The Role Of Cyclooxygenase-2 Inhibitors In Perioperative Medicine

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Citation

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Abstract

Cyclooxygenase-2 (COX-2) inhibitors can be found in numerous nourishments. Curcumin (diferuloyl methane) is one of the components of turmeric, a yellow spice that is frequently used in the Indian cuisine,
which has been shown to have anti-inflammatory and analgesic properties [14].

Resveratrol, a natural product derived from grapes, is frequently used in traditional Chinese herbal medicine. In 1997 its anti-inflammatory properties have been shown in an animal model for the first time, at that time inhibition of cyclooxygenase-1 was thought to be responsible for that effect [5]. Later it could not only be shown that these effects are depending on inhibition of COX-2 [15], but also that they were completely independent of effects on COX-1 [8].

PERIOPERATIVE USE OF COX-2 INHIBITORS

In a study on perioperative bleeding, the influences of either nonsteroidal anti-inflammatory drugs (NSAIDS) and rofecoxib, a selective COX-2 inhibitor, were compared. 100 patients undergoing elective total knee arthroplasty discontinued their use of NSAID 10 days before surgery and were assigned randomly to receive either placebo or rofecoxib, 25 mg daily for 5 consecutive days starting 3 days before surgery. The administration of rofecoxib resulted in no increase of the perioperative bleeding, but improved preoperative pain scores. The authors conclude that rofecoxib does not need to be discontinued before elective total knee arthroplasty [13].

Other investigators evaluated the efficacy of preoperative administration of rofecoxib, two doses of 50 mg daily, on postoperative pain after single-level lumbar microdiscectomy. The randomized, double-blind, placebo-controlled clinical trial showed less morphine requirements and less pain scores greater than 7 at admission to the PACU. There were no differences between the groups concerning incidence of nausea, time to discharge from the PACU, or hospital stay. The authors conclude that preoperative rofecoxib does effectively decrease postoperative narcotic consumption in patients undergoing single-level lumbar microdiscectomy [1].

In a randomized, double-blind trial on 218 patients in post-orthopedic surgery pain, placebo, rofecoxib 50 mg, or naproxen sodium 550 mg were compared. Rofecoxib was superior to placebo and similar to naproxen sodium for all single-dose measures of pain relief. Patients in both the rofecoxib group and the naproxen sodium group used less supplemental narcotic analgesia and reported less pain on global evaluations when compared with the placebo group [10].

Reuben et al. compared the analgesic efficacy of preoperatively given single doses of the COX-2 inhibitors celecoxib (200 mg) and rofecoxib (50 mg), and placebo after spinal stabilization in a randomized trial [11]. The doses used were the maximum doses of the drugs that had been shown to be effective in earlier studies on postoperative pain [2, 7, 9]. The outcome measures for the 60 patients included pain scores and morphine use at six times during the first 24 postoperative hours. The total dose of morphine and the cumulative doses for each of the six time periods were significantly higher in the placebo group than in the other two groups. The morphine dose was significantly lower in five of the six time intervals in the rofecoxib group compared with the celecoxib group. The pain scores were significantly less in the rofecoxib group than in the other two groups at two of the six intervals. Although both rofecoxib

and celecoxib produce similar analgesic effects in the first 4 h after surgery, rofecoxib demonstrated an extended analgesic effect that lasted throughout the 24-h study.

USE OF COX-2 INHIBITORS IN AMBULATORY SURGERY

Reuben also investigated the analgesic effect of administering rofecoxib either before or after surgical incision in patients undergoing ambulatory arthroscopic knee surgery under local anesthesia. Sixty patients undergoing arthroscopic meniscectomy were randomized into three groups. All patients received intraarticular bupivacaine 0.25% pre- and postsurgery together with IV sedation using midazolam and propofol. In addition they received either a single 50 mg dose of rofecoxib 1 h before surgery, rofecoxib 50 mg after the completion of surgery, or a placebo tablet before surgery. Analgesic duration, defined as the time from completion of surgery until first opioid use, was significantly longer both groups receiving rofecoxib. The opioid use was less in the preincisional rofecoxib group versus the postincisional group or the placebo group. Pain scores with movement were lower in the preincisional group at all postoperative time intervals over a 24 hour period. The authors discuss an preemptive effect of rofecoxib, modulating spinal wind-up phenomena. Early intervention by administration of rofecoxib result in lower pain scores [12].

In a study on 112 healthy outpatients scheduled for elective otolaryngologic surgery, the subjects were randomly assigned to 4 study groups. Patients received orally either placebo, acetaminophen 2000 mg, celecoxib 200 mg, or acetaminophen 2000 mg and celecoxib 200 mg 1 h prior to surgery. During the postoperative period, pain was assessed using a 10-point verbal rating scale. Celecoxib or acetaminophen alone was not significantly more effective than placebo in reducing postoperative pain. The patients receiving a combination of acetaminophen and celecoxib suffered from significantly less postoperative pain than all others. placebo in reducing postoperative pain [4].

In a similar setup for outpatients undergoing orthopedic surgery, the patients received orally either placebo, ibuprofen 800 mg, celecoxib 200 mg, or rofecoxib 50 mg 30-90 minutes prior to surgery. All analgesics improved postoperative pain levels and decreased opioid consumption. Only patients receiving rofecoxib 50 mg had a shorter time to discharge from the PACU [3].

White reviewed the role of non-opioid analgesics in the management of pain after ambulatory surgery. Analyzing the literature he drew the conclusion that preoperatively administered rofecoxib in a dose of 50 mg provides both more effective analgesia and lower opioid requirements than celecoxib 200 mg. He compares the analgesic potency of celecoxib 200 mg with acetaminophen 2000 mg [17].

USE OF COX-2 INHIBITORS IN AMBULATORY SURGERY

In a study on the analgesic efficacy and the opioid-sparing effect of rofecoxib in otolaryngologic surgery, 60 patients undergoing nasal septal or sinus surgery were randomized to receive either oral placebo or rofecoxib 50 mg 1 h before surgery. All patients received analgosedation with propofol and fentanyl, and local anesthesia at the operative site. Pain scores were obtained at 5, 15, 30 45, and 60 min during surgery and 30 min, 2, 4, 6, 12, and 24 h after completion of the procedure. For pain scores >4 or on the patient's request, additional fentanyl dosages were given intraoperatively, during the postoperative period, diclofenac 75 mg IM was administered. Compared with the placebo group, pain scores, intraoperative fentanyl and postoperative diclofenac requirements were significantly smaller in the rofecoxib group. The times to first analgesic request were also significantly less in the rofecoxib group. The authors concluded that the preoperative administration of oral rofecoxib provided a significant analgesic benefit and decreased the need for opioids in patients undergoing nasal septal and nasal sinus surgery [16].

INTRATHECAL APPLICATION OF COX-2 INHIBITORS

In animal models of inflammatory pain, intrathecal COX-2 selective inhibitors suppress hyperalgesia. A study of Kroin et al. investigated whether the water-soluble COX-2 selective inhibitor L-745337 can modify allodynic responses in a rat model of postoperative pain. Allodynia was induced in the left plantar hindpaw of the animals by surgical incision. Animals then received intrathecal or subcutaneous L-745337 coadministered with intrathecal morphine. Mechanical allodynia (increased withdrawal threshold) was quantified with calibrated von Frey hairs. The COX-2 selective inhibitor alone, whether intrathecal or systemic, had no effect on withdrawal threshold. When intrathecal L-745337 at doses of 40 to 80 micro g was combined with a subthreshold dose of morphine, withdrawal thresholds were increased in a dose-dependent manner. Adding 80 micro g L-745337 to 1 nmol morphine produced an antiallodynic effect greater than that of morphine at twice the dose.

Subcutaneous application of L-745337 did not influence the effect of intrathecal morphine on antiallodynic response. These results suggest a spinal interaction of COX-2 inhibition with opiate analgesia. This effect may allow a reduction of postoperative pain with lower doses of opioids.

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