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Pharmacokinetics of testosterone after percutaneous gel or buccal administration

Cristin C. Slater, M.D., Irene Souter, M.D., Chunying Zhang, M.D., Chaxiang Guan, M.D., Frank Z. Stanczyk, Ph.D., and Daniel R. Mishell, Jr., M.D.

Department of Obstetrics and Gynecology, University of Southern California, Keck School of Medicine, Los Angeles, California

Objective: To determine the pharmacokinetics of testosterone following its administration using transdermal gel or buccal lozenges.

Design: Pilot study.

Setting: University-based hospital.

Patient(s): Ten bilaterally oophorectomized women.

Intervention(s): Daily micronized testosterone gel (1 mg) and testosterone propionate lozenge (1 mg).

Main Outcome Measure(s): Total testosterone, androstenedione, dihydrotestosterone, 3α–androstanediol glucuronide, and sex hormone–binding globulin were measured in serum by specific radioimmunoassays; free testosterone levels were also calculated.

Result(s): Before treatment, serum testosterone levels in the groups using the lozenge and gel were 16 ± 4.0 and 20 ± 6.0 ng/dL, respectively. Mean maximum testosterone levels obtained with the lozenge occurred 1 hour after administration on days 1 (692 ± 236 ng/dL) and 14 (836 ± 309 ng/dL) of treatment and fell precipitously thereafter. In contrast, testosterone levels obtained with the gel showed a prolonged rise reaching maximal levels of 97 ± 78 and 100 ± 60 ng/dL after 18 hours. The serum level patterns of free testosterone, dihydrotestosterone, and 3α–androstanediol glucuronide were similar to the corresponding total testosterone levels.

Conclusion(s): Administration of testosterone lozenge by buccal absorption produced a rapid and brief elevation of testosterone levels, with levels reaching upper limits of the male range. In contrast, transdermal testosterone gel absorption resulted in a prolonged elevation of testosterone levels, which were in the hyperandrogenic female range but resembled steady state pharmacokinetics. (Fertil Steril® 2001;76:32–7. ©2001 by American Society for Reproductive Medicine.)

Key Words: Postmenopausal testosterone replacement, transdermal testosterone gel, testosterone lozenge

Advanced age is associated with a significant decrease in the rate of production of androgens (1–5). Following menopause, there is a drop in the blood production rate of not only estrogens, but also of both the adrenal and ovarian androgens, namely, dehydroepiandrosterone (DHEA), DHEA sulfate (DHEAS), androstenedione, and testosterone. Approximate average total daily production rates for androstenedione and testosterone in premenopausal women are 3 mg/24 hours and 250 μg/24 hours, respectively, and in postmenopausal women they decrease to 1.5 mg/24 hours and 180 μg/24 hours, respectively (6). Total testosterone production decreases by approximately 28% after menopause (6). This decrement in daily production rate is largely accounted for by a decrease in testosterone production by nonovarian sources. The premenopausal ovary directly contributes 25% of daily testosterone production, whereas the postmenopausal ovary directly contributes 40% of the daily production of testosterone (7). This accounts for the 40%–50% decrease in circulating testosterone levels noted after removal of postmenopausal ovaries (5–8).

Menopausal estrogen replacement causes an increase in sex hormone–binding globulin (SHBG), which reduces the amount of circulating, bioavailable free testosterone. Thus, estrogen replacement after menopause, particularly after surgical menopause, is probably not an adequate total hormonal replacement.

Possible effects of decreased testosterone include osteoporosis, loss of energy, muscle wasting, and depression, in addition to de-

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Reprint requests: Cristin C. Slater, M.D., 1240 North Mission Road, room 8K-9, Los Angeles, California 90033 (FAX: 323-226-2850; E-mail: coulam@hsc.usc.edu).

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creased libido. Oral methyltestosterone is currently the most commonly prescribed testosterone replacement for women. However, there is concern about possible methyltestosterone-induced liver toxicity. Orally administered testosterone is degraded in the liver, and very little reaches the systemic circulation. Therefore, its absorption is erratic and inefficient and can adversely affect lipid profiles (9). In addition, oral testosterone decreases HDL cholesterol and increases LDL cholesterol (9). An ideal testosterone replacement therapy should achieve physiologic serum testosterone levels, while avoiding hepatic effects. New postmenopausal testosterone preparations with this goal have been marketed; however, there is a scarcity of data available on these formulations.

Transdermal testosterone gel and testosterone lozenges are compounded and sold in pharmacies in the United States. Little is known regarding the pharmacokinetics of these two androgen replacement therapies. Transdermal or buccal absorption avoids the first-pass effect of the liver and thus may be a more effective delivery mode than oral absorption. Thus, the objective of this pilot study was to determine the pharmacokinetics of testosterone administered either as buccal lozenges or transdermal gel in doses that are commonly prescribed for postmenopausal women. In addition, we studied the effects of testosterone administered by these routes on free testosterone, testosterone metabolites, and SHBG.

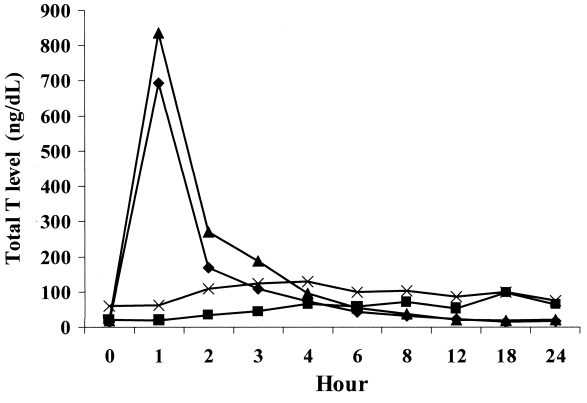
MATERIALS AND METHODS

Ten healthy postmenopausal women between the ages of 51 and 58 were studied in this pilot investigation. The Institutional Review Board approved this study, and informed consent was obtained from all of the subjects. All of the women had undergone bilateral oophorectomies in the past for benign indications. They had body mass indices between 26 and 29 and denied a history of any known endocrine diseases. Nine of the 10 women were taking estrogen replacement daily. The subjects were randomly assigned into two groups by drawing a sealed envelope. Group 1 (n = 5) applied 1 mg of micronized gel containing testosterone on the inner thigh. Group 2 (n = 5) applied one lozenge containing 1 mg testosterone propionate to the buccal mucosa. The study subjects took their designated dose of testosterone replacement daily at the same time each morning for 14 days.

Blood samples were collected at baseline (before the first testosterone dose) and at hours 1, 2, 3, 4, 6, 8, 12, 18, and 24 after starting treatment on days 1 and 14. The serum samples were then used for analysis of total testosterone, androstenedione, and dihydrotestosterone by radioimmunoassay after organic solvent extraction and Celite column partition chromatography of the analytes as described elsewhere (10–13). Then 3α–androstanediol glucuronide and SHBG were analyzed by highly specific direct radioimmunoassays (14, 15). Free testosterone was calculated by a validated computer algorithm (16). Area under the curve (AUC) was calculated using the trapezoidal method for each analyte measured on days 1 and 14 of treatment.

FIGURE 1

Mean serum total testosterone (T) levels on treatment days (D) 1 and 14. Subjects used one application daily of either 1 mg of micronized testosterone transdermal gel or 1 mg of testosterone propionate buccal lozenge. Blood samples were studied at hours 0 (before administration of testosterone), 1, 2, 3, 4, 6, 8, 12, 18, and 24. Diamond = lozenge D-1; square = gel D-1; triangle = lozenge D-14, X = gel D-14.



Slater. Postmenopausal testosterone replacement. Fertil Steril 2001.

RESULTS

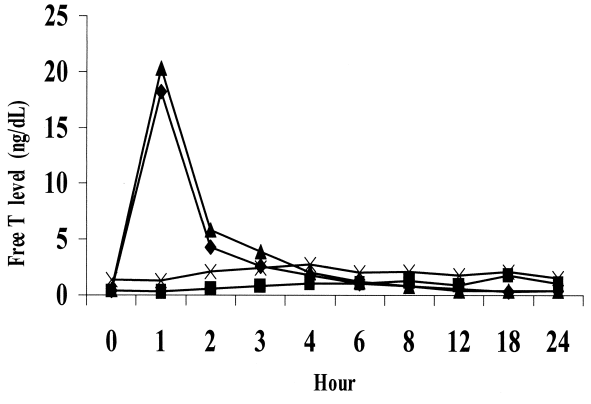
Figures 1–3 depict mean serum levels of total testosterone, free testosterone, and dihydrotestosterone measured in samples obtained on day 1 and day 14 following treatment with testosterone gel or testosterone lozenge.

Table 1 shows mean baseline (day 1) serum concentrations and day 1 and day 14 C_{max} concentrations, percentage increase of C_{max} from baseline concentration (day 1), and mean T_{max} for the analytes measured in both the testosterone gel and lozenge groups (day 1). The C_{max} concentration is the maximum concentration obtained after administration of testosterone supplement. T_{max} is the time, in hours, to reach maximum concentration after administration of testosterone supplement.

Maximum testosterone levels obtained on day 1 with the lozenge, ranged from 418 to 1,275 ng/dL and occurred 1 hour after administration, reaching the upper range of normal male levels (300–1,200 ng/dL). The levels fell precipitously thereafter. With regard to the testosterone gel, maximum testosterone levels on day 1 of treatment ranged from 36 to 331 ng/dL and occurred at 4–18 hours after administration. Testosterone levels on day 14 of treatment followed the same pattern as day 1 of treatment for both of the testosterone preparations studied. The patterns of serum levels of free

FIGURE 2

Mean serum free testosterone (T) levels on treatment days (D) 1 and 14. Subjects used one application daily of either 1 mg of micronized testosterone transdermal gel or 1 mg of testosterone propionate buccal lozenge. Blood samples were studied at hours 0 (before administration of testosterone), 1, 2, 3, 4, 6, 8, 12, 18, and 24. Diamond = lozenge D-1; square = gel D-1; triangle = lozenge D-14; X = gel D-14.



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testosterone (Fig. 2), dihydrotestosterone (Fig. 3), and 3α–androstanediol glucuronide were similar to the pattern of mean total serum testosterone level on both days of sampling in each treatment group. Higher androstenedione levels were reached with the lozenge (range = 0.27–1.1 ng/mL), compared with the gel (range = 0.27–0.86 ng/mL). The patterns of serum levels of androstenedione did not follow that of total testosterone, free testosterone, dihydrotestosterone, and 3α–androstanediol glucuronide. Thus, the testosterone formulation was preferentially converted to dihydrotestosterone over androstenedione. SHBG levels remained relatively constant during treatment days 1 and 14, with average values ranging from 26 to 57 nmol/L for both testosterone formulations.

FIGURE 3

Mean serum dihydrotestosterone levels on treatment days (D) 1 and 14. Subjects used one application daily of either 1 mg of micronized testosterone transdermal gel or 1 mg of testosterone propionate buccal lozenge. Blood samples were studied at hours 0 (before administration of testosterone), 1, 2, 3, 4, 6, 8, 12, 18, and 24. Diamond = lozenge D-1; square = gel D-1; triangle = lozenge D-14; X = gel D-14.

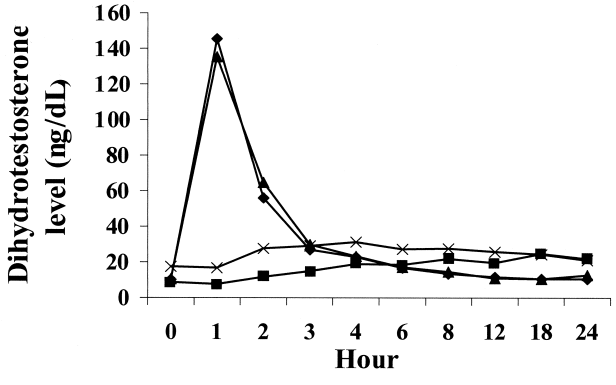

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Table 2 shows comparisons of mean AUC values between testosterone gel and testosterone lozenge for total testosterone, free testosterone, dihydrotestosterone, 3α–androstanediol glucuronide, and androstenedione on treatment days 1 and 14. AUC values increased on day 14 compared with day 1 for all androgens measured except androstenedione. The AUC on day 14 was higher with the testosterone gel compared with the buccal testosterone lozenge for total and free testosterone and dihydrotestosterone. Although the AUC values were higher with the gel, these values were not statistically significant. However, statistical significance is difficult to achieve with such a small sample size.

DISCUSSION

There are no known published reports evaluating the pharmacokinetics of buccal testosterone absorption in women. Studies of buccal testosterone absorption in men show results similar to those found in the present study: there is an acute rise in testosterone after administering a buccal testosterone tablet (17, 18). Both Kim et al. (17) and Dobs et al. (18) found that the maximal concentration of testosterone levels occurred at 30 minutes after transbuccal administration of testosterone, which is similar to our finding of a maximal increase in testosterone noted approximately 60 minutes after treatment. Since we did not collect a blood sample 30 minutes after dosing in this study, it is possible that we could have detected an earlier peak in testosterone level before 60 minutes if we had chosen an earlier sampling time point.

The data in this study, along with those of Kim et al. (17) and Dobs et al. (18), show that the pattern of free testosterone levels is similar to that of total testosterone. Kim et al. (17) found there was a 5.3-fold mean increase from baseline to peak free testosterone levels after buccal administration to eugonadal men of a tablet containing 10 mg of testosterone. This is in contrast to the 50-fold corresponding increase found in the present study using a lozenge containing 1 mg of testosterone. The larger increase to mean testosterone maximum in this study may be due to either absorption differences between a lozenge and a tablet and/or gender differences in absorption and metabolism of testosterone.

Dobs et al. (18) found that the total and free testosterone levels returned to baseline in 4–6 hours after transbuccal absorption of a tablet containing 10 mg testosterone, whereas

TABLE 1

Mean (± SD) baseline (day 1) and day 1 and day 14 C_{max}, % increase of C_{max} from baseline and T_{max} for androgens and sex hormone–binding globulin (SHBG) for testosterone lozenge (n = 5) and gel (n = 5) groups.

	Baseline		C_{max} (day 1)		C_{max} (day 14)		% Increase C_{max} from baseline (day 1)		T_{max} (day 1)	
Hormone	Gel	Lozenge	Gel	Lozenge	Gel	Lozenge	Gel	Lozenge	Gel	Lozenge
Total T (ng/dL)	20 ± 6.0	16 ± 4.0	96 ± 78	692 ± 236	130 ± 104	836 ± 309	380	4,225	18	1
Free T (ng/dL)	0.4 ± .20	0.4 ± 0.1	1.8 ± 1.2	1.8 ± 0.7	2.1 ± 1.8	2.0 ± 0.7	368	386	18	1
DHT (ng/dL)	9.0 ± 3.0	10 ± 3.0	25 ± 15	145 ± 63	31 ± 24	135 ± 69	183	1313	18	1
3 AG (ng/mL)	1.4 ± 0.8	1.4 ± 0.6	1.7 ± 1.1	4.3 ± 2.1	2.1 ± 1.7	4.7 ± 2.0	21	207	24	1
A (ng/mL)	0.7 ± 0.5	0.6 ± 0.1	0.7 ± 0.1	1.0 ± 0.2	0.6 ± 0.2	0.9 ± 0.2	−1.0	66	24	1
SHBG (nmol/L)	55 ± 29	29 ± 14	57 ± 29	31 ± 18	45 ± 26	40 ± 17	4.0	6.0	—	—

Note: A = androstenedione; DHT = dihydrotestosterone; 3 AG = 3α-androstanediol glucuronide.

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the data in this study show that although free testosterone levels decrease rapidly after 60 minutes, levels do not return to baseline until 12–18 hours after administration of the testosterone lozenge.

Because of the known effect of estrogens on SHBG levels, and because 9 of the 10 subjects in this study were taking estrogen therapy, it should be noted that our findings regarding the absolute free androgen levels apply only to oophorectomized women taking estrogen replacement therapy.

Transdermal testosterone delivery is commonly used for testosterone replacement in hypogonadal adult men, but there is a scarcity of published data regarding the pharmacokinetics of testosterone delivery by this route in women. Buckler et al. (19) studied a novel matrix/patch transdermal delivery system for testosterone in postmenopausal women. They report that serum testosterone levels rose rapidly after a single daily application and remained relatively constant for 18 hours. In that study, the mean peak level of testosterone with approximately 1.1 mg of daily testosterone administration was 118 ± 46 ng/dL, which fell to baseline levels 6 hours after patch removal. In contrast, the transdermal testosterone gel in this study maintained peak testosterone levels for up to 18 hours after application. Data from this study and the study by Buckler et al. (19) indicate that transdermal testosterone delivery appears to be an effective route to deliver physiologic levels of testosterone.

Large increases of total and free testosterone and dihydrotestosterone were found between baseline mean serum levels and C_{max} on day 1 of treatment with both the testosterone gel (380%, 386%, 183%) and testosterone lozenge (4,225%, 368%, 1,313%). Mean maximum testosterone values in the lozenge group reached male levels. In the gel group, the mean testosterone level remained in the hyperandrogenic female range.

Mean free testosterone values reached male levels with the lozenge, whereas they remained in the normal female range with the gel. Peak dihydrotestosterone and 3α–androstanediol glucuronide levels were above the male range for the lozenge group yet remained within the premenopausal female range in the gel group. The lozenge group had a 207% increase in serum 3α–androstanediol glucuronide lev-

TABLE 2

Mean (± SD) area under the curve after daily application of either 1 mg of transdermal micronized testosterone gel or buccal lozenge containing 1 mg testosterone propionate.

Hormone	Gel, day 1	Gel, day 14	Gel, % increase	Lozenge, day 1	Lozenge, day 14	Lozenge, % increase
Testosterone (ng/hr/dL)	1,580 ± 1,185	2,267 ± 1,393	43	1,518 ± 349	1,949 ± 629[a]	28
Free testosterone (ng/hr/dL)	28 ± 17	47 ± 30	68	38 ± 10	44 ± 11	16
Dihydrotestosterone (ng/hr/dL)	484 ± 307	601 ± 364	24	494 ± 155	506 ± 171	2
3α-androstanediol glucuronide (ng/hr/mL)	30 ± 16	43 ± 30	43	46 ± 16	46 ± 23	0
Androstenedione (ng/hr/mL)	105 ± 22	101 ± 33	−4	133 ± 35	128 ± 46	−4

[a] P = .04.

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els at C_{max} on day 1, while the gel group had only a 21% increase in serum levels at C_{max} when compared with baseline levels.

Higher androstenedione levels were reached with the lozenge compared with the gel. Androstenedione levels, however, remained within premenopausal ranges for both the gel and the lozenge. Mean levels of SHBG remained physiologic and did not change during the individual treatment days after administration of either testosterone preparation.

The AUC for total and free testosterone increased between treatment days 1 and 14 for both the gel (43% and 68%, respectively) and the lozenge (28% and 16%, respectively). The change in AUC for total testosterone between treatment days 1 and 14 is statistically significant only in the testosterone lozenge group at ($P = .04$). The relatively large increases in the AUCs between days 1 and 14 are probably due to steady state conditions not being achieved until sometime between the two sampling periods.

The AUC for dihydrotestosterone and 3α–androstanediol glucuronide increased by 24% and 43%, respectively, from treatment day 1 to 14 for the gel group, whereas in the lozenge group, the AUC of dihydrotestosterone increased by only 2% and there was no change in the AUC of 3α–androstanediol glucuronide. The discrepancy between the transbuccal and transdermal groups with respect to the AUCs of dihydrotestosterone and 3α–androstanediol glucuronide is most likely due to the fact that the testosterone gel was applied on the skin and skin contains a high abundance of the enzyme, 5α-reductase. This enzyme transforms testosterone to dihydrotestosterone, which is subsequently converted to its distal metabolite, 3α–androstanediol glucuronide. It is now well established that 3α–androstanediol glucuronide correlates highly with 5α-reductase activity (20).

The AUCs on treatment day 14 for total testosterone and free testosterone and dihydrotestosterone were all greater in the testosterone gel group when compared with the testosterone lozenge group. Although these AUCs were greater in the gel group, statistical significance was not achieved. Statistical significance was not a focus of this pilot study because of the difficulty in achieving statistical significance with small sample sizes. The larger AUCs on treatment day 14 for total testosterone and free testosterone in the gel group when compared with the lozenge group results from the continuous, prolonged elevation in hormone levels throughout the 24-hour period after administration of the testosterone gel, but not the lozenge.

The mean serum total testosterone level before applying the testosterone gel on treatment day 14 was still elevated at 60 ng/dL, whereas the corresponding level in the lozenge group at that time was only 19 ng/dL.

As evidenced by these markedly increased hormone values, the commonly prescribed doses of 1 mg of micronized testosterone gel and 1 mg of buccal testosterone propionate appear to be excessive. Long-term studies are needed to determine if accumulation of these androgens occurs with prolonged administration and what, if any, adverse effects these androgen levels may have. It is possible that the degree of conversion of testosterone to dihydrotestosterone would have even been greater if the testosterone gel were placed onto the labia rather than on the inner thigh, since there is more 5α-reductase activity in the genital skin. Further long-term studies are also needed to determine the critical amount of testosterone that produces undesirable symptoms such as acne, hirsutism, and alopecia when it is prolonged indefinitely.

Testosterone supplementation has been used to treat diminished libido in postmenopausal women who have had breast cancer. A concern of prescribing physicians in this situation is the possibility that testosterone could be aromatized to estradiol and would elevate estrogen levels in these women. Our data revealed that estrogen levels did not appear elevated during this 2-week course of testosterone administration, where each woman was used as her own control.

In summary, lozenge administration of testosterone propionate (1 mg) by buccal absorption produced an acute elevation of serum testosterone levels reaching upper limits of the male testosterone range approximately 1 hour after administration. In contrast, transdermal gel absorption of testosterone (1 mg) resulted in a prolonged elevation of testosterone levels. Free testosterone, dihydrotestosterone, and 3α–androstanediol glucuronide were all elevated and followed the same pattern of serum levels as the corresponding testosterone levels. Androstenedione levels increased but remained within physiologic premenopausal levels. The larger AUC of dihydrotestosterone found with testosterone gel compared with the lozenge is not surprising because of the known abundance of 5α-reductase activity in the skin. These data suggest that testosterone gel is the preferable route of administration of testosterone because the gel provides prolonged levels of total testosterone. The commonly prescribed doses of 1 mg of micronized testosterone gel and 1 mg of buccal testosterone propionate appear to be excessive. However, further studies using different testosterone doses and their effects on metabolic parameters, e.g., lipids and lipoproteins, are required to achieve optimum androgen replacement for postmenopausal women.

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