

ABSTRACT

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Inhaled GLP-1 and Exenatide: Different Effects on Pancreatic and Gastric Activity Following a Single Dose in Type 2 Diabetes Mellitus

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Background and aims: MKC253 is GLP-1 adsorbed onto Technosphere[®] microparticles for oral inhalation. A single MKC253 dose in healthy, normal volunteers produced high circulating concentrations of GLP-1 (10 min) with a dose-dependent insulin release, a reduction in fasting plasma glucose, and no nausea or vomiting. This double-blind, double-dummy, placebo-, and active-control crossover trial compared the effects of MKC253 (1.5 mg) and sc injection of exenatide (EXE; 10 µg) on postprandial glucose (PPG) excursions, postprandial insulin, gastric emptying, and GLP-1 pharmacokinetics.

Materials and methods: Included were 20 nonsmoking subjects with type 2 diabetes mellitus (HbA1c 6.2%-8.5%) on a stable oral antidiabetic regimen. Subjects received five treatments 2 days apart. All received MKC253 or inhaled placebo (InhP) while fasting. EXE or sc placebo (SCP) was given 15 min premeal, and MKC253 or InhP was given premeal (Pre) or 30 min postmeal (Post). Subjects received in randomized order: SCP + MKC253 Pre + InhP Post; SCP + MKC253 Pre + MKC253 Post; EXE + InhP Pre + InhP Post; or SCP + InhP Pre + InhP Post. Gastric emptying was measured by absorption of ¹³C-octanoate from a 575 kcal standardized meal.

Results: MKC253 produced a rapid spike in insulin. Mean maximum insulin concentration occurred < 10 min after dosing and fell sharply thereafter. Mean peak insulin was 60 µU/mL. Mean pharmacokinetics of insulin release closely tracked mean GLP-1 kinetics. The insulin response following EXE was slower and less pronounced. In fasting subjects with baseline glucose < 9 mmol/L, MKC253 produced a mean maximal decrease in glucose of 0.75 mmol/L about 30 min after inhalation. Subjects with baseline glucose > 9 mmol/L had a 1.2 mmol/L decrease in glucose ~45 min after inhalation. MKC253 reduced PPG excursions. Compared with InhP, MKC253 Pre decreased PPG by ≥ 1 mmol/L for > 1 h and MKC253 Pre + Post decreased PPG for > 3 h. Reductions were longer than that predicted by a GLP-1 half-life of < 2 min. MKC253 had little or no effect on gastric emptying. In contrast, EXE also reduced PPG but acted by delaying gastric emptying. More than 90% of ¹³C-octanoate ingested was unabsorbed 4 h after the meal compared with < 60% with MKC253. After EXE injection, the insulin response to meal challenge was much smaller than with MKC253. Only 1 of 20 subjects reported nausea with MKC253 vs rates > 66% from literature with injected GLP-1.

Conclusion: Both MKC253 and EXE reduce PPG excursions, but appear to do so by different mechanisms.