# Drug Disease Interactions: Role of Inflammatory Mediators in Pain and Variability in Analgesic Drug Response

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## ABSTRACT

Pain has both physical and emotional components. Physical noxious stimuli activate peripheral sensory neurons that, in turn, relay signals to the spinal and supraspinal nuclei. Subsequently, these signals activate areas within the brain associated with pain. Despite considerable knowledge in this area, analgesics may provide pain complete relief in only one out of five patients. Failure to manage pain may be due to a lack of understanding of the neurobiological processing of pain. Factors such as anticipation, anxiety and pain history play roles in the perception of pain. Non-neuronal cells such as those of the immune system influence perception and modulation of pain by the nervous system. In post-dental surgery patients, the severity of the pain and the relief following administration of anti-inflammatory analgesics has been linked to the time course of inflammatory mediators. Similarly, the relief of post-operative pain after abdominal surgery is also associated with a reduction in expression of pro-inflammatory mediators. Administration of anti-cytokines to sciatica patients and subsequent pain relief further emphasizes the role of pro-inflammatory mediators in modulation of pain. Increased expression of inflammatory mediators may also alter response to analgesia. For example, rheumatoid patients with temporal mandibular joint disease with increased expression of interleukins prior to treatment demonstrate inadequate pain relief after administration of anti-TNF-$\alpha$. In addition, pain or its trauma impairs absorption of oral analgesics causing therapeutic failure. Improved analgesic pharmacotherapy may require a better understanding of the involvement of the inflammatory pathways.

## THE INFLAMMATORY RESPONSE SYSTEM AND PAIN

Pain research typically has focused on its physical and emotional components. For example there is considerable knowledge as to how noxious stimuli activate peripheral sensory neurons that, in turn, relay signals to the spinal and supraspinal nuclei. These signals then activate areas within the brain associated with the perception of pain (1-3). However, attempts to alleviate pain often fail. Indeed, analgesics may provide relief for only one out of five patients (4-6). This is especially relevant to the elderly who have a prevalence of pain ranging from 67-80% (7-9). A probable explanation for unsuccessful analgesic treatment is that often only the neuronal system of signaling is targeted. Somatic and psychological factors such as anticipation, anxiety, and pain history, however, may also contribute to perception and intensity of pain (1, 10, 11). Importantly, failure to manage pain may be due to a lack of understanding of the neurobiological processing of pain. Non-neuronal cells such as those of the immune system influence perception and modulation of pain by the nervous system (12-15).

Several reports have demonstrated the involvement of the immune system in both manifestation of pain and analgesia. Various cells of the immune system that express mediators of inflammation are involved in neuronal modulation of pain (6, 16, 17).

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Inflammation is the result of increased capillary blood flow and permeability that allows cells of the immune system to enter the affected region (18, 19). Excessive production of inflammatory mediators such as cytokines by the adaptive (T-lymphocytes) and innate (macrophages, monocytes, neutrophils) immune systems modulate painful syndromes. Cytokines are soluble messenger proteins involved in the control of immune events, regulation, and repair of cells (20). During an inflammatory response secretion of pro-inflammatory cytokines by CD-4+ T-lymphocyte helper (Th)-1 cells [e.g., interferon (IFN)-γ, interleukin (IL)-2, tissue necrosis factor (TNF)-α] is increased and anti-inflammatory cytokines by Th-2 cells (e.g., IL-4, -10, 13) is decreased (3, 20).

Pro-inflammatory cytokines expressed by Th-1 cells degrade phospholipids in membranes of monocytes and macrophages resulting in production of arachidonic acid that is further metabolized via the cyclooxygenase pathway to prostaglandins and thromboxanes [e.g., prostaglandin $E_2$ ($PGE_2$), thromboxane $B_2$ ($TxB_2$)], mediators of inflammation (21, 22). Various cells of the immune system such as mast cells reside in tissues and upon stimulation also express a variety of pro-inflammatory mediators (e.g., cytokines, prostaglandins) contributing to pain (16, 22, 23). For example, patients afflicted with chronic pancreatitis and concomitant pain show over a 3-fold increase in mast cell expression compared to patients without pain (24). Similar to mast cells, activated macrophages reside and/or are recruited to an injured area contribute to development of pain via release of pro-inflammatory mediators [e.g., TNF-α, IL-1β nerve growth factor (NGF), bradykinin] that either act directly on nociceptors (i.e., pain receptors) or indirectly through release of other mediators (e.g., prostaglandins) and recruitment of other immune cells (16-19, 22, 23). In addition, B and T-lymphocytes through release of pro-inflammatory cytokines, for example, can stimulate production of nitric oxide from immune cells and tissues causing pain (25-29). Nitric oxide has been shown to be involved in development and maintenance of hyperalgesia (30).

Immune cells through release of inflammatory mediators play a major role in peripheral as well as central sensory processing of neuropathic pain (12, 13, 31). Pro-inflammatory cytokines are large hydrophilic molecules thus penetration through the blood brain barrier are thought to be restricted and involvement in pain limited. However, cytokines may enter the brain through regions where the blood brain barrier is absent (e.g., circumventricular organs), limited (e.g., median eminence), compromised by disease (e.g., multiple sclerosis) or by active transport. Production of cytokines also occurs within the CNS (25-28). Pro-inflammatory cytokines can stimulate production of other inflammatory mediators within the CNS modulating pain (25-29).

Expression of pro-inflammatory cytokines by Th-1 cells leads to generation of kinins that are involved in the perception and progression of pain. Kinins are small peptides that are normally inactive in the blood stream. Tissue injury activates kinins such as bradykinin causing vasodilation, increased vascular permeability, smooth muscle contraction and pain. After stimulation of pain receptors by bradykinin, the individual attempts to protect the affected area to aid in relief of pain (22, 23, 32). However, continual increased expression of inflammatory mediators may also lead to persistent painful syndromes (31, 33, 34). Pain and hyperalgesia due to inflammation may also result from release of inflammatory mediators by neuronal tissues and direct actions of inflammatory mediators on nociceptive nerve terminals innervating inflamed tissues as neurons express receptors for mediators of inflammation, for example, TNF-α, IL-6, NGF, bradykinin, and prostaglandins (12, 13, 22).

Inflammation and/or inflammatory mediators have been shown to be involved in many diseases and may alter response to drugs such as cardiovascular agents (35-37). In addition, during pain episodes, gastrointestinal absorption of the orally administered analgesics may be impaired resulting in therapeutic failures (38). Indeed, during acute pain following oral surgery, absorption of ibuprofen is significantly delayed which results in subtherapeutic drug concentrations during the first few hours post-dose (Fig. 1). The delayed absorption is attributed to a suppression of the vagus nerve by pain itself or by its associated trauma, thereby, prolongation of gastric emptying and subsequently a delay for the drug to reach the major site of absorption, i.e., the intestine (38). A similar observation has also been made with the 5-hydroxytryptamine inhibitor, naratriptan (39).

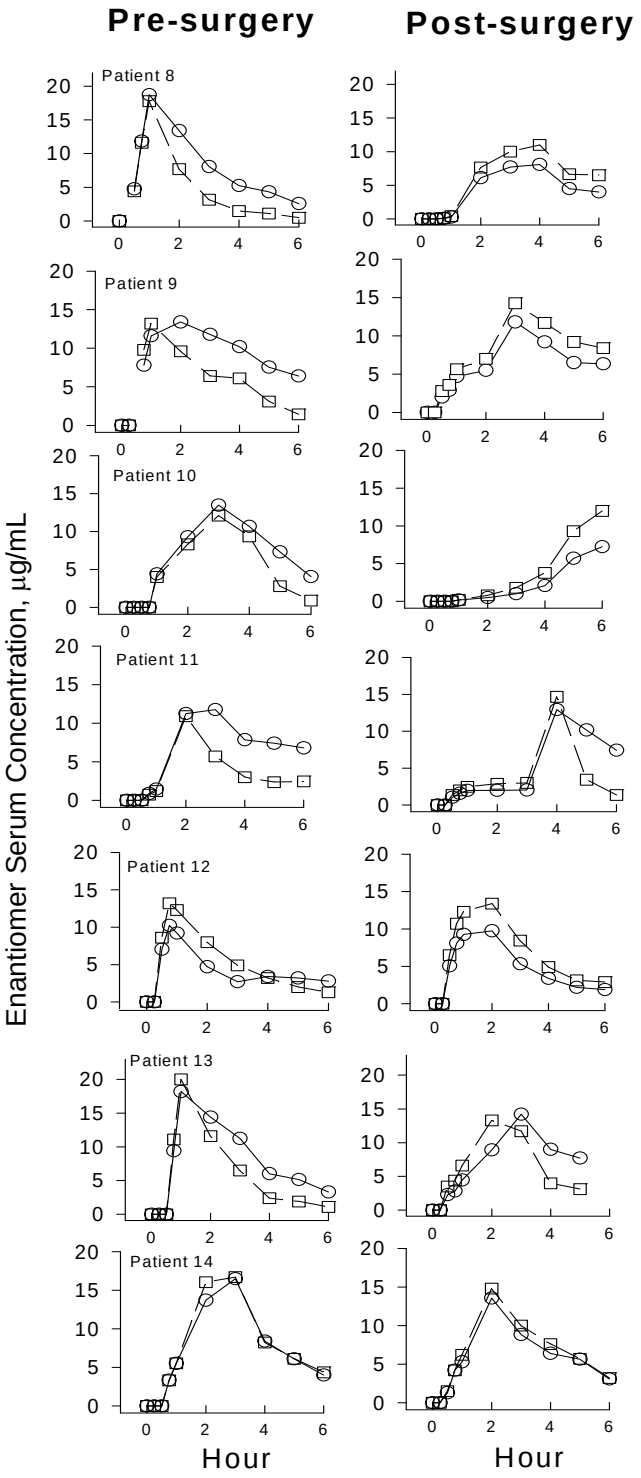


**Figure 1.** Plasma ibuprofen enantiomers concentrations in the patients receiving oral doses of 600 mg racemic ibuprofen. The same patient was administered ibuprofen a week prior and subsequently after emergence of moderate to severe pain following extraction of third molar teeth. The delayed absorption during the post surgery phase as compared with the healthy phase was significant. From reference 38.

## Inflammatory Mediators and Acute Pain

To investigate the role of inflammation in acute pain, oral surgery models have been used. These models are widely accepted and applied to evaluate the efficacy of analgesics with results extrapolated to other painful conditions (40-43). For example, in a randomized, double-blind study (42), following third molar teeth extraction, patients were treated with either dexamethasone or placebo until the loss of the subjective signs of anesthesia and time of pain emergence. Subsequently, they received either placebo or the anitiinflammatory ketorolac (Fig. 2). Pain intensity and relief expressed on a visual analog scale (VAS) were recorded. To measure local levels of $PGE_2$ and $TxB_2$ a microdialysis probe was implanted at each surgical site and dialysis fluid, sterile lactated Ringer's solution, was collected at timed intervals.

Surgery significantly decreased PGE2 and caused an insignificant declining trend for TxB2. Ketorolac but not placebo was effective in reducing pain intensity. The pain relief coincided with a corresponding decrease in PGE2. TxB2 concentrations declined significantly faster in response to ketorolac than placebo (Fig. 2). The observed pain relief, therefore, was attributed to a decreased expression of pro-inflammatory mediators $PGE_2$ and $TxB_2$ at the surgical site. The observed lack of effect of dexamethasone to reduce pain intensity was attributed to the small size of the dose (42).

Similarly $PGE_2$ concentrations at site of extracted impacted third molars significantly decreased following oral administration of anti-inflammatory agent flurbiprofen. The suppressing effect on PEG2 correlates well with both the onset of analgesia and the pain relief caused by flurbiprofen (44).

In another study the synergic effect of the analgesic anti-inflammatory drug, ibuprofen and analgesic agent acetaminophen on the potency of oxycodone and hydrocodone to relieve pain was measured in post-dental surgery patients (45). Oxycodone 5 mg plus 400 mg ibuprofen was significantly more effective that 5 mg oxycodone plus 325 mg acetaminophen or 7.5 mg hydrocodone plus 500 mg acetaminophen (Fig. 3). The potent synergic effect of ibuprofen relative to that of acetaminophen has been attributed on the ability of

the former analgesic to inhibit prostaglandins synthesis (45, 46).

Cytokine expression in patients that had undergone a transabdominal hysterectomy was investigated to determine whether preemptive analgesia followed by patient-controlled analgesia decreased pro-inflammatory cytokine expression and concurrent pain following the operation (47). Patients were randomly assigned to one of two groups: patient-controlled epidural analgesia (PCEA) in the post-operative period or preemptive epidural analgesia (PA) followed by patient-controlled epidural analgesia post-operatively (PCEA+PA). Post-operative pain was assessed using VAS in which endpoints ranged from no pain to worst possible pain. Patients that received PA were administered an epidural mixture of bupivacaine plus fentanyl 20-25 minutes before surgery. For post-operative pain management both groups received bupuvicaine and fentanyl per demand (i.e., PCEA) as well as a continuous background infusion. Cytokines (IL-1β, TNF-α, IL-6, IL-1ra, IL-10 and IL-2) production by lipopolysaccharide stimulated peripheral blood mononuclear cells were determined over 72 h post-operation.

Patients treated with pre-operatively analgesia exhibited lower pain scores (Fig. 4). In support, perioperative administration of dexketoprofen markedly improved analgesia and decreased opioid requirements following elective hip arthroplasty (48). Pre-operative treatment with anti-inflammatory agents is reported to reduce synthesis of inflammatory mediators and subsequent pain before oral surgery supporting decreased inflammatory mediator expression and pain experienced by patients in the PA+PCEA group (43, 49).

The stimulated peripheral blood mononuclear cells of patients who received both post-operative and preemptive analgesia produced more IL-2 but less IL-1β, IL-6, IL-1ra and IL-10 as compared with those who received only preemptive treatment (Fig, 4). The authors (47) explained these findings by tissue and peripheral nerve injury initiating inflammation accompanied by elevated levels of pro-inflammatory cytokines. In turn, pro-inflammatory cytokines induced peripheral and central nervous system sensitization resulting in hyperalgesia. IL-1β induces synthesis and release of substance P from peripheral nerve terminals of primary afferent neurons that contributes to neurogenic inflammation. In addition, glia cells in the central nervous system increase production of pro-inflammatory cytokines after injury. IL-1β induces central sensitization to pain via IL-1 receptors on neurons and by activating glia cells that produce mediators of pain such as substance P, glutamate, nitric oxide that alter pain processing in the central nervous system. Elevation of IL-1β in the central nervous system leads to production of $PGE_2$ that further increases pain sensitivity. The lack of elevation of TNF-α in the PCEA group was explained by lipopolysaccharide stimulating maximum release of TNF-α by peripheral blood mononuclear cells before the first sampling time point.

Increased IL-2 as shown in Fig 4 suggests less attenuated suppression of Th-1 responses in the PA+PCEA group. Less suppression of IL-2 was suggested by the authors to contribute to a decrease in pain perception in the PA+PCEA group as IL-2 resembles opiate peptides and is reported to have analgesic effects in the peripheral and central nervous systems.

**Inflammatory Mediators in Neuropathic Pain**

Neuropathic pain occurs in various conditions such as diabetes, acquired immunodeficiency disease, post-herpetic neuralgia and trauma (50). Peripheral nerve injury in neuropathic pain causes a series of changes in the central processing of pain at the spinal level (31, 50). Astrocytes, microglia and oligodendrocytes form a large group of CNS glial cells (51-54). Microglia cells become activated during pain leading to production of cytokines, chemokines and other pain producing substances that contribute to perception of neuropathic pain after peripheral nerve injury (51-55). Disease or injury that directly affects the CNS may also induce immune responses, for example, pain produced in multiple sclerosis and spinal cord injury patients. Pro-inflammatory mediators such as TNF-α are reported to have considerable involvement in neuropathic pain. Development of allodynia and hyperalgesia are linked to increased TNF-α expression (31). In animal models, TNF-α is involved in onset of nerve pain.

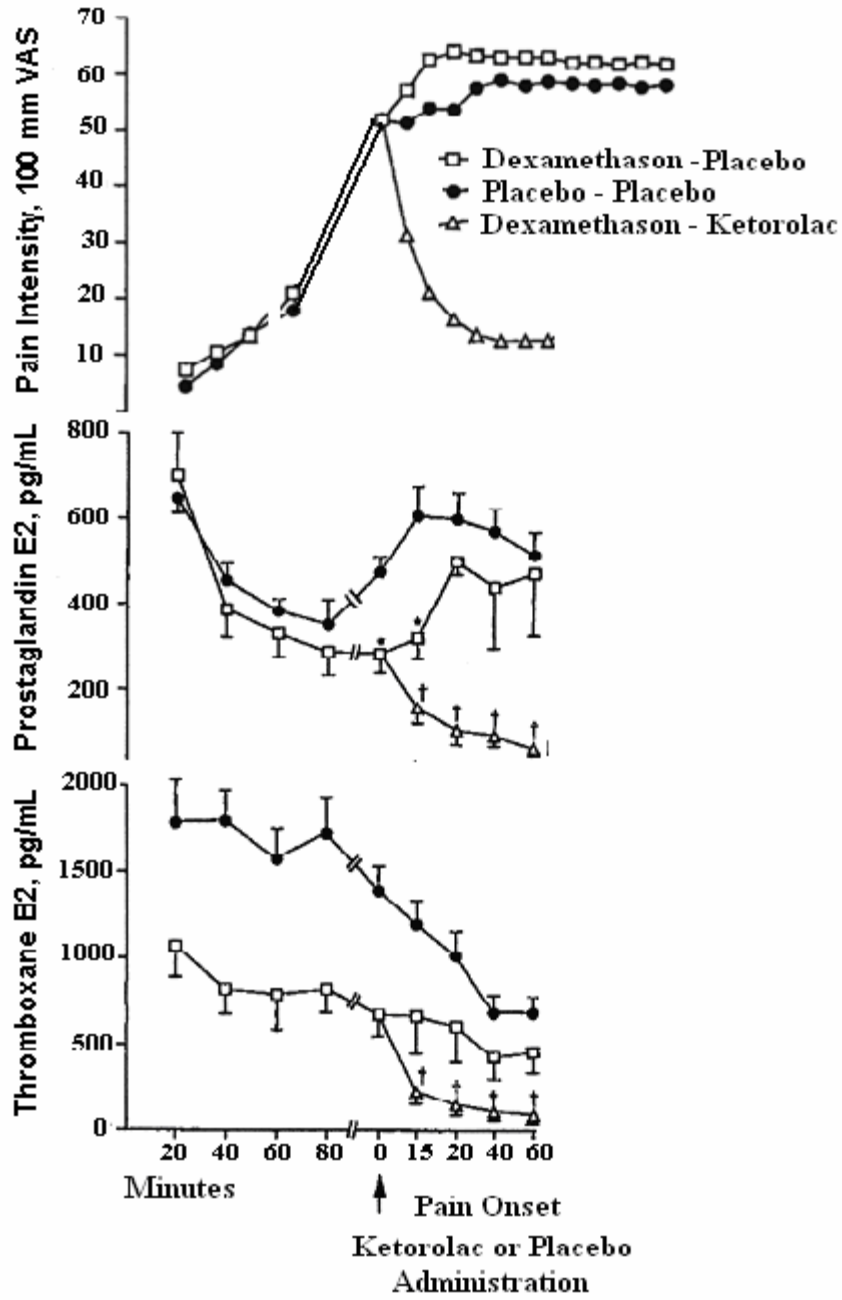


**Figure 2.** The time course of $PGE_2$ and $TxB_2$ concentrations and of pain intensity measured by the visual analog scale (VAS) dental surgery patients. Surgery was performed at time zero. Patients received dexamethasone or placebo just after surgery followed by placebo or ketorolac when anesthesia was worn out and pain emerged (*$p<0.05$ versus placebo, †$p<0.05$ versus dexamethasone and placebo). Adopted from reference 42.

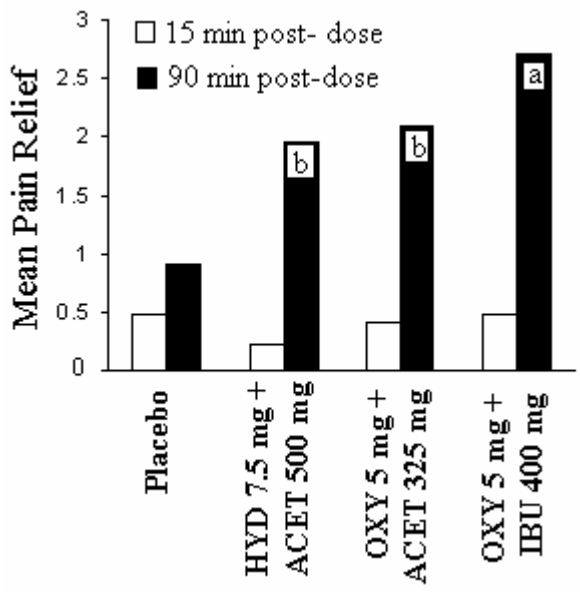


**Figure 3.** Mean pain relief scores over time in patients receiving placebo (PLA) or oxycodone (OXY) in combination with ibuprofen (IBU) or acetaminophen (ACET) or hydrocodone (HYD) in combination with ACET. Pain relief scale ranged from 0 (none), 1 (a little), 2 (some), 3 (a lot) and 4 (complete), *$p<0.05$ versus PLA; †$p<0.05$ versus HYD 7.5/ACET 500 mg; ‡$p<0.05$ versus all other treatments. Adopted from reference 45.

This prompted clinical studies in which anti-TNF-α was administered to patients with disk-related sciatica pain (56, 57).

Involvement of TNF-α in pathogenesis of neuropathic pain has been investigated. In a study by Karppinen et al (58), ten patients with a 2-12 week history of herniated intervertebral disc sciatica received a single intravenous infusion of infliximab. Relief of leg pain was the primary outcome. After administration of infliximab mean leg pain score decreased by 50% in 1 hour and 90% after three months. In a 1-year follow-up study with these same patients eight still had a 75% reduction in pain from baseline score (59). In another study, patients with chronic, moderate-to-severe intensity, disc-related back or neck pain resistant to traditional treatment were administered enanercept followed by a one-month follow-up. Significant improvements in pain and neurological abnormalities were reported (60). Although preliminary, numerous open label studies and case reports show benefit of anti-TNF-α therapy in alleviation of sciatica pain (61, 62).

Korhonen et al also carried out an open-label double-blind clinical study on the effect of anti-TNF-α, infliximab, on herniation-induced sciatica (63). In this study, pain relief after anti-TNF-α treatment did no differ from placebo. The authors stressed that the results of this trial do not definitively confirm that the theoretical framework for anti-TNF-α therapy should be disregarded. A factor that may have contributed to the discrepancy with open label studies is that the controlled trial consisted of a small number of heterogeneous patients. It is also probable that concurrent inflammatory disorders (e.g., rheumatoid arthritis), degree of inflammation present, severity, and site of the disk herniation influenced the response to the anti-cytokine. Benefit may also possibly be confined to the early stages of pathophysiological processes leading to nerve pain (i.e., anti-cytokines may be ineffective unless administered early).

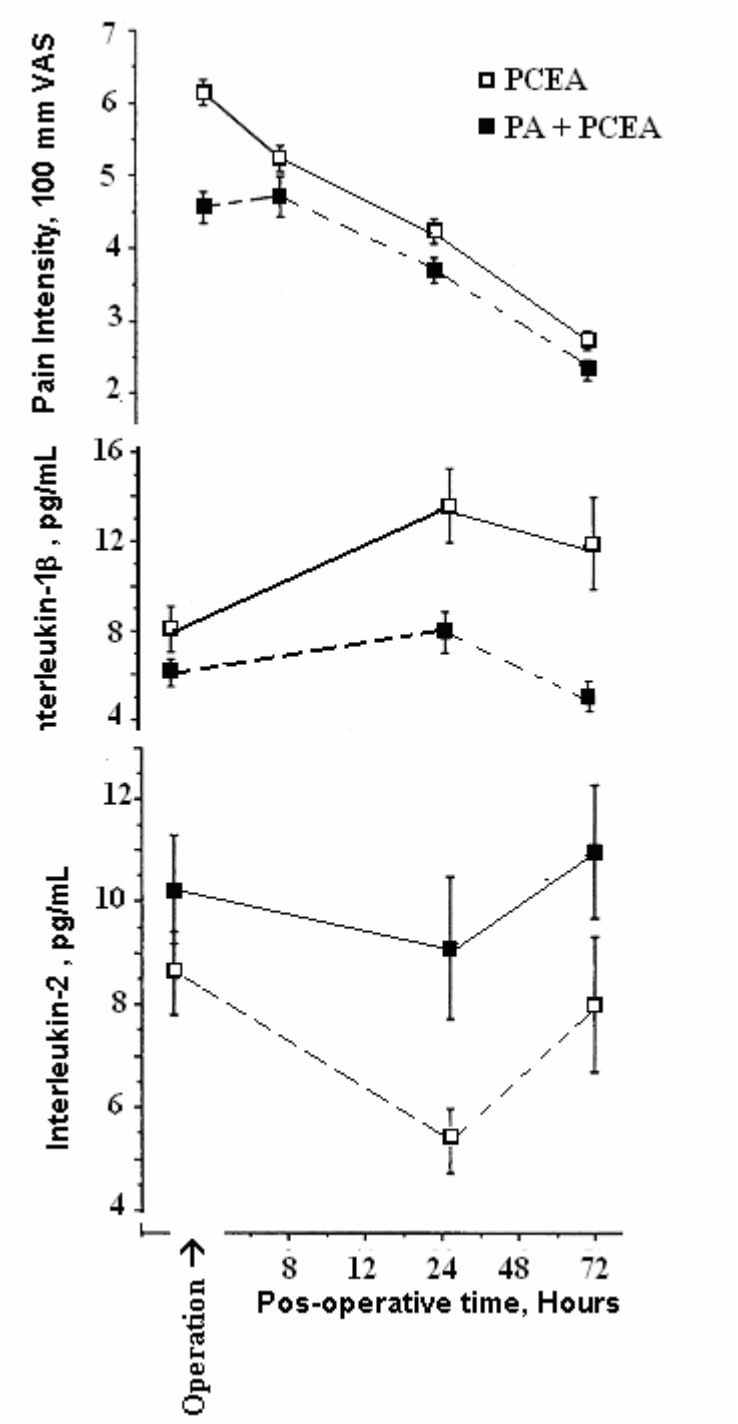


**Figure 4.** The time course of pain intensity, IL-1β and IL-2 in peripheral blood mononuclear cells of subjects under patient-controlled epidural analgesia (PCEA) in post-operative period alone or along with preemptive epidural analgesia (PA). Values are mean±standard error of the mean. The difference between the two groups were significant for all three observations ($p<0.05$). From reference 47.

The route of administration may also play a role in pain relief, for instance, epidural administration may lead to more effective pain relief than systemic route in some patients. Further controlled trials are required to address these concerns. Similar to TNF-α, the inflammatory cytokine IL-1β in animals is reported to have a role in neuropathic pain as expression of IL-1β is increased after nerve injury and administration of neutralizing antibodies reduces pain-associated behaviors (64-66). Involvement of inflammatory pathways in pain sensation and modulation emphasizes a role for anti-inflammatory therapy for relief of pain (67).

**Inflammatory Mediators in Migraine**

Migraine is a neurovascular pain syndrome triggered by abnormal neuronal excitability in the cerebral cortex that in turn sensitizes the trigeminal vascular system resulting in pain (68). Studies conducted in Europe and the United States show that 6-8% of men and 15-18% of women experience migraine each year (69). Cytokines can mediate pain in neurovascular inflammation hence potential exists for involvement in migraine pain (70). The majority of studies investigating cytokines in migraine pathogenesis have focused on peripheral and central expression of cytokines and produced inconsistent results. In one study, TNF-α levels in patients with migraine during an attack and at attack free periods did not differ significantly with respect to healthy controls (71). In contrast, another study suggested that inflammatory cytokines might be involved during an episode (72). Clinical data showing effectiveness of nonsteroidal anti-inflammatory agents in relief of migraine pain indicate inflammation may be an important component in a subset of individuals that suffer from migraine (70). Despite conflicting data, it is probable that immunological changes occur in a subset of migraine patients. For example, genetic polymorphisms in TNF-α genes in association with migraine is reported (73). In fact emerging options for migraine treatment involves reduction in pro-inflammatory mediators such as nitric oxide by administration of compounds that have anti-inflammatory properties (74, 75). In cervicogenic headache that manisfests itself by symptoms similar to those of migraine TNF-α expression increases (76). An open label pilot study was conducted in which six patients afflicted with severe cervicogenic headache were administered anti-TNF-α (76). Anti-cytokine treatment resulted in rapid and sustained relief of cervicogenic headache pain and decreased analgesic consumption. Although preliminary, this suggests a role of inflammatory mediators in pain mediation for patients afflicted with various headache syndromes.

**Inflammation and Variability in Response**

The plasma concentrations of inflammatpry mediators exhibit remarlable variability in disease states (35-37) including pain (77). To assess the influence of inflammatory mediators on treatment of pain, Kopp et al measured the effect of anti-TNF-α on temporomandibular joint (TMJ) pain in patients with active rheumatoid arthritis (77). Plasma and synovial fluid levels of TNF-α, IL-1β, IL-6, soluble TNF receptor II (TNF-sRII), IL-1ra, soluble IL-1 receptor II (IL-1sRII) and IL-10 were measured before and during treatment. Anti-TNF-α and methotrexate was administered to fifteen patients initially then at 2, 6 and 14 weeks after initial treatment. Pain was assessed using a visual analog scale with endpoints denoted as no pain to worst pain ever experienced. The circulating cytokine concentrations were analysis prior to initiation of treatment and at 14 and 22 weeks, post-dose.

The effect of anti-TNF-α and methotrexate treatment on pain relief was influenced by pretreatment plasma levels of IL-1β, IL-1ra, IL-10 and pretreatment levels of IL-1sRII in TMJ synovial fluid (77). Higher pre-treatment levels of IL-1β, IL-1ra, IL-10 in plasma and IL-1sRII in synovial fluid resulted in none or only minor pain relief. The presence of rheumatoid factor in 11 of the 15 patients was also associated with poor treatment response. Anti-TNF-α treatment seems to be most successful when levels inflammatory cytokines such as IL-1β were not elevated or the absence of rheumatoid factor. As depicted in Fig. 5, increased pretreatment plasma levels of IL-1β can be associated with failure to relieve pain.

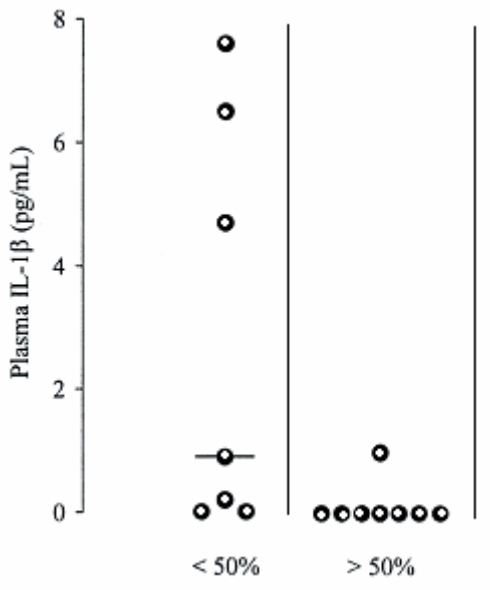


**Figure 5.** Pretreatment levels of IL-1β in relation to reduction in temporalmandibular joint pain intensity upon mouth opening using a visual analog scale to rate pain. In patients that had >50% reduction in pain all but one patient had undetectable plasma levels of IL-1β (p=0.012). Adopted from reference 77.

## CONCLUSION

Inflammatory mediators appear to play significant roles in modulation of inflammatory and neuropathic pain. Many inflammatory disorders such as rheumatoid arthritis, Crohn's disease, multiple sclerosis as well as conditions associated with neuropathy such as vasculitis, acquired immunodeficiency and diabetes have pain as a their main syndrome (34, 50, 78-85). This may lead to a lack of predictability of clinical response to pharmacotherapy. Interestingly, through their anti-inflammatory properties, the cholesterol lowing agents, 3-hydroxy-3-methyl-glutaryl-CoA reductase inhibitors (statins) appear to control hypernociception (86) and other symptoms associated with inflammation (87). Further investigation of the analgesic effects of anti-cytokines/chemokine therapies (88) is expected to provide more insight onto the relationship between pain and inflammatory cascade and provide more effective pharmacotherapy.

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