Role of Analgesics in Medical & Dental discipline- a literature review

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Abstract

Everyone has had a personal experience of inflammation and pain in day-to-day life with significant number of long term sufferers amongst us. One of the greatest services, we as doctors can provide to the society, is to acquire skill in the management of pain and to understand the phenomenon of pain and inflammation. Among the various novel methods for control of pain, the NSAIDS are the most frequently used for relief of pain and inflammation. The present review article provides a sound knowledge of the various NSAIDS and their pharmacological actions along with their effective application in medicine.

Keywords: Pain, NSAIDS, Stimulus, Drugs, Sensation

Introduction

Pain is an unpleasant sensory & emotional experience associated with actual or potential tissue damage, or described in terms of such damage. The word "unpleasant" comprises the whole range of disagreeable feelings from mere inconvenience to misery, anguish, anxiety, depression & desperation, to the ultimatum of suicidal death in severe cases.

On the other hand inflammation is defined as the local response of the living mammalian tissues to injury due to any agent. It is a body defense reaction in an attempt to eliminate or limit the spread of injurious agent as well as to remove the consequent necrosed cells & tissues. The ability to mount an inflammatory response is essential for survival in the face of environmental pathogens & injury, although in some situations & diseases, the inflammatory response may be exaggerated & sustained for no apparent beneficial reasons. Anti-Inflammatory Agent is a drug that relieves inflammation. Analgesic is a drug that relieves pain due to multiple causes. Eg: aspirin, paracetamol, morphine, etc. Drugs that relieve pain due to single cause or specific pain syndrome are not classified as analgesics. E.g.: Ergotamine in the treatment of migraine, Carbamazepine in the treatment of neuralgias & Glyceryl trinitrate in the treatment of angina pectoris.[1,2]

Classification of Analgesics

1. Narcotic / Opiod Analgesics - Act on CNS
2. Non-Narcotic / Non-Opiod Analgesics - Act Peripherally.

Ranking of an Analgesic for Clinical Use

Mild Pain – Conventional NSAIDS. Eg: Aspirin, Paracetamol, Ibuprofen, etc

Moderate Pain – Low efficacy opiods &/or NSAIDS. Eg: Codeine, Pentazocine, etc

Severe Pain – High efficacy opiods. Eg: Morphine, &/or NSAIDS

Overwhelmingly Acute Pain - High efficacy opiods. Eg: Morphine + Sedatives/Anxiolytics/Tranquilisers

Anti-Inflammatory Analgesics: The anti-inflammatory, analgesic, and antipyretic drugs are a heterogeneous group of compounds, often chemically unrelated (although most of them are organic acids), which nevertheless share certain therapeutic actions and side effects. The prototype is aspirin; hence these compounds are often referred to as aspirin-like drugs; they also are frequently called *Nonsteroidal anti-inflammatory drugs,* or NSAIDs.

These drugs are weaker analgesics compared to opiods, do not depress the Central nervous system, do not produce physical dependence and do not have abuse liability. However, they are efficient in relieving pain of inflammatory origin primarily by peripheral pain mechanisms but also in CNS to raise pain threshold. Moreover, they are particularly effective in settings in which inflammation has caused sensitization of pain receptors to normally painless mechanical or chemical stimuli. Pain that accompanies inflammation and tissue injury probably results from local stimulation of pain fibers and enhanced pain sensitivity (hyperalgesia), in part a consequence of increased excitability of central neurons in the spinal cord a process known as" central sensitization". (*Kohttinen et aI, 1994*).

The mechanism of Pain and Inflammation: The inflammatory process involves a series of events that can be elicited by numerous stimuli (*e.g.,* infectious agents, ischemia, antigen-antibody interactions, and thermal or other physical injury). Each type of stimulus provokes a characteristic pattern of response that represents a relatively minor variation on a theme. At a macroscopic level, the response usually is accompanied by the familiar clinical signs of erythema, edema, tendemess (hyperalgesia), fever and pain; both of which is associated with the production of mediators which include:

Pain Mediators:[3] These mediators of pain and inflammation invariably liberate prostaglandins (PGs) and probably other mediators that promote Hyperalgesia. These prostaglandins sensitize pain receptors to stimuli by lowering the threshold of polynodal nociceptors of 'C' fibers. They also interact with cytokines resulting in pyrexia. Thus inhibition of prostaglandin synthesis forms the basis for the various pharmacological actions of NSAIDS.

Prostaglandins: These exist in virtually every mammalian tissue, acting as local hormones; which exert important physiologic and pharmacologic activities, associated with various regulatory functions and reactionary responses, before undergoing rapid, spontaneous decay, or are enzymatic destruction. They represent one of the key chemicals involved in the sensitization of peripheral nociceptors, contributing to the development of primary hyperalgesia and subsequently to secondary hyperalgesia. They are synthesized in vivo by the cyclooxygenase pathway along with leukotrienes and lipoxins, each derived by the action of specific enzyme. Of these, The Prostanoid PGE2 is especially important in inflammatory pain and these levels of PGE2 correlate with pain intensity levels

Pain, Inflammation & Immunity: PGEs cause pain when injected intradermally; these effects are generally not as immediate (since they are not present in normal tissues at significant levels to be active and need to be synthesised) or intense as those caused by bradykinin or histamine, but they outlast those caused by the other autacoids. PGS appear in significant concentration just one hour after trauma. PGEs and PGs sensitize the afferent nerve endings to the effects of chemical or mechanical stimuli by lowering the threshold of the nociceptors. Hyperalgesia also is produced by LTB4. The release of these prostaglandins and of LTB4 during the inflammatory process thus serves as an amplification system for the pain mechanism. (Savage et al *2004*). PGs and LTs are released by a host of mechanical, thermal, /chemical, bacterial and other insults contributing significantly to the genesis of the signs and symptoms of inflammation. Although, they do not appear to have direct effects on vascular permeability, both PGE2 & PGI2 markedly enhance edema formation and leukocyte infiltration by promoting blood flow in the inflamed region. Moreover, they potentiate the pain – promoting activity of bradykinins and other autacoids.

However, PGEs inhibit the lymphocytic participation in delayed hypersensitivity reactions. They also inhibit the release of hydrolases and lysosomal enzymes from human neutrophils. It is also found that in some experimental tumors in animals and certain spontaneous human tumors (thyroid, renal, breast) are accompanied by an increase concentration of local or circulating PGs, bone metastasis and Hypercalcemia.

The Anti- Inflammatory Analgesics
History of NSAIDS: The medicinal effect of the bark of willow and certain other plants has been known to several cultures for centuries. In England in the mid-eighteenth century, Reverend Edmund Stone described in a letter to the president of the Royal Society "an account of the success of the bark of the willow in the cure of agues" (fever). Since the willow grew in damp or wet areas "where agues chiefly abound," Stone reasoned that it would probably possess curative properties appropriate to that condition. The active ingredient in the willow bark was a bitter glycoside called Salicin, first isolated in a pure form in 1829 by Leroux, who also demonstrated its antipyretic effect. On hydrolysis, Salicin yields glucose and salicylic alcohol. The latter can be converted into salicylic acid, either *in vivo* or by chemical manipulation. Sodium salicylate was first used for the treatment of rheumatic fever and as an antipyretic in 1875, and the discovery of its Uricosuric effects and of its usefulness in the treatment of gout soon followed.[4,5]

The enormous success of this drug prompted Hoffman, a chemist employed by Bayer, to prepare acetylsalicylic acid based on the earlier, but forgotten, work of Gerhardt in 1853. After demonstration of its anti-inflammatory effects, Dreser introduced this compound into medicine in 1899 under the name of aspirin. The name is said to have been derived from *Spiraea,* the plant species from which salicylic acid was once prepared. The synthetic salicylates soon displaced the more expensive compounds obtained from natural sources. By the early years of this century, the chief therapeutic benefits of aspirin were known. Toward the end of the nineteenth century, other drugs were discovered that shared some or all of these actions; among these, only derivatives of para-aminophenol *(e.g.,* acetaminophen) are used today.

The next major advance was the development of phenylbutazone in 1949 having anti-inflammatory activity almost comparable to that of steroid; which led to the introduction of the term NSAIDS. N-Fenemic acid was introduce by *Dr.Prahlad B.sattur in 1982* as an anti inflammatory agent that exhibited strong anti platelet activity. Beginning with the introduction of indomethacin for the treatment of rheumatoid arthritis in 1963, a host of other agents with similar actions have been introduced over the years, culminating in the recent development of selective inhibitors of COX-2 and the most recent lox – cox inhibitors.

Mechanism of Action: The most convincing MOA of NSAIDS was established by VANE and associates, smith and Willis in 1971, who demonstrated that low concentration of aspirin and indomethacin inhibited the enzymatic production of PGs, as the principle basis for the therapeutic effects of NSAIDS. (Bergstrom, Samuelsson and vane were awarded the noble prize in 1982 for their work on PGs and LTs). Thus NSAIDS

are known to produce anti-inflammatory, analgesic and antipyretic effects by inhibiting the PG synthesis.

In general, NSAIDS do not affect the hyperalgesia or pain caused by the direct action of PGs (which is consistent with the notion associated with the analgesic effect of these agents) and the pain relief exerted by these compounds is known to occur via mechanisms other than the inhibition of PG synthesis, including antinociceptive effect at peripheral and central neurons.

The first enzyme in the prostaglandin synthetic pathway is prostaglandin endoperoxide synthase, or fatty acid *cyclooxygenase*. This enzyme converts arachidonic acid to the unstable intermediates PGG2 and PGH2. It is now appreciated that there are two forms of cyclooxygenase, termed *cyclooxygenase-l* (COX-I) and *cyclooxygenase-2* (COX-2) *(Vane et aI.,*1998). COX-I is a constitutive isoform found in most normal cells and tissues, while COX-2 is induced in settings of inflammation by cytokines and inflammatory mediators. However, COX-2 also is constitutively expressed in certain areas of kidney and brain. Importantly, COX-I, but not COX-2, is constitutively expressed in the stomach. This accounts for the markedly reduced occurrence of gastric toxicity with the use of selective inhibitors of COX-2. The fate of PGG2/PGH2 cyclooxygenase products differs from tissue to tissue, depending on the particular PGG2/PGH2-metabolizing enzymatic activities present.

Arachidonic acid also can be converted, *via* the 5-lipoxygenase pathway, to a variety of leukotrienes. Aspirin and NSAIDs inhibit the cyclooxygenase enzyme and prostaglandin production; they do not inhibit lipoxygenase pathways and, hence, do not suppress leukotriene formation. Glucocorticoids suppress the expression of COX-2 and thus COX-2-mediated prostaglandin production. This effect may contribute in part to the anti-inflammatory actions of Glucocorticoids.

Aspirin covalently modifies both COX-I and COX-2, thus resulting in an irreversible inhibition of cyclooxygenase activity. This is an important distinction for aspirin, as the duration of the effects of aspirin is related to the turnover rate of cyclooxygenases in different target tissues. In the structure of COX-I, aspirin acetylates serine 530, preventing the binding of arachidonic acid to the active site of the enzyme and thus the ability of the enzyme to make prostaglandins. In COX-2, aspirin acetylates a homologous serine at position 516. Although covalent modification of COX-2 by aspirin also blocks the cyclooxygenase activity of this isoform, an interesting property of COX-2, not shared by COX-I, is that acetylated COX-2 now synthesizes 15(R)-hydroxyeicosatetraenoic acid (I5(R)-HETE). Interestingly, this aspirin-induced product can undergo transcellular metabolism by the 5-lipoxygenase enzymes to yield 15-epilipoxin A4, which exerts potent anti-inflammatory actions and therefore may potentiate

the anti-inflammatory action of aspirin.

The vast majority of NSAIDs is organic acids and, in contrast to aspirin, acts as reversible, competitive inhibitors of cyclooxygenase activity. Even the nonacidic parent drug, Nabumetone, is converted to an active acetic acid derivative *in vivo.* As organic acids, the compounds generally are well absorbed orally, highly bound to plasma proteins, and excreted either by glomerular filtration or by tubular secretion. In contrast to aspirin, whose duration of action is determined by the rate of synthesis of new cyclooxygenase enzyme, the duration of action of all other NSAIDs, which are reversible inhibitors of cyclooxygenase, is primarily related to the pharmacokinetic clearance of the drugs from the body. Because aspirin and other NSAIDs are organic acids, they accumulate at sites of inflammation, which is an attractive pharmacokinetic property of drugs intended as anti-inflammatory agents.

Most NSAIDs developed before the availability of selective COX-2 inhibitors inhibit both COX-1 and COX-2 with little selectivity or have modest selectivity for the constitutive COX-1 isoform. The hope that it would be possible to retain the anti-inflammatory effects of aspirin like drugs with a lower ulcerogenic potential has propelled efforts to design NSAIDs with greater selectivity for COX-2 *versus* COX-1.

Shared therapeutic activities and side effects of NSAIDS:[6] Analgesic, Antipyretic and Anti-Inflammatory Effects: All NSAIDs, including selective COX-2 inhibitors, are antipyretic, analgesic, and anti-inflammatory. One important exception is acetaminophen, which is antipyretic and analgesic but is largely devoid of anti-inflammatory activity. This can be explained by the fact that acetaminophen effectively inhibits cyclooxygenases in the brain but not at sites of inflammation in peripheral tissues.

When employed as analgesics, these drugs usually are effective only against pain of low-to-moderate intensity, such as dental pain. Although their maximal effects are much lower, they lack the unwanted effects of the opiods on the central nervous system (CNS), including respiratory depression and the development of physical dependence. NSAIDs do not change the perception of sensory modalities other than pain. Chronic postoperative pain or pain arising from inflammation is particularly well controlled by NSAIDs, whereas pain arising from the hollow viscera usually is not relieved. As antipyretics, NSAIDs reduce the body temperature in febrile states. The fact that selective COX-2 inhibitors are effective antipyretic agents indicates that the COX isoform predominantly involved in thermoregulation is COX-2.

NSAIDs find their chief clinical application as anti-inflammatory agents in the treatment of musculoskeletal disorders, such as rheumatoid arthritis, Osteoarthritis, and ankylosing spondylitis. . In general, NSAIDs provide only symptomatic relief from the pain and inflammation associated with the disease and do

not arrest the progression of pathological injury to tissue.

Side Effects

1. Gastric ulceration and / or intolerance – dyspepsia, heart burn, ulceration, blood loss and anemia
2. Inhibition of platelet function
3. Inhibition of induction of labor – prolongation of gestation / spontaneous labour
4. Premature closure of PDA in infants
5. Alterations in renal function
6. Hypersensitivity reactions

Drug Interactions: Being organic acids, NSAIDS are highly bound to the plasma proteins and therefore predisposed to interactions with drugs, which express similar characteristics or those whose mechanism of action depends on physiological levels of these mediators (PGs).

1. Anti – Hypertensives
ACE inhibitors – which act by influencing renal PGs
Diuretics – which act by NA+ retention and plasma renin activity
Beta – blockers – which act by increasing PG levels
A meta-analysis has shown that, on an average, NSAIDS raise a mean B.P by 5mm Hg that can significantly increase the risk of Stroke by approx 45 to 67% and coronary artery disease by 15%, when prescribed over a period of two to six weeks. However, the short-term use in dentistry is not contraindicated since the minimum period required for clinically significant interaction is around 7 to 8 days for the commonly prescribed NSAIDS.

2. *Anti – Coagulants* – due to its inherent anti-coagulant effects and high dose Aspirin, mefenamates and ketoprofen should be avoided in patients receiving Warfarin.
3. *Lithium* – greatest interaction with indomethacin and coxibs.
4. *Methotrexate* – NSAIDS reduce the renal clearance of Methotrexate
5. *Ethanol* – NSAIDS potentiate the GI damage.
6. *Digoxin* - Nephrotoxicity
7. *Cyclosporine-* Nephrotoxicity
8. *Sulfonyl Ureas* - exacerbates hypoglycemic effect
9. *Anti – Convulsants* – serum levels are increased resulting in neurological, hematological complications.
10. Carbonic Anhydrase Inhibitors – serum levels increased resulting in lethargy and incontinence.
11. *NSAIDS & Other NSAIDS/ Acetaminophen* – Nephrotoxicity.

NSAIDS in orofacial diseases:[7] Orofacial diseases and their treatment are almost always associated with varying degrees of pain ranging from mild to severe pain which are at times associated with patient's anxiety. The most common forms of dental surgery are brief and relatively noninvasive procedures often performed on an outpatient basis except during emergencies like orofacial trauma and operative procedures like radical head neck surgeries that require hospital management.

Procedures and conditions such as TMJ pain and chronic orofacial pain are further associated with patient's anxiety which is frequently disproportionate to the safety of the procedure. Mild pain associated with most forms of uncomplicated dental care such as simple tooth extractions, endodontic therapy, or scaling of the periodontal area or of a previously asymptomatic tooth is well managed by oral administration of an NSAID such as aspirin or Ibuprofen.

Dental procedures such as surgical removal of bony impactions, osseous periodontal surgery, management of fractures and soft tissue injuries are more traumatic and typically produce intense and prolonged postoperative pain. The onset of such pain can be delayed by preoperative treatment with ibuprofen and /or application of a long-acting local anesthetic such as bupivacaine during the procedure.

Conditions such as TMJ pain are best treated with NSAIDS such as diclofenac sodium and piroxicam, which accumulate in synovial fluid after oral administration. Further they inhibit MMPs in cartilage and are also capable of modifying cartilage activity. Dispersible tablets of piroxicam 20mg (Nugesic) are available for sublingual use and are found to be effective in treating articular pain. Conditions such as non-articular TMJ pain and chronic orofacial pain are best treated pharmacologically by NSAIDs such as ibuprofen, naproxen in combination with muscle relaxants, opiods and anxiolytics.

There are certain procedures involving oral cavity, which preclude use of oral medications postoperatively (e.g., wiring the mouth closed after an operation on a mandibular fracture). Alternative therapy should be based on the severity of the surgical procedure and expected pain associated with it, as well as the surroundings in which it will be managed. Formulations of NSAIDs such as rectal suppositories (indomethacin) or intramuscular injection (ketorolac) are now commonly available. The use of intramuscular and local infiltration of ketorolac is found to be effective in relieving severe pain of endodontic emergencies and post op dental pain. In endodontic emergencies, 1ml is given intramuscularly and 1.8ml Periapical Infiltration in relation to the vestibule of the offending tooth. Analgesia is comparable to 12mg morphine sulfate with onset within 40mins and minimal side effects. It is administered with a Loading dose - 40 to 60mg followed by 20 mg/day for not more than five days.

Preoperative analgesia with IBUPROFEN:[7] Preoperative administration of ibuprofen appears to delay the onset of postoperative pain and lessen its severity (Jackson, Moore, and Hargreaves, 1989). For patients unable to tolerate aspirin or ibuprofen, acetaminophen can provide an acceptable analgesic

effect. Vogel et al 1992 compared the presurgical and immediate post surgical analgesic effect of 600mg Ibuprofen on post operative periodontal pain in 60 patients divided into three groups and the results indicated that dosing with 600mg Ibuprofen either immediately before or immediately after periodontal surgery significantly delays onset of pain as compared to placebo, with dosing after surgery demonstrating a significantly greater delay of onset of pain as compared to dosing pre surgically. Li Wan Po and. Zhang in 1998, in a meta-analysis evaluated the analgesic efficacy of Ibuprofen alone and in combination with codeine or caffeine in post-surgical pain. They concluded that Ibuprofen is effective in dental pain, episiotomy pain and other post-operative pain. There is a dose-response relationship over the range 50-400 mg. The difference in total pain-relief score relative to placebo was found to be 19-31%. The analgesic effect of ibuprofen 400 mg by about 8% is found to be enhanced by addition of Codeine 60 mg in the total pain-relief scale, but also increases its adverse effects. The additive effect of caffeine was inconsistent requiring validation.

Presurgical considerations for patients on aspirin therapy: Aspirin (ASA) therapy has long been associated with an increase in BT and risk of postoperative hemorrhage. For most elective surgeries, it has typically been recommended that the patient stop taking ASA 7 to 10 days before the procedure. This recommendation was based on general surgical studies, which reported an increase in intra operative and postoperative bleeding in patients taking ASA.

Ardekian et al maintained that a daily dose of 100 mg of ASA did not significantly increase intraoperative and postoperative bleeding during tooth extractions.

Sonksen et al showed that the increase in BT caused by daily ASA in doses of up to 300 mg did not exceed normal limits in most patients.

Madan G.A et al evaluated minor oral surgery patients, from May 2002 to May 2003, who were on long-term low-dose aspirin therapy regimens (acetylsalicylic acid 75 mg to 100 mg/day). If investigation of bleeding time and platelet count were within normal limits, aspirin was not stopped before surgery. Patients were operated under local anesthesia on an outpatient basis. All wounds were sutured and followed up at 24, 48, and 72 hours, 1 week, and 2 weeks after the procedure. There was no excessive intraoperative bleeding in all cases except one case, concluding that most minor oral surgery procedures can be carried out safely without stopping long-term low-dose aspirin regimen. Thus, patients need not stop taking ASA before dental surgery, provided the hemorrhagic risk is not greater than the thromboembolic risk associated with interrupting use of the drug. When intraoperative or postoperative bleeding does occur, local hemostatic methods are generally very effective.

In the situations, associated with high hemorrhagic risk as in patients with qualitative or quantitative platelet anomalies, with congenital or acquired coagulopathies, chronic kidney or liver failure, and alcoholic patients, a medical consultation should be requested and ASA should be stopped 7 days before surgery to minimize the hemorrhagic complications. If interruption of ASA therapy is contraindicated, the patient should receive specialized treatment in hospital.

Analgesic combinations used in dentistry

- ANACIN - ASA 400mg + caffeine 325mg
- EXCEDRIN – 250mg ASA + 250mg PCT + 65mg caffeine
- EMPIRIN WITH CODEINE – 325mg ASA + 15/30/60 mg codeine
- TYLENOL WITH CODEINE – 300mg PCT + 15/30/60 mg codeine
- PERCODAN – 325mg ASA + 2.44/4.88 mg oxycodone
- PERCOCET – 325mg PCT + 5mg oxycodone
- TALWIN – 325mg ASA + 12.5mg pentazocine
- TALACEN – 650mg PCT + 25 mg pentazocine
- ULTRACET – 325mg PCT +37.5 mg tramadol
- VICOPROFEN – 200mg ibuprofen + 7.5mg hydrocodone

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