



Fig. 1. (A) Equilibrium fluorescence intensity of Dns-C₆-Chol under conditions of energy transfer from nAChR tryptophan residues in the presence of nonanesthetics. The excitation wavelength was 290 nm, and emission was recorded above 560 nm. The predicted EC₅₀s for 1,2-dichlorohexafluorocyclobutane and 2,3-dichlorooctafluorobutane are 16 μ M and 4.5 μ M, respectively. Data are the means (\pm SD) of at least three determinations. (B) Stern-Volmer plots for nAChR-rich membrane intrinsic fluorescence quenching by halothane. Data are the means (\pm SD) of at least three determinations.

avoiding compounds that seemed to offer the greatest probability of quenching.

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Enoxaparin and Epidural Analgesia

To the Editor:—Enoxaparin sodium (Lovenox), a low molecular weight heparin (LMWH) manufactured by Rhone-Poulenc Rorer Pharmaceuticals, has a new warning included in its recently changed package insert. This change can have significant implications for anesthesiologists. It states "Lovenox injection, like other anticoagulants, should be used with extreme caution in conditions with increased risk of hemorrhage, such as . . . in patients with indwelling intrathecal or epidural catheters, . . ." Because of this warning, some orthopedic surgeons at our institution have decided against the use of an epidural catheter for postoperative pain management in patients receiving Lovenox for deep venous thrombosis (DVT) prophylaxis after total hip and knee replacement surgery.

Lovenox was released for use in Europe in 1987 and in the United States in 1993. Bergqvist *et al.*¹ reported that of more than one million patients receiving LMWH, there was one case of a spinal hematoma. In other controlled studies of at least 10,000 patients who received

epidural/spinal anesthesia or analgesia during LMWH prophylaxis, this combination of treatments did not produce any catheter-related complication.^{1,2} A similar safety record was observed in three other studies of 1,792 patients.²⁻⁴ In contrast, during post-market clinical use in the United States since 1993, Rhone-Poulenc Rorer Pharmaceuticals reports that there have been seven cases of epidural hematoma formation after epidural anesthesia/analgesia in association with Lovenox use. All but two cases were associated with an epidural catheter that was inserted or removed, either before the patient was started on Lovenox. Because of this new development, the drug manufacturer recently changed the package insert to reflect the perceived increased risk of epidural hematoma formation in patients with an epidural catheter during Lovenox prophylaxis.

Epidural hematoma formation in patients receiving anticoagulation therapy is a known but rare complication irrespective of central neuraxial blockade. Is the risk of spontaneous or catheter-related spinal

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hematoma greater with Lovenox than with other effective forms of anticoagulant DVT prophylaxis? Is it safe to leave an indwelling epidural catheter for postoperative analgesia or to remove it during Lovenox therapy? Although we are now aware of the seven cases of epidural hematoma reported by Rhone-Poulenc Rorer in the past 2 yr, we cannot estimate the incidence of epidural hematoma formation in patients receiving Lovenox and have an epidural catheter, because the number of patients receiving intraoperative and/or postoperative epidural anesthesia and/or analgesia is unknown. The perceived "high" incidence of epidural hematoma formation in patients receiving Lovenox may be explained by the increased use of epidural analgesia after total joint replacement surgery. Therefore, it may appear that specifically having a catheter in place increases the risk of epidural hematoma formation.

We must identify whether the risk of epidural hematoma formation is related to the timing of epidural catheter insertion or catheter removal, or related to the duration of catheter indwelling; whether there is a relation between the administered dose of Lovenox and epidural hematoma formation. Information regarding the circumstances under which epidural hematoma occurred in the reported cases is lacking or incomplete. A cause-effect relation cannot be established at this time. A prospective determination of the incidence of epidural hematoma formation in patients with epidural catheters removed at the end of surgery and in patients whose catheter is left in place for postoperative analgesia is needed. There is no evidence in the literature that removal of an epidural catheter portends greater risk of epidural hematoma formation than does epidural catheter insertion.

Finally, further studies are needed to delineate the role and effectiveness of epidural anesthesia and analgesia in improving outcome. Postoperative epidural analgesia is an excellent method for providing postoperative pain control, particularly in patients undergoing total

hip and knee joint replacement. It would be unfortunate to abandon this form of postoperative pain management without further elucidation of the risk-benefit profile for Lovenox and epidural anesthesia and analgesia.

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In Reply:—Rhone-Poulenc Rorer (RPR) Pharmaceuticals Inc. thanks Weitz and Chan for the questions they have raised concerning the risk of epidural hematoma formation in patients who have received anticoagulation after neuraxial anesthesia. These questions are important and remain unanswered. Recent reviews¹⁻⁵ discussed the use of postoperative indwelling catheters in anticoagulated patients. Rhone-Poulenc Rorer has received approximately 14 worldwide reports of epidural hematoma, which have been shared with worldwide regulatory authorities and expert anesthesiologists in the United States and Europe, including board members of the American Society of Regional Anesthesia (ASRA) and the Anesthesia Patient Safety Foundation (ASPF). We asked these experts for their analysis and advice, and encouraged them to disseminate this information in their literature and presentations.

We agree with Weitz and Chan that the often sketchy information we can obtain from spontaneous case reports limits our analyses, but some consistencies emerge from the cases we were able to review in depth and in conversations with the involved anesthesiologists.

First, we discovered that many anesthesiologists were unaware of the postoperative administration of anticoagulants in their patients,

nor were they aware of the differences in the pharmacokinetics of low molecular weight heparins and customary anticoagulants such as warfarin or heparin. A survey done in 1995 with U.S. anesthesiologists who frequently care for hip and knee replacement patients revealed that only 14% knew about low molecular weight heparin (LMWH), and only 4% could name enoxaparin sodium as a marketed LMWH. Although understandable, because anesthesiologists do not prescribe these agents, this survey illustrates an information gap that might have contributed to the problem.

Second, almost all of the cases involved postoperative indwelling epidural catheters. This was also noted in Dahlgren and Tornebrandt's retrospective review of one hospital's experience.⁵ Also emphasized by Dahlgren and Tornebrandt, delayed diagnosis of the hematoma was noted in many of the cases we reviewed.

Perhaps most importantly, the majority of the reported cases involved dosing the anticoagulant either preoperatively or close postoperatively (including an intraoperative dose in one case). Spinal puncture or catheter manipulation during times of anticoagulant activity has been linked to the formation of epidural hematoma.^{1,2,5} The three hematomas (noted in 9,000 cases) reported by Dahlgren