Testosterone administration frequency, estradiol, and AAS in relation to growth plates

intelligentanabolism.com

This article addresses multiple different topics, from pharmacokinetics of testosterone, estradiol related issues, AAS in relation to growth plate closure, and injection frequency.

Pharmacokinetic context

Many of the common lower danger side effects of injectable testosterone use largely appear to be caused by hormone fluctuations. The pharmacokinetics of injectable testosterone esters are relatively straightforward. Upon administration of enanthate or cypionate esters of testosterone (which behave the same, the difference is found in the 7 carbon enanthate tail v.s. The 8 carbon cypionate tail); the molecule slowly exits the carrier oil into the body system. Both enanthate and cypionate tails of these molecules are lipophilic, meaning they "prefer" to stay in the carrier oil. This prevents rapid release and therefore rapid elimination within the body, giving both test E and test C a half life of ~4.5 days.

When the ester molecules leave the carrier oil, they are targeted by carboxylesterases, and plasma esterases. These specialized proteins are part of the serine hydrolase superfamily, and have the primary task of breaking down ester bonds using water. These can be seen as chemical scissors, specialized to target fats, lipids, and medications and foreign substances.

These enzymes introduce a water molecule, and break the ester linkage which is located at the 17-beta hydroxyl position of the steroid core.

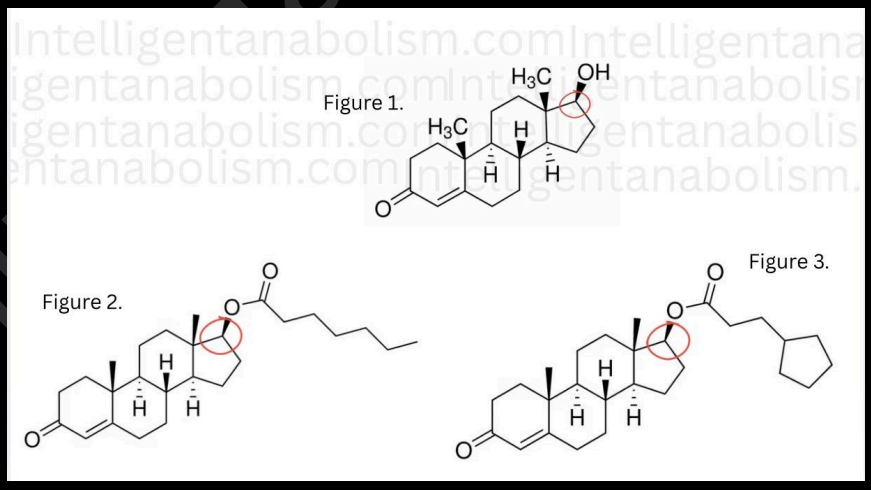


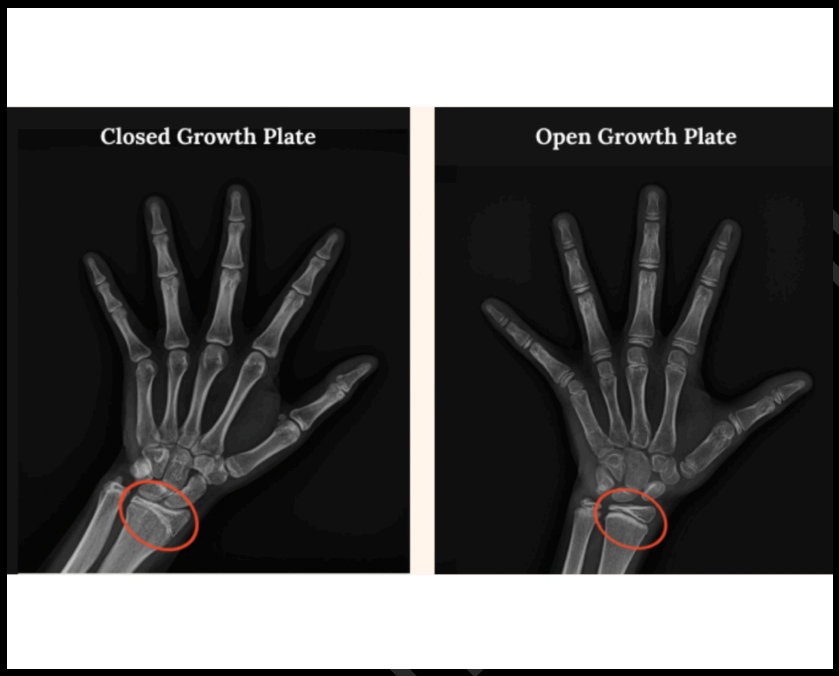
Figure 1. Non-esterified testosterone molecule Figure 2. Testosterone molecule with added Enanthate ester 7-carbon tail Figure 3. Testosterone molecule with added Cypionate ester 8-carbon tail.
The 17-beta hydroxyl position is circled, showing where on the molecule the ester is attached to. Non-esterified testosterone administration is very subpar, as it is eliminated rapidly, whereas the added esters allow for a longer elimination time. The circled hydroxyl position is also where the enzymes mentioned in the above text cleave the ester from the molecule.

Once the ester is split from the testosterone molecule, we are left with 2 products. The main one that actually matters is the free testosterone, which is bioidentical to endogenous testosterone. This androgen is now free to bind to androgen receptors in various tissues. We also now have enanthic acid or cypionic acid (depending on ester used), and these are inert fatty acids that are rapidly oxidized via cellular metabolic pathways.

Hormonal effects on the body and development

Common injection frequencies include bi-weekly, weekly, and daily. Daily is less commonly used, but can provide us a positive benefit when it comes to maintaining the most stable serum levels possible. For people using TRT level doses, this is slightly less important, but the theory still applies. For people using supraphysiological doses, it is important to mitigate hormone fluctuation as much as possible, as an ideal scenario is balanced hormones, particularly when it comes to estradiol (e2). The reason we want balanced estradiol is due to the issues associated with both too high, and too low levels. High estradiol comes with issues such as low sex drive, low energy, and more. Two of the most common side effects that testosterone and androgen use in general is known for is mood swings and gyno. My opinion is that people's perception of steroid use is skewed by a misunderstanding that "roid rage"-like mood swings, gynecomastia, and acne is caused by the androgens themselves (with the exception of certain AAS that do indeed cause extreme mood swings). In reality it can be avoided with properly controlled e2, but this is a simple misunderstanding of the actual mechanisms that relate to this topic. Low e2 is a less common issue unless you are running a base-less cycle (a cycle with no aromatizing base compound to provide estradiol) or are using too much of an aromatase inhibitor (a compound that causes the aromatase enzyme that turns a portion of testosterone into estradiol to kill itself). Low e2 issues include similar issues, such as low libido, mood swings, and brain fog. Gynecomastia is not an issue associated with low e2. Another issue that is misunderstood and less talked about outside of certain circles is the risk of premature growth plate closure from using androgens during developmental years. This is also blamed solely on AAS (anabolic-androgenic steroids) rather than the root cause, which is estrogen. The primary factor in the body that signals the cartilage in the epiphyseal plate to close is estrogen. This causes the cartilage to mature into solid bone (epiphyseal closure). It does so through a few mechanisms, including estrogen receptor binding within the growth plate; the primary receptor that it does so with is located across various cell layers of the growth plate, and is known as Estrogen Receptor-alpha (ER***α***). The irreversible exhaustion/depletion of progenitor cells that reside in the resting zone of the epiphyseal plate is triggered (progenitor cells are slowly cycling stem cell descendants that drive longitudinal bone growth by feeding into the rapidly dividing proliferative zone). The senescent decline of chondrocytes (these also drive the bone lengthening during development, through cell division, then enlargement, and then calcification) is sped up through estrogenic mechanisms. As this pool of active growth starts to run out, ossification takes over. The cartilage matrix is replaced by solid bone tissue, and the plate fuses into a solid line. This brings into question androgen use in puberty and how it causes premature growth plate closure if not approached intelligently. Excess estradiol that causes this early closure can be avoided, theoretically, with non-aromatizing compounds. A base-less cycle would

theoretically avoid this issue, but crushing e2 during development may have adverse effects. Estradiol appears to shape the developing brain in many ways, from synaptic growth to chemical balance. There is evidence that it promotes the creation, rearrangement, and the fine tuning of connections between neurons in development. Estradiol plays a role in building the architecture on a cellular level necessary for learning and memory. The role played by estradiol in regional maturation of the brain seems to be similar to a clock, and when e2 is crushed during development, the timeline has the potential of being skewed. This may lead to altered regional volumes, and asymmetrical maturation in certain brain areas. E2 also appears to play a role in white v.s. grey matter volume, and can subsequently be disrupted by being crushed. Ultimately, to avoid these issues, hypothetically you would need to design a protocol that allows for reaching maximum height potential, but also mitigates irregular brain development.



Growth plate xray visual (wrist)
In the xray on the left we can see the epiphyseal plate (the dark line separating the epiphysis from the metaphysis) is completely gone, having been replaced by the solid white line of fused bone.

How can we avoid these issues? One is ensuring that we have our estradiol balanced in a middle range. This range varies by individual, as some people naturally have a higher or lower ideal e2 range. How do we find out what our e2 sits at? We use bloodwork to evaluate, specifically a high-sensitivity estradiol (e2) test. In my opinion bloodwork is a non-negotiable tool for risk mitigation when using anabolic-androgenic steroids, and should be taken both before, during, and after a cycle for the valuable information it provides. Ideally bloodwork should be taken as often as you can afford, as the more data you have the more you can understand your personal biology, and how you react to different compounds. This is also a main tool for compound selection long term, some people do better with different compounds than others do. This is part of my personal approach, which is a holistic approach to enhancement, meaning

looking at the whole system and how different sub-systems in our body interact and balance each other.

Daily injection frequency

One way that we can avoid hormone fluctuations on top of pharma intervention (leveraging things such as aromatase inhibitors or Equipoise) is our injection frequency. For this theory, let's propose that someone was using 250mg of testosterone enanthate per week. Weekly injection would be 250mg, biweekly would be roughly 120-125mg every 3 days, and daily would be 35mg per day. Pharmacokinetically with a weekly injection, we would see a large spike and gradual decline that reached its bottom near day 6. With biweekly, we would see essentially the same, but slightly less of a spike, but still a gradual decline that bottoms out before the next injection. The least fluctuation in this scenario would be found with the highest injection frequency, which is daily.

The image above shows a visual representation of serum testosterone levels with different frequencies for testosterone injections. As you can see the least fluctuation is found with daily dosing.

When serum testosterone levels fluctuate, downstream hormones such as estradiol follow a similar curve. Daily injections give you a more stable and predictable hormone profile in your body. Ideally when you are on a cycle trying to put yourself in a higher level of anabolic state, there are variables you can control and variables you can't. One of these variables is predictability in your androgen use and therefore, the effect in your body. This is why I personally advocate for everyone to do daily injections rather than a lower frequency, as it seems to be the optimal option.