

# 3rd International Workshop on Adverse Drug Reactions and Lipodystrophy in HIV



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## THE HIV PROTEASE INHIBITOR INDINAVIR ACUTELY INHIBITS INSULIN-STIMULATED GLUCOSE DISPOSAL: A RANDOMIZED, PLACEBO-CONTROLLED STUDY

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**BACKGROUND:** Therapy with HIV protease inhibitors (PIs) causes insulin resistance even in the absence of HIV infection, hyperlipidemia or changes in body composition. The mechanism of the effects on insulin action is unknown. *In vitro* studies suggest that PIs selectively and rapidly inhibit the activity of the insulin-responsive glucose transporter Glut4.

**OBJECTIVE:** We hypothesized that a single dose of the PI indinavir resulting in therapeutic plasma concentrations would acutely decrease insulin-stimulated glucose disposal in healthy human volunteers.

**METHODS:** Randomized, double-blind, cross-over study comparing the effect of 1200 mg of orally administered indinavir and placebo on insulin-stimulated glucose disposal during a 180-min euglycemic, hyperinsulinemic clamp. Six healthy HIV-seronegative adult male volunteers were studied twice with 7-10 days between studies.

**RESULTS:** There were no significant differences in baseline fasting body weight, or plasma glucose, insulin, lipid and lipoprotein levels between placebo and indinavir studies. During steady-state ( $t_{60-180}$  min), insulin reached comparable levels ( $394 \pm 13$  placebo versus  $390 \pm 11$  pmol/l indinavir) and glucose was clamped at approximately 4.4 mmol/l under both conditions. The average maximum concentration of indinavir was  $9.4 \pm 2.2$   $\mu$ M; and 2-h area under the curve was  $13.5 \pm 3.1$   $\mu$ M/h. Insulin-stimulated glucose disposal per unit of insulin (M/I) decreased in all subjects from  $14.1 \pm 1.2$  to  $9.2 \pm 0.8$  mg/kg/min per  $\mu$ UI/ml (95% CI for change 3.7-6.1,  $P < 0.001$ ) on indinavir (average

decrease  $34.1 \pm 9.2\%$ ). The nonoxidative component of total glucose disposal (storage) decreased from  $3.9 \pm 1.8$  to  $1.9 \pm 0.9$  mg/kg/min,  $P < 0.01$ . Free fatty acid levels were not significantly different at baseline and were suppressed equally with insulin administration during both studies.

**CONCLUSIONS:** A single dose of indinavir acutely decreases total and non-oxidative insulin-stimulated glucose disposal during a euglycemic, hyperinsulinemic clamp. Our data provide the first evidence of an acute effect of indinavir on glucose disposal in humans, consistent with the proposed mechanism that PI-induced insulin resistance is mediated by a direct blockade of Glut4 transporters.

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