SAFE AND SUCCESSFUL CLINICAL USE OF THE DEFBIRINOGENATING AGENT ANCROD

To the Editor:

Recently, Krishnamurti et al. cautioned against the use of the defibrinogenating agent ancrod as being potentially thrombosis-promoting in patients with hypofibrinolysis. They based their concern on the use of ancrod in rabbits in which pretreatment with endotoxin had typically induced high levels of plasminogen activator inhibitor-1 (PAI-1). In this setting, ancrod administration resulted in renal fibrin deposition.²

We have been using ancrod safely and successfully in patients...
with thrombotic disease. The majority of patients presented with elevated levels of PAI-1, which in some instances reached extremely high levels (40 to 50 IU/mL; normal range, 3 to 10 IU/mL). After ancrod administration (1 U/kg), a significant decrease in PAI-1 to normal levels, accompanied with a significant increase of initially unmeasurable tissue plasminogen activator levels, strongly correlated with a beneficial clinical response. In systemic lupus erythematosus patients, the striking concordance between normalization of laboratory values and favorable biologic effects was evidenced by improved renal function. This was associated with effective fibrin removal from the glomeruli, as shown by a significant decrease in the microvascular thrombosis index in posttreatment renal biopsies.

Likewise, in a double-blind, placebo-controlled pilot study on the use of ancrod in acute ischemic stroke, 2 a constant-rate slow intravenous infusion of ancrod (0.5 U/kg) was followed by a rapid and significant decrease of initially high PAI-1 levels (12 to 30 IU/mL), the appearance of plasmin-antiplasmin complexes, and increases in fibrin(ogen) degradation products and D-dimer. These changes are consistent with an effective activation of the endogenous fibrinolytic system. Importantly, the reduction in PAI-1 levels significantly correlated with improved stroke scores (Scandinavian stroke scale; P < .05).

A recently completed double-blind, placebo-controlled, multicenter study agreed with the pilot study and, furthermore, showed a significant reduction in mortality in the ancrod-treated stroke group. Whether a demonstrated early activation of the protein C system in the ancrod-treated group was a causative factor in the reduction of PAI-1 levels is presently being evaluated. Thrombotic complications (ie, myocardial infarction, pulmonary embolism, thrombophlebitis, recurrent stroke) were rare and occurred with equal frequency in both groups.

The multiple pathogenetic factors, in addition to a sixfold to sevenfold increase in PAI-1 levels, involved in the rapid development of a net procoagulant state in experimental endotoxemia and clinical sepsis, may differ from underlying mechanisms at work in a variety of clinical situations leading to an overexpression of PAI-1.

We conclude that high PAI-1 levels per se are not a contraindication for the administration of ancrod. In the conditions described above, ancrod is a hemostatically safe drug effectively triggering thrombolysis.

REFERENCES


RESPONSE

Our previous letter discussed the role of the fibrinolytic system in the degradation of non–cross-linked fibrin formed by the action of ancrod on fibrinogen. We have shown that ancrod induces renal fibrin deposition in endotoxin-treated rabbits with increased levels of endogenous PAI-1. In more recent studies, we have found that ancrod can also induce renal fibrin deposition in rabbits with increased levels of PAI-1 achieved through the continuous infusion of human recombinant PAI-1. In rabbits with an intact fibrinolytic system, fibrin deposition does not occur after ancrod infusion.

Glas-Greenwalt presents evidence from clinical studies that indicates that high PAI-1 levels per se are not a contraindication for the use of ancrod. We agree that it is difficult to extrapolate from animal studies to the human situation. Additional information is needed to determine the relevance of PAI-1 in impairing fibrinolysis and thereby promoting thrombosis, especially when an agent such as ancrod is used. Currently, there are no standardized units for expression of PAI-1 activity, and a variety of assays are used for the measurement of PAI-1. Thus, it is difficult to compare studies from different laboratories.

PAI-1 has a very short half-life in the circulation (approximately 7 minutes) and synthesis can be rapidly increased (by as much as 40-fold) in many clinical situations, including endotoxemia. In some clinical settings, synthesis may only be transiently stimulated, whereas in others, the increased production may be more sustained. In patients who have endotoxemia, the hemostatic balance also may be tipped toward thrombosis by increased expression of tissue factor as well as downregulation of thrombomodulin.

Because ancrod has been used with apparent safety for numerous clinical conditions, these issues may not be applicable to the majority of recipients. Ancrod is available for compassionate use under an IND by the Knoll Pharmaceuticals for the treatment of well-defined situations of heparin-induced thrombocytopenia. It is not to be used in patients with clinically significant renal failure or in patients who have sepsis. In our initial animal studies, ancrod was infused intravenously during 1 hour at a dose of 2 U/kg. The currently recommended initial dose for patients is 1 U/kg, which is to be infused intravenously during 12 hours with a maintenance dose of 1 U/kg infused during every 24-hour period. These doses are guidelines to maintain the fibrinogen level between 20 and 70 mg/dL. (Dr Keiko Aogaichi, Knoll Pharmaceuticals, Whippany,
The careful screening of patients and adherence to the recommended dosing regimen should enhance the safety of ancrod until further information can be obtained about the clinical significance of elevated plasma levels of PAI-1.

CHITRA KRISHNAMURTI
CHARLES D. BOLAN
THOMAS J. REID
BARBARA M. ALVING
Department of Hematology
Walter Reed Army Institute of Research
Washington, DC

REFERENCES
Safe and successful clinical use of the defibrinogenating agent ancrod [letter; comment]

P Glas-Greenwalt