Oral agents in type 2 diabetes (1)

A PPAR-sparing insulin sensitizer is effective in type 2 diabetic patients without causing weight gain

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Background an.
Aim: We have suggested that insulin sensitizing activity of the thiazolidinediones (TZDs) can be separated from their ability to activate the nuclear transcription factor PPARg. Since PPARg-driven transcription has been implicated in many negative effects of both TZD and nonTZD-related insulin sensitizers, a PPAR sparing analog might be expected to have a superior profile of activity. We hypothesized such a compound would exert beneficial pharmacology without causing plasma volume expansion and weight gain. We have previously identified PPAR-sparing analogs with similar insulin sensitizing pharmacology to pioglitazone in preclinical animal models. Here we directly compare the prototypical PPAR-sparing analog, MitoglitazoneTM (MSDC-0160), to pioglitazone hydrochloride (Actos®) in type 2 diabetic patients. MSDC-0160 is an isomer of a known pioglitazone metabolite, Methods: A double bind, placebo and comparator-controlled phase IIA study was carried out in 76 type 2 diabetic patients at 12 US sites. MSDC-0160 (Mito) was given as two doses of bulk drug [90 mg (Mito1) or 220 mg (Mito2)] chosen to bracket exposures (AUC) predicted for pioglitazone and its active metabolites. Subjects were either drug-free or on a stable dose of metformin. Participants underwent a two week single blind placebo lead-in followed by four weeks of active double blind treatment and a one week follow-up. The primary endpoint was change in postprandial glucose determined by mixed meal tolerance tests.
Results: Mito was well tolerated and no serious adverse events were observed. Exposures of Mito and its metabolite were reached that should not be sufficient to activate PPARg. Both Mito2 and pioglitazone (Pio) significantly ($p < 0.05$ versus placebo) reduced circulating postprandial blood glucose, triglycerides, and free fatty acids. High molecular weight adiponectin was increased by 102 %, 223%, and 215% for Mito1, Mito2, and Pio, respectively. Both Pio and Mito2 produced a statistically significant time-dependent decrease in circulating fasting glucose (1.1 mM and 0.98 mM, respectively) and a statistically significant time-dependent increase in HDL cholesterol (0.119 and 0.130 mM, respectively). Over this short study period, Pio resulted in a small
(1.14 kg), but statistically significant increase in weight gain that was not seen in the Mito-treated patients. Conclusions: This study suggests that it is possible to achieve clinical responses with a non-PPAR activating thiazolidinedione similar to pioglitazone without the associated weight gain.
Conflict of interest:
Stock ownership: J.R. Colca, R.F. Kletzien, J.T. VanderLugt- Metabolic Solutions Development Company Employee: J.R. Colca, R.F. Kletzien, J.T. VanderLugt- Metabolic Solutions Development Company Commercially-sponsored research: Metabolic Solutions Development Company