PROJECT REVIEW

"Detection of recombinant human LH as a doping agent."

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The project aims are to establish parameters to allow the detection of the use of recombinant human Luteinizing Hormone (LH) as a sports doping agent. LH is a natural pituitary hormone which, although on the banned list, has never been available previously but has become available as a commercial recombinant hormone marketed in Europe (Nov 2000). Clinically, LH is intended for use to trigger ovulation in anovulatory infertile women as well as potentially in in vitro fertilization hyperstimulation regimens. In men it is the natural stimulus to testicular Leydig cells to increase synthesis and secretion of testosterone. The availability of the recombinant LH as a potential doping agent for male athletes requires the development of a reliable and valid detection test. Like hCG, LH is most likely to be used mainly by athletes who have reduced testicular size and suppressed endogenous testosterone production due to use of synthetic androgens, but (in contrast to hCG) without risk of detection. As LH and hCG act upon the same LH/CG receptor, their biological effects are likely to be very similar. However, as hCG has a much longer circulating half-life than LH due to the C-terminal sialic acids residues in the CG β subunit, the effects of LH are likely to be of shorter duration making it easier to continue use closer to competition events which are subject to doping tests. Furthermore, in contrast to hCG, LH occurs normally in easily detectable concentrations in blood and urine so it also becomes necessary to distinguish between exogenous recombinant LH from endogenous LH.

Results and Conclusions

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This one year project aimed to undertake clinical administration studies using single doses of recombinant human LH (rhLH) and recombinant hCG (rhCG) to determine their effects on (a) conventional urine steroid profiles, (b) blood hormone analyses and (c) to provide samples for development of novel tests for rhLH and rhCG as sports doping agents in men.

The clinical studies recruited healthy young men to have one of two rhLH doses (75 IU, 225 IU) with or without prior suppression of endogenous testosterone (T) by a single dose of 200 mg nandrolone decanoate.

The original target of 32 men in a balanced design (2 LH doses [75 I, 225IU], with or without 200 mg nandrolone decanoate pre-treatment and 8 per group) was modified in the light of the interim analysis. This showed no consistent or significant effects on urinary LH or T at either LH dose. We therefore decided to incorporate a higher rhLH dose. A protocol amendment was approved and we completed the 4 original groups with 5 (rather than 8) men per dose but added 3 more men studied at a higher LH dose (750 IU, in two evenly divided doses 4 hr apart) without nandrolone pre-treatment.
The LH component of this project was completed with 23 men having rhLH without adverse effects. Analysis of the time-course of serum LH and testosterone as well as urinary LH, testosterone and testosterone/epitestosterone ratio are consistent in showing no significant effects of any LH dose on blood or urinary LH or testosterone. Artefacts influencing urinary LH measurements were identified and shown to be rectified by redissolving the urinary sediment (to correct for non-specific adsorption of LH onto urinary sediment) and correcting for urinary creatinine or specific gravity (to correct for time of sampling and urine dilution effects).
The hCG component of the study was completed with 24 men having one of two rhCG doses. The pharmacokinetics and pharmacodynamics of rhCG was defined with dose-proportionality of peak serum and urinary hCG levels but no effect of concurrent gonadal suppression by nandrolone. By contrast neither serum nor urinary LH or testosterone were influenced by rhCG dose and serum but not urinary T was lowered by concurrent nandrolone treatment.

The T/LH ratio was highly sensitive to rhCG administration with a progressive and steep rise lasting well over a week after a single rhCG dose but without influence by rhCG dose or nandrolone treatment. rhCG and nandrolone had modest effects of increasing the T/E ratio.

Subject to standardisation and validation of specific commercial LH immunoassays, the T/LH ratio remains a useful screening test for hCG doping.