ABSTRACT

Using a Göttingen mini-pig model, we evaluated the impact of OrbeShield on the clinical signs and structural and functional markers of gastrointestinal (GI) radiation damage. OrbeShield is a proprietary formulation, including both immediate release (IR) and delayed release (DR) tablets containing beclomethasone 17,21-dipropionate (BDP). OrbeShield has low systemic delivery of BDP, allowing topical treatment of the GI tract while minimizing the adverse effects associated with systemic steroid administration. OrbeShield has been administered to 382 human subjects demonstrating a good safety profile. Pharmacokinetic studies in normal and irradiated mini-pigs revealed that irradiated animals are unable to consistently pass the intact DR tablets from the stomach to the lower GI tract, suggesting a potential impact of irradiation on gastric emptying. Testing of the IR tablets (which dissolve in the stomach) revealed partial coverage of the lower GI tract tissues with both the parent steroid, BDP, and its more potent metabolite beclomethasone 17-monopropionate (BMP). Administration of BDP (IR tablets) to hemi-body shielded Göttingen mini-pigs yielded improvement in a number of clinical signs, structural parameters and functional measurements. BDP administration was associated with marginal increases in survival, which were not statistically significant due to the low mortality rate in the placebo population. Daily treatment with BDP, starting 24 hours post-irradiation, was associated with a significant improvement in body weight loss over 30 days post-irradiation, a statistically significant reduction in the amount of collagen deposition (fibrosis) at Day 30 semi-quantitatively evaluated in mid-jejunum tissue, and a statistically significant increase in the absorption of simple nutrients at 15 days post-irradiation, with a trend towards continuing improvement through to 30 days post-irradiation. These results justify further investigation of OrbeShield as a potential medical countermeasure.

This program has received both Orphan and Fast Track Designations from US FDA and this work was supported by BARDA contract HHSO100201300023C. These are the personal views of the individual authors and do not necessarily express the opinions or policies of the US Department of Health and Human Services or its components.

STUDY DESIGN

Male and female Göttingen mini-pigs between 6 and 7 months of age and 9 to 13 kg body weight were exposed to 14 Gy irradiation at 50 cGy/min using a Cobalt-60 source (Therantron-1000). Supportive care included anti-emetics, prophylactic antibiotic (Erythromycin, SC; Days 1-30), nutritional support, oral fluid support, analgesics and anesthetic (Isoflurane) for blood draws and oral dosing. All animals were hemi-body shielded (head, trunk, front legs). BDP was administered as IR tablets, each containing 1 mg of BDP.

RESULTS

BDP & Its Metabolites All Have Steroidal Activity and are Delivered Primarily to the GI Tract

RESULTS

Treatment with BDP Improves Body Weight Maintenance

RESULTS

BDP Reduces Incidence of Hemorrhages

BDP Does NOT Induce Hematopoietic Suppression

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