Stimulatory effects of the long-acting kisspeptin analogue TAK-448 on serum testosterone in men with type 2 diabetes and hypogonadotropic hypogonadism

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Background and aims: Exogenous kisspeptin stimulates testosterone in hypogonadal men with type 2 diabetes (T2DM); long-acting kisspeptin analogues may have therapeutic potential. The study aimed to evaluate serum testosterone (ST) responses to different doses and frequencies of TAK-448, an oligopeptide analogue of the fully active 10-amino acid C terminus of kisspeptin-54.
Materials and methods: Open-label, adaptive design assessing ST responses to varying doses of TAK-448 in hypogonadotropic hypogonadism (HH) males recruited at a Clinical Research Unit Centre for Diabetes, Endocrinology and Metabolism. Fifteen overweight men with T2DM and HH, defined as two morning total ST values ≤12 nmol/L and normal luteinizing hormone, were given TAK-448 0.3, 1.0 or 3.0 mcg once- or twice-weekly. Primary outcome measures were trough ST concentrations and area under the effect curve (AUEC)(0-72h) percentage changes after 4 weeks of TAK-448 administration.
Results: TAK-448 was well tolerated. First dose mean ST AUEC(0-72h) responses ranged from 11% after 0.1 mcg to 53% after 3 mcg. In contrast, after the last dose, a marginal benefit (9%) was seen for 1 mcg once-weekly with a reduction (-4%) for 3 mcg once-weekly. Following 0.3 mcg weekly or 0.1 mcg twice weekly similar levels of responses were seen after the first and last dose. 0.3 mcg given twice weekly showed a reduction in response compared to baseline (-4.4%). No regimen increased mean post dose trough ST levels above 10.4 nmol/L. Once-weekly 3.0 and 1.0 mcg dosing produced trough ST levels below baseline, indicating desensitization. Twice-weekly 0.3 and 0.1 mcg dosing also showed desensitization. Once-weekly 0.3 mcg did not show desensitization overall but did for some individual profiles.
Conclusion: TAK-448 stimulated ST secretion acutely in a dose dependent manner. Repeated administration produced desensitization of ST responses for all regimens except 0.3 mcg once-weekly. No dosing regimen that maintained testosterone secretion within the normal range could be identified.
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