Correspondence

A Letter to the Editor must be signed by all authors, typewritten, and double spaced (including references), and must not exceed one and one-half typed pages in length. To be considered for publication, a letter referring to a recent Journal article must be received within a reasonable period after the article’s publication. All such correspondence, including the reply of the author or authors, will be subjected to the editorial process, including possible abridgment. However, no letter will be printed without the final approval of the correspondents.

TO THE EDITOR:

I read the article “Effect of Ketorolac Tromethamine on Bleeding and on Requirements for Analgesia after Total Knee Arthroplasty” (77-A: 998-1002, July 1995), by Fragen et al., with great interest. I find it hopeful that excellent analgesia can be obtained with a non-opiate substance in order to limit side effects in an often elderly population at risk for complications. I am still concerned, however, about bleeding and wound complications in the total joint population. These very important complications, which may prove catastrophic, were not addressed in this study.

As we know from the literature regarding prophylactic therapy with low-dose warfarin and low-molecular-weight heparin, substantial bleeding episodes occur in as many as 5 per cent of treated patients. In these reports, a major bleeding episode was defined as a decrease in hemoglobin of 0.002 gram per deciliter or more, the need for a transfusion of two units of blood or more after twenty-four hours, bleeding into the retroperitoneum, intracranial hemorrhage, or bleeding into the site of a major prosthetic joint. None of the fifty-nine patients reported on by Fragen et al. had a substantial bleeding episode. I therefore question if enough patients were included for the authors to determine whether bleeding complications were affected or if the definition of a substantial bleeding complication was similar to that in previous studies of warfarin and low-molecular-weight heparin.

Also, speaking anecdotally from clinical observations of our patients with a joint replacement, persistent serous drainage seems to occur with the use of anticoagulants in general. This drainage was more substantial when our patients were managed with ketorolac tromethamine and especially when it was used simultaneously with low-molecular-weight heparin. I would be interested to learn if these observations were made in the reported population and also if there was a difference in complications with respect to the use of warfarin and low-molecular-weight heparin.

Hypothetically, given the rapid onset of both ketorolac and low-molecular-weight heparin, it would not be surprising to see more bleeding complications with this combination of agents. Since low-molecular-weight heparin interferes with factor Xa at the level of the common clotting pathway, there is a dependence on platelet function to form a loose platelet aggregate. The reversible and immediate cyclooxygenase-mediated platelet inhibition of ketorolac would then theoretically predispose the patient to bleeding because of a lack of formation of this so-called plug during primary hemostasis, which occurs within seconds after an injury of a vessel. Conversely, as the half-life of warfarin is approximately 7.5 hours, a steady state is not reached for approximately thirty-six to seventy-two hours. The use of ketorolac in patients managed with warfarin allows formation of a clot with compaction to an organized and irreversible plug in the presence of fibrinogen, which is not immediately inhibited. Thus, fewer bleeding episodes may result.

I hope that this study continues to include more patients, with specific observations regarding the cited parameters so that these critical issues may be addressed before the widespread simultaneous administration of these potentially interacting agents.

Douglas Linville, M.D.: Department of Orthopedics, State University of New York at Stony Brook, Stony Brook, New York 11794

Dr. Fragen, Dr. Stulberg, Dr. Wisson, Dr. Glisson, and Ms. Librojo reply:

Dr. Linville correctly expresses concern regarding our article. Total knee arthroplasty was chosen for the study only because it is one of the few operations for which most of the blood loss is measured rather than estimated. The results should be applicable to other types of operations of the same or lesser severity, but we realize that they cannot be applied to all operations, such as, possibly, total hip arthroplasties. In our study, we found no wound infections or bleeding other than at the operative site.

According to the definition of a major bleeding episode cited by Dr. Linville, twenty-five of the twenty-nine patients who received ketorolac and twenty-three of the thirty patients who received the placebo in our study had a decrease in hemoglobin of 0.002 gram per deciliter or more. However, these numbers are meaningless because many of the preoperative laboratory values were obtained before the patients donated blood for autologous transfusion. Furthermore, these numbers appear similar for the two types of treatment. A better variable for comparison is the number of patients who received transfusion of more than one unit of blood (some of the transfused blood came from the Hemovac drainage system). Twelve of the twenty-nine patients who received ketorolac received more than one unit of blood. Six of these twelve were given warfarin and six, low-molecular-weight heparin. Thirteen of the thirty patients who received the placebo received more than one unit of blood. Four of these thirteen were given warfarin and nine, low-molecular-weight heparin. Furthermore, with regard to the patients who had the greatest blood loss, seven who received the placebo and five who received ketorolac lost 750 to 1000 milliliters; two patients who received the placebo and one who received ketorolac lost more than 1000 milliliters. Of these fifteen patients, seven were given warfarin and eight were given low-molecular-weight heparin. It appears from these data that ketorolac was not associated with greater blood loss compared with the placebo regardless of whether warfarin or low-molecular-weight heparin was used for anticoagulation to prevent deep-vein thrombosis. We doubt if a larger number of participants would change the results, and we have not expanded the study.

Despite our results, we reiterate part of our summary paragraph: “It is still possible that a bleeding problem could occur postoperatively with the combination of ketorolac and anticoagulants.” This may be a special concern when preoperative platelet function may be abnormal from other causes, but ketorolac was recently shown not to worsen platelet function when platelets are healthy.

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To The Editor:

I read with interest "Effect of Ketorolac Tromethamine on Bleeding and on Requirements for Analgesia after Total Knee Arthroplasty" (77-A: 998-1002, July 1995), by Fragen et al. This is a useful contribution to the literature, but I think that some points should be raised.

The benefits of parenteral administration of non-steroidal drugs for postoperative analgesia have been well shown before, and indeed many patients are maintained preoperatively on a treatment regimen that incorporates oral administration of non-steroidal drugs. The use of these drugs in combination with low-molecular-weight heparin, as was done in the study by Fragen et al., has two potential hemorrhagic interactions: (1) prolonged bleeding time caused by a direct suppressive effect on platelet production of thromboxane A2 and other prostanoids endoperoxides and (2) decreased renal excretion of low-molecular-weight heparin, caused by a diminished rate of renal glomerular filtration, and a consequent prolongation of its half-life.

Ketorolac tromethamine has a rapid onset and a relatively short duration of action; in addition, it is believed to have a minimum effect on platelet activity and clotting of platelets. This is in contrast to other non-steroidal drugs, in particular indomethacin, which have more profound effects on platelet activity and renal function, with clofonac falling somewhere in between. Fragen et al. gave no information regarding the renal function of their patients. To my knowledge, there are no studies at present that answer the question of whether non-steroidal drugs administered orally in conjunction with low-molecular-weight heparin have a significant clinical interaction that causes increased postoperative bleeding, and Fragen et al. did not attempt to answer this. It would therefore be wrong to extrapolate the results of this study to non-steroidal drugs in general.

It is interesting to note that a similar study in Britain was curtailed when the data sheet for ketorolac was amended to advise that it should not be used in conjunction with heparins, although this was because of anecdotal concern regarding bleeding problems rather than because of data from clinical trials. Studies such as those of Fragen et al. are therefore welcome, and I look forward to the subsequent publication of a study on the use of non-steroidal drugs administered orally in conjunction with low-molecular-weight heparin for postoperative analgesia.

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We did not extrapolate our finding of no apparent adverse drug interaction to other non-steroidal anti-inflammatory analgesics, and we agree that it would be wrong to do so. An examination of the effects of any of the orally administered non-steroidal anti-inflammatory analgesics on the rate of glomerular filtration, renal excretion, elimination half-life of anticoagulants, and blood loss when they are given in conjunction with low-molecular-weight heparin would be an interesting and possibly valuable study, but it is not in our immediate plans to undertake such an investigation.

Cyclooxygenase is an important enzyme in the prostaglandin synthesis pathway. If the enzyme is inhibited by non-steroidal anti-inflammatory analgesics, the kidneys are susceptible to the systemic vasoconstrictive effect of angiotensin II and other catecholamines secreted to preserve intravascular volume and perfusion in hypotensive states. This is a problem with ischemic kidneys but not with normal kidneys, and it is more likely to be a problem after the administration of indomethacin.

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To The Editor:

In "Non-Unio of the Scaphoid. Revascularization of the Proxi­
mal Pole with Implantation of a Vascular Bundle and Bone-Grafting" (77-A: 883-893, June 1995), by Fernandez and Eggi, the implan­
tation of a vascular bundle may have been unnecessary because there was already blood circulation. The authors described changes of the supposedly avascular proximal poles evident on plain radiographs. The cystic changes and collapse of the subchondral bone, which were observed in most of the patients, are the result of active resorptive processes that require a vascular supply. Thus, the radiographs indicated that, although the bone tissue may have been necrotic, the narrow compartment of the proximal pole had already revascularized spontaneously.

The authors cited a study regarding proximal scaphoid frag­
ments that were all macroscopically judged to be necrotic and un­
salvageable by the surgeon; in all cases, the histological studies showed areas of living vascularized tissue.

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Dr. Fernandez and Dr. Eggi reply:

The scaphoids treated in our series had radiographic and clinical evidence of impaired circulation, erroneously called avascular necrosis. According to the observations of Green, the total absence of bleeding points and sclerotic bone in the proximal scaphoid segment is associated with a high rate of failure when conventional bone-grafting techniques are used. Although we totally agree that cystic changes and collapse of subchondral bone are the result of active bone resorption, which requires some vascularity, this does not mean that the proximal pole had sufficient vascularity to pro­