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Pharmacokinetics and Degree of Aromatization Rather Than Total Dose of Different Preparations Determine the Effects of Testosterone: A Nonhuman Primate Study in *Macaca fascicularis*

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Currently available testosterone (T) preparations differ substantially in their pharmacokinetic profile that might influence their androgenic properties in terms of suppression of the gonadal axis, effects on anabolic parameters, lipid metabolism, and erythropoiesis. The present work was undertaken to determine the physiological effects of three T preparations with different serum kinetics. Twenty adult male cynomolgus monkeys (Macaca fascicularis) were randomly assigned to receive treatment for 28 weeks with either T enanthate (TE) every 4 weeks, T buciclate (TB) every 7 weeks, or T undecanoate (TU) every 10 weeks or remaining untreated (controls). Each injection delivered 20 mg pure T per kilogram body weight. Pharmacokinetic profiles demonstrated higher peak levels of T for TE-treated animals; serum half-lives were longer for TU or TB. Estradiol levels (area under the curve) were significantly higher in TB vs TU or TE. All T regimens suppressed serum luteinizing hormone bioactivity and testicular volumes declined (all $P < .001$ vs controls). Sperm counts were markedly lowered in all animals but least in TE ($P < .01$ vs TB or TU). During recovery phase, return to normal for all three parameters occurred significantly earlier in TE-treated animals, followed by those given TU, compared with TB (all $P < .001$ between groups). Body weight increased significantly during T exposure. This effect was stronger and more sustained in TB vs TU or TE (both $P < .001$). Serum creatinine and hemoglobin increased with high significance in all T-treated animals (all $P < .001$ vs controls). The lowering impact of T on serum lipids was markedly stronger in the longer-acting T preparations in comparison with TE, as were effects on purine metabolism (all $P < .001$). The pattern of exposure and degree of aromatization rather than overall exposure to T determine its effects in the preclinical primate model. Both fluctuations of androgen concentrations and the conversion rate to estradiol influence gonadal suppression as well as metabolism. These results have to be considered in men receiving treatment for hypogonadism or regimens for hormonal contraception.

Key words: Spermatogenesis, testis, male contraception, clinical chemistry, primates

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