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COMPARATIVE EFFECTS OF ATAZANAVIR ALONE AND IN COMBINATION WITH LOW CONCENTRATION OF RITONAVIR ON TRIGLYCERIDE AND CHOLESTEROL SYNTHESIS *IN VITRO*

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OBJECTIVE: Treatment with some protease inhibitors (PIs) is associated with dyslipidaemia. Proposed mechanisms include effects on lipid and lipoprotein production in hepatocytes and adipocytes. Atazanavir is a potent once-daily PI that in combination with low-dose ritonavir showed comparable clinical efficacy to lopinavir/ritonavir in treatment-experienced patients. Compared with ritonavir and lopinavir, atazanavir is associated with less or no dyslipidaemia clinically and less effect on lipogenesis *in vitro*. We hypothesized whether combining atazanavir with ritonavir at low concentration ($\leq 2 \mu\text{M}$) would negate the favourable *in vitro* effect of atazanavir on lipogenesis reported previously.

METHODS: Lipogenesis was assayed as [¹⁴C]2-acetate incorporation into triglyceride and cholesterol in human primary adipocytes and HepG2 hepatoma cells. Triglyceride and cholesterol synthesis were quantified in triplicates in the presence of atazanavir and lopinavir alone or in combination with ritonavir at various doses approximating therapeutic and boosted PI levels expected *in vivo*. Comparisons are by *t*-test versus control.

RESULTS: As a single drug at boosted-equivalent concentration ($\leq 2 \mu\text{M}$), ritonavir did not affect lipogenesis in either cell line. At 3 μM , ritonavir modestly inhibited (15–30%) triglyceride and cholesterol synthesis in adipocytes ($P < 0.05$ for both). At therapeutic concentration (10 μM), ritonavir inhibited triglyceride synthesis in adipocytes and increased triglyceride synthesis in HepG2 cells by 50% ($P < 0.01$). Atazanavir as a single drug up to 10 μM or in combination with ritonavir ($\leq 2 \mu\text{M}$) had little effect on triglyceride or cholesterol synthesis in HepG2 or adipocytes ($< 15\%$ effect, $P > 0.2$). In

contrast, lopinavir as a single drug at 10 μM increased (~50%) triglyceride synthesis in HepG2, and inhibited synthesis of triglycerides (~30%) and cholesterol (~50%) in adipocytes ($P < 0.01$ for all). Combination of lopinavir and ritonavir ($\leq 2 \mu\text{M}$) had no additive effect.

CONCLUSIONS: Atazanavir as a single drug at 10 μM or combined with ritonavir up to 2 μM has very little effect on lipogenesis, whereas lopinavir as a single drug at 10 μM or combined with ritonavir up to 2 μM affects lipogenesis. The data are consistent with the current hypothesis that ritonavir-boosted atazanavir used clinically will maintain the favourable lipid profile of unboosted atazanavir. Confirmatory clinical data are needed.

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