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Testosterone, an endogenous androgenic hormone, is commonly supplemented exogenously in patients, and the number of patients being treated with exogenous testosterone has only grown in recent years. Reports indicate an increase in testosterone therapy prescriptions of 350% between 2001 and 2011 and the number of prescribers writing for testosterone prescriptions increased 8.8% annually from 2016 to 2019.1,2 To cater to this increasing demand, there are a wide variety of commercially available FDA approved products for testosterone supplementation including transdermal gels, oral in-oil capsules, buccal tablets, injections, nasal gels, and transdermal patches among others. Despite the wide variety of options, compounded formulations are sometimes necessary, perhaps due to allergies to certain excipients or difficulty achieving the correct dose with a commercially available product. Additionally, there are currently no FDA approved products for testosterone therapy in women, often resulting in a need for compounding to achieve the correct dose in female patients.3 Despite the many commercially available products via different routes of administration, there is limited information on the best way to assist patients who must switch from one route of administration to another in terms of how to convert dosages, when to implement testing, and what the pros and cons are of various routes of administration. In this blog we discuss some of the reasons patients may switch between routes of administration, and how we might assist practitioners with identifying a reasonable starting dose for patients who are switching.

Why Switch Between Routes?

There are a multitude of reasons a patient may need to switch from one form of testosterone supplementation to another. Patient preference certainly plays a role, for example, patients who experience pain on injection

may prefer a transdermal route of administration, or patients with gum or mouth irritation upon using buccal dosage forms may prefer a switch to an oral option or to a transdermal option. Some patients may also have a lack of success with one method as compared to another, for example, patients applying transdermal testosterone may struggle with transference, issues with compliance given recommended rotation schedule application, or issues with absorption impacting the efficacy of therapy.4,5 Patients taking buccal testosterone may struggle to use the dosage form ideally and may swallow a relatively large portion of the testosterone, resulting in compromised bioavailability via this route. Another potential contributing factor is the adverse event profile.

Despite their popularity, testosterone injections have been associated with increased risk of cardiovascular events, hospitalizations, and deaths compared with other forms of testosterone supplementation such as transdermal gels.6 Studies have also noted that short acting testosterone injections are associated with greater risk of erythrocytosis evidenced by elevated hemoglobin and hematocrit. One comparison of injectable testosterone esters found a much higher rate of erythrocytosis with testosterone enanthate and cypionate as compared to longer acting forms like testosterone undecanoate or transdermal or oral testosterone replacement options.7 Other studies comparing the impact of testosterone gels, injections, and pellets on hemoglobin and hematocrit found significantly higher hemoglobin and hematocrit with injections as compared to transdermal gels or subcutaneous pellets.8 This elevation in hematocrit is significant as it is associated with increased risk of major cardiovascular events.9 Though the reason for these differences has not been fully elucidated, one study hypothesized that the impacts on hemoglobin and hematocrit are more significant with high transient testosterone spikes associated with injectable testosterone, leading to an exacerbated impact of injectable testosterone esters on these parameters.10

Pharmacokinetic profile can impact a patient's choice of therapy as well. Comparisons of the pharmacokinetic profile of testosterone injection, patch, implant, oral, buccal, nasal, and transdermal gel use reveal that between these various routes of administration, transdermal options appear to have the smoothest pharmacokinetic profile (smallest gap between peaks and troughs once steady state is reached).11,12 Though testosterone endogenously follows a cycle of diurnal variation, with highest levels in the morning and lowest values in the afternoon and early evening, the pharmacokinetic profile provided by testosterone supplementation options with a high Cmax, such as IM injection, exceed the ranges seen with typical diurnal variation and are not good mimics of this natural variation in daily testosterone levels.13

How to Switch Between Routes?

For patients who desire a switch due to one or more of the above reasons, finding the ideal dose can be a challenge. Oftentimes, dosage adjustment is needed after switching routes of administration, and monitoring to verify patients are in safe and effective therapeutic ranges is often recommended with these switches.14 When selecting a starting dose for a new route of administration for a patient who desires to switch therapies but was already within an acceptable range per testosterone levels and symptomatic control, we can use bioavailability estimates as a starting point for selecting a dose.

Oral testosterone bioavailability varies depending on the form in question. Bioavailability of testosterone micronized orally is low and highly variable, with estimates putting it at 3.56 +/-2.45%, with testosterone undecanoate having higher bioavailability at 6.83 +/- 3.32%, and methyltestosterone having the highest bioavailability at around 70%.15,16 It should be noted that this superior bioavailability of methyltestosterone due to avoiding first pass metabolism is associated with increased hepatotoxicity, whereas regular oral micronized testosterone and testosterone undecanoate salt, though they are significantly less bioavailable via the oral route, are not anticipated to present significant hepatotoxicity.17

Information on buccal testosterone bioavailability is limited, with some animal studies estimates putting bioavailability around 14.1%.18 Though different pharmacokinetic profiles should be considered as well, we can see this reflected in starting dosing of commercially available products. Testosterone undecanoate minimum starting dose per the package insert is 158mg testosterone undecanoate (~100mg as testosterone)

twice daily, whereas buccal dosing per the commercially available Striant product starts at 30mg of testosterone twice daily.19,20 These dosing ranges (approximately 3x more testosterone undecanoate adjusted for amount as testosterone orally as compared to the buccal dose) are approximately in line with the range we would expect based on the bioavailability information in the literature.

Transdermal testosterone has a wider range of expected bioavailability, with estimates putting it between 9 to 14%.21 This can be further complicated by the influence of bioavailability at specific sites, for example, one study of testosterone gel applied to the abdomen as compared to the upper arms or shoulders found 30 to 40% lower bioavailability when applied to the abdomen as compared to the arms or shoulders.22 This bioavailability is not dissimilar from buccal use, though, unlike buccal use, transdermal testosterone is typically dosed just once daily. Though starting doses of commercially available testosterone transdermal gels vary, some such as AndroGel recommend a starting dose of 50mg testosterone per day,23 similar to the total daily dose of buccal testosterone (60mg of Striant) which is what we may expect based on the limited data we have on bioavailability via these two routes.

While exact bioavailability comparisons were not available in the literature, subcutaneous dosing and intramuscular dosing of testosterone via injection or pellet is thought to be very high. Testosterone pellets are typically dosed at 150 to 450mg every 3 to 6 months. The package insert estimates that patients receiving 50mg testosterone propionate via injection per week may be switched to 300mg total testosterone via subcutaneous pellet for a 3 month period (equivalent to about 25mg per week, though, note that the package insert states that 1/3rd of the pellet is thought to be absorbed during the first month, followed by just 1/4th in the second month and 1/6th in the third month).24

Given the wide range of variability that can occur with patient use, such as swallowing some of the dose impacting buccal bioavailability, or application related factors contributing to a wide range of transdermal bioavailability, patients may often need further adjustment, even when using bioavailability as a ballpark for dose conversion. Though bioavailability studies offer a way to compare testosterone supplementation via different routes, often monitoring is indicated. The timing of monitoring testosterone levels can vary depending on the route of administration the patient switches to. For example, instructions for testosterone transdermal products and monitoring vary, but some recommend checking serum testosterone levels 14 days after initiation of therapy with variable recommendations on whether to measure before or after application (given testosterone transdermal offers a smoother pharmacokinetic profile, though consistency is important, measuring prior to or 2 hours after a dose could be reasonable if done consistently). For buccal dosage forms, information suggests steady state may be reached quickly, and monitoring by taking levels immediately before the first dose in the morning even just one week after initiation may be reasonable. For testosterone injectable dosage forms such as cypionate, monitoring serum levels just 1 week after the first dose is sometimes recommended.12

Patients may desire to switch testosterone route of administration for a variety of reasons including preference, adverse events, or ease of use among other potential factors. When helping patients to find a starting point for a new route of administration, information on bioavailability from the literature can help to guide us initially, but follow up monitoring is often indicated as well.

Interested in compounding topical, transdermal, or vaginal testosterone? Check out our recent stability study published in the International Journal of Pharmaceutical Compounding (ijpc.com)

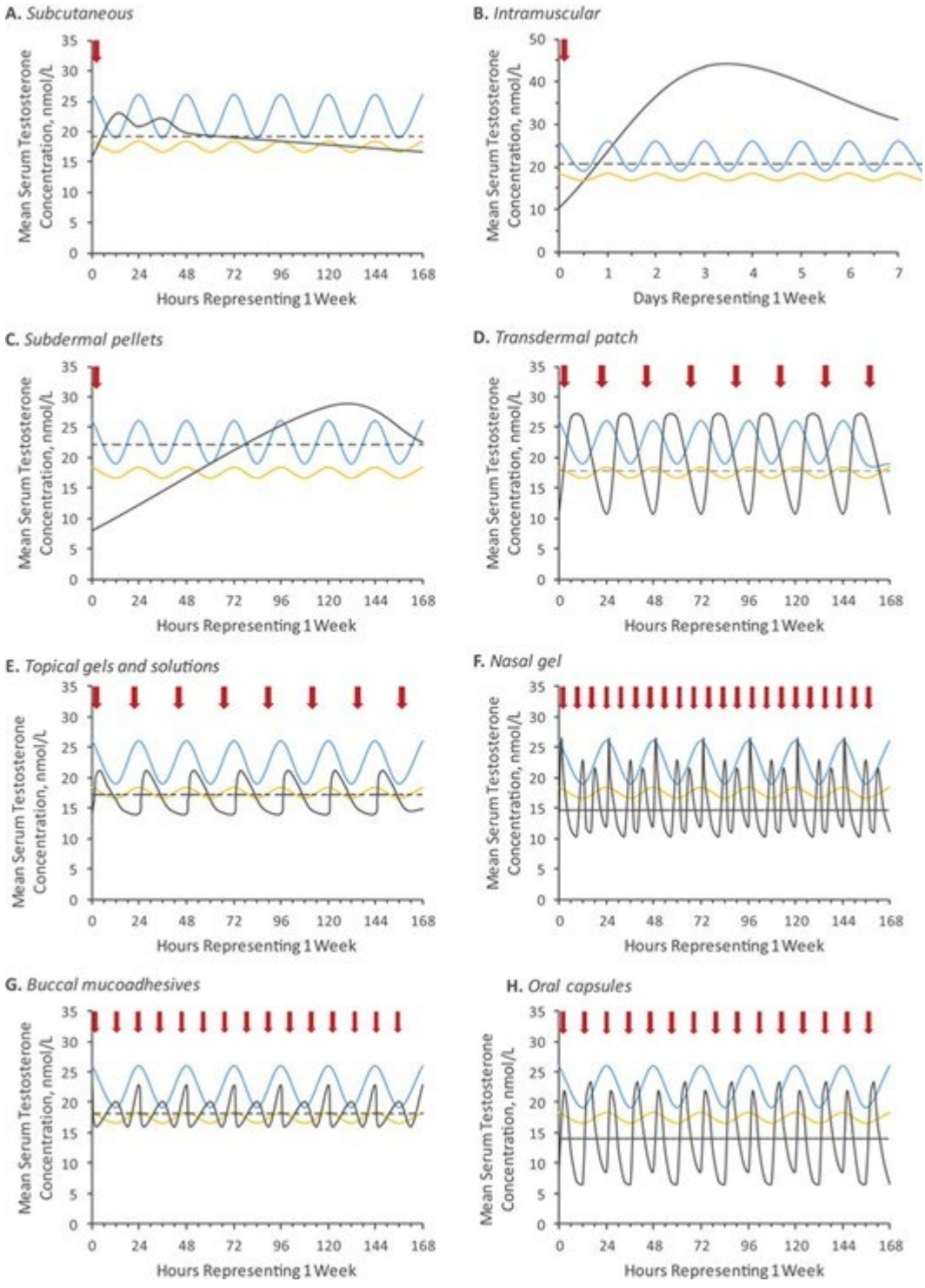

Figure from Pastuzak AW et al. [13], the black line represents pharmacokinetic profile of the dosage form on the Y-axis, the blue line is diurnal variation of young men between the ages of 23 and 28 years of age and the yellow line represents the diurnal variation of older men between the ages of 58-82 years of age.

References:

1. Zhou CK, Advani S, Chaloux M, et al. Trends and Patterns of Testosterone Therapy among U.S. Male Medicare Beneficiaries, 1999 to 2014. J Urol. 2020;203(6):1184-1190. doi:10.1097/JU.0000000000000744
2. Sellke N, Omil-Lima D, Sun HH, et al. Trends in testosterone prescription during the release of society guidelines. Int J Impot Res. 2024;36(4):380-384. doi:10.1038/s41443-023-00709-1
3. Donovitz GS. A Personal Prospective on Testosterone Therapy in Women-What We Know in 2022. J Pers Med. 2022;12(8):1194. Published 2022 Jul 22. doi:10.3390/jpm12081194
4. Rolf C, Knie U, Lemmnitz G, Nieschlag E. Interpersonal testosterone transfer after topical application of a newly developed testosterone gel preparation. Clin Endocrinol (Oxf). 2002;56(5):637-641. doi:10.1046/j.1365-2265.2002.01529.x
5. Lakshman KM, Basaria S. Safety and efficacy of testosterone gel in the treatment of male hypogonadism. Clin Interv Aging. 2009;4:397-412. doi:10.2147/cia.s4466
6. Layton JB, Meier CR, Sharpless JL, Stürmer T, Jick SS, Brookhart MA. Comparative Safety of Testosterone Dosage Forms. JAMA Intern Med. 2015;175(7):1187–1196. doi:10.1001/jamainternmed.2015.1573
7. Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis following testosterone therapy. Sex med rev. 2018; 6(1):77-85.
8. Pastuszak AW, Gomez LP, Scovell JM, Khera M, Lamb DJ, Lipshultz LI. Comparison of the Effects of Testosterone Gels, Injections, and Pellets on Serum Hormones, Erythrocytosis, Lipids, and Prostate-Specific Antigen. Sex Med. 2015 Sep;3(3):165-73. doi: 10.1002/sm2.76. Epub 2015 Aug 12. PMID: 26468380; PMCID: PMC4599554.
9. Kohn TP, Agrawal P, Ory J, Hare JM, Ramasamy R. Rises in Hematocrit Are Associated With an Increased Risk of Major Adverse Cardiovascular Events in Men Starting Testosterone Therapy: A Retrospective Cohort Claims Database Analysis. Journal of Urology [Internet]. 2024 Feb 1 [cited 2024 Jul 30];211(2):285–93. Available from: https://doi.org/10.1097/JU.0000000000003786
10. Coviello AD, Kaplan B, Lakshman KM, Chen T, Singh AB, Bhasin S. Effects of graded doses of testosterone on erythropoiesis in healthy young and older men. J Clin Endocrinol Metab. 2008 Mar;93(3):914-9. doi: 10.1210/jc.2007-1692. Epub 2007 Dec 26. PMID: 18160461; PMCID: PMC2266950.
11. Kalinchenko, S., Tyuzikov, I., Mskhalaya, G., Tishova, Y. (2023). Testosterone Therapy: Oral Androgens. In: Hohl, A. (eds) Testosterone. Springer, Cham. https://doi.org/10.1007/978-3-031-31501-5_13
12. Shoskes JJ, Wilson MK, Spinner ML. Pharmacology of testosterone replacement therapy preparations. Transl Androl Urol. 2016;5(6):834-843. doi:10.21037/tau.2016.07.10
13. Pastuszak AW, Gittelman M, Tursi JP, Jaffe JS, Schofield D, Miner MM. Pharmacokinetics of testosterone therapies in relation to diurnal variation of serum testosterone levels as men age. Andrology. 2022;10(2):209-222. doi:10.1111/andr.13108
14. Petering RC, Brooks NA. Testosterone Therapy: Review of Clinical Applications [published correction appears in Am Fam Physician. 2019 Oct 1;100(7):393.]. Am Fam Physician. 2017;96(7):441-449.
15. Schroder T, Dusterberg B, Matthes H. Absolute bioavailability of testosterone after oral administration of tesotsterone undecanoate and testosterone. European Journal of Drug Metabolism and Pharmacokinetics; 1986; 11(2): 145-149.
16. Thomas L. Lemke; David A. Williams (24 January 2012). Foye's Principles of Medicinal Chemistry. Lippincott Williams & Wilkins. pp. 1360–. ISBN 978-1-60913-345-0.
17. Schroder T, Dusterberg B, Matthes H. Absolute bioavailability of testosterone after oral administration of tesotsterone undecanoate and testosterone. European Journal of Drug Metabolism and Pharmacokinetics; 1986; 11(2): 145-149.
18. Schroder T, Dusterberg B, Matthes H. Absolute bioavailability of testosterone after oral administration of tesotsterone undecanoate and testosterone. European Journal of Drug Metabolism and Pharmacokinetics; 1986; 11(2): 145-149.
19. Jatenzo (testosterone undecanoate) [package insert]. Fort Collins, CO. Tolmar Inc. 2023.
20. Striant (testosterone) [package insert]. Austin, TX. PharmaForm LLC. 2009.

21. Swerdloff RS, Wang C, Cunningham G, et al. Long-term pharmacokinetics of transdermal testosterone gel in hypogonadal men. J Clin Endocrinol Metab. 2000;85(12):4500-4510. doi:10.1210/jcem.85.12.7045
22. Miller J, Britto M, Fitzpatrick S et al. Pharmacokinetics and relative bioavailability of absorbed testosterone after administration of a 1.62% testosterone gel to different application sites in men with hypogonadism. Endocrine Practice. 2011; 17(4): P574-583.
23. AndroGel (testosterone) [package insert]. Thousand Oaks, CA. Rebel Distributors Corp. 2010.
24. Testopel (testosterone) [package insert]. Malvern, PA. Endo USA Inc. 2024.

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