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INDINAVIR WITH AND WITHOUT NUCLEOSIDES ACCELERATE THE DIABETES PHENOTYPE IN MALE ZUCKER DIABETIC FATTY (ZDF FA/FA) RATS

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BACKGROUND: The male Zucker diabetic fatty rat (zdf fa/fa) is a well-characterized animal model of NIDDM. It progressively develops worsening hyperglycaemia and hyperinsulinaemia from 5-10 weeks of age, and becomes insulinopenic at about 14 weeks of age. Adipose deposition in muscle and pancreas are believed to contribute to the development of NIDDM in this animal model.

OBJECTIVE: We tested whether twice-daily administration of didanosine (60 mg/kg/day), stavudine (12 mg/kg/day), zidovudine (88 mg/kg/day) all in combination with lamivudine (44 mg/kg/day) and with or without indinavir (320 mg/kg/day) exacerbates or accelerates the diabetic phenotype in these rats.

METHODS: Thirty-two zdf rats (Genetic Models, Indianapolis, Ind., USA) were randomly assigned to one of eight treatment groups: placebo, didanosine+lamivudine, stavudine+lamivudine, zidovudine+lamivudine, indinavir, didanosine+lamivudine+indinavir, stavudine+lamivudine+indinavir and zidovudine+lamivudine+indinavir. Medications were suspended in water and administered orally twice daily for 7 weeks starting at 5 weeks of age. Fasting glucose, insulin and triglyceride levels were measured weekly. Muscle mitochondrial enzyme activities were measured at the end of week 7.

RESULTS: Food consumption and weight gain were similar in all groups during the 7 week treatment period. In comparison to placebo, fasting glucose levels were higher in all indinavir-treated groups starting at week 3 of treatment ($P<0.05$). Fasting glucose levels

were higher in rats treated with NRTIs only, but this was not different from placebo until week 6-7 of treatment ($P<0.05$). Fasting insulin levels increased similarly in all groups until week 6 when they failed to increase in all groups treated with indinavir ($P<0.05$). In stavudine+lamivudine and zidovudine+lamivudine, fasting insulin levels tended to be lower than placebo at week 7. Fasting triglyceride levels tended to be greater than placebo in nucleoside reverse transcriptase inhibitor (NRTI) animals starting at treatment week 5, but lower in indinavir and still lower in indinavir+NRTI animals starting at week 3 ($P<0.05$). Muscle citrate synthase and cytochrome oxidase enzyme activities tended to be lower in NRTI-treated groups.

CONCLUSIONS: In rodents genetically predisposed to develop diabetes, indinavir alone and indinavir+NRTIs accelerated the development of diabetes more than NRTIs alone. We propose that these medications accelerate diabetes through a sequential injury mechanism that involves impairments in mitochondrial function, insulin sensitivity and insulin secretion.

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