Novel oral FXa shows initial anticoagulation promise

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MedWire News: A novel oral selective factor (F)Xa inhibitor could help prevent and treat thromboembolism, scientists say.

DU-176b is an orally active form of an earlier FXa inhibitor, DX-9065a, that had potent anticoagulant and antithrombotic effects but poor low oral bioavailability, Yoshiyuki Morishima (Daiichi Sankyo Co, Tokyo, Japan) and co-workers explain.

Laboratory examination demonstrated that DU-176b was highly specific for FXa, showing a greater than 10,000-fold potent inhibition of FXa compared with the serine proteases thrombin and FIXa. The agent showed concentration-dependent inhibition of both animal and human FXa.

The researchers examined the bioavailability of the drug in animals and found significant FXa inhibition for up to 4 hours in rats, whereas the drug peaked at 4 hours in monkeys and was still active 24 hours after administration.

In rat and rabbit models of venous stasis thrombosis, oral DU-176b 0.5, 2.5, and 12.5 mg/kg significantly reduced thrombus formation in a dose-dependent manner and prolonged the prothrombin time.

Rat tail bleeding times were not significantly prolonged with an oral DU-176b dose of 3 mg/kg compared with control, but the drug prolonged bleeding 1.9-fold in animals given 10 mg/kg and 30 mg/kg doses.

"DU-176b is a potent and highly selective direct FXa inhibitor and represents a remarkable improvement in the potency, selectivity, and oral bioavailability compared with DX-9065a," Morishima *et al* report in the *Journal of Thrombosis and Haemostasis.*

"The present study demonstrates that DU-176b has potential as an oral antithrombotic agent and a promising novel anticoagulant for the prophylaxis and treatment of thromboembolic diseases."

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