P4464

Significative role of edoxaban on endotelial cell functions

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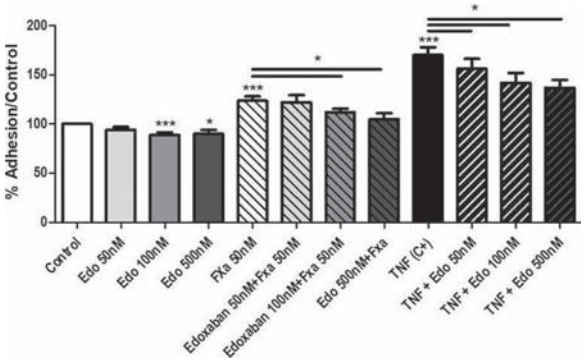
Background: Edoxaban is a new oral anticoagulant with factor X activated (FXa) inhibition properties. It is approved for the prevention of ictus and embolism in patients with atrial fibrillation and for the treatment of venous thrombosis and lung embolism. However, little is known about its effects on endothelial cell functions.

Objectives: To study the edoxaban effects on key endothelial functions as proliferation, wound-healing, angiogenesis and peripheral blood mononuclear cells (PBMCs) adhesion.

Methods: Human umbilical endothelial cells (HUVECs) were obtained from donated umbilical cords after signed informed consent of the mothers. Cell proliferation and viability were measured by a real-time cell analyzer by noninvasive electrical impedance monitoring. Migration was study in wound-healing assays. Angiogenesis was measured after 16 hours of HUVECs' seeding in a three dimensional matrix and PBMCs adhesion to HUVECs' monolayers was assessed in the presence or in the absence of edoxaban and/or FXa. Measurements on each assay was compared between control conditions and edoxaban's or FXa's treatments and between treatments with FXa and the combination of FXa and edoxaban.

Results: Edoxaban (1 Nm – 1 μm) was a safe, non-toxic molecule for HUVECs. It significantly promoted HUVECs' growth at concentrations between 10–500 Nm, been the maximal response at 100 nM. The proliferative effect of edoxaban 100 nM was also observed in the presence of FXa 9 nM, which also induced proliferation by itself. In spite of this proliferative effect, edoxaban (50–100 nM) did not increased healing (cells' migration) after a wound, but counteracted the healing effects of FXa 9 nM. Edoxaban (100–500 nM) alone did not influence angiogenesis, but partially restore the anti-angiogenic effect of FXa on HUVECs. Finally, and very interestingly, edoxaban (50–500 nM) significantly inhibited PBMCs adhesion to endothelial cells' monolayers, and even blocked the FXa (50 nM)- and tumor necrosis factor (TNF; 10μg/ml)-induced adhesion.

Conclusions: Edoxaban is a safe and proliferative-inducer drug in endothelial cells in vitro. It counteracts the anti-angiogenic and pro-migratory effects of FXa on HUVECs, but more importantly, edoxaban significantly reduced PBMCs adhesion to endothelial cells monolayers in comparison to control experiments and compared to stimulated cells, independently of the pro-inflammatory drug used.



PBMCs adhesion to endothelial cells