COMPARATIVE PRE-CLINICAL STUDY ON THE EFFECTS OF APIXABAN AND DABIGATRAN ON INTESTINAL MUCOSA

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Novel oral anticoagulants (NOACs) display good efficacy and greater safety as compared to old ones. However, some of NOACs can increase the risk of gastrointestinal (GI) bleeding. Data from clinical trials showed that apixaban (API, selective factor Xa inhibitor) appears to carry a lower risk of GI bleeding as compared to dabigatran (DAB, selective factor IIa inhibitor), particularly when the latter is employed at its higher dosage (Holster et al., 2013). This difference could result from differential indirect modulation by these NOACs on type 1 and 2 protease-activated receptors (PAR1 and PAR2, known to exert protective and detrimental effects on the GI tract, respectively), via inhibition of factor Xa (active both on PAR1 and PAR2) and/or factor IIa (active on PAR1). This study evaluated the bowel damaging effects of API and DAB in a model of enteropathy induced by indomethacin (IND, non-steroidal anti-inflammatory drug) NSAID, and examined the putative involvement of PAR1 and PAR2 receptors in these effects.

Enteropathy was induced in male rats by intragastric (i.g.) indomethacin administration (1.5 mg/kg BID) for 14 days. API (10 mg/kg/BID, i.g.) and DAB (10 mg/kg/BID, i.g.) were administered daily 1 hour before IND. The doses were selected on the bases of preliminary experiments and were endowed with similar effects on bleeding time. Subgroups of rats were treated with TFLLR-NH2 (PAR1 agonist; 2 mg/Kg i.p.), AC55541 (PAR2 agonist; 10 mg/Kg i.p.) or ENMD-1068 (PAR2 antagonist; 4 mg/Kg i.p.). At the end of treatments, fecal samples were collected for the assay of calprotectin (CAL) levels, and blood hemoglobin (Hb) concentration was evaluated (as an indirect index of digestive bleeding). The small intestine was processed for the assay of tissue myeloperoxidase (MPO) levels, as an index of neutrophil inflammatory infiltration, and the assay of tissue malondialdehyde (MDA) concentration, as an index of lipid peroxidation.

IND elicited a decrease in blood Hb levels (-31%) and significantly increased mortality (+20%), CAL (+102%), MPO (+128%) and MDA (+353%). In this setting, the concomitant administration of the PAR1 agonist or PAR2 antagonist significantly reduced the mortality rate, as well as MPO and CAL levels, while the PAR2 agonist was without effects. In IND-treated rats, DAB worsened mortality (+40%), Hb decrease (-65%) and CAL increase (+308%), while API was without any significant effect. In rats treated with IND+DAB, the PAR1 agonist or PAR2 antagonist ameliorated significantly all tested parameters. In rats treated with IND+API, the PAR1 agonist ameliorated the Hb decrease, as well as MDA and calprotectin increments, while the PAR2 agonist worsened only the mortality rate.

In the presence of NSAID-induced enteropathy, DAB exerts more detrimental effects on intestinal mucosal integrity and bleeding as compared with API. The effects of DAB appear to result from its

indirect inhibition of the PAR1 protective pathway and its lack of interference with the damaging PAR2 pathway.

Holster et al. (2013). Gastroenterology. 145:105-12