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Intrathecal Cyclooxygenase Inhibitors in Humans

Don't Throw in the Towel!

THE role of spinal cyclooxygenase and prostaglandins in nociceptive processing has been examined, corroborated, and reported in more than 100 publications describing animal and bench studies during the past 3 decades. Relevant observations include the constitutive expression of cyclooxygenase 1 and 2 in the spinal cord, up-regulation of cyclooxygenase 2 (primarily) and cyclooxygenase 1 after peripheral injury, release and production of spinal prostaglandins in response to tonic and often inflammatory nociceptive input, and an association between an increase in spinal prostaglandins and nociceptive behavior. Conversely, intrathecal injection of prostaglandins, most notably prostaglandin E2, causes hyperalgesia and allodynia.[1] Studies in animals further suggest that intrathecal injections of cyclooxygenase inhibitors attenuate both the concentration of spinal prostaglandins and nociceptive behavior, implying that targeted inhibition of spinal cyclooxygenase may be a viable strategy for treating pain in humans.[2,3]

In this issue of ANESTHESIOLOGY, two companion articles by Eisenach *et al.*[4,5] report results from studies in human volunteers and patients receiving a single intrathecal bolus dose of the nonsteroidal antiinflammatory drug (NSAID), ketorolac, for alleviating experimental or clinical pain. These studies are significant because they are the first to systematically examine the analgesic effects of an intrathecal NSAID in humans. They represent the culmination of a dogged effort to translate the promising results in animals into clinically useful therapies, including preclinical toxicology, regulatory approval for human use, and a phase I safety study in volunteers.[6,7]

Eisenach *et al.* documented that intrathecal ketorolac is ineffective against the brief pain evoked in unaltered tissue, which is not unexpected. The studies in patients either undergoing surgery or suffering from chronic nonmalignant pain provided negative results, neither detecting an effect of intrathecal ketorolac on spontaneous pain nor time to rescue analgesia. These results are disappointing and imply that intrathecal NSAIDs are of limited utility for alleviating pain in humans.

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However, the studies in volunteers paint a more complex picture regarding the effects of intrathecal ketorolac on hyperalgesia and allodynia. These phenomena are associated with tissue injury and chronic pain. In the context of this study, hyperalgesia and allodynia largely reflect the amplification of nociceptive input within the central nervous system. The results suggest modest antihyperalgesic and antiallodynic activities in inflammatory pain states but not in capsaicin-induced pain states.

Early proof-of-concept studies in humans are critical for guiding future research efforts, but the limitations must be understood before drawing overly broad conclusions. There are two obvious limitations in this work. First, the drug was given by a single bolus. Second, only 109 volunteers and patients, a relatively small number, were enrolled in seven different protocols. Let us consider each of these.

The pharmacokinetics of ketorolac in cerebrospinal fluid and spinal tissue are largely unknown. Data obtained in dogs suggest fast elimination of ketorolac from cerebrospinal fluid with an estimated half-life of 53 min.[7] Ketorolac is also one of the most hydrophilic NSAIDs with limited and delayed tissue uptake.[8] A sophisticated pharmacometric analysis suggested that maximum analgesic effects lag behind peak plasma concentrations by about 1 h after systemic drug administration.[9] Assuming fast elimination and slow-tissue distribution of ketorolac, bolus administration may result in marginally effective concentrations in spinal tissue. A slow uptake of ketorolac into spinal tissue is consistent with the observation that a bolus injection of 5 mg in dogs produced high cerebrospinal fluid concentrations (~400 μg/ml) 30 min after administration that were accompanied by a 48% decrease of prostaglandin E2, whereas continuous administration of 1.2 mg for 24 h produced cerebrospinal fluid concentrations that were 100-fold lower but were accompanied by a 96% decrease of prostaglandin E2. Given these considerations, continuous infusion of intrathecal ketorolac may be a more effective strategy than bolus administration.

◆ This Editorial View accompanies the following two articles: Eisenach JC, Curry R, Tong C, Houle TT, Yaksh TL: Effects of intrathecal ketorlac on human experimental pain. ANESTHESIOLOGY 2010; 112:1216–24; and Eisenach JC, Curry R, Rauck R, Pan P, Yaksh TL: Role of spinal cyclooxygenase in human postoperative and chronic pain. ANESTHEISOLOGY 2010; 112:1225–33.

Intrathecal ketorolac was studied in patients scheduled for vaginal hysterectomy under spinal anesthesia and in patients suffering from chronic nonmalignant back or leg pain requiring intrathecal morphine *via* implanted infusion pumps. These patients represent target populations for the potential clinical use of intrathecal ketorolac. However, the concomitant use of a local anesthetic in patients undergoing surgery may have prevented or delayed the up-regulation of spinal prostaglandins. Therefore, the current results do not preclude that intrathecal ketorolac may be effective for alleviating pain associated with acute tissue injury. Most chronic pain patients suffered from back or leg pain of degenerative causes and received a daily median morphine dose of 4.6 mg. Patients on chronic intrathecal morphine likely represent a population that has failed previous treatments, including the systemic administration of NSAIDs. The possibility that these patients may be particularly resistant to the effects of intrathecal NSAIDs should be considered.

The studies by Eisenach *et al.*[3,4] illustrate the complexity of translating promising preclinical findings into human biology and pharmacology. They raise doubts about the clinical utility of intrathecal NSAIDs for alleviating pain and describe circumstances where potential benefits were absent. However, the current data do not rule out that intrathecal NSAIDs may be effective for certain pain conditions. Future studies will need to determine whether intrathecal NSAIDs have any role in pain management. Preclinical evidence and data presented in the two companion articles provide some guidance on what may be sensible next steps in evaluating the analgesic efficacy of intrathecal NSAIDs. Pain conditions associated with significant inflammation seem to be particularly responsive. In the domain of chronic pain, conditions may include cancer-related pain or certain forms of neuropathic pain. Anecdotal evidence suggests that intrathecal NSAIDs could be effective for some of these conditions.[10,11] Given the pharmacokinetic profile of intrathecal ketorolac, comparing the effectiveness of continuous infusion techniques with bolus administration may be of use.

Targeting spinal cyclooxygenase in the treatment of acute pain may prove more difficult. Bolus administration in the likely clinical setting of co-injecting local anesthetics is of little benefit. An attractive option may include the prolonged administration of NSAIDs by the epidural route. However, it is not clear that this approach would result in effective central nervous system drug concentrations and offer an improved safety profile compared with systemic drug administration.

I applaud the efforts of Eisenach *et al.* to translate many years of animal research on the role of spinal cyclooxygenase in nociception into human pain therapy. Similar to the investigators, I was disappointed with the mostly negative results. We have learned from these seminal studies that intrathecal cyclooxygenase inhibitors are not a panacea for all types of pain. However, there is much we do not know, including the optimal method of drug delivery, and whether there are specific pain states that might prove responsive. It is too early to throw in the towel on the potential utility of intrathecal cyclooxygenase inhibitors in the management of pain.

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