THE IMPACT OF PROTHROMBIN COMPLEX CONCENTRATE ON THE ANTICOAGULATORY EFFECTS OF EDOXABAN

Poster Contributions
Hall C
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Authors: Karen Brown, Prachi Wickremasingha, Dolly Parasrampuria, Jarema Kochan, Victor Dishy, Minggao Shi, Daiichi Sankyo Pharma Development, Edison, NJ, USA, Certified Consultant Pharmacists Inc, Chatham, NJ, USA

Background: Edoxaban (Edox) is a novel oral, once-daily, direct factor Xa inhibitor currently under clinical investigation. To date, there is no established paradigm to reverse Edox activity in cases of clinically relevant bleeding. We evaluated the use of 3-factor prothrombin complex concentrate (PCC; Bebulin® VH) to reverse the anticoagulatory effects of Edox on thrombin generation (TG) and prothrombin time.

Methods: In this phase 1, single-dose, placebo-controlled, 2-arm, 3-way crossover study, 24 healthy subjects, aged 18-45 y, were randomized to either Edox 60 mg QD (cohort 1) or Edox 180 mg QD (cohort 2). Within each cohort, subjects were randomized to 1 of 6 treatment (Tx) sequences with: A (Edox + PCC placebo), B (Edox + PCC 25 IU/kg), and C (Edox + PCC 50 IU/kg). For all treatments, 1 Edox dose was followed 1 h post-dose with a 1-2 h IV infusion of PCC or placebo. Edox pharmacokinetics, TG, and prothrombin time were measured. Endogenous thrombin potential (ETP) and other TG parameters were calculated. Treatment-emergent adverse events were recorded.

Results: Twenty subjects completed the study. All treatments were well tolerated. Mean percent change from baseline reductions in ETP were -39.5, -30.4, and -33.4% for Txs A, B and C, respectively, in cohort 1 and -49.9, -37.8 and -58.9% for Txs A, B and C, respectively, in cohort 2. Mean ETP returned to baseline with PCC administration within 3.5 h (cohort 2, Tx B) or 3 h (all other PCC Tx). With Tx A, ETP had not returned to baseline at 72 h (both cohorts). PCC treatment led to an increased mean percent change from baseline to maximum observed ETP (ΔAmax) compared with placebo (21.6 and 32.9% for Txs B and C, respectively, vs 3.1% for Tx A in cohort 1; 18.4 and 32.4% for Txs B and C vs -1.0% for Tx A in cohort 2). Similar trends were observed for TG peak and velocity. There were no changes in TG lag or time to peak. High variability was observed in the TG data for all parameters assessed. Effects on prothrombin time were not reversed.

Conclusions: Both doses of PCC 25 and 50 IU/kg reversed Edox-induced TG inhibition as measured by ETP. However, the results should be interpreted with caution due to the high variability observed for TG. Co-administration of PCC with Edox was well tolerated.