IN NEONATAL PIGLETS WITH SHORT BOWEL SYNDROME AND JEJUNOCOLIC ANASTOMOSIS, A NEW GLP-2 ANALOGUE ENHANCES BOTH STRUCTURAL ADAPTATION, INCLUDING GROWTH IN SMALL BOWEL LENGTH, AND NUTRIENT ABSORPTION

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BACKGROUND

- Glucagon-like peptide-2 (GLP-2) is a trophic factor released predominantly from neuroendocrine L cells in the ileum
- Loss of ileum is common in severe neonatal short bowel syndrome (SBS), requiring long-term parenteral nutrition (PN)
- We have shown that ileal resection is associated with limited intestinal adaptation and reduced endogenous GLP-2 secretion
- In this study we aimed to examine the effects of a novel long-acting subcutaneous GLP-2 analogue, FE203799 (FE)
  - To enhance structural adaptation
  - To enhance functional adaptation
  - To make the intestine grow in length

METHODS

- Saline
  - n=8
  - Treatment day 0 and 4
- FE
  - n=8
  - Treatment day 0 and 4 at 5mg/kg

Surgery (day 0)

- Insertion of a Jugular and gastric catheters
- 75% intestinal resection with a jejunocolic anastomosis
- Measure intestine length

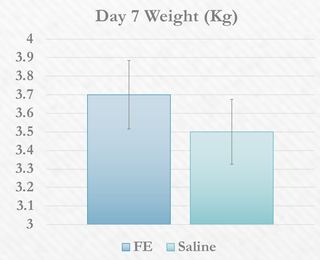
Trial period

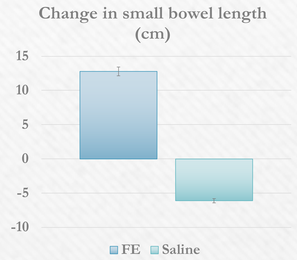
- Parenteral Nutrition 100% total requirements
- Enteral Nutrition Trophic only at 20%
- Day 5: 24 hour fecal collection

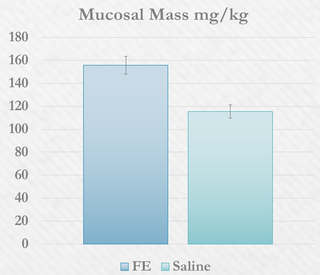
Surgery (day 7)

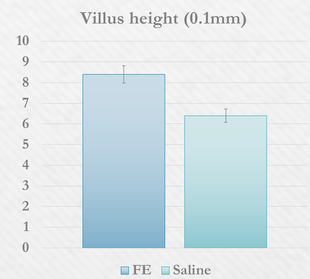
- Small intestinal length and weight measured
- Intestinal tissue collection

RESULTS







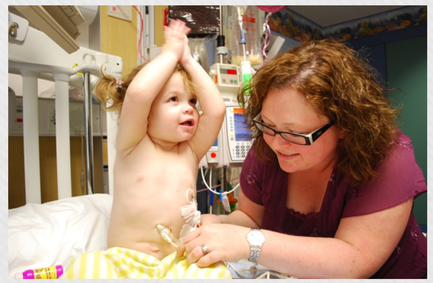


All piglets had similar weight on day 7 (3.7 vs 3.5kg; p=0.1; FE treated piglets had growth in intestinal length (+12.8 vs -6.1cm; p<0.001), greater small intestinal mass (155.8 vs 115.4mg/cm; p=0.014). longer villus height (0.86 vs 0.66mm; p=0.015)

Fecal Nutrient Data	Saline (n=8)	FE treated 5mg/kg (n=8)	P value
Measured total energy (J/g)	2198 (2037-2769)	1697 (1297-1976)	0.02
Calculated total energy (J/g)	2018 (1788-2184)	1328 (1058-1514)	0.01
Fat (mg/g)	31.1 (28.3-33.7)	20.1 (15.2-24.6)	0.02
Carbohydrate (mg/g)	16.8 (5.2-37.5)	8.8 (4.0-10.9)	0.35
Nitrogen (mg/g)	2.3 (1.8-3.4)	2.2 (1.7-3.0)	0.75

CONCLUSION

- FE203799, enhanced structural and functional intestinal adaptation in a neonatal model of SBS with total ileal resection
- The increase in intestinal length noted with this GLP-2 analogue has important clinical implications for treating SBS in neonates and infants, given that at this developmental age there is potential for linear gut growth that does not exist at later ages
- The long half-life (30hours) and need for only twice weekly subcutaneous administration is also a potential advantage of this treatment
  - Currently clinical trials with FE203799 are being undertaken in adult patients with intestinal failure using only a weekly administration.
- Future directions:
  - Direct comparison to other GLP-2 analogues in piglets
  - Characterization of the molecular affects of FE203799 that lead to intestinal lengthening and determination of durability of the effect of FE203799 in piglets
  - Determination of optimal dosage for pediatric studies



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