP),7,8 and/or activation of products of polymorphonuclear cells. Inhibition of prostaglandins or leukotrienes by NSAIDs results in analgesia.

Central Mechanism

Evidence now indicates that NSAIDs are antihyperalgesic through a direct action on the spinal cord (central mechanism).9 This effect can be dissociated from the peripheral action of NSAIDs and may be dissociated from their anti-inflammatory mechanism.

As a painful stimulus activates the peripheral nociceptor, stimuli are sent along the afferent C fibers into the dorsal horn where they synapse with second-order neurons for transmission to higher centers. One of these mechanisms, known as windup, allows for amplification of an incoming signal in both intensity and duration to create a state of hyperalgesia. With repetitive C-fiber nociceptor stimulation from the periphery, excitatory amino acids (neurotransmitters) such as glutamate and aspartate, as well as several peptides (including substance P) are thought to increase. These cause activation of NMDA (N-methyl D-aspartate) receptors of the postsynaptic second neuron in the dorsal horn. Activation of these receptors is not thought to function to transmit nociceptive information evoked by a peripheral stimulus, but rather to facilitate the processing of such incoming signals to create a state of hyperalgesia (windup in the dorsal horn). Experiments utilizing intrathecal NSAIDs in the rat model,9 as well as antagonists to the NMDA
receptor, suppressed the hyperalgesic component but not the acute pain behavior of the pain stimulus. In addition, intrathecal injection of several cyclooxygenase products such as PGE$_2$, PGD$_2$, and PG also functioned in this model to induce a hyperalgesic state. NSAIDs are thought to block activation of the NMDA receptor induced by excitatory amino acids released by repetitive C-nociceptor firing. This is thought to occur through calcium-induced release of prostaglandins in the dorsal horn. By blocking this activation in the experimental model, NSAIDs are thought to be antihyperalgesic. Lastly, NSAIDs block windup at doses much lower than doses required for systemic effects.

Thus, NSAIDs work in the periphery by decreasing the sensitivity of the nociceptor to painful stimuli induced by heat, trauma, or inflammation. In the central nervous system, they are thought to function as antihyperalgesics and block the increased transmission of repetitive incoming signals to higher centers. In effect, they modulate perception of pain (which is enhanced through windup in the dorsal horn) caused by repetitive stimulation from the periphery. Since they function by modulation of the perception of pain, they may be useful when given in the preoperative period and may reduce the need for postoperative analgesia.

**Efficacy of NSAIDs**

A considerable number of NSAIDs with proven efficacy and safety are currently available for prescription and nonprescription use. Many patients with acute pain obtain good pain relief with these drugs. Pharmacotherapy may be an important component of a multimodal or balanced approach to the management of pain.\textsuperscript{10}

"Drug therapy is the mainstay of treatment for the management of acute pain," according to the American Pain Society. Three facts relative to the efficacy of non-opioid analgesics for acute pain management need mention: (1) NSAIDs possess proven efficacy for mild to moderate acute pain, (2) The potency of some NSAIDs is greater than that of others. Several of the newer NSAIDs have demonstrated potency comparable to or greater than that of opioid agents and are indicated for postoperative pain management.\textsuperscript{11,13} (3) Since individual patient response varies considerably,\textsuperscript{11,13,14} therapeutic failure with one agent does not preclude success with another. Analgesics may require adjustment until the patient reports adequate pain relief. Such an adjustment can be guided by the "analgesic ladder" promulgated by the Cancer Pain Relief and Palliative Care Program of the World Health Organization (Figure).\textsuperscript{14}

**Potency of Nonnarcotic Analgesics**

Nonnarcotic analgesics have been differentiated into two broad levels of potency: (1) low or moderate potency and (2) potency comparable to that of opioids.\textsuperscript{15}

**NSAIDs of Moderate Potency**

A considerable number of nonnarcotic analgesics can provide effective pain relief. However, clinically important differences have been shown among agents of moderate potency. Therefore, it is useful to differentiate between those NSAIDs with a half-life of less than 6 hours and those with a half-life of more than 10 hours.\textsuperscript{13} As a rule, agents with long half-lives will have a slower onset of action. The use of a medication with a rapid onset is helpful to patients with acute conditions.

Acetaminophen is comparable to the potency of aspirin in its analgesic and antipyretic effects. It has no known antiplatelet and little anti-inflammatory activity. Clinicians should be aware of the total amount of acetaminophen being taken by a patient per day.\textsuperscript{16,18}

Etodolac may be used to provide relief for postoperative pain and pain associated with gouty conditions and traumatic injury.\textsuperscript{19} Etodolac, nabumetone, and COX-2 selective agents are associated with less gastric injury when prescribed at doses commonly used to treat osteoarthritis.\textsuperscript{20,21}

Mefenamic acid is approved for analgesia of moderate pain. It is determined to possess efficacy for pain of dysmenorrhea.\textsuperscript{22,23}

Naproxen has a half-life of 12 to 14 hours, and twice-a-day dosing may be employed. Peak plasma levels are attained 2 to 4 hours following administration.\textsuperscript{24} It provides effective relief in acute traumatic injury and for acute pain associated with migraine, tension headache, postoperative pain, postpartum pain, pain consequent to various gynecologic procedures, and the pain of dysmenorrhea.\textsuperscript{25}

Sulindac is specifically indicated for acute painful shoulder (acute subacromial bursitis/supraspinatus tendinitis).\textsuperscript{23} The slow accumulation of sulindac sulfide has led some authorities to conclude that other NSAIDs should be preferred for the management of acute pain.\textsuperscript{26}

**NSAIDs of Efficacy Approximately Equal to That of Opioids**

The potency of the following drugs is comparable to that of certain opioids. Moderate postoperative pain, for example, may be managed using these agents. These drugs should not be used to treat mild pain. The major NSAIDs of potency comparable to opioids are diclofenac and ketorolac.
The overall analgesic effect of 30 mg of ketorolac is equivalent to that of 6 to 12 mg of morphine, and efficacy has been demonstrated for postsurgical pain including oral, orthopedic, gynecologic, and abdominal procedures. Efficacy for acute musculoskeletal pain has also been shown. Its antipyretic activity is significant. Anti-inflammatory activity is achieved only at doses higher than those needed for analgesia.

Clinical Guidelines

The following recommendations may facilitate clinical decisions relative to the efficacy of NSAIDs:

- Combinations of NSAIDs with opioids should be favored because synergy has been demonstrated. Administration of more than one NSAID should be avoided because superior efficacy has not been proven, while risks associated with NSAID toxicity may be increased. NSAIDs are characterized by dose ceilings; thus, administration of increasingly greater doses provides no more analgesia than does the maximum effective dose.

- The use of corticosteroids, anticonvulsants, antidepressants, muscle relaxants, and antispasmodics may increase pain relief. Some patients may benefit from antidepressants, anxiolytics, and antipsychotics to address anxiety and psychiatric symptoms that frequently accompany pain. For the anxiety that often accompanies pain, benzodiazepines or hydroxyzine may be prescribed.

- Placebos should rarely be used to assess the severity or genesis of pain, except as part of a clinical trial that has received adequate investigational review board approval. Placebos may correctly be used to supplement a course of drugs in an attempt to gain added benefit.

- For patients with such conditions as dysmenorrhea who need management over long periods of time, failure to achieve adequate pain relief with the NSAID first recommended may be followed by a trial of an analgesic of the same or another class. Good management of pain may be achieved with such a "second choice" agent, if two NSAIDs of two different classes have been tried individually, further attempts to obtain benefit from NSAIDs are unlikely to succeed.

- Doses of NSAIDs should be modified over time to maximize benefits and minimize risks.

- Elderly patients may obtain great benefit from NSAIDs. Dosing should be addressed carefully, and reevaluation of the therapy should be performed regularly.

Conclusions

The investigation of analgesics has grown in sophistication, and clinical studies have demonstrated the efficacy of NSAIDs in the management of acute pain. The potency of NSAIDs is founded on a mechanism of action that appears to affect both peripheral and central activity. A number of nonnarcotic agents provide effective pain relief for mild to moderate acute pain.

In recent years, progress in the area of pain management has been enhanced by the development of NSAIDs whose potency is equal to or greater than that of opioids. Because synergy has been demonstrated, the combinations of NSAIDs with opioids may demonstrate a number of advantages. The development of highly selective COX-2 agents, which may offer increased safety margins, is progressing.

References


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