In Reply:—I agree with Steinberg and Tessier that “therapeutic advances rarely come without risk; a note of caution may be appropriate.” The three cases of serious gastrointestinal bleeding that they report in conjunction with the use of parenoetal ketorolac are worthy of review. Their subsequent effort to “supervise the use of ketorolac more scrupulously,” including medical staffing and a drug-use evaluation program, is a model program that we all should follow at our own institutions.

As Steinberg and Tessier point out, ketorolac is approved for as many as 5 days of use in dosages of 15-50 mg intramuscularly every 6 h after a loading dose of 30-60 mg. The lower end of the dosage range is recommended for patients less than 50 kg, for patients older than 65 yr, and for patients with reduced renal function. The dose guidelines are not “loosely based on a patient’s weight, age, and general medical condition” but rather on carefully derived pharmacokinetic data from normal subjects, healthy elderly subjects, patients with hepatic dysfunction, patients with renal impairment, and patients on renal dialysis, all of which were subjected to rigorous scrutiny by the Food and Drug Administration. According to these guidelines, all three patients mentioned by Steinberg and Tessier should have received the lower end of the dosage range (30 mg followed by 15 mg every 6 h), and the third patient should have received this lower dosage range for no more than 5 days, “because adverse reactions may increase with longer use at recommended doses.” Thus, if indeed ketorolac was a significant factor in the development of gastrointestinal bleeding in these patients, we cannot conclude that it would have been a significant factor had proper dosing guidelines been followed.

Although we concluded in our study that ketorolac had no clinically significant effect on postoperative bleeding, our sample size (n = 20 per group) was not sufficiently large to detect a potentially catastrophic adverse outcome that may be clinically significant even in very low frequency of occurrence. Nonetheless, although multiple-dose studies in humans have shown that ketorolac inhibits platelet aggregation1-3 while prolonging bleeding time to a degree similar to that observed with other nonsteroidal antiinflammatory drugs,4-5 in controlled clinical studies in which ketorolac was administered postoperatively, the incidence of clinically significant postoperative bleeding was 5 in 1,170 (0.4%) for ketorolac, compared to 1 in 570 (0.2%) in the control groups receiving opioid analgesics.*

Patients who have coagulation disorders or who are receiving therapeutic doses of anticoagulants are probably at increased risk of bleeding complications if given ketorolac concurrently; we avoid the use of ketorolac in all such patients. The concurrent use of ketorolac in patients receiving prophylactic low-dose heparin (2,500-5,000 units every 12 h) has not been studied extensively, but we do not currently believe this to be a contraindication to the use of ketorolac in our practice. Based on the Agency for Healthy Care Policy and Research Clinical Practice Guideline for Acute Pain Management recommendation that "unless contraindicated, every patient should receive an around-the-clock postoperative regimen of an nonsteroidal antiinflammatory drug,"† we have administered ketorolac to more than 1,000 patients at our institution, typically as adjuvant therapy to epidural analgesia or intravenous patient-controlled analgesia for 24-72 h with strict compliance to dosing guidelines, without any clinical incidence of gastrointestinal bleeding or other significant adverse outcome.

Conversely, the inhibition of platelet aggregation achieved with ketorolac and other nonsteroidal antiinflammatory drugs may be of therapeutic benefit in reducing the incidence of vascular graft occlusion, coronary artery occlusion, and deep venous thrombosis postoperatively, analogous to the antiplatelet and fibrinolytic effects of epidural anesthesia and analgesia in preventing vascular graft occlusion6 or prophylactic antiplatelet therapy in preventing heart attacks in the general population.7 Carefully controlled clinical investigations addressing these outcome end-points are warranted.

Jeffrey A. Grass, M.D.
Director, Acute Pain Service
Assistant Professor
Department of Anesthesiology/Critical Care Medicine
Johns Hopkins Medical Institutions
600 North Wolfe Street, Osler 304
Baltimore, Maryland 21287-5354

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