A Comparison of the Trophic Effects of Two Glucagon like Peptide 2 Analogues Studied in Neonatal Piglets with Short Bowel Syndrome Without Ileum

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Introduction

Short bowel syndrome (SBS) the leading cause of neonatal intestinal failure, traditionally had a 25% mortality rate. While survival has improved, dependence on long term parenteral nutrition (PN) negatively impacts quality of life and incurs significant healthcare costs.

Glucagon like peptide-2 (GLP-2) is a trophic peptide secreted by the small intestine endocrine L cells that can stimulate adaptation and so promote autonomy from PN.

Teduglutide and Apraglutide are long acting analogues of GLP2 with the $T_{1/2}$ Teduglutide 2 hours and $T_{1/2}$ Apraglutide is 30 hours.
Teduglutide is approved for the treatment of SBS in adults (US, Canada) and in adults and children (Europe).

The aim of this study was to compare Teduglutide and Apraglutide head to head using pharmacologically comparable doses using our neonatal piglet model of short bowel syndrome with total ileal resection, which is known to have limited capacity for adaptation without trophic treatment.

Methods

Neonatal piglets 2-5 days in age were randomized to four groups:

- Teduglutide (n=8): 0.05mg/kg sc daily for 7 days
- Teduglutide (n=8): 0.05mg/kg sc BID for 7 days
- Apraglutide (n=8): 5mg/kg sc twice in 7 days
- Saline (n=8): control given sc daily for 7 days

Day 0, Surgery resection 75% distal small intestine; insertion of G tube for enteral nutrition (EN) and jugular venous catheter for PN.

Day 0-7, piglets were maintained in metabolic cages, PN delivered at 100% requirements; was delivered at 20% (trophic) requirements.

Day 0-5, PK measurements were undertaken (data not included).
Day 5-6, Fecal fat collections were undertaken.

Day 7, length of small intestine was re-measured, total wet small intestine was weighed; 20cm scarped jejunal mucosa was weighed; jejunum was collected for villus and crypt histology performed by an animal pathologist blinded to anatomical group.

Statistical analysis used ANOVA with post-hoc Tukey.

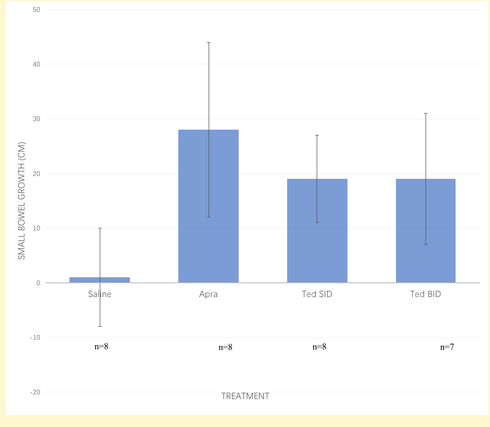
Results

Table 1. Comparison Saline, Apraglutide, Teduglutide SID and BID treatments (data expressed as mean ±SD)

Note n as shown except #*except where indicated n=7
Superscripts indicate post hoc differences.

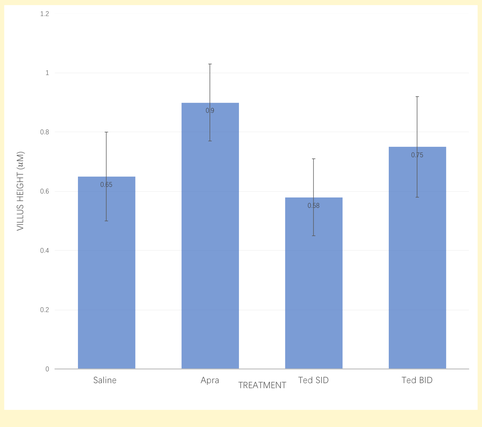
	Saline (n=8)	Apraglutide 5mg/kg twice week (n=8)	Teduglutide 0.5mg/kg SID (n=8#)	Teduglutide 0.5mg/kg BID (n=8*)	ANOVA p value
Age (day)	3.6(0.7)[1]	3.5(0.8)[1]	3.6(0.7)[1]	4.8(1.0)[2]	0.02
Weight (kg)	2.3(0.2)	2.2(0.2)	2.2(0.2)	2.4(0.1)	0.43
End weight (kg)	3.5(0.4)	3.5(0.4)	3.6(0.4)	3.6(0.3)	0.93
Weight gain (kg)	1.3(0.3)	1.2(0.2)	1.3(0.2)	1.2(0.2)	0.55
Baseline SBL (cm)	555(47)	553(54)	520(68)	587(24)	0.09
Post resection SBL (cm)	138(12)	138(14)	134(13)	146(6)	0.19
End SBL (cm)	140(17)	166(14)	153(13)	165(13)	0.003
SB growth (cm)*	1(9)[1]	28(16)[2]	19(8)[1,2]	19(12)[2]	0.001
% Change SBL (%)*	0.7(6.8)[1]	20.8(12.6)[2]	14.4(6.6)[2]	9.2(11.6)[1,2]	0.003
SB weight (g)	25(4)[1]	33(6)[2]	28(3)[1,2]	32(3)[2]	0.003
Jej weight(g)/cm	0.11(0.02)	0.13(0.03)	0.11(0.03)	0.12(0.03)	0.18
Villus height (µm)	0.65(0.15)[1]	0.90(0.13)[2]	0.58(0.13)[1]	0.75(0.17)[1,2]	0.001
Crypt depth (µm)	0.17(0.27)	0.15(0.14)	0.16(0.19)	0.14(0.15)	0.09
Fat delivery (g/kg/d)#*	1.96(0.13)	1.95(0.54)	1.93(0.53)	2.02(0.58)	0.99
Fat absorbed (g/kg/d)#*	1.63(0.34)	1.86(0.54)	1.74(0.51)	1.93(0.58)	0.70
% Fat absorbed#*	82.7(15.2)	95.0(3.1)	87.2(16.4)	95.1(4.8)	0.11

Figure 1. The Effect of Saline, Apraglutide, Teduglutide SID and BID Treatment on Small Bowel Linear Growth



All trophic treatments increased the linear growth of the small intestine compared to saline. Apraglutide increased linear growth more than other treatments (statistically significant compared to Teduglutide SID, which was not different to BID).

Figure 2. The Effect of Saline, Apraglutide, Teduglutide SID and BID Treatment on Villus Height (n=8 all groups)



Apraglutide increased villus height statically more than saline or Teduglutide SID. Teduglutide BID was not statistically different or to Teduglutide SID, which was not statistically different to saline.

Conclusion

Compared to saline control long acting GLP-2 analogues, Teduglutide and Apraglutide, both increase intestinal adaptation as evidenced by:

- Increased small bowel lengthening
- Increased small bowel weight
- Increased jejunal villus height

With a markedly longer half life (15-fold), Apraglutide administered twice in one week increases intestinal adaptation to the same degree as Teduglutide twice daily and is superior to Teduglutide administered daily.

PK data - not shown - supports comparable area under the curve for BID Teduglutide compared to Apraglutide

At trophic feeding (only 20% EN) no significant differences in fat absorption were shown. However, on average Apraglutide and Teduglutide BID had fat absorption 12% more than saline and 8% more than Apraglutide SID.

Functional differences are likely given higher EN rates.

The neonate with intestinal failure may have a unique benefit from these trophic factors in producing intestinal growth; however, PK studies will be essential to dose optimize.

In the pediatric population Apraglutide offers the potential to promote autonomy from PN while requiring less injections than shorter acting GLP-2 analogues.

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