Nonpeptide factor Xa inhibitors: I. Studies with SF303 and SK549, a new class of potent antithrombotics.

Wong PC¹, Quan ML, Crain EJ, Watson CA, Wexler RR, Knabb RM.

Abstract
A series of benzamidine isoxazoline derivatives was evaluated for their inhibitory potency against purified human factor Xa (fXa) and in a rabbit model of arteriovenous shunt thrombosis for their antithrombotic activities, expressed as K(I) and IC(50), respectively. A highly significant correlation was found between K(I) and IC(50) (r = 0.93, P < .0001). The antithrombotic effects of SF303 [mol. wt. 536; K(I): fXa, 6.3 nM; thrombin, 3,100 nM; trypsin, 110 nM; tissue plasminogen activator >20,000 nM; plasmin, 2,500 nM] and SK549 [mol. wt. 546; K(I): fXa, 0.52 nM; thrombin, 400 nM; trypsin, 45 nM; tissue plasminogen activator >33,000 nM; plasmin, 890 nM] were compared with recombinant tick anticoagulant peptide [K(I)(fXa) = 0.5 nM], DX-9065a [K(I)(fXa) = 30 nM], and heparin or low molecular weight heparin (dalteparin) in a rabbit model of arteriovenous shunt thrombosis. ID(50) values for preventing arteriovenous shunt-induced thrombosis were 0.6 micromol/kg/h for SF303, 0.035 micromol/kg/h for SK549, 0.01 micromol/kg/h for recombinant tick anticoagulant peptide, 0.4 micromol/kg/h for DX-9065a, 21 U/kg/h for heparin, and 23 U/kg/h for low molecular weight heparin. SK549 produced a concentration-dependent antithrombotic effect with an IC(50) of 0.062 microM. To evaluate its potential oral efficacy, SK549 was given intraduodenally at a dose of 5 mg/kg; it produced a peak antithrombotic effect of 59 +/- 4% with a duration of action greater than 6.7 h. Therefore, our study suggests that SF303, SK549, and their analogs represent a new class of synthetic fXa inhibitors that may be clinically useful as antithrombotic agents.

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