

Fig. 14.12 Serum concentrations (mean  $\pm$  SEM) of testosterone after single-dose intramuscular injections of 1000 mg testosterone undecanoate in tea seed oil in 7 hypogonadal men (squares) or castor oil in 14 hypogonadal men (circles). Broken lines indicate normal range of testosterone (adapted from Behre *et al.* 1999a, reproduced by permission of the European Journal of Endocrinology).

patients (Behre *et al.* 1999a). Follow-up examinations were performed 1, 2, 3, 5 and 7 days after injection and then weekly up to study week 8. Whereas no prolonged increase of testosterone was observed in the 250 mg-group, serum levels of testosterone in the higher dose group increased from  $4.8 \pm 0.9$  nmol/l (mean  $\pm$  SEM) to maximum levels of  $30.5 \pm 4.3$  nmol/l at day 7 ( $t_{\max}$ ). Testosterone levels remained within the normal range up to week 7 ( $13.5 \pm 1.2$  nmol/l). Non-linear regression analysis revealed a terminal elimination half-life for intramuscular testosterone undecanoate of  $20.9 \pm 6.0$  days (Fig. 14.12).

Similar to the preclinical study in monkeys, the clinical study in hypogonadal men demonstrated favourable pharmacokinetics of intramuscular testosterone undecanoate. Because of the relatively low concentration of 125 mg testosterone undecanoate per milliliter tea seed oil, however, administration of the 1000 mg dose requires an injection volume of 8 ml which renders intramuscular administration impracticable. Therefore, the preparation was reformulated and testosterone undecanoate dissolved in castor oil at a higher concentration of 250 mg/ml. 14 hypogonadal patients received one intramuscular injection of 1000 mg of the reformulated testosterone undecanoate preparation (Behre *et al.* 1999a). Maximal serum levels with the reformulated preparation were lower than with the Chinese preparation and remained within the mid-normal range (Fig. 14.12). Pharmacokinetic analysis revealed a long terminal elimination half-life of  $33.9 \pm 4.9$  days (Table 14.2).

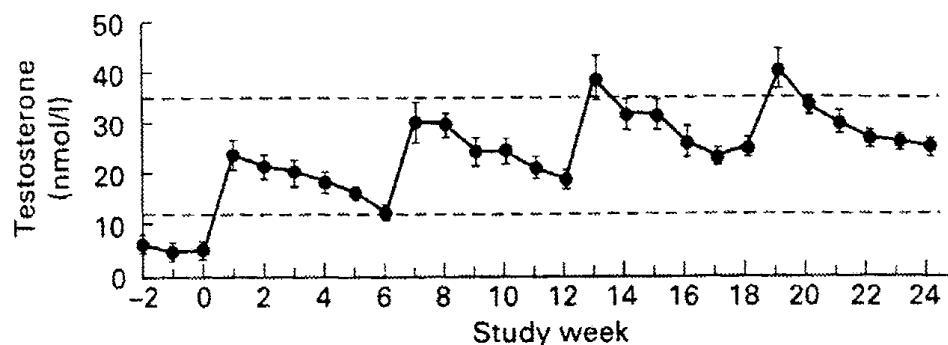


Fig. 14.13 Serum concentrations (mean  $\pm$  SEM) of testosterone after multiple intramuscular injections of 1000 mg testosterone undecanoate in castor oil in 13 hypogonadal men. Broken lines indicate normal range of testosterone (adapted with permission from Nieschlag *et al.* 1999, copyright 1999, Blackwell Publishing).

Due to these favourable pharmacokinetics a first, prospective, open-label study with repeated intramuscular injection was initiated (Nieschlag *et al.* 1999). 13 hypogonadal men received four intramuscular injections of 1000 mg testosterone undecanoate in castor oil at six-week intervals. Following the first injection, mean serum levels of testosterone were never found below the lower limit of normal (Fig. 14.13). However, peak and trough serum concentrations of testosterone increased during the six-month treatment, with testosterone levels above the upper normal limit after the third and fourth injection. Therefore, in seven of the 13 hypogonadal men injections were given at gradually increasing intervals between the fifth and tenth injection, and from then on every 12 weeks (von Eckardstein and Nieschlag 2002). During steady state, serum levels of testosterone remained in the normal range with maximal concentrations of  $32.0 \pm 11.7$  nmol/l (mean  $\pm$  SD) one week after injection and nadir levels before the next injection of  $12.6 \pm 3.7$  nmol/l (Fig. 14.14). As this preparation has been approved for clinical use in Europe, intramuscular testosterone undecanoate in castor oil will become a significantly improved testosterone preparation for treatment of male hypogonadism as well as for male contraception (see Chapter 23).

#### 14.3.6.7 Testosterone decanoate

Testosterone decanoate differs from testosterone undecanoate by one carbon atom in the ester side chain. It has been widely administered for many years as part of a mixture with shorter-action testosterone esters, however, it has not been available as a single preparation. To date there are no detailed studies published on the pharmacokinetics of administration of testosterone decanoate to hypogonadal men. Recently, intramuscular injections of 400 mg of testosterone decanoate were given four times every four weeks to normal men in a contraceptive study (Anderson *et al.* 2002). Endogenous testosterone was suppressed by concomitant administration