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Regular Article

Pharmacokinetics of UH and LMWH are similar with respect to antithrombin activity

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Abstract

Background: The ability to administer low molecular weight heparins (LMWH) subcutaneously without laboratory monitoring contributes to their popularity for the treatment of thrombotic disorders. Subcutaneous unfractionated heparin, although less expensive, is deemed to require routine laboratory monitoring on the basis of more variability in drug effect compared to LMWH. However, the more predictable pharmacokinetic profiles of low molecular weight heparins are largely based on anti-Xa activity, while antithrombin activity may be at least as important to their mechanisms of action.
Methods: We performed a clinical pharmacokinetic trial to compare the variability in peak antithrombin effect between subcutaneous unfractionated heparin and various LMWHs, all given in recommended weight-adjusted treatment doses. Sixty-one patients enrolled in a warfarin clinic were randomized to receive one of four different weight-adjusted subcutaneous heparin doses: unfractionated heparin, 250 units/kg (n=15); tinzaparin, 175 units/kg (n=15); dalteparin, 200 units/kg (n=15); or enoxaparin, 1 mg/kg (n=16). The areas under the curves of antithrombin levels during the first 3 h after administration were determined for each patient, and the coefficients of variation and 95% confidence intervals of the AUCs were compared among the treatment groups.
Results: There was no statistically significant difference in the coefficients of variation of antithrombin effect between unfractionated heparin (52.8, 95% CI: 32.6—72.9) and enoxaparin (56.5, 95% CI: 35.7—77.4) or dalteparin (43.5, 95% CI 25.4—61.6). Tinzaparin had statistically significant decrease in coefficients of

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variation (21.6, 95% CI: 12.2—30.9) relative to unfractionated heparin, dalteparin and enoxaparin.
Conclusions: LMWHs, as a class of drugs, are no more predictable in antithrombin effect after subcutaneous injection than unfractionated heparin. There were considerable differences among LMWHs in the observed variability of antithrombin effects, with tinzaparin being somewhat more predictable than the other drugs tested.

Introduction

Subcutaneous low molecular weight heparins have become increasingly popular for the treatment of venous thromboembolic disease and other disorders [1]. Both subcutaneous unfractionated heparin and subcutaneous low molecular weight heparin have been demonstrated to be safe and effective for venous thromboembolism treatment. Subcutaneous low molecular weight heparin has the significant practical advantage that most clinical uses do not involve plasma monitoring, which is routinely performed for unfractionated heparin [2]. The different requirements for plasma monitoring between the two drug types have never been tested in comparative trials. Current recommendations for different monitoring requirements are based in part on the belief that subcutaneously administered low molecular weight heparins are associated with more predictable pharmacokinetic profiles than those of subcutaneous unfractionated heparin. The parameter typically used to compare the pharmacokinetics of the two drug types has been the potency for catalyzing the inhibition of unbound factor Xa in plasma (anti-Xa activity). However, since the mechanism of action for both drugs involves thrombin inhibition as well as factor Xa inhibition, potency for inhibiting thrombin (antithrombin activity) may be an appropriate parameter for comparing these drugs.

Inhibition of thrombin (antithrombin activity) has been proposed as the major action of both unfractionated and low molecular weight heparins [3]. Animal experiments suggest that the antithrombotic potencies of unfractionated heparin and of low molecular weight heparins correlate more highly with plasma antithrombin activity than with plasma anti-Xa activity [4,5]. In clinical trials, anti-Xa activity did not correlate well with antithrombotic effect or bleeding risk [6] in patients given low molecular weight heparins. For these reasons, the pharmacokinetic "superiority" of any subcutaneous heparin preparation may depend on its ability to achieve a low level of variability in antithrombin activity when administered to a variety of patients.

We performed a randomized clinical trial to determine if several types of subcutaneous low molecular weight heparin have more predictable pharmacokinetics than subcutaneous unfractionated heparin, with respect to their antithrombin activities. We compared the variability in plasma antithrombin levels measured serially in patients who had received the recommended treatment doses of unfractionated heparin or one of the low molecular heparins available in the United States: enoxaparin, dalteparin or tinzaparin.

Materials and methods

Patient population

Subjects were recruited from participants in a clinical study (to be published separately) determining the effect of subcutaneous heparins on prothrombin time measurements in patients taking warfarin. (Warfarin should have no effect on the primary pharmacokinetic variables measured in the current study.) Inclusion criteria for the parent study were as follows: warfarin administration for at least 6 weeks, no oral contraceptives, no known sensitivity to heparin and no use of heparin for at least 12 h prior to the study. Patients were excluded from the current study only if plasma sampling did not include all time points necessary for pharmacokinetic analysis (see below).

The Veterans Administration Medical Center, Loma Linda California Institutional Review Board approved the project. Informed consent was obtained from all human subjects.

Drug administration and blood sample collection

Patients were randomly assigned to receive one of the following four medications subcutaneously: