Testosterone Replacement Therapy

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Guideline for use of testosterone replacement therapy for induction of and progression through puberty in hypogonadotrophic hypogonadism (HH), androgen deficiency secondary to testicular failure and in constitutional delay of growth and puberty (CDGP).

Background:

The aim of testosterone replacement therapy is to mimic the normal cadence of puberty [1] and match requirements at different stages of pubertal development in patients with HH, androgen deficiency secondary to testicular disease (hypergonadotrophic hypogonadism) and in CDGP. Testosterone replacement therapy is used to induce development of secondary sexual characteristics and promote linear growth, normal accrual of muscle mass and bone mineral density while avoiding mistimed epiphyseal plate closure [2,3].

In androgen deficiency secondary to congenital hypogonadism (hypogonadotrophic or hypergonadotrophic), testosterone replacement therapy may be given in the neonatal 'mini-puberty' for a short period but is then usually started at between 12 to 14 years of age and life-long treatment is required [4].

In boys with CDGP, testosterone replacement therapy may also be commenced to alleviate the distress boys often suffer because of their lack of growth and pubertal progression, which can affect their school performance and social relationships [2]. Low dose, intermittent testosterone should be used in CDGP to avoid suppression of endogenous axis.

Licenced testosterone preparations (in BNFc [5] and BNF [6]):

NB. Sustanon 250® and testosterone enantate are not licensed for use in children

IM testosterone:

- **'Mini-Puberty' in infants**: A long-acting testosterone ester (testosterone propionate (Virormone®, Nordic)) at 25 mg/month for 3 months can be used [7,8]. It does not contain benzyl alcohol [9]. Other testosterone preparations such as testosterone enantate, or mixture of esters (Sustanon 250®) need to be treated with caution as they are made up in vehicles which may be toxic to neonates. Sustanon 250® contains benzyl alcohol and is contraindicated in neonates as there is risk of a severe and potentially fatal toxic reaction to benzyl alcohol [10,11,12]. The reports were in preterm babies, given benzyl alcohol intravenously in the first weeks of life and the risk is highest during the neonatal period, with risk decreasing with age up to 3 years although the European Medicine Agency recommendation is to avoid parenteral administration up to aged 3 years [13]. Sustanon preparations also contain arachis oil so are contraindicated in those with a nut allergy [10]. Testosterone enantate contains benzyl benzoate and castor oil for injection. Castor oil when used as a vehicle in intravenous injection have been associated with severe

anaphylactoid reactions [14]. There was no information available about benzyl benzoate safety in neonates.

- **Pubertal induction**: Long-acting testosterone esters (testosterone enantate, testosterone proprionate (Virormone®, Nordic) or mixture of esters (Sustanon 250®

  - 50–75 mg/month is used initially and escalated gradually every 6 months to 100–150 mg/month before changing to 250mg 3 weekly after 3–4 years [1,4].

  Or

  - For children over 12 years: 25–50 mg/m2 every month increasing dose every 6–12 months according to response [5].

- **Post-pubertal maintenance:** Testosterone undeconate (Nebido®, Bayer) is licensed in men over 18 years (not licensed for children). Dose: 1 g every 10–14 weeks; if necessary, second dose may be given after 6 weeks to achieve rapid steady state plasma testosterone levels and then every 10–14 weeks. This should not be used for induction of puberty or progression through early stages of puberty (and CDGP) as it is not appropriate for dose titration. Testosterone enantate (Dose: 250 mg every 2–3 weeks; maintenance 250 mg every 3–6 weeks), Sustanon 250®, or Virormone®, Nordic (Dose: 50 mg weekly for delayed puberty; 50 mg 2–3 times weekly for androgen deficiency) may also be used.

Oral testosterone:

- **Pubertal induction:** Testosterone undecanoate (Restandol® Testocaps)

  - Started at 40 mg once daily, and gradually titrated up every 6 months to a maximum dose of 80 mg tds after 2–3 years [1,4].

  Or

  - For children over 12 years: 40 mg on alternate days increasing according to response up to 120 mg daily [5]

  - Oral testosterone has a short half-life and must be taken with food for satisfactory absorption, and has a tendency to be 5a-reduced to DHT in the gut [1].

Testosterone cream:

- Testosterone 5% cream can be used for treatment of microphallus in gonadotrophin deficiency to stimulate phallic growth.
- Dose: apply cream three times daily for 3 weeks [5].
- Testosterone propionate 5 % cream is an unlicensed special available from Special Labs on a bespoke basis. The only constituents of this preparation is the active ingredient and aqueous cream.

- Dihydrotestosterone (andractim 2.5 % gel) can be used in neonates for treatment of microphallus or for 'mini-puberty in hypopituitary babies. It is not licensed in the UK, but licensed elsewhere in the world and imported into the UK. Recommended doses (GOS) are as follows:
    - **<3kg:0.625g**
    - **3-6kg: 1.25g**
    - **6-9kg: 1.875g**
    - **9-12kg: 2.5g**
    - **>12kg: 5g**

However andractim contains 96 % alcohol. The use of a preparation which has high content of alcohol is cautioned in neonates, due to their large body surface area in relation to body mass increases susceptibility to toxicity from systemic absorption of substances applied to the skin. Furthermore, high alcohol containing preparations can dehydrate the skin, cause skin irritation and can cause necrosis. In pre-term neonates, the skin is more fragile and offers a poor barrier, especially the first fortnight after birth and especially if below 32 weeks corrected gestational age.[16]

Other options (in BNF [6]):

The following preparations are unlicensed for use in children.

Buccal tablets:

- Striant® SR (The Urology Co.): 30 mg every 12 hours; not recommended for use in children or adolescents under 18 years.

Transdermal gel:

- 1% testosterone strength (Testogel®, Bayer or Testim®, Ferring):
    - Adult dose: 50–100 mg of testosterone in 5–10 g gel sachets.
    - For children: the starting dose should be around one-third of a 50mg/5g satchet ie. 10-20mg daily or every second day [1,4] for the first year, and gradually increasing by one-third of a satchet daily every year to a final dose of 50 mg daily in the third year [1].

- Metered-dose 2% testosterone gel (Tostran®, ProStrakan) 10mg/metered application:
    - Adult dose: apply 60–80mg of testosterone (3–4 g of gel) daily.
    - For children: 10-20mg (1-2 metered applications) daily or every second day[4] (extrapolated from adult dose, no evidence in literature).
    - Metered dose 2% testosterone gel allows much easier titration compared with 1% testosterone sachet preparations.

- Advice for application:

- Apply thin layer of gel on clean, dry, healthy skin such as shoulders, arms or abdomen. Allow to dry before dressing.
- Be careful to avoid potential cross-contamination - wash hands with soap and water after applying gel.
- Preferably apply at bedtime, avoid shower or bath for at least 6 hours.
- Gels should not to be applied on genital area as high alcohol content may cause local irritation.

NB Testogel and testim gel would be unsuitable for babies. They contain high alcohol contents and propylene glycol.

Transdermal patch:

- Andropatch® (Glaxo-SmithKline): 2.5-5mg/24hrs
- Intrinsa® (Warner Chilcott): 300mcg/24hrs.
- Evidence for use in children: A study by Mayo et al. [15] assessed the pharmacokinetics and effects on pubertal status, short-term growth and bone turnover of transdermal testosterone application. The study was a prospective randomized, crossover study over 26 weeks, involving 8 boys aged 12.4 to 14.9 years. It was found that use of a 5mg/24hrs patch (Virormone®, Nordic) applied overnight for 8-12hrs may be a potentially acceptable method to induce puberty and stimulate short-term growth and bone turnover.
- Patches should be applied to dry skin on the back or buttocks and have been associated with localised skin irritation.

None of the transdermal preparations (gels, patches or implants) have been licensed for induction of puberty in the UK and experience of their use is limited in adolescent practice [1]. By contrast, in adults, transdermal systems provide testosterone pharmacokinetics that most closely mimic natural diurnal variation in testosterone concentrations and are convenient when changing from the IM route at late puberty to adult replacement therapy [1].

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