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Development of clinical trials using injectable testosterone and norethisterone

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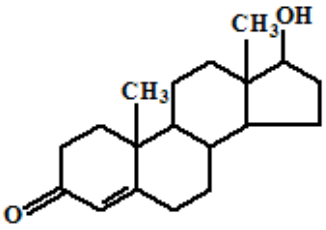
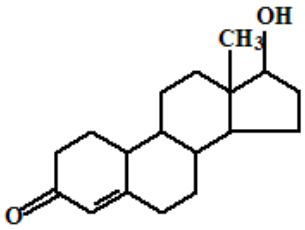
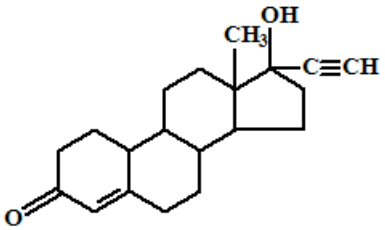
The requirements for male hormonal contraception (MHC) were defined more than four decades ago, namely that MHC should be effective as comparable female methods, acceptable to both partners, easily applicable, rapidly effective, independent of the sexual act, free of side-effects, especially without influence on masculinity, libido and potency, without influence on progeny, reversible, and financially affordable. However, despite numerous attempts to date no MHC product has reached the market. To illustrate the long-winding road to MHC a series of developments tested by our team is summarized.



Testostérone



19-Nortestosterone



Norethisterone

Since an orally applicable modality for MHC would be favored by a majority of possible users, we first performed a trial using oral testosterone undecanoate (TU), but learned that despite suppression of spermatogenesis the short-lived kinetic peaks produced by TU were insufficient for MHC (Nieschlag et al. 1978). Inspired by azoospermia observed in athletes doped by anabolic androgenic steroids, we next tested the injectable T derivative 19-nortestosterone-hexoxyphenyl-propionate which effectively suppressed sperm when applied in clinical doses to a small group of volunteers (Schürmeyer et al. 1984).. WHO concluded from multicenter clinical trials that weekly injections of T enanthate would suffice for MHC (1996). Since the frequency of these injections and the dose would be too high, a search for long-acting T-preparations in combination with a progestin was initiated. We had identified intramuscular TU as a candidate well suited for prolonged androgen action (Nieschlag & Nieschlag 2017) and combined it with the 19-nortestosterone derivative

norethisterone-enanthate (NETE), the first synthetic gestagen with a long history in female contraception (Kamischke et al. 2002). These studies were so successful that, after further dose-finding studies (Meriggola et al. 2005), WHO initiated a ten-center safety and efficacy trial using this steroid combination. Although 266 couples entered the efficacy phase and the trial was very successful in terms of contraceptive protection (Pearl Index 2.2) and acceptability by the couples, it was early terminated and only preliminary results are published (2016). Nevertheless, investigators were not demotivated by this sad outcome of the WHO trial and are continuing their efforts for MHC supported by the NIH and Population Council, as the next presentation at this ICMC Congress will show.

References

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