ENTERALLY ADMINISTERED LB1148, A SERINE PROTEASE INHIBITOR, RESULTS IN SIGNIFICANTLY FASTER RETURN OF GUT FUNCTION COMPARED TO PLACEBO IN RATS UNDERGOING LAPORATOMY AND BOWEL RESECTION/ANASTAMOSIS

LB04

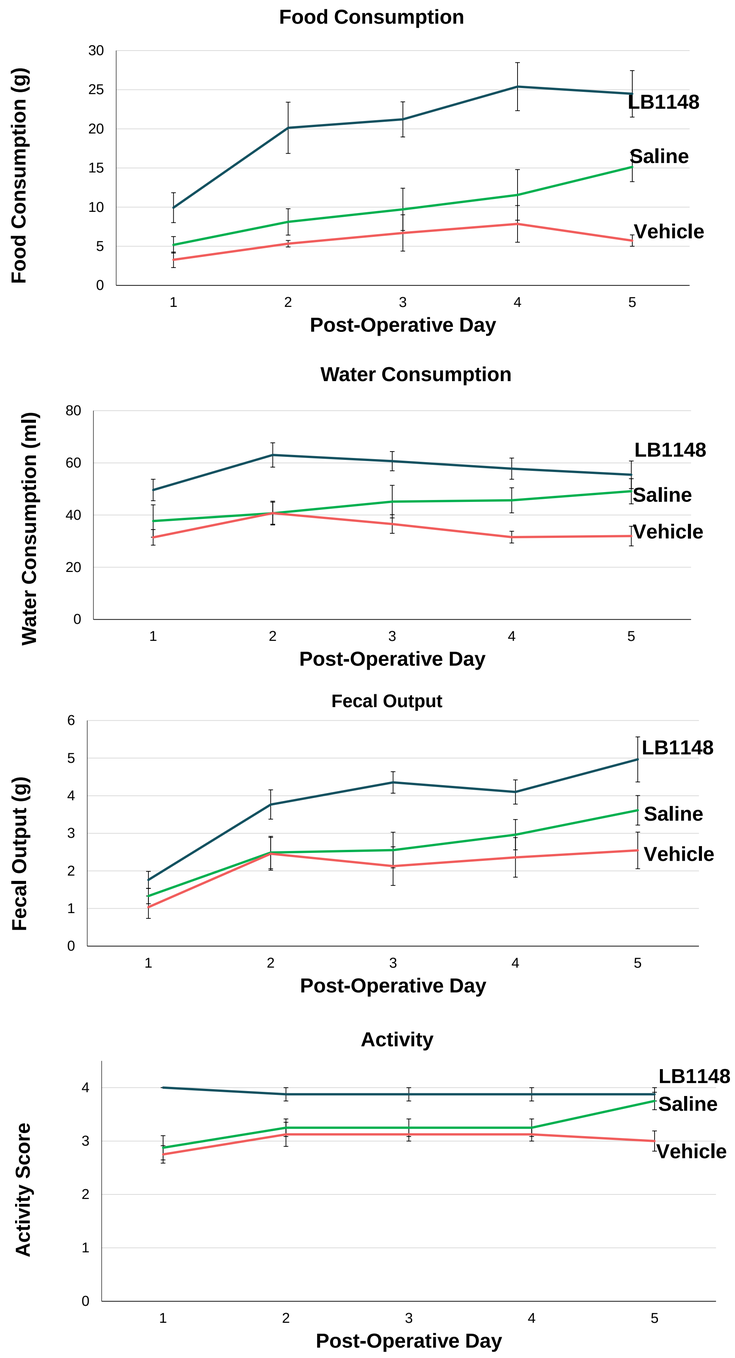
H. C. Dittrich, J. J. Rodenrys, T. M. Hallam Leading BioSciences Inc. San Diego, CA USA

Background and Rationale

The exact cause of postoperative impaired GI function including ileus remains elusive but is likely multifactorial, involving the autonomic nervous system, inflammation, the enteric nervous system, hormones and neuropeptides, anesthesia and narcotics. In their work on multi-organ dysfunction in shock, Schmid-Schönbein and co workers have established the deleterious effects of pancreatic enzymes remotely when mesenteric hypoperfusion is present and the GI mucosal barrier is compromised. Further, they demonstrated that enteral administration of a serine protease inhibitor will, if given prophylactically, limit the injury caused by these enzymes, thereby significantly limiting end organ dysfunction.[1] These findings have now been extended to mechanical injury of the GI mucosal barrier, which is seen with surgery of the bowel and the potential benefit of a serine protease inhibitor on improvement of postoperative ileus (POI).

Objectives

The objective of the current study was to compare the efficacy of enterally administered saline, vehicle, and LB1148 on return of GI function in a rat model of bowel resection and anastomosis. The hypothesis being tested is that enteral LB1148 will be superior to saline and vehicle in return of GI function in a rat model of surgical bowel resection.



Results

Mean/SD by Postoperative Day

			Day 1	Day 2	Day 3	Day 4	Day 5	p value
Food Consumption (gm/day)								
LB1148	Mean		9.93	20.13	21.21	25.4	24.48	
	SD		5.4	9.26	6.35	8.68	8.41	
Vehicle	Mean		3.27	5.33	6.7	7.85	5.73	<0.001
	SD		2.81	1.18	6.55	6.63	2.07	
Saline	Mean		5.18	8.11	9.71	11.56	15.14	<0.001
	SD		2.98	4.78	7.63	9.15	5.33	
Water Consumption (mL/day)								
LB1148	Mean		49.62	63.03	60.67	57.77	55.46	
	SD		11.62	13.19	10.47	11.5	14.98	
Vehicle	Mean		31.45	40.76	36.56	31.55	31.94	<0.001
	SD		8.42	12.82	10.11	6.38	10.69	
Saline	Mean		37.71	40.72	45.15	45.68	49.13	<0.01
	SD		17.5	11.98	17.69	13.6	13.65	
Fecal Output (gm/day)								
LB1148	Mean		1.76	3.77	4.35	4.1	4.97	
	SD		0.64	1.11	0.81	0.91	1.69	
Vehicle	Mean		1.04	2.46	2.13	2.36	2.55	<0.01
	SD		0.84	1.23	1.45	1.49	1.38	
Saline	Mean		1.33	2.49	2.55	2.96	3.61	<0.01
	SD		0.58	1.22	1.34	1.14	1.11	
Activity (0-4)								
LB1148	Mean		4	3.88	3.88	3.88	3.88	
	SD		0	0.35	0.35	0.35	0.35	
Vehicle	Mean		2.75	3.13	3.13	3.13	3	<0.001
	SD		0.46	0.64	0.35	0.35	0.53	
Saline	Mean		2.88	3.25	3.25	3.25	3.75	<0.01
	SD		0.64	0.46	0.46	0.46	0.46	
Body Weight (gm, change from baseline)								
LB1148	Mean		-17.81	-17.01	-3.03	0.71	2.47	
	SD		10.17	8.48	7.09	6.94	3.69	
Vehicle	Mean		-15.89	-7.81	-5.65	-4.05	-5.21	NS
	SD		16.25	13.36	7.88	2.63	7.51	
Saline	Mean		-18.01	-15.64	-5.9	-4.65	-1.59	NS
	SD		7.15	7.26	5.5	6.96	4.05	

Methods

Population: 24 Wistar male rats were assigned to one of three treatment groups (n=8) to receive a single enteral administration of LB1148, LB1148 minus TXA (vehicle), or saline.

Study drug: Treatment was given via gavage 2 hours prior to surgery. The volume of study drug was a rat dose equivalent to the daily dose of LB1148 employed in clinical studies of LB1148. Timing of dose was based on estimates of GI transit time in rats to allow complete intestinal coverage of study drug. LB1148 is composed of specific concentrations of TXA, PEG, electrolytes, glucose, and water.

Anesthesia: Animals were anesthetized with ketamine/xylazine (75/4 mg/kg, I.M.). Supplemental anesthesia (ketamine/xylazine 10 % initial dose, I.M.) was administered as indicated following response to tail/toe pinch. Anesthesia was maintained throughout the experimental shock period.

Surgery: A small skin incision in the midline of the abdomen was made for isolation of small intestine. A one centimeter ileal resection six centimeters from the ileo-cecal valve and primary anastomosis was performed. Laparotomy was then sutured and the animal allowed to recover.

Efficacy Observations: A single observer, blinded to treatment assignment, measured water consumption, food intake, fecal output, activity level*, and body weight at the same time daily for the first 5 postoperative days. *Activity level was graded on a scale of 0 (moribund) to 4 (attempting cage escape).

Conclusions

LB1148 enhances early GI recovery as measured by food and water consumption, fecal output, and general activity in this model of open bowel surgery. These results, in addition to the findings from numerous preclinical studies and the well-described safety of parenteral TXA in tens of thousands of patients worldwide form the basis for pursuing the clinical development of LB1148 in early recovery of function and reduction of postoperative ileus. A multinational phase 2 clinical trial is planned for 2016.

Statistics

Data analysis was performed using JASP software. Return of function data for each dependent variable was analyzed using repeated-measures ANOVA with assessment days as the repeated variable within subjects. A Bonferroni correction was used to compare LB1148 vs vehicle and LB1148 vs saline. Results are reported as mean and SD (table) and SEM (figure).

Safety

All animals tolerated the study drug, anesthesia, and surgery well. One saline treated animal developed a surgical complication of anastomotic leak, peritonitis and death on Day 21.

References

1. Schmid-Schönbein GW, Chang M, The Autodigestion Hypothesis for Shock and Multi-organ Failure. Annals of Biomedical Engineering 42: 405-14, 2014
2. Penn AH, Hugli TE, Schmid-Schonbein GW. Pancreatic enzymes generate cytotoxic mediators in the intestine. Shock. 2007;27:296 –304.
3. Altshuler AE, Lamadrid I, Li D, Ma SR, Kurre L, Schmid-Schonbein GW and Penn AH. Transmural intestinal wall permeability in severe ischemia after enteral protease inhibition. PLoS ONE. 2014 May;9(5):e96655.

Contact

Thomas Hallam, PhD tom.hallam@leadingbiosciences.com
Website: www.leadingbiosciences.com