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Efficacy and safety of linagliptin (BI 1356), a novel inhibitor of dipeptidyl-peptidase 4 (DPP-4), in animal models and clinical studies in healthy volunteers and patients with type 2 diabetes mellitus.

Promotionsfach: Innere Medizin
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This work was undertaken to gain a better understanding of the safety, efficacy and glucose lowering mechanism of linagliptin, a novel DPP-4 inhibitor for the treatment of patients with type 2 diabetes under development by Boehringer Ingelheim. To this end, first the existing pre-clinical and clinical data to date were reviewed and summarized. Thereafter a new clinical trial was designed, conducted, and analyzed that studied the effect of linagliptin (5 mg) and sitagliptin (100 mg) on parameters of glucose control (e.g. 24-h glucose control) in patients with type 2 diabetes and inadequate glycaemic control. In addition, various pharmacodynamic parameters (e.g. plasma levels of GLP-1, insulin, as well as inhibition of plasma DPP-4 activity) were investigated to study the entire "linagliptin chain of efficacy" and thereby contribute to a more complete understanding it's mechanism of action.

As the responsible physician for the trial the author had the overall responsibility for planning, conduct, analysis and interpretation of the study from the early planning phase to the finalization of the clinical trial report (CTR). Patients with type 2 diabetes not on anti-diabetes medication for at least 4 weeks, were randomized to receive 5 mg linagliptin, 100 mg sitagliptin or placebo once daily for 28 days. Meal tolerance tests (MTT) were performed for the determination of intact GLP-1, glucagon and various other parameters. Samples for 24-hour glucose profiles were collected to calculate weighted mean glucose (WMG), and markers of long-term glycaemic control (HbA1c, fructosamine, 1,5-anhydroglucitol) were analysed. Plasma DPP-4 activity was measured as a direct pharmacodynamic response marker. The trial included MTTs performed 24h and 48h after the last dose.

Already a single dose of linagliptin led to a median DPP-4 inhibition of 79.8% at through, resulting in a statistically significant increase of post-prandial GLP-1 concentrations ($AUEC_{0-2h}$ +10.5 ±2.0 pmol*h/L, $p<0.001$, placebo-corrected adjusted means ±SE) and a significant decrease of post-prandial glucagon concentration ($AUEC_{O-2h}$ -23.4 ±6.7 pg*h/mL, $p<0.001$). The post-prandial glucose excursion was significantly reduced by 58.6 ±14.2 mg*h/dl ($AUEC_{0-3h,}$ $p<0.001$) and 24-hour glucose control was improved significantly (WMG -9.2 ±2.1 mg/dl, $p<0.0001$).

Treatment with linagliptin for 28 days led to an inhibition of plasma DPP-4 activity of >80% over the entire 24h dosing interval and effects on post-prandial GLP-1 and improvements of glucose control were even more pronounced:
Post-prandial intact GLP-1 increased by +18.1 pmol*h/L ±2.1 ($AUEC_{0-2h}$, $p<0.001$) and glucagon concentrations were decreased by -18.7 pg*h/mL ±9.2 ($AUEC_{O-2h}$, $p<0.05$). Glucose control was improved in the fasted state (FPG -11.0 ±4.9 mg/dl, $p<0.05$), after a MTT ($AUEC_{0-3h}$ -105.6 ±20.5 mg*h/dl, $p<0.001$) and over the entire day (WMG -19.8 ±4.1 mg/dl, $p<0.001$). Interestingly, in this patient population with comparatively good glycaemic control (baseline HbA1c =7.3%) the effect of linagliptin on postprandial glucose excursions was more pronounced than the effect on fasting glucose levels. 1,5-anhydroglucitol increased by 1.8

±0.4 µg/mL ($p<0.0001$) while the level of fructosamine decreased by 9.0 ±4.4 µmol/L ($p<0.05$). HbA1c was lowered by 0.2 ±0.07 % ($p<0.01$), even though the treatment duration was only 28 days.

Interestingly, DPP-4 inhibition and improvements in glucose control were largely preserved 24h and 48h after the last dose. These findings clearly suggest that linagliptin is a "true once daily drug" providing sufficient DPP-4 inhibition during the entire dosing interval. It is even tempting to speculate that in case a patient misses a dose, DPP-4 inhibition may still be sufficient to guarantee adequate efficacy.

Overall, linagliptin treatment was well tolerated and the safety laboratory data and the assessment of vital signs revealed no changes of clinical relevance.

In conclusion, this thesis was aimed at a better understanding of the safety, efficacy, and mechanism of the novel DPP-4 inhibitor linagliptin. Pre-clinical and clinical data to date were reviewed and summarized and a new clinical trial was designed, conducted and analyzed. This trial demonstrated for the first time that linagliptin treatment leads to statistically significant, beneficial changes of GLP-1 and glucagon both acutely and after four weeks of treatment. Changes were associated with significant and clinically meaningful improvements of 24h glucose control.

Linagliptin was shown to be a "true once daily drug" and treatment with linagliptin was safe and well tolerated.