OrbeShield® Efficacy in a Preclinical Partial Body Irradiation Göttingen mini-pig Model of Acute Radiation Syndrome

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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.

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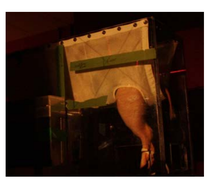
STUDY DESIGN

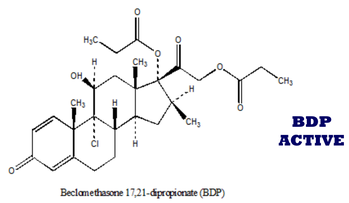
Male and female Göttingen mini-pigs between 6 and 7 months of age and 9 to 13 kg body weight were exposed to 14 Gy irradiation at 50 cGy/min using a Cobalt-60 source (Theratron-1000). Supportive care included anti-emetics, prophylactic antibiotic (Enrofloxacin, SC, Days 1-30), nutritional support, oral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

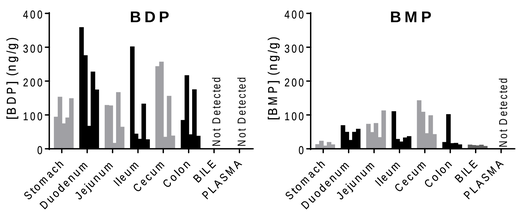
Group	Treatment	Necropsy Day 30 M	Necropsy Day 30 F	Necropsy Day 60 M	Necropsy Day 60 F
1	Placebo (4 mg IR Tablets, BID)	5	5	5	5
2	BDP (4 IR Tablets, BID)	5	5	5	5



RESULTS

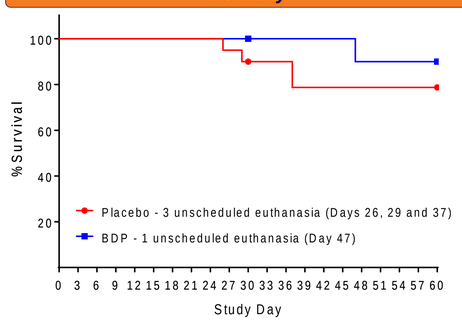
BDP & Its Metabolites all have Steroidal Activity and are Delivered Primarily to the GI Tract





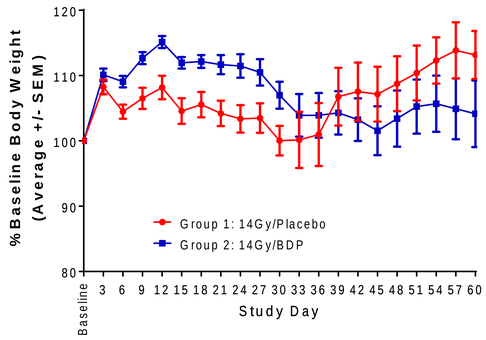
The predominant molecular species in GI tissue is BDP and BMP, when dosed with a combination of IR and DR tablets, despite significant retention of the DR tablets in the stomach of the mini-pig. The predominant species in plasma is BOH. Results are shown for mini-pigs after 16 Gy irradiation (from an earlier study), similar results are observed with 12 Gy irradiation. Each tissue is shown with collection at the following timepoints: Day 1, 4 hours post-dose, Day 8 at 1, 4, 7, 12 and 24 hours post-dose.

Mortality



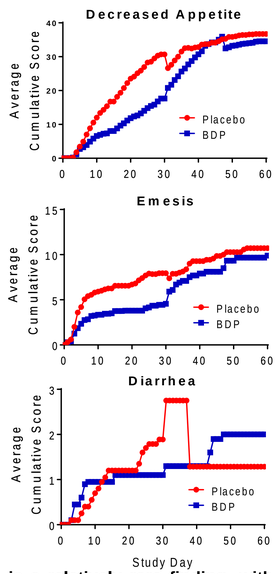
RESULTS

Treatment with BDP Improves Body Weight Maintenance



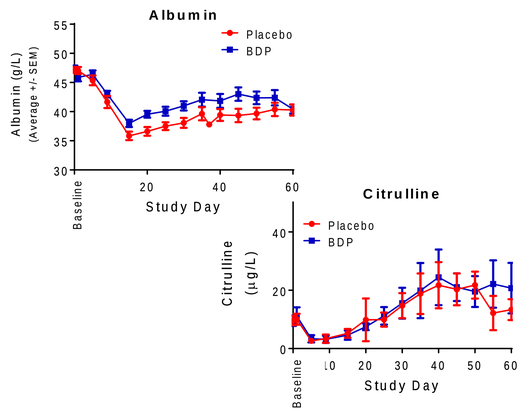
Due to scheduled (Day 30) and unscheduled euthanasia, sample sizes post Day 30 are small, yielding large error bars and no significant differences

Reduction in Clinical Signs Correlated with Improved Body Weight Maintenance



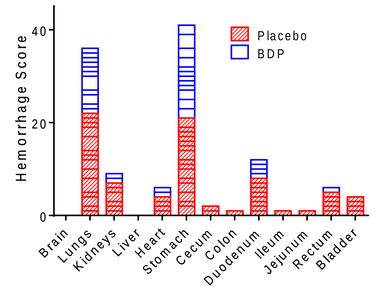
Diarrhea is a relatively rare finding, with decreased appetite occurring most commonly.

Reduced Albumin Loss with Unchanged Citrulline Profile

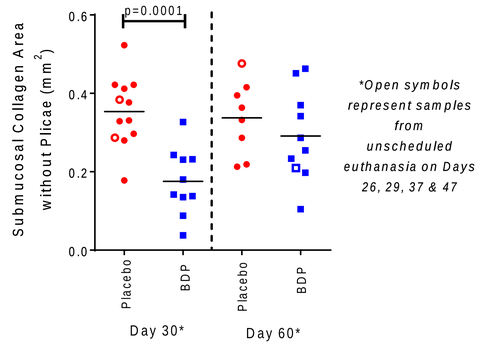


RESULTS

BDP Reduces Incidence of Hemorrhages



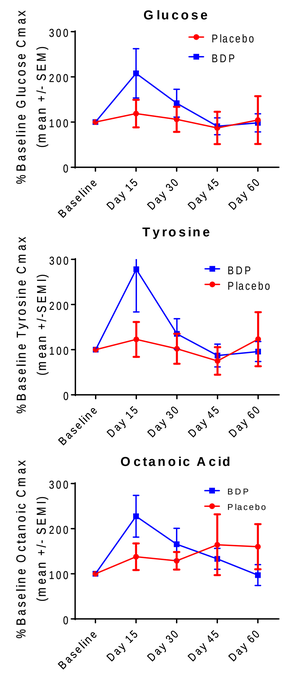
Reduced Collagen Deposition in the GI Tract



Open symbols represent samples from unscheduled euthanasia on Days 26, 29, 37 & 47

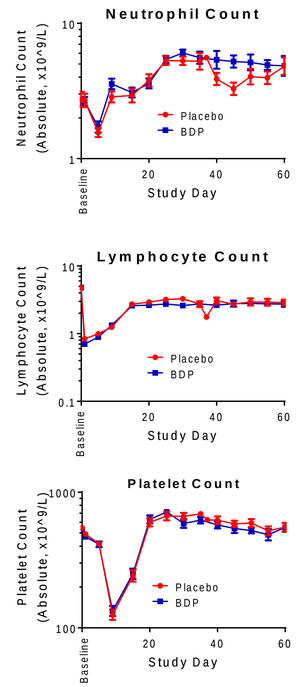
Increased Nutrient Absorption

Nutrient absorption was assessed by direct endoscopic delivery of nutrients (D-Glucose-1,2,3,4,5,6,6-d_7, L-Tyrosine-(phenyl-$^{13}C_6$), Octanoic acid-1,2,3,4-$^{13}C_4$) to the duodenum. Blood samples were taken at 15, 30, 60 and 180 minutes post-endoscopy. These simple nutrients require absorptive processes only and do not depend on the activity of brush border enzymes.



RESULTS

BDP Does NOT Induce Hematopoietic Suppression



DISCUSSION

- Treatment with OrbeShield was designed to provide topical anti-inflammatory treatment without systemic side effects (e.g., neutrophil suppression). In the context of acute radiation exposure, BDP treatment does not cause further hematopoietic suppression.
- Treatment resulted in improved mini-pig health including:
  - Better maintenance of body weight;
  - Reduced clinical signs; and
  - Reduced incidence of hemorrhage as observed on necropsy.
- GI functional markers also demonstrated improvement, including increased absorption of simple nutrients and reduced albumin loss. Citrulline measures were unaffected but citrulline is believed to be a marker of initial enterocyte loss due to direct radiation damage and secondary to apoptosis, which would not be impacted by BDP.
- GI structure, as examined with histopathology, demonstrated a reduction in collagen deposition (fibrosis) with BDP treatment.
- The mini-pig model is a valid model of BDP efficacy since the use of *both* IR and DR tablets in humans would be expected to further improve outcomes.

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