HIGHLIGHTS

Assessment of Ketorolac as an Adjuvant to Fentanyl Patient-controlled Epidural Analgesia after Radical Retropubic Prostatectomy

Jeffrey A. Grass, M.D., Neal T. Sakima, M.D., Marc Valley, M.D., Karl Fischer, R.N., Catherine Jackson, R.N., Patrick Walsh, M.D., Denis L. Bourke, M.D.

POSTOPERATIVE pain management is undergoing significant changes. The U.S. Department of Health and Human Services Agency for Health Care Policy recently published "The Clinical Practice Guidelines on Acute Pain Management," which reflects the growing belief that adequate treatment of pain has benefits beyond patient satisfaction and comfort. Opioids have been used to provide postoperative analgesia, but they often are associated with significant side effects, including nausea, pruritus, sedation, and respiratory depression. Furthermore, opioids may cause urinary retention and may slow the return of bowel function, both of which are undesirable in surgical patients. Opioids may be administered *via* several routes, including intravenous, intramuscular, intrathecal, and epidural. While epidural or intrathecal administration of opioids provides superior analgesia, the incidence of side effects remains a significant problem. In the past, research on acute pain management primarily has compared opioids or modes of administration. The discovery of new pharmacologic agents is allowing us to expand our horizons past the opiate receptor in an effort to provide improved analgesia with fewer side effects. The recent addition of ketorolac to our armamentarium may decrease the dose of opioids required to provide adequate pain control while minimizing opioid-related side effects.

Ketorolac is an injectable, nonsteroidal antiinflammatory agent (NSAID) with potent analgesic and moderate antiinflammatory and antipyretic effects. Ketorolac inhibits synthesis of prostaglandin (one of the mediators in the inflammatory response known to cause pain) by reversible blockade of cyclo-oxygenase. Currently only approved for intramuscular injection, ketorolac is absorbed rapidly, reaching its peak plasma concentration at 45–50 min. The plasma half-life is 4 to 6 h and is prolonged in the elderly and patients with renal insufficiency.

Ketorolac offers several advantages over opioids. The analgesia provided by a 30-mg dose of ketorolac is believed to be comparable to 12 mg intramuscular morphine. Ketorolac does not have hemodynamic effects or cause pruritus, significant respiratory depression, urinary retention, or slow gastric emptying.

The most common side effects of ketorolac include drowsiness, gastrointestinal upset, abdominal pain, and nausea. Less common side effects include edema, diarrhea, dizziness, headache, sweating, and pain at the injection site. Ketorolac, as with other NSAIDs, may cause significant renal toxicity, particularly in hypovolemic patients or those with preexisting renal disease. It also inhibits platelet aggregation, thereby raising concern for potential bleeding complications.

Ketorolac, because it acts at a site other than the opiate receptor, is proving to be an excellent adjunct to opioid analgesia. In this issue, Grass *et al.* (page 642) describe their well designed, well executed clinical study to evaluate the role of ketorolac in postoperative pain management. They demonstrate that periodic administration of ketorolac provides better analgesia with a smaller opioid requirement than that required following placebo. In addition, bowel function, which is affected by opioid administration, improves more rapidly in patients receiving ketorolac, and perioperative bleeding was not a problem.

The use of new pharmacologic agents, of which ketorolac is an example, as adjuvants to conventional therapy may revolutionize the field of postoperative pain management. By targeting multiple sites along the pain pathway, we may be able to provide significantly better analgesia with fewer side effects.

Postoperative Pulmonary Complications: Epidural Analgesia Using Bupivacaine and Opioids *Versus* Parenteral Opioids

Christian Jayr, M.D., Hermès Thomas, M.D., Annie Rey, M.Sc., Fayezi Farhat, M.D., Philippe Lasser, M.D., Jean-Louis Bourgain, M.D.

THE paper by Jary *et al.* (page 666) should be read by both clinicians and clinical investigators. Careful attention to the issues raised will improve the reader's ability to critically evaluate clinical studies in the future. It demonstrates how prospective involvement of an epidemiologist/statistician can profoundly affect how a clinical study is designed, carried out, and interpreted.

The results of intra- and postoperative management over 5 days comparing the effects of epidural local anesthetic plus opioid *versus* parenteral opioid administration on pulmonary complications are presented in a randomized, blinded study of 153 consecutive patients undergoing major abdominal surgery. The patients were stratified for respiratory disease by history, physical examination, and pulmonary function testing, and the results statistically adjusted for a history of smoking. Important components of the study, addressed and illustrated in this paper, include: defining the patient randomization and exclusion criteria; the prospective stratification and calculation of population size based on prospective definitions of acceptable types I and II errors with the difference expected between groups; understanding the difficulties in balancing standard procedures of patient care with blinding the caretakers to different therapeutic approaches; prolonged observation; multiple quantifiable endpoints; and post-data acquisition statistical adjustments to account for population differences impossible to prospectively randomize.

No major differences in quantifiable pulmonary complications were observed between the two groups, nor in the stratified subgroups with a history of respiratory illness or smoking. Little difference was observed in the nighttime measurements of hemoglobin oxygen saturation. Better early postoperative pain relief using an epidural approach was observed, but no difference was found after 2 days. Vital capacity was better on day 1 for the epidural group, but no difference was observed later, whereas systemic blood pressure was lower in the epidural group, as would be expected. Finally, no difference in duration of hospital stay was found. This paper responds to the demand on rounds of "Show me the study."