NSAIDs in postoperative pain

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The objectives of this presentation are to give an update on clinical pharmacology of non-steroidal anti-inflammatory analgesics (NSAIDs) in management of postoperative pain and discuss use of these drugs in specific patient groups.

Prostaglandins play important roles in many cellular responses and pathophysiologic processes including modulation of the inflammatory reaction, turnover of cartilage and bone, gastrointestinal cytoprotection, angiogenesis and cancer, hemostasis and thrombosis, and renal hemodynamics. The major target for NSAIDs is the cyclo-oxygenase pathway in the peripheral tissues. NSAIDs have also central actions in the spinal cord and brain. The relative contribution of peripheral and central sites of action is variable in different pain states is not complitely understood. It has been suggested that pharmacokinetic factors, such as the relative distribution to effect sites and sites where COX-inhibition is harmful (eg kidney), might partly explain differences in the efficacy and safety between various NSAIDs.

NSAIDs are effective analgesics in acute postoperative pain, especially when there is an inflammatory component. In severe postoperative pain it is not possible to study the effect of NSAIDs alone, but most commonly the opioid-sparing effect is studied, despite the shortfalls of the method. NSAIDs have been shown to relatively consistently reduce postoperative opioid consumption in average by 30–50%, and to reduce opioid-induced adverse effects, such as nausea & vomiting and sedation.

NSAIDs and coxibs have deleterious effect on renal function that can lead to both acute and chronic renal failure. The risk of acute renal failure associated to NSAID is increased in patients with hypertension, diabetes, and pre-existing renal diseases, including previous episodes of acute renal failure, exposure to other nephrotoxic drugs and contrast media, and the length of use. In patients with previously normal renal function and no perioperative problems with homeostasis, of NSAIDs for postoperative pain can be relatively safe to kidneys.

COX-1 has a key role in production of gastroprotective prostaglandins, and NSAIDs produce dyspepsia and peptic ulcer disease in chronic use. Coxibs are not completely devoid of adverse gastrointestinal effects, but the risk is significantly lower. In acute postoperative pain NSAIDs are usually used for a short period, and the risk of gastrointestinal problems is lower than in chronic use.

NSAIDs can lead to the development of congestive heart failure in susceptible individuals, but there are only few epidemiological investigations on this “forgotten” adverse effect. Since 2004 a lot has been written on thrombotic cardiovascular events associated to coxibs. In postoperative pain, NSAIDs or coxibs are in most cases used for a relatively short time, and therefore the cardiovascular risk profile is different from that in chronic use. Other risk factors for cardiovascular disease are importan for risk assessment for postoperative analgesia. NSAIDs (except ASA) reversibly inhibit COX-1 in platelets, and the effect on platelet aggregation and risk of bleeding is dependent on the half-life of the compound.

Prostaglandins are important in the regulation of osteoblast and osteoclast functions, and inhibition of prostaglandin production affect bone formation. COX-2 controls osteoclastogenesis, mechanotransduction, bone formation and fracture repair constitutively in the skeleton. Reports of impaired bone healing associated with NSAID treatment have therefore raised a concern, but here are no good clinical studies on this matter. Based on the importance of inflammation of the tissue healing in general, concern on the effect of NSAIDs on healing of surgical injury in other tissues, such as intestinal anastomoses, has also been raised. However, there is very little clinical evidence on this.

When considering the use of NSAIDs in postoperative pain, the analgesic good efficacy must be balanced against the known and assumed adverse effects. The assessment must be based on the individual characteristics of each patient, and compared to the risk profile of alternative methods of pain management.

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How should we prevent persistent postoperative pain?

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Persistent pain after surgery has received increased attention during the last 15 years, and reported incidence has been reported as between 5 and 50% [1]. A recent large epidemiological study using population-based data confirms these previous cohort studies [2].

Several risk factors for persistent postoperative pain have been identified and can logically be divided into preoperative, intraoperative and postoperative risk factors [1,3,4]. Better knowledge of risk factors may allow preventive strategies. The preoperative risk factors include psychosocial factors [5], genetic factors [6] and preoperative pain - both pain in the area of surgery and other preoperative pain syndromes. Surgery with increased risk of nerve injury is also a prominent risk factor, and severe postoperative pain is strongly associated with persistent pain [3]. For most of these factors it remains to confirm whether the relationship with persistent postoperative pain is causal.

No preventive strategy is yet fully documented, but several interventions are promising [3]. The idea of preventive analgesia has evolved from preemptive analgesia by shifting the focus from timing of treatment to aiming at blocking noxious stimuli across the entire perioperative period. Such intensified perioperative pain treatment including regional anaesthesia and antihyperalgesic drugs like ketamine, gabapentin and pregabalin has been studied a lot, but still there are diverse findings. A recent systematic review and meta-analysis did find support for perioperative pregabalin/gabapentin [7]. Of special interest is also the finding that anaesthetic technique may be of importance. Spinal anaesthesia may be protective, and use of nitrous oxide during surgery might prevent persistent pain [8].

Since most interventions have potential side-effects it would be advantageous to reserve the most intense treatments to those at greatest risk only. Preoperative assessment of nociceptive function together with knowledge about inherent risk with the planned procedure may help identify a high risk group.Those patients who have severe pain and abnormal sensory changes four to six weeks after surgery are risk patients for persistent pain [9]. Thus, it may be an interesting approach to treat more aggressively patients with severe acute postoperative pain and signs of neuropathic components 1–3 weeks after surgery, at a time when pain subsides in most patients.

The lecture will review the most recent findings and discuss the current research agenda.

Recommended reading

[1] Kehlet H, Jensen TS, Woolf CJ. Persistent postsurgical pain: risk factors and prevention. Lancet 2006;367:1618–25.

[2] Johansen A, Romundstad L, Nielsen CS, Schirmer H, Stubhaug A. Persistent postsurgical pain in a general population: prevalence and predictors in The Tromsø Study. Pain 2012. Mar 23 (PMID: 22445291).