Safety of C1-Inhibitor for Clinical Use

To the Editor:

Horstick and colleagues1 recently reported detrimental side effects of C1-esterase inhibitor (C1inh) in pigs with myocardial ischemia. Local complement activation contributes to ischemic myocardium injury, and complement inhibition constitutes a novel therapeutic approach for coronary syndromes. C1inh reduces reperfusion injury in various animal models of myocardial infarction (MI). In dogs, we found that C1inh also reduced myocardial injury after permanent coronary occlusion2 and did not reduce tensile strength of the scar area. C1inh prepared from human plasma has been given safely for 30 years to patients with angio-edema. We initiated a pilot study of C1inh in 22 patients with MI. The highest dose given was 100 U/kg, followed by 2 U·kg⁻¹·h⁻¹ for 48 hours. C1inh was well-tolerated, and infarct size was reduced by 40% to 50%.³

Our results differ from those of Horstick et al., who found no cardioprotection of C1inh at 100 U/kg in a pig model, but claimed detrimental side effects consisting of “severe coagulation disorders.” Their data do not support this; however, apart from clotted catheters, often observed in non-heparinized animals, no signs of thrombosis were documented. Actually, animals receiving 100 U/kg had results similar to those of controls. Thus, lack of efficacy, not “detrimental side effects,” was observed. These findings were related to a report of thrombosis in neonates receiving high dose C1inh for cardiac surgery. A follow-up randomized study not quoted by Horstick et al., however, demonstrated clinical benefit of 100 U/kg in neonates undergoing arterial switch operations.⁴

C1inh has opposite effects on coagulation and fibrinolysis; it inhibits contact system proteases and plasmin on the one hand, and factor Xa and thrombin on the other. Horstick et al. showed reduction of thrombin-antithrombin complexes by lower doses of C1Inh. This indicates that C1inh at low doses reduces thrombin formation, which may explain why at these doses catheters were not occluded. We found no effect of up to 5 U/mL of C1inh on clot formation and lysis in plasma (Hack et al., unpublished data, 1999). Several studies show safety of C1inh in sepsis and capillary leak syndrome. Hence, a pro-thrombotic effect of C1inh is likely minimal. The study by Horstick et al. does not provide data regarding this risk in MI.

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Response

Our study was conducted without heparinization because heparin potentiates the complement-inhibitory effect of C1-inhibitor (C1inh).¹ The concerns of Hack et al are correct; in heparinized patients, the detrimental effects of high dose C1inh are avoidable. We have unpublished data that support this statement. Our data, however, make it clear that in the absence of adequate heparinization, high dose C1inh can have serious side effects. Inadequate heparinization might be a reason for the reported adverse events² in contrast to further studies with C1inh treatment.³,⁴

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