

Editorial Focus

Differences in the safety profiles of two low-molecular-weight heparins

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Low-molecular-weight heparins (LMWH) approved for use to prevent post-operative thrombosis, and to treat venous and arterial thrombosis have several recognizable differences, including differences in molecular weight distribution and the proportions of molecules possessing the pentasaccharide sequence with high affinity for antithrombin. The two major differences above probably account for the variations in the ratios of the anti-factor Xa and anti-thrombin activities of LMWH (1). In the absence of compelling evidence to the contrary, LMWH are currently viewed as separate drugs for regulatory purposes (1). Largely for this reason, all currently approved LMWH required pre-clinical toxicological and pharmacological studies before the various clinical trials demonstrating the prophylactic and therapeutic efficacy and safety (acceptable bleeding side effects) of LMWH in venous and arterial thrombosis were conducted (1–3).

While the prophylactic and/or therapeutic doses of most LMWH are generally stated in anti-factor Xa units/patient or anti-factor Xa units/kg, no clinical studies have reported direct evidence consistent with increased antithrombin-mediated inhibition of factor Xa by any LMWH in man. Similarly, no study has reported the sustained normalization of prothrombin activation (as the concentrations of prothrombin fragment 1+2) in man by the prophylactic or therapeutic dose of any LMWH. Furthermore, evidence for direct contributions of the anti-thrombin activities of LMWH to their antithrombotic effects in venous and arterial thrombosis in man remains to be demonstrated (4). Finally, definitive relationships between the ex-vivo anti-factor Xa activities and minor or severe bleeding side effects of LMWH have also not been established.

The lack of direct relationships between the demonstrated effective prophylactic and therapeutic anti-factor Xa doses of LMWH and their bleeding side effects largely explain why routine laboratory monitoring of the concentrations of LMWH in patients' plasmas is generally not warranted (5, 6). This lack of direct relationships between the anti-factor Xa doses and clinical effects, when LMWH are compared, and the dearth of results from large clinical studies that refute this regulatory stance

largely validate the current position of regulatory agencies that LMWH should be viewed as separate drugs (1).

Results of a few studies that appear to contradict this stance have reported the therapeutic equivalence of the recommended doses of four approved LMWH in patients who had elective total knee or hip replacement surgery and each study enrolled up to 600 patients (7–10). However, another study that compared the efficacy (prevention of death at day 12 and prevention of symptomatic deep vein thrombosis or pulmonary embolism) and safety (major bleeding) in 1,296 patients randomized to receive either nadroparin (2,850 IU of anti-factor Xa) or enoxaparin (4,000 IU anti-factor Xa) per day after colorectal cancer found the former to be significantly safer and more effective than the latter (11). Thus, there currently are two views on whether approved LMWH can be used in an interchangeable manner (12, 13).

The study by Kistler et al. that appears in this issue of *Thrombosis and Haemostasis* enrolled over 8,000 consecutive patients who had a variety of orthopedic surgical procedures over an eighteen-month period at a clinic in Zurich, Switzerland. Nearly half the patients received nadroparin in the first nine-month period while the other patients received enoxaparin in the second nine-month period to prevent venous thrombosis after their orthopedic surgeries (14). The two major strengths of this non-randomized study by Kistler et al. are the large number of patients enrolled in the two phases, and the six different orthopedic surgeries that were performed at this single institution over 18 months. In particular, groups consisting of at least a thousand patients had total hip replacement, total knee replacement, spine, shoulder, or foot surgeries. Thus, the authors could make more definitive statements about the comparative efficacy and safety of the two LMWH studied than could be made from the results of previous smaller studies (7–10).

Kistler et al. found nadroparin and enoxaparin to be equally effective in preventing objectively confirmed symptomatic post-operative thromboembolic events, while approximately 30% fewer patients on enoxaparin had clinically significant bleeding complications than the patients on nadroparin. The authors ac-

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knowledge, as noted by others previously (15–17), that this study “probably missed several potential thrombotic events that the patients experienced after discharge and that could be reasonably be attributed to their previous orthopedic surgeries”(14). Even though this was not a randomized control trial, this study has set

an important bar regarding the number of patients suitable for future studies aimed at determining the prophylactic and/or therapeutic equivalence or non-equivalence of other LMWH. The issue of whether LMWH can be used interchangeably for other approved indications also remains to be resolved.

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