Oral Insulin: A comparison with Subcutaneous Regular Human Insulin in patients with Type 2 Diabetes

Time-Action Profile of Oral Insulin

Christoph Kapitza, MD
Eric Zijlstra, PHD
Lutz Heinemann, PHD
M. Cristina Castelli, PHD
Gary Riley, DVM, PHD
Tim Heise, MD

1Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany.
2Emisphere Technologies, Cedar Knolls, New Jersey, USA.

CORRESPONDING AUTHOR
Christoph Kapitza, MD
e-mail: christoph.kapitza@profil-research.de

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**Objective** - To determine the pharmacokinetic and pharmacodynamic properties of an oral insulin (OI) formulation in comparison to subcutaneously injected regular human insulin (RHI).

**Research Design and Methods** - Ten male patients with type 2 diabetes (mean±SD, HbA1c 7.0±1.1%, BMI 28.3±2.7 kg/m²) received either 300 U insulin combined with 400 mg delivery agent orally or 15 U RHI subcutaneously under isoglycaemic clamp conditions.

**Results** - Maximum insulin concentration was greater and onset of action was faster with OI ($C_{max} 93±71$ vs. $33±11 \mu U/mL$; $AUC_{GIR(0-1h)} 173±86$ vs. $27±32$ mg/kg, $P < 0.05$). Mean insulin concentration and glucose infusion rate (GIR) returned to baseline within three hours after OI administration. Relative bioavailability of OI was $7±4\%$ (first two hours).

**Conclusion** - This proof-of-concept study demonstrated that absorption of OI is feasible under fasting conditions. OI has a fast onset and a short duration of action, but also shows a rather high between-subject variability in absorption.
Oral administration of insulin has the potential advantage of a more physiological action by its direct effect on hepatic glucose production (1,2). Thus far various oral insulin approaches have however only partially produced satisfactory results (1,3,4). Gastrointestinal absorption of insulin is hampered e.g. by enzymatic degradation and lack of permeation through epithelial cells (5). Noncovalent interaction of the novel drug-carrier molecule monosodium N-(4-chlorosalicyloyl)-4-aminobutyrate (4-CNAB) with insulin might create more favourable physico-chemical properties for gastrointestinal insulin absorption (6,7). In this study, 4-CNAB has been combined with human insulin to facilitate gastrointestinal insulin absorption.

**RESEARCH DESIGN AND METHODS**

A single-centre, open-label, randomized, two-period cross-over, isoglycaemic glucose clamp study was used to determine the pharmacokinetic and pharmacodynamic properties of an oral insulin (OI) formulation with 4-CNAB in comparison to subcutaneous regular human insulin (RHI). The protocol was approved by an independent ethics committee and the study was performed in accordance with the Declaration of Helsinki. A total of 14 male adult patients diagnosed with type 2 diabetes for over a year and without insulin therapy were screened after providing written informed consent (see the Online Appendix, available at [http://care.diabetesjournals.org](http://care.diabetesjournals.org), for all inclusion and exclusion criteria). Ten patients were enrolled. One patient withdrew consent during the first clamp visit and was replaced, resulting in ten patients (age 55±9 years [mean±SD], HbA1c 7.0±1.1%, BMI 28.3±2.8 kg/m²) completing the study. Subjects received either 300 U OI combined with 400 mg 4-CNAB in two capsules (each containing 150 U OI plus 200 mg 4-CNAB) or a subcutaneous injection of 15 U RHI (Humulin R 100 U/mL, Eli Lilly and Company, Indianapolis, USA) on two separate dosing days separated by 1-20 days. Patients did not take oral hypoglycaemic agents 24 hours prior to each dosing.

**Glucose Clamp Procedure.** After an overnight fast, patients were connected to a Biostator (MTB Medizintechnik, Ulm, Germany). The clamp level, set to the subject’s fasting blood glucose concentration, was established by intravenous infusions of insulin (Actrapid, Novo Nordisk, Bagsvaerd, Denmark, 0.2 mU/kg/min from 2 hours pre-dosing until the end of the experiment) and a variable infusion of glucose. At t=0, one of the two study medications was administered. The pharmacokinetic (insulin levels) and pharmacodynamic (glucose infusion rates – GIR) responses to the study medication were measured for six hours. Safety parameters studied included adverse events, laboratory data, vital signs, physical examinations, and ECGs.

**Statistical analysis methods.** Area under the curve for plasma insulin concentration (AUC$_{INS}$) and GIR (AUC$_{GIR}$) were calculated with the trapezoidal rule. Insulin and GIR values were corrected for the baseline intravenous insulin infusion by subtracting the mean insulin concentrations or GIR in the last hour before study drug administration from all post-dosing values. Individual GIR profiles were then smoothed using a polynomial function of 6th order and maximum GIR (GIR$_{max}$), time to GIR$_{max}$ (T$_{GIR_{max}}$), and time to half-maximum GIR before and after reaching GIR$_{max}$ (T$_{GIR-50%-early}$ and T$_{GIR-50%-late}$) were calculated. Relative bioavailability and biopotency were calculated as the dose-corrected ratios of individual AUCs below insulin or GIR profiles after oral and subcutaneous application (8).
One subject was excluded from the bioavailability and biopotency analysis due to a very low pharmacokinetic and metabolic response to RHI administration. In addition, two subjects with an absent metabolic response to RHI administration in the first hour after application were excluded from the biopotency analysis in the first hour. Two-sided signed Wilcoxon rank tests and Kruskal-Wallis non-parametric tests were used for comparisons between treatments. $P < 0.05$ was considered to be statistically significant.

RESULTS

Figure 1 shows the pharmacokinetic (1A) and pharmacodynamic (1B) responses to oral and subcutaneous insulin administrations. All subjects showed early enhanced pharmacokinetic and pharmacodynamic responses after OI administration. Maximum plasma insulin concentration ($C_{\text{max}}$) was significantly higher ($93\pm71$ vs. $33\pm11$ µU/mL) and time to $C_{\text{max}}$ ($T_{\text{max}}$) was significantly shorter ($27\pm9$ vs. $161\pm83$ min) with OI administration. Relative bioavailability of OI for the 0-1h, 0-2h and 0-6h period were $26\pm28\%$, $7\pm4\%$ and $2\pm1\%$. Respective values for biopotency were $55\pm92\%$, $12\pm9\%$ and $3\pm1\%$. Plasma C-peptide concentrations showed no significant increase in any of the experiments and were not significantly different between the two treatments.

No adverse events and no clinically relevant changes in vital signs, ECGs or standard safety laboratory parameters were observed.

CONCLUSION

This is the first glucose clamp study demonstrating that OI is absorbed under fasting conditions and exhibits early enhanced pharmacokinetic and pharmacodynamic responses. The duration of action of OI was much shorter than that of RHI with a return to the baseline effect within 2-3 hours. No safety concerns arose from this short-term study with single dose administrations.

The fast pharmacokinetic and metabolic time-profiles of OI observed in this study may be advantageous in patients with type 2 diabetes by restoring normal first phase insulin secretion (9) potentially leading to an improvement in glycaemic control (10). OI's onset of action seems to be in the range of (or even faster than) that published for subcutaneous fast-acting analogues (11), but a head-to-head comparison has yet to be done.

OI should also have the advantage of reaching the liver in high concentration through the portal vein after gastrointestinal absorption. Thereby having a more physiological and stronger effect on hepatic glucose production and weaker effect on the peripheral tissues (potentially avoiding hypoglycaemia) than subcutaneous insulin preparations.

In this small proof-of-concept study only a relatively small amount, 7% for the 2-hour period after drug administration, of OI is absorbed under fasting conditions with a standard deviation of 4%. Thus, variability in absorption (CV 60-70%) is about as high for OI as that reported for NPH-insulin (11) but may increase further with prandial administration. In view of the narrow therapeutic window for insulin, this high between-subject variability might restrict clinical use of OI to patients with a high endogenous insulin secretion capacity. This first pilot study just provides a proof-of-concept for OI under fasting conditions. Additional investigations are therefore needed in particular to determine the pharmacodynamic (intra-individual) variability and the effect of food on oral insulin absorption, before longer-term studies could further elucidate the clinical potential of this OI formulation.

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FIGURE LEGEND

Figure 1 (A) Pharmacokinetic (plasma insulin concentration) response to administration of an oral insulin formulation (uninterrupted line) and subcutaneous regular human insulin (dotted line) at time = 0h. Plasma insulin concentrations are presented as mean+SEM. AUC_{INS(0-1h)}: 2559±1831 vs. 542±296 µU·min/mL, P<0.05. AUC_{INS(0-6h)}: 3225±2320 vs. 7004±2440 µU·min/mL, P<0.05. (B) Pharmacodynamic (GIR) response. GIRs are given for mean raw (thin line) and smoothed (bold line) data. AUC_{GIR(0-1h)}: 173±86 vs. 27±32 mg/kg, P<0.05. AUC_{GIR(0-2h)}: 297±143 vs. 137±107 mg/kg, P<0.05. AUC_{GIR(0-6h)} (374±135 vs. 651±380 mg/kg). T_{GIRmax}: 40±16 vs. 255±108 min, P<0.05. T_{GIR-50%-early}: 13±6 vs. 150±87 min, P<0.05. T_{GIR-50%-late}: 115±79 vs. >360 min, P<0.05. GIR_{max}: 4.4±2.2 vs. 3.6±1.8 mg/kg/min. GIR = glucose infusion rate; sc = subcutaneous.
REFERENCES


Figure

A

B