Canadian Agency for Drugs and Technologies in Health

HTA

HEALTH TECHNOLOGY INQUIRY SERVICE (HTIS)

Title: Non-Steroidal Anti-Inflammatory Drugs for Analgesia in Patients with Fracture: Evidence for Use

Date: 03 June 2008

Context and policy issues:

In 2000 - 2001, 3.4 million Canadians aged 12 years or older sustained an injury severe enough to limit their usual activities. Approximately 18.6% of these injuries were attributed to fractures.[1] This represents a substantial proportion of the Canadian population. Several acute pain management guidelines recommend non-steroidal anti-inflammatory drugs (NSAIDS), which are commonly used analgesic and anti-inflammatory drugs,[2] as an initial treatment option in the management of mild to moderate pain.[3,4] Although there is some concern about the use of NSAIDS in patients with fractures, when used concurrently with opioids in patients with moderate to severe pain, NSAIDS can reduce opioid requirements. This translates to lower incidence of dose-dependent opioid adverse effects such as nausea, vomiting, dizziness, and constipation. As well, NSAIDS cause less respiratory depression and sedation than opioids.[3,5] This is not to say that NSAIDS are not without important adverse effects, themselves, including gastro-intestinal side effects and impairment of clotting and renal function, which may be important considerations in trauma patients.[6] Thus, it is important to consider both the risks and benefits of all treatment options when selecting an analgesic.

NSAIDS exert their effects through the inhibition of cyclooxygenase 1 and 2 (COX-1 and COX-2), enzymes that produce prostaglandins. Prostaglandins have numerous effects in the body. Prostaglandins produced via COX-1 are involved in the regulation of normal cellular processes,[7] while prostaglandins associated with inflammatory processes are generally produced via COX-2.[2] By inhibiting the production of prostaglandins via COX-2, NSAIDS reduce fever, pain and inflammation.[8] One class of NSAIDS, COX-2 inhibitors, preferentially inhibits COX-2 over COX-1, which reduces the potential for some adverse effects related to COX-1 inhibition. There are many NSAIDS currently on the Canadian market, some of which include acetylsalicylic acid (ASA), ibuprofen, diclofenac, indomethacin, naproxen (traditional NSAIDS) and celecoxib (a COX-2 inhibitor).[9]

In addition to its roles in the inflammatory response, COX-2 also has a role in the fracture healing process.[8] During the initial stages of fracture healing, COX-2 production is increased in order produce prostaglandins which are needed for bone repair.[7,10] Because of this, there is theoretical concern that inhibiting COX-2 would decrease prostaglandin levels and, subsequently, impair fracture healing. There is evidence that NSAIDS impair fracture healing in animals, but this evidence is somewhat controversial. While well-designed animals studies do suggest that NSAID use is associated with impaired bone healing, it is not clear whether this evidence should be extrapolated to humans given that there are important differences between species in the COX expression and in bone healing itself.[6] As well, the dosages and duration of treatment used in the animal studies were not necessarily reflective of what would be used to manage acute pain in clinical practice.[11]

Concerns about the potential for impaired bone healing with NSAIDS may be an additional consideration in managing acute pain in individuals who present with a fracture. This report will review the evidence that NSAIDS impair fracture healing, which could potentially help in decision-making at the level of the healthcare system.

Research questions:

1. What is the evidence that the use of NSAIDS for analgesia will delay healing or increase the incidence of non-union in patients with fractures?

2. Is there any evidence that multiple doses of an NSAID versus a single dose of an NSAID have an effect on healing time or incidence of non-union in patients with fractures?

Methods:

A limited literature search was conducted on key health technology assessment resources, including PubMed, OVID Embase, The Cochrane Library (Issue 2, 2008), University of York Centre for Reviews and Dissemination (CRD) databases, ECRI, EuroScan, international HTA agencies, and a focused Internet search. Results include articles published between 2000 and May 2008 and are limited to English language publications only. No filters were applied to limit the retrieval by study type.

HTIS reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews and meta-analyses are presented first. These are followed by randomized controlled trials and observational studies.

Summary of findings:

No health technology assessment reports, systematic reviews or meta-analyses on the effects of NSAIDS on fracture healing were identified; however, one randomized control trial (RCT) and two observational studies were identified.

Randomized controlled trials

Burd et al. (2003)[12] analyzed data from an RCT that compared the efficacy of indomethacin 25mg three times daily for six weeks to low dose radiation therapy for preventing heterotopic ossification (abnormal formation of true bone within extraskeletal soft tissues)[13] in 282 patients with acetabular fracture, a fracture of the socket of the hip joint. This post-hoc analysis was performed on a subgroup of patients who had a long-bone fracture in addition to the acetabular fracture to determine if indomethacin increased the risk of non-union in this subgroup. Non-

union was defined as any fracture which required further treatment for failed healing (clinical or radiographic) after a minimum of three months. Of the 282 patients enrolled in the original RCT, 112 had concomitant fractures of the femur, tibia, humerus, radius or ulna and were included in this analysis. Of these 112 patients, 38 had received indomethacin, 38 received radiation and 36 did not receive any prophylactic treatment. Adherence to indomethacin was not monitored and patients were not given specific instructions about the use of nonprescription NSAIDS. The use of nonprescription NSAIDS was not assessed.

The average age in the indomethacin group was 39.5 years versus 38.1 years in the participants who were not treated with indomethacin. The sex of the participants was not reported. A total of 16 patients required additional treatment for non-union of a long-bone fracture. Approximately 29% of patients who received indomethacin had non-union of a fracture compared to 7% of patients ($p = 0.004$) who did not receive indomethacin (i.e., the 74 patients who received radiation or no prophylaxis). The odds ratio for this comparison was 5.32 (p-value not reported). When comparing the no treatment and radiation groups separately, the indomethacin group was 6.9 and 4.3 times, respectively, more likely to experience non-union (p-values not reported). When looking at the total number of fractures with non-union (rather than number of patients), non-union occurred in 4.2% of fractures in patients who did not receive indomethacin and 15.3% in those that did receive indomethacin ($p = 0.029$). The authors concluded that indomethacin increased the risk of non-union of long-bone fractures compared to radiation or no prophylaxis.

This study had a number of limitations. First, while data were obtained from an RCT, this was a retrospective analysis of data from 112 of the 282 original patients and not truly an RCT itself, which increases the risk of bias in the study. For example, the study groups were unbalanced with respect to injury severity score, which was highest in the indomethacin group. Another limitation of the study was that the investigators did not collect data on how long bone fracture was treated which could affect outcome in terms of non-union. Finally, the use of non-prescription NSAIDS was not reported, which could also impact non-union.

Observational studies

Bhattacharyya et al. (2003)[14] analyzed the relationship between non-union of humeral shaft fractures and NSAID and opioid use in 9,995 patients from a Medicare database. Humeral shaft fractures were identified through diagnosis and procedure codes, while prescription NSAID and opioid use were determined through pharmacy claims data 90 days following the initial fracture code. For the purposes of analysis, the 90-day follow-up period for medication use was broken out into three 30-day time periods (1 to 30 days; 31 to 60 days; and 61 to 90 days). Non-union was defined by the presence of procedure codes for repair of non-union 90-365 days after the initial fracture code.

The average age of the cohort was 77 years and 88% were female. The relative risk (RR) of fracture was 3.7 (95% CI: 2.4 – 5.6) in individuals who used NSAIDS within 1 to 90 days of the fracture compared to non-users and 1.6 (95% CI: 1.1 – 2.5) for opioid users compared to non-users. The association between NSAID use and non-union of fracture was statistically significant for each 30-day time period when they were analyzed separately. When the three time periods were entered into a single analysis, NSAID use 61-90 days post-fracture was significantly associated with non-union (RR 3.9, 95% CI 2.0-6.2), whereas NSAID use from days 1 to 30 or days 31 to 60 were no longer associated with non-union. A similar association was found between opioids and non-union, with exposure to opioids between 61 and 90 days being associated with non-union (RR 2.7, 95% CI 1.5-5.2). The authors concluded that exposure to nonselective NSAIDS or opioids in the period 61-90 days after a humeral shaft fracture was

associated with non-union. However, the authors felt that these relationships were more likely to reflect the use of analgesics by patients with painful non-healing fractures than causal associations between NSAID or opioid use and non-union.

Given the design of the study, there are a number of limitations. First, confounding could be an issue given that many other factors associated with non-union could not be identified or controlled for in a data-base study. Little clinical data were available about the patients or their exposure to over-the-counter NSAIDS. Exposure to NSAIDS was defined as 10 days of medication dispensed during each 30 day period. Using pharmacy claim data, there is uncertainty that the patient actually consumed the medication on all or any of the 10 days. Further, the authors of the study pointed out that the effect they observed for NSAID use in the 61 to 90 days post-fracture is not consistent with biology of fracture healing where COX-2 activity is increased in the first 14 days of fracture. As well, the authors pointed out that use of opioids were also found to be a risk for non-union, when there is no data to suggest they impair fracture healing. Based on this, they felt that medication use was really just a marker for pain associated with non-union (i.e. non-union leads to NSAID use, not NSAID use leads to non-union). Finally, identification of fractures and non-union was based on procedure codes, which may or may not be entered accurately.

In a second observational study, Giannoudis et al. (2000)[15] assessed factors associated with non-union of diaphyseal fractures of the femur. Thirty-two patients with non-union of a fracture and 67 comparable patients whose fracture had united (control group) were identified through retrospectively reviewing records of 377 patients who had underwent intramedullary nailing for femoral shaft fractures. Non-union was defined by clinical and radiological criteria and by the need for further surgery. Relationships between non-union and the following variables were assessed first independently and then in a single model: surgical technique, smoking and NSAID use. NSAID use appeared to be collected via self-report and was not clearly defined in the article in terms of dose or duration of treatment; ibuprofen and diclofenac were most commonly used.

The average age in the non-union group was 35 years compared to 38 years in the control group. There was no relationship between the rate of non-union and the type of implant, mode of locking, reaming, distraction (surgical techniques) or smoking. A larger proportion of patients in the non-union group took NSAIDS (62.5% compared to 13.4%) and took them for a longer period of time on average (21.2 weeks compared to 1 week) compared to the control group. The odds ratio for non-union was 10.74 (95%: 3.55 – 33.23; $p<0.001$) for NSAID users compared to non-users, after adjusting for smoking and reaming. Based on this finding, the authors stated that they no longer used NSAIDS in patients with diaphyseal fractures. Average healing time in the control group was prolonged in those patients who took NSAIDS compared to those who did not: 7.5 months (range: 6 to 10) compared to 5.5 months (range: 3 to 8; p-value not reported).

Given the retrospective nature of this study, a number of limitations should be considered in interpreting the results. Again, it is difficult to draw any inferences about causality, given that the timing of NSAID use is not clear (i.e., whether exposure to NSAIDS preceded non-union). As with the previous study, it is possible that NSAID use was for the treatment of pain associated with non-union and not a causal factor. Further, the report did not include information about the dose of NSAIDS taken in each group and appeared to be based on patient report. Finally, a number of factors associated with non-union could not be controlled for given that the study was retrospective and non-randomized.

Limitations

Overall, the evidence of a relationship between non-union of fractures and NSAID use is weak, given the small number of studies and methodological shortcomings within each study. While one study used RCT data, it was not truly an RCT and the other two were retrospective analyses. The ability to make any causal inferences about the relationship between NSAID use and non-union was limited by the retrospective nature of the studies and the inability to control for other factors which may have affected non-union. Further, given that two of the three studies included only surgical patients with long-bone fractures,[12,15] and the other study included only patients with humeral fractures,[14] it is not clear whether the results would be generalizable to other fractures as well.

Conclusions and implications for decision or policy making:

The evidence that the use of NSAIDS for pain management delays healing or increases the incidence of non-union in patients with fractures is limited. Given the available human studies, it is difficult to draw any strong conclusions about the association between non-union of fractures and NSAID use. Without detailed information about the specific NSAIDS and dosages used or the duration of treatment, it cannot be determined whether multiple doses compared to a single dose of a NSAID has more of an effect on healing time or incidence of non-union in patients with fractures. Overall, concern about fracture healing and NSAID use appears to be based upon animal studies, with little human data to support these concerns. Regardless, in treating pain in patients with fractures, the risks versus benefits of any treatment option, beyond adverse effects on bone healing, should be considered.

Prepared by:
Ron Pohar, BScPharm, Clinical Pharmacist
Carolyn Spry, MLIS, Information Specialist
Health Technology Inquiry Service
Email: htis@cadth.ca
Tel: 1-866-898-8439

References:

1. Wilkins K, Park E. Injuries. *Health Rep* 2004;15(3):43-8. Available: http://www.statcan.ca/english/freepub/82-003-XIE/0030382-003-XIE.pdf (accessed 2008 May 28).

2. Solomon DH. NSAIDs: mechanism of action. In: *UpToDate* [database online]. Version 16.1. Waltham (MA): UpToDate; 2008.

3. *Assessment and management of acute pain*. Bloomington (MN): Institute for Clinical Systems Improvement (ICSI); 2008 Mar. Available: http://www.icsi.org/pain_acute/pain__acute__assessment_and_management_of__3.html (accessed 2008 May 23).

4. Assessment and management of pain. In: *Nursing best practice guidelines* [website]. Toronto: Registered Nurses Association of Ontario (RNAO); 2007. Available: http://www.rnao.org/Page.asp?PageID=924&ContentID=720 (accessed 2008 May 28).

5. Gajraj NM. The effect of cyclooxygenase-2 inhibitors on bone healing. *Reg Anesth Pain Med* 2003;28(5):456-65.

6. Langford RM, Mehta V. Selective cyclooxygenase inhibition: its role in pain and anaesthesia. *Biomed Pharmacother* 2006;60(7):323-8.

7. Williams A. Should non-steroidal anti-inflammatory drugs be given to orthopaedic patients with fractures? *Br J Hosp Med* 2007;68(8):452.

8. Vuolteenaho K, Moilanen T, Moilanen E. Non-steroidal anti-inflammatory drugs, cyclooxygenase-2 and the bone healing process. *Basic Clin Pharmacol Toxicol* 2008;102(1):10-4.

9. *e-CPS: compendium of pharmaceuticals and specialties*. [database online]. Ottawa: Canadian Pharmacists Association; 2008.

10. Wheeler P, Batt ME. Do non-steroidal anti-inflammatory drugs adversely affect stress fracture healing? A short review. *Br J Sports Med* 2005;39(2):65-9.

11. Reuben SS, Ekman EF. The effect of cyclooxygenase-2 inhibition on analgesia and spinal fusion. *J Bone Joint Surg Am* 2005;87(3):536-42.

12. Burd TA, Hughes MS, Anglen JO. Heterotopic ossification prophylaxis with indomethacin increases the risk of long-bone nonunion. *J Bone Joint Surg Br* 2003;85(5):700-5.

13. Moore DS, Cho G. Heterotopic ossification. In: *eMedicine specialties* [website]. New York: WebMD; 2007. Available: http://www.emedicine.com/radio/topic336.htm (accessed 2008 May 28).

14. Bhattacharyya T, Levin R, Vrahas MS, Solomon DH. Nonsteroidal antiinflammatory drugs and nonunion of humeral shaft fractures. *Arthritis Rheum* 2005;53(3):364-7.

15. Giannoudis PV, MacDonald DA, Matthews SJ, Smith RM, Furlong AJ, De Boer P. Nonunion of the femoral diaphysis. The influence of reaming and non-steroidal anti-inflammatory drugs. *J Bone Joint Surg Br* 2000;82(5):655-8.