Heparin: Applications and Future Prospects

Donald Quick, M.D.; and Arthur A. Trowbridge, M.D.

It is challenging to consider why a drug which has been in widespread clinical use for over 40 years and has been the subject of thousands of carefully conducted investigations at both the biochemical and clinical levels continues to generate the degree of controversy and intrigue surrounding the drug heparin. In his article “The New Understanding of the Drug Heparin,” (see page 751) Dr. Jaques presents strong arguments in support of what he has termed “the new paradigm” of the drug heparin. This paradigm, evolved over a lifetime devoted to the study of heparin, proposes that heparin should be thought of in terms of a group of similar compounds (linear anionic polyelectrolytes) of varying molecular weight, each component possessing different anticoagulant properties. Moreover, these components also possess a variety of other biochemical properties, ranging from immunologic mediation to hormone suppression. Protection from thrombosis, he contends, is provided by heparin's ability to electrostatically protect vessel wall endothelium, the target organ of the drug. He proposes that heparin's anticoagulant and potentially hemorrhagic action is more or less an undesirable property or side effect of the drug and its antithrombotic ability lies in properties other than coagulation inhibition. The author further proposes that an alternative heparin administration technique (ie, intrapulmonary delivery) may possess the pharmacokinetic attributes necessary for the optimum delivery of this agent to its target organ without the concomitant undesirable systemic anticoagulant and hemorrhagic side effects.

This article raises several interesting points which deserve comment, including (1) the properties and uses of heparin other than as an anticoagulant, (2) the heterogeneity of heparin and how this relates to the study of heparin fractions and heparin analogs, and (3) the published work on intrapulmonary delivery as an alternative method of heparin administration.

First, many clinicians do not well appreciate heparin's many biochemical properties distinct from its well known anticoagulant abilities. Jaques has elegantly summarized many of these properties in a recent extensive review. Heparin, for instance, has been shown to exhibit multiple immune-mediatory effects. These actions include stimulation of lymphocytes; inhibition of C-esterase; antagonization of the action of histamine, bradykinin, and prostaglandin E; and attenuation of anaphylaxis. There has been, however, a rather limited clinical applicability for these mediating effects of heparin. There are scattered reports of favorable effects on certain autoimmune disorders such as pulmonary alveolar proteinosis, experimental allergic encephalomyelitis, and certain subgroups of migraine. However, these claims are disputed by others; for instance, in the case of pulmonary alveolar proteinosis, heparin lavage has been felt by most authorities to be no more effective in this disorder than normal saline lavage. Perhaps one of the reasons for its limited use as an immune mediator (in fact, major immunology texts do not discuss any possible role for heparin) is the reported variability of the drug's effects on these immune processes. For example, findings conflict regarding heparin's effect on polymorphonuclear leukocyte aggregation and degranulation, with reports of both significant inhibitory and stimulatory effects. In part, however, these conflicting drug effects may be either dose related, or may be due to the specific type of heparin (source, weight, etc) tested. Such is true of immune-mediated thrombocytopenia, where it has been shown that beef lung heparin initiates immune-associated platelet aggregation at a rate of two to three times that of hog intestine heparin. Similarly, fractions of high molecular weight heparin were found to be more reactive with the platelets than were fractions of low molecular weight. Obviously, further studies defining the exact activities of specific heparin types on these immune processes must precede further clinical studies examining potential beneficial immune-mediation.

Heparin possesses further properties which are often not appreciated but have prompted interesting studies. Some of the claims of heparin's activity are apparently overstated, while other drug actions of possible benefit might deserve closer attention. For example, early reports gave indication that heparin might prove effective in gallstone dissolution, though later work did not support this, and further investigation of heparin for this purpose was made obsolete by the favorable reports of the effectiveness of chenodeoxycholate and ursodeoxycholate for this purpose. On

*From the Division of Hematology/Oncology, Scott and White Clinic, Temple, Texas. Reprint requests: Dr. Trowbridge, Scott and White Clinic, Temple, Texas 76508
the other hand, heparin’s proposed usefulness as a modifier of coronary artery disease probably deserves more attention. Heparin has been shown to liberate lipoprotein lipase, lower serum triglycerides, augment the level of HDL, and favorably affect platelet aggregation in low doses. Studies are incomplete but, in a convincing summary of the drug’s potential benefits on the atherogenic processes, Engelberg6 concludes that heparin’s use merits wider application.

A second point of discussion are implications expressed by Jaques regarding heparin’s heterogeneity. As pointed out, there are over 100 different “heparins” in each commercial preparation. Investigation and development of these various heparin fractions are underway. The excitement in this area lies in the potential development of an effective antithrombotic agent which avoids undesirable side effects such as hemorrhage and thrombocytopenia. Heparin fractions with low-molecular weights tend to potentiate inactivation of factor Xa and factor Xlla but seem to show less reactivity with thrombin.14 These low-molecular weight fractions also exhibit more specific antifactor Xa activity than anticoagulant activity, as measured by the traditional activated partial thromboplastin time. In vivo testing has shown low-molecular weight heparins to be at least as effective as unfractionated heparin, and early clinical trials indicate that a single daily injection of low-molecular weight heparin is a convenient and apparently effective agent of thrombosis prophylaxis.16-17 Low-molecular weight heparins also have additional potential advantages. They have less platelet aggregating activity than their higher molecular weight counterparts yet retain some of the desirable properties of high molecular weight fractions, such as their inability to cross the placenta during pregnancy.10, 18

Heparin analogs are now being evaluated to find a drug with effective antithrombotic properties and no significant effect on overall clotting. The semi-synthetic heparin analog (SSHA) was noted by Thomas24 to exhibit factor Xa inhibition without significant effect on overall clotting as measured by the APTT. In early clinical trials, this drug was as effective as continued low dose heparin, though more extensive studies are needed before safety and specific indications for use can be determined. Another heparin analog, pentosan polysulphate (SP54), offers similar hopes as an antithrombotic agent. This drug appears to act by a mechanism independent of antithrombin III, probably through potentiation of heparin cofactor II.19 Again, early clinical trials show favorable results.20 Due to its antithrombin-III independent mechanism, SP54 may offer an alternative form of treatment in patients with antithrombin-III deficiency.21

The final point raised by Jaques is that of intrapulmonary heparin administration. The fact that intrapulmonary heparin exerts a prolonged anticoagulant effect on blood raises further speculation about the true mechanism(s) of the drug’s anticoagulation effects. Traditionally, heparin is considered to exert its effect via the activation of its cofactor antithrombin-III (ATIII), although the exact mechanism of heparin-ATIII interaction is still disputed.22 It is perhaps less well recognized that heparin may act via a number of other mechanisms to prompt antithrombosis, including (as stated in the article) the drug’s electrostatic effect on endothelial tissue lining. The work of Glimelius et al23 showing that heparin combines reversibly with cultured human endothelial cells; Sawyer’s demonstration of heparin’s protective effect on traumatized, damaged vessel endothelium; and recent studies in ultra-low dose heparin by Negus24 and Hladovec25 tend to support Jaques’ proposal that heparin in low doses may act preferentially via endothelial cell uptake and redistribution.

It is because of this mechanism that Jaques and co-workers propose that intrapulmonary heparin would be an effective alternative route of heparin delivery. Intrapulmonary administration was first introduced over 20 years ago with initially disappointing results in terms of achieving what was felt to be significant anticoagulant levels.27 In 1976, Jaques and co-workers28, 29 successfully adminstered heparin intratraechally into dogs and later, via inhaled nebulizers into human volunteers. A dose of 1,300 units per kg body weight delivered to human subjects over 1½ hours of inhalation resulted in a prolonged state of moderate hypocoagulability for approximately two weeks. In subsequent studies, this method appeared safe and the hypocoagulability induced was easily reversed by repeated protamine administration.30-35 Pharmacokinetic studies demonstrated a delayed endothelial cell uptake of heparin with slow release back into the plasma after several days. In theory, this delivery method would allow a single administration of heparin during hospitalization and avoid the need for uncomfortable twice-a-day subcutaneous injections. In practice, however, clinical trials of intrapulmonary heparin have not been published and its advantages over other routes are uncertain. Intrapulmonary heparin will have to compete in terms of safety, efficacy, and cost effectiveness with other proven and unproven methods of thrombosis prophylaxis such as adjusted-dose heparin, ultralow dose IV heparin, dihydroergotamine-heparin prophylaxis, infusion pumps, and possibly even enteral administration of heparin (eg, via facilitation by Cetomacrogol 1000).35-37 Until such trials have been performed, intrapulmonary heparin administration will remain an interesting observation, but an uncertainty in terms of potential therapeutic applicability.

We would, with the data available, strongly support Dr. Jaques’ “new paradigm.” Commercial heparin is in
fact a mixture of complex, functionally multifaceted, individual molecules whose biologic properties are largely unknown.

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