12 Clinical pharmacology of testosterone pellet implants

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12.1 Introduction

Androgen therapy may be divided into physiological and pharmacological applications. The pharmacological applications usually involve non-physiological doses of synthetic androgens as second-line, empirical treatment
where more specific medical therapy is not yet available. The physiological applications consist of androgen replacement therapy, the treatment of androgen deficiency in hypogonadal men. Androgen replacement therapy aims to replicate physiological actions of endogenous testosterone by steadily maintaining physiological blood levels of testosterone. Since the underlying disorders are virtually always irreversible, this requires life-long administration of testosterone, making it desirable that the testosterone formulations be long-acting. Reliable therapeutic compliance over the lifetime of the patient depends heavily on a convenient formulation which ensures the continuity of treatment. The pharmacological properties of testosterone, notably its rapid hepatic metabolism and very low oral bioavailability, dictate the need for development of depot, sustained-release testosterone formulations (Parkes 1938; Wilson 1980). The perfect depot would be safe, effective, inexpensive, convenient, and long-acting with a reproducible, zero-order release profile. Not surprisingly, even six decades after entry of testosterone into clinical use (Foss 1939; Hamilton 1937), this ideal has not been achieved. Nevertheless one of the oldest testosterone formulations, the subdermal testosterone implant, provides a very close approximation to this ideal in providing stable blood testosterone levels lasting 4–6 months after a single implantation. Curiously this cheap, safe and effective treatment modality was neglected for decades despite its many advantages for androgen replacement therapy but is now undergoing a revival of interest, particularly since its desirable pharmacological properties have been outlined (Cantrill et al. 1984; Conway et al. 1988; Handelsman et al. 1990, 1997; Jockenhövel et al. 1996; Nieschlag 1996; Zacharin and Warne 1997).

12.2 History

Remarkably by modern standards, testosterone entered clinical usage (Hamilton 1937) within two years of its chemical identification (David et al. 1935) and synthesis (Butenandt and Hanisch 1935; Ruzicka and Wettstein 1935) in 1935. During its purification it became apparent that testosterone had negligible oral bioavailability and a very short duration of action parenterally (Foss 1939; Parkes 1938), later shown to be due to rapid hepatic metabolism (Frey et al. 1979; Hellman et al. 1956; Nieschlag et al. 1975, 1977). These pharmacological features led to an early recognition of the need for long-acting depot testosterone (Foss 1939; Parkes 1938). Within the few years until the hiatus created by World War II, numerous formulations of testosterone and its derivatives were reported. Subdermal pellet implantation was among the earliest effective modalities employed for clinical application of testosterone (Deansley and Parkes 1937; Howard and Vest 1939; Vest and Howard 1939). The experimental observation that subdermal implants showed the most potent, lasting effects of any steroid formulation (Deansley and Parkes 1938; Hamilton and Dorfman 1939) was quickly applied by clinical investiga-