Pharmacokinetic Modeling of Heparin and Its Clinical Implications

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Experimental work on heparin has indicated that its half-life increases with dose. Two models to describe heparin's pharmacokinetic behavior are proposed, and the parameters in the models are fitted to experimental data. Both models exhibit an apparent first-order decay with a "half-life" that increases with dose. It is shown that, even though both models exhibit a bolus half-life of from 1 to 2 hr, over 2 days can be required for true steady-state conditions to be achieved in these models when a constant intravenous infusion of drug is given. The clinical implications of these models are discussed. Suggestions are made for further research on heparin kinetics.

KEY WORDS: heparin; metabolite-inhibition model; phagocytosis.

INTRODUCTION

In this report the pharmacokinetic modeling and clinical implications of drugs whose half-life increases with dose will be examined. The report will focus on the anticoagulant drug heparin. However, many of the conclusions drawn for heparin are generally applicable. As discussed in detail in a companion report (1), the work of Estes et al. (2-5) and Olsson et al. (6) indicates that the elimination of heparin, as measured by bioassay, follows an apparent first-order response whose half-life increases with dose. Essentially all of the studies which report on the pharmacokinetics of heparin have involved a single bolus of the drug.
Several other drugs are known to exhibit this same type of apparent first-order behavior with a dose-dependent half-life. Product inhibition may produce such behavior in the pharmacodynamics of phenylbutazone (7) and diphenylhydantoin (8,9). Estes et al. (2) also list the following drugs as possibly exhibiting a dose-dependent half-life in humans: indanediones, methotrexate, probenecid, and rifampicin. Dicumarol (10) and a number of other drugs (11) have been demonstrated to exhibit an increasing half-life response.

If a drug exhibits an increasing half-life with dose behavior, then, in fact, a mathematical contradiction exists, and linear models cannot be used. Perrier et al. (12) have described a one-compartment model which exhibits an increasing half-life with dose behavior. Their model is based on a Michaelis-Menten drug elimination mechanism in which the major metabolite competes with the drug for binding sites on the metabolizing enzyme. Two nonlinear differential equations are necessary to describe the system.