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Oral Testosterone-Triglyceride Conjugate in Rabbits: Single-Dose Pharmacokinetics and Comparison With Oral Testosterone Undecanoate

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Development of a safe and effective oral form of testosterone has been inhibited by the rapid hepatic metabolism of nonalkylated androgens. Since triglycerides are absorbed via lymphatics and bypass the liver, we hypothesized that a testosterone-triglyceride conjugate (TTC) might allow for safe and effective oral testosterone therapy. Therefore, we studied the single-dose pharmacokinetics of oral administration of TTC in rabbits. Female New Zealand rabbits were administered 2, 4, or 8 mg/kg of TTC in sesame oil by gastric lavage. Testosterone undecanoate (TU) by gastric lavage was used as a positive control. Blood was sampled from a catheter in the auricular artery at 0, 15, 30, 60, 90, 120, 180, 240, 360, 480, and 600 minutes after drug administration. Samples were assayed for testosterone by a fluoroimmunoassay. Mean serum testosterone, area under the curve (AUC), and terminal half-life were calculated. Oral TTC administration resulted in rapid and marked increases in serum testosterone. Oral TTC resulted in higher maximum serum testosterone concentrations than oral TU at 8 mg/kg (TTC: 28.6 ± 7.9 nmol/L vs TU: 11.9 ± 2.1 nmol/L; $P < .001$) and 4 mg/kg (TTC: 11.5 ± 4.2 nmol/L vs TU: 3.6 ± 1.0 nmol/L; $P < .001$). In addition, the AUC was 1.8 to 2.6 times greater for TTC than TU at both doses ($P < .05$). The terminal half-life for both TU and TTC was between 3 and 5 hours and was not significantly different. We conclude that oral TTC is rapidly absorbed from the rabbit intestine and results in elevated concentrations of serum testosterone. The absorption of TTC appears to be superior to that of TU; however, the in vivo persistence of the 2 compounds is similar. TTC may offer an alternative to the use of TU for oral testosterone therapy. Further testing of this compound is warranted.

Key words: Hypogonadism, androgen, lymphatics