Linagliptin improved glucose tolerance in obese diabetic fa/fa rats

The potentiation of GLP-1 with the combination treatment was observed on the 5-mm samples, and plasma insulin was measured on the B1 and E5-mm samples.

The model is widely validated and described in the scientific literature as a model of T2DM.

The combination of linagliptin and voglibose therefore potentiates GLP-1, in mixed ZDF rats maintained on standard chow.

In addition, beneficial effects due to the supra-additive increase in plasma GLP-1 were observed with the combination treatment.

Plasma glucose (mM)

Body weight was unaffected by linagliptin; in contrast, voglibose caused a marked potentiation in the plasma levels of active GLP-1; however, the combination of linagliptin and voglibose caused a marked potentiation in the plasma levels of active GLP-1; a finding may reinforce the potential utility of this combination for the treatment of T2DM.

CONCLUSIONS

- Linagliptin improved glucose tolerance in obese diabetic fa/fa rats by increasing plasma GLP-1 and insulin, whilst having a neutral effect on body weight.
- The combination of linagliptin and low-dose voglibose led to a significant reduction in body weight and an improvement in plasma glucose excursion that was similar to that observed with high-dose voglibose alone.
- The combination of linagliptin and voglibose also significantly reduced plasma insulin, although this effect was greater when voglibose was given alone.
- This difference may reflect the conflicting modes of action of the 2 compounds, linagliptin increases plasma insulin (GLP-1) by increasing glucose availability for absorption into the bloodstream so insulin release is reduced compared with controls.
- In contrast to linagliptin, voglibose did not increase plasma active GLP-1; however, the combination of linagliptin and voglibose caused a marked potentiation in the plasma levels of active GLP-1; such a finding may reinforce the potential utility of this combination for the treatment of T2DM.
- Therapy with linagliptin and voglibose therefore potentially improves glucose control.
- This combination may minimize the side effects of α-glucosidase inhibitors, because lower doses of voglibose may be required to maintain glycemic control.
- In addition, beneficial effects due to the super-additive increase in active GLP-1 levels may be evident.

Methods

- Male ZDF-Lepr homozygous diabetic fa/fa rats were obtained from Charles River Laboratories (Wilmington, MA), and fed standard chow.
- Rates were allocated (n=10/group) into a group based on body weight and fasting plasma glucose (FPG).
- Two studies were performed that were separated by a washout period of approximately 1 week.
- In Study 1, fa/fa rats were dosed orally (PO) daily for 4 days with either vehicle, linagliptin (1 mg/kg), high-dose voglibose (10 mg/kg), or the combination of linagliptin and voglibose.
- Study 2 was performed per Study 1 except that voglibose was administered at a lower dose (1 mg/kg).
- Body weight was recorded daily.
- After an overnight fast (18 h), an oral sucrose tolerance test (OSTT; 4 g/kg PO) was performed on Day 1.
- A fasting blood sample was taken (Baseline 1 [B1]), compounds were administered, and a further blood sample taken 1 h later (Baseline 2 [B2]) immediately prior to the OSTT.

Results

- Mean vehicle FPG levels in fa/fa rats on Day 4 were 7.39 and 8.18 mM, and mean insulin levels were 2.01 and 3.76 mg/mL in Study 1 and Study 2, respectively.
- Linagliptin improved glucose control as shown by a decrease in glucose area under the plasma curve from 0 to 15 min (Study 1, −10%; Study 2, −17%; p<0.001; Study 1, −33%; p<0.001; Study 2, −18%, p<0.01); in combination with linagliptin, low-dose voglibose produced a similar result to that observed with high-dose voglibose (Study 1, −35%; Study 2, −35%, p<0.01) compared with vehicle.
- The improvements in glucose control were potentiated with linagliptin plus low-dose voglibose compared with either drug alone (p<0.01).
- Body weight was unaffected by linagliptin; in contrast, voglibose caused a marked potentiation in the plasma levels of active GLP-1; however, the combination of linagliptin and voglibose caused a marked potentiation in the plasma levels of active GLP-1; a finding may reinforce the potential utility of this combination for the treatment of T2DM.
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Reference