Testosterone therapy for adolescents/adults with sex chromosome aneuploidies: What’s available and what’s new?

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Disclosures

- Consultant to and scientific advisory board
  - Acerus Pharma
  - Aytu BioScience

Both market nasal testosterone gel
Outline

• Testosterone preparations
  • Injectable
  • Transdermal
  • Intra-nasal
  • Buccal
  • Implantable
  • Oral

• Time course

• Advantages and disadvantages

• Adverse events

• Cost
Testosterone
Testosterone preparations

• Injectable
  • Cypionate and enanthate (generic and branded)
  • Undecanoate (Aveed®)

• Transdermal
  • Patch (Androderm®)
  • Gel (branded and generic)

• Intranasal
  • Natesto®

• Buccal
  • Testim®

• Implantable
  • Testopel®

• Oral
# FDA Thresholds for Testosterone Products

## Table 1.

<table>
<thead>
<tr>
<th>Observed $C_{\text{max}}$ Limit (ng/dl)</th>
<th>Success Criteria (% participants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1,500 or Less</td>
<td>85% or Greater</td>
</tr>
<tr>
<td>1,800–Less than 2,500</td>
<td>5% or Less</td>
</tr>
<tr>
<td>2,500 or Greater</td>
<td>None</td>
</tr>
</tbody>
</table>

1 nmol/L = ~ 30 ng/dL
Testosterone Preparations

• Oral
  • Alkylated (methyl T)
  • Undecanoate
  • oxandrolone

• Transdermal
  • scrotal patch
  • Non-scrotal patch
  • gel (packets and pump)
Testosterone Preparations (cont.)

• Oral androgens
  • T (unmodified)
  • 17α-alkylated
    • Hepatotoxic
    • ↑ transaminases
    • Cholestasis
    • *Peliosis hepatis*
Testosterone Preparations (cont.)

• Oral androgens (cont.)
  • Undecanoate
    • 17β-ester, absorbed in lymph
    • high inter-individual variability in absorption, time-to-peak, maximal concentration
    • multiple doses per day with fatty meal
  • Not approved in the US, although several companies working on new formulations
Testosterone Preparations (cont.)

• Oral androgens (cont.)
  • Oxandrolone
    • Nonaromatizable
    • treatment
      • boys with CDGP
      • girls with Turner syndrome
Testosterone Preparations (cont.)

- Injectable
  - short- and long-acting esters
- Longer-acting preparations
  - microcapsules (Testopel)
  - buciclate
Testosterone Preparations (cont.)

- Injectable
  - Propionate
    - unsuitable because of short half-life
  - Enanthate
    - ~200-250 mg every 2 weeks leads to *virtually* physiological levels of T with peaks just above the upper limit of normal and nadirs just below the lower limit of normal
- Cypionate
  - indistinguishable from enanthate
Testosterone enanthate or cypionate

• Dose
  • 75 to 100 mg/week
  • 150 to 200 mg/2 weeks

• Testosterone levels rise to supraphysiological range and then decline into the hypogonadal range before the next dose

• Cost: ~$12 to ~$18/month + (perhaps) administration fee, 2/mo
Testosterone (implantable pellets)

• 3 to 6 (75 mg) pellets
  • Testosterone peaks at about 1 month and remains within the normal range for 3-6 months

• Adverse events—surgical incision (trocar) and potential extrusion
Testosterone Preparations (cont.)

• Subdermal
  • Pellets
    • effective modality for more than 50 y
    • newer formulations (100 and 200 mg)
      • multiple pellets per implantation
      • highly reproducible and dose-dependent time course for circulation total and free T
    • 6 month intervals
Testosterone enanthate or cypionate (im)
Testosterone gel (various strengths)

- Available in sachet packets, tubes and by pump
  - 5-10 g/day T gel containing 50 to 100 mg testosterone
- Restores T and estradiol levels to the physiologic range
- Adverse events
  - Potential for transfer to a partner or child
- Cost: branded *versus* generic
Pharmacokinetics and bioavailability of a new testosterone gel formulation in comparison to Testogel® in healthy men
Testosterone Preparations (cont.)

• Transdermal
  • scrotal patch
    • highest rate of steroid absorption
    • high concentration of $5\alpha$-reductase
    • problem-to deliver 5-15 mg T/day
    • stable levels of T, DHT, $E_2$ with daily application
Testosterone Preparations (cont.)

• Transdermal (cont.)
  • nonscrotal patch
    • enhancers to facilitate sufficient T passage through the skin (drug delivery system)
    • skin irritation-up to 60% (alcoholic enhancer and occlusive nature of system)
Testosterone Preparations (cont.)

• Transdermal (cont)
  • gel (packets and pump)
    • hydroalcoholic gel to contain 25 to 50 mg T in 2.5 or 5 g doses
  • physiologic levels of T, DHT, E₂
Testosterone Preparations (cont.)

• Transdermal (cont.)
  • gel (packets and pump)
    • advantages
      • ability to deliver T dose to low, mid or high physiologic range
      • lower incidence of skin irritation
      • ease of application
      • invisibility of dried gel
    • disadvantages
      • transfer to women and children
Testosterone (transdermal patch)

• One or two patches to deliver 5 to 10 mg Testosterone per day
• T:DHT and T:E2 within the physiologic range
• Adverse events-skin irritation is common
Testosterone (buccal adhesive)

• 30 mg controlled release twice daily
• Normalizes T, DHT and E2 levels
• Adverse events - gum irritation in ~ 16 %
Testosterone (nasal gel)

• 22 or 33 µg/day given twice or three times
• Relatively low total dose because it is directly absorbed
  • Very short acting
• Adverse events
  • No transfer to partners or children
  • ? Ameliorative effect with rhinitis
Natesto™, a novel testosterone nasal gel, normalizes androgen levels in hypogonadal men

(A) 

(B) 

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Testosterone undecanoate
Testosterone undecanoate (injectable)

- 750 to 1,000 mg at 0 and 6 weeks
- 750 to 1,000 mg every 10 to 14 weeks
- Levels of T, DHT, E2 mainly within the physiologic range
- Adverse events-injection of a large volume (4 mL) and lipid droplets in lungs (cough)
Testosterone undecanoate (injectable)

- 1000 mg deep IM initial
- Second dose 6 weeks later of 1000 mg
- Then 1000 mg every 10 to 14 weeks
- Caution that oil can travel to lung or be associated with anaphylaxis (0.4 cases per 10,000 men)
Monitoring Testosterone Treatment

- Adolescent development
  - Testicular size
- Height velocity
- Serum testosterone level
Bone Mass

- Improve Bone Acquisition
- Build Bone
- Reduce bone loss & prevent falls

- Childhood
- Adulthood
- Elderly

Bone Mass
<table>
<thead>
<tr>
<th>Form</th>
<th>Cost/month (without markup)</th>
<th>Dosing Interval</th>
<th>Adverse Events</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injectable</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>propionate</td>
<td>~3 da</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyp/enanthate</td>
<td>~$25-50</td>
<td>1-2 wk</td>
<td>Pain and redness at injection site; relatively higher risk of polycythemia</td>
<td>Longer dosing interval</td>
<td>Wide fluctuations in T levels</td>
</tr>
<tr>
<td>Undecanoate</td>
<td>~$900/3 mo</td>
<td>~10-12 wk</td>
<td>Lipid in lung; anaphylaxis</td>
<td>Long dosing interval</td>
<td>Difficult to change dosing</td>
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<tr>
<td>Implant</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Testopel</td>
<td>~$950/10 pellets</td>
<td>Multi pellets 4-6</td>
<td>extrusion</td>
<td>Long dosing interval</td>
<td>Surgical procedure</td>
</tr>
<tr>
<td>Form</td>
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<tr>
<td>Transdermal</td>
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<td></td>
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<tr>
<td>Gel/other</td>
<td>~$5-600/mo (no discount); ~150 with discount</td>
<td>daily</td>
<td>2⁰ exposure [BBW]</td>
<td>Mimics morning T peak; simple administration</td>
<td>Transference; daily administration</td>
</tr>
<tr>
<td>patch</td>
<td>~$550/mo (no discount); ~$125 with discount</td>
<td>daily</td>
<td>Cutaneous inflammation</td>
<td>Mimics morning T peak</td>
<td>Skin irritation; may not stick</td>
</tr>
<tr>
<td>buccal</td>
<td>~$600/mo (no discount)</td>
<td>2/da</td>
<td>Gum/mouth irritation</td>
<td>Ease of use; rapid kinetics</td>
<td>In mouth 12 h</td>
</tr>
<tr>
<td>nasal</td>
<td>~$250-750/mo (no discount)</td>
<td>2-3/da</td>
<td>Nasal symptoms</td>
<td>Ease of use; rapid kinetics</td>
<td>3x/da</td>
</tr>
</tbody>
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## Testosterone Pharmaceuticals (3)

<table>
<thead>
<tr>
<th>Form</th>
<th>Cost/month</th>
<th>Dosing Interval</th>
<th>Adverse Events</th>
<th>Advantages</th>
<th>Disadvantages</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oral</td>
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<tr>
<td>oxandrolone</td>
<td>~$60-120</td>
<td>daily</td>
<td>Hepatic AE’s</td>
<td>Oral convenience</td>
<td>Hepatic AE’s</td>
</tr>
<tr>
<td>Undecanoate (not available US)</td>
<td>$50-100</td>
<td>tid</td>
<td></td>
<td>Oral convenience; modifiable dose</td>
<td>Very variable responses; taken with a fatty meal</td>
</tr>
</tbody>
</table>
THANK YOU