Pharmacokinetics, safety and tolerability of three dosage regimens of buccal adhesive testosterone tablets in healthy men suppressed with leuprorelin

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Abstract

We used a randomised, double-blind, crossover design to evaluate the pharmacokinetics, safety and tolerability of three doses of buccal adhesive testosterone tablets (BATT). Twenty-four healthy men, whose endogenous testosterone was suppressed to $\leq$5·38 nmol/l with leuprorelin acetate, took BATT (10, 20 or 30 mg) daily for 10 days. There was a 4-day washout between treatments. Substantial testosterone absorption occurred from BATT, and mean serum testosterone, free testosterone and dihydrotestosterone (DHT) concentrations over 24 h showed circadian variation. Steady state was reached by day 5. Average 24-h concentrations for the three BATT doses were within the normal range for eugonadal men: testosterone 11·67–14·57 nmol/l, free testosterone 0·026–0·33 nmol/l and DHT 1·66–2·03 nmol/l. On all three doses, peak testosterone and free testosterone was reached 8–9 h after tablet application; DHT peaked about 1–2 h later, and declined more slowly. Hormone concentrations increased with BATT dose, but increases were less than dose-proportional. There was no evidence of testosterone accumulation. BATT was well tolerated.
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Introduction

Testosterone, the main circulating androgen in men, is secreted predominantly by the testes. Normal serum testosterone concentrations are 10·41–34·70 nmol/l, and show circadian variation with peak concentrations in the morning (Bremner *et al.* 1983, Place & Nichols 1991). In extragonadal tissues, circulating testosterone is enzymatically converted to dihydrotestosterone (DHT) by 5α-reductase.

The main indication for androgen replacement therapy in men is primary or secondary hypogonadism associated with a deficiency of endogenous testosterone (Bhasin 1992, Snyder *et al.* 2000). The restoration of testosterone concentrations to normal maintains or induces male secondary sexual characteristics, sexual behaviour, energy, mood and muscle development (Matsumoto 1994, Dobs *et al.* 1999, Wang *et al.* 2000*b*, Basaria & Dobs 2001). Various exogenous testosterone formulations have been developed, including injectable, oral and dermal preparations. Intramuscular injections often yield testosterone concentrations greatly above normal during the first few days after administration, and do not produce daily variation in testosterone concentrations (Behre *et al.* 1994, Matsumoto 1994, Dobs *et al.* 1999). Oral testosterone undecanoate, used in Europe, is a lipid-soluble preparation that is absorbed directly into the lymphatic system, thereby avoiding first-pass metabolism in the liver (Conway *et al.* 1988). However, because of the poor oral bioavailability of testosterone, the levels of circulating testosterone obtained with such treatment are unpredictable (Cantrill *et al.* 1984, Conway *et al.* 1988, Bagatelle & Bremner 1996). Transdermal delivery of testosterone, widely prescribed in the USA as either a patch or gel, can yield physiological concentrations of testosterone, and a circadian pattern close to that of healthy men (Meikle *et al.* 1996, Dobs *et al.* 1999). Transdermal patches often cause local skin reactions (Arver *et al.* 1997, Parker & Armitage 1999), and the scrotal patch produces very high concentrations of DHT, owing to high 5α-reductase activity in scrotal skin (Cunningham *et al.* 1989, Meikle *et al.* 1992). Testosterone gel causes only minimal skin irritation (Wang *et al.* 2000*a*), but it must be applied over a large surface area of skin (Wang *et al.* 2000*a*,*b*), and thus may not be acceptable to all patients.

In this study, we evaluated the pharmacokinetics, tolerability and safety of three dosage strengths of a buccal adhesive testosterone tablet (BATT), under development by Abbott Laboratories (Abbotts Park, IL, USA). Buccal administration 'bypasses' the liver and so avoids first-pass

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clearance (Dobs *et al.* 1998). To study BATT, we used a model of artificial hypogonadism in healthy men, by temporarily suppressing their endogenous testosterone secretion with a gonadotrophin-releasing hormone agonist, leuprorelin acetate (Linde *et al.* 1981, Frick & Aulitzky 1986, Leibenluft *et al.* 1997). We evaluated serum testosterone, free testosterone and DHT concentrations on 10, 20 and 30 mg BATT.

Materials and Methods

Subject population

Our subjects were twenty-four healthy men, aged 22–66 years (mean = 37·5 years; S.D. = 12·5 years), body mass index 21·1–31·8 kg/m^2 (mean = 25·2 kg/m^2; S.D. = 2·7 kg/m^2). Twenty-two subjects were Caucasian, one was Black and one was Asian. All were deemed healthy by medical history and examination, standard 12-lead electrocardiogram (ECG) and clinical laboratory tests, including morning serum testosterone. Mean testosterone concentration was 18·89 nmol/l (range 11·00–34·98).

The study complied with the Declaration of Helsinki and the protocol was approved by the local ethics committee. All subjects gave fully informed, written consent.

Study design

The study was a randomised, double-blind, three-way crossover comparison of multiple doses of identical tablets of BATT (10, 20 and 30 mg) in healthy men whose endogenous testosterone secretion had been suppressed with leuprorelin. It consisted of four consecutive phases: screening, baseline, treatment and follow-up. During the screening phase, subjects received two to three injections of 3·75 mg leuprorelin acetate (Wyeth, Maidenhead, Berks, UK), 3 weeks apart, to suppress their endogenous testosterone, and took androgen replacement therapy (oral testosterone undecanoate; Organon, Oss, The Netherlands). We measured their morning serum testosterone for 3 weeks, at 1-week intervals, starting 1 week after their second leuprorelin injection. Subjects stopped testosterone replacement therapy $\geq$48 h before we evaluated their serum testosterone. Those whose morning testosterone had fallen to $\leq$5·38 nmol/l were randomised, and entered the baseline and treatment phases of the study.

During the baseline phase (day −1), all subjects received one placebo tablet identical to the BATT tablets. The treatment phase consisted of three periods, during which we evaluated the pharmacokinetics, safety and tolerability of the BATT. The periods each lasted 10 days, and were separated by 4-day washouts. We gave all subjects a third injection of leuprorelin (3·5 mg) on day 10 of the first period, after the 24-h blood collection.

In the follow-up phase, which began 1 day after the last BATT dose, we measured subjects' morning serum testosterone every 2 weeks, until in the normal range. Subjects took oral testosterone undecanoate, but stopped taking it $\geq$48 h before we measured their serum testosterone.

BATT treatment

Subjects applied the BATT to the gingiva, in the region of the infranasal fossa, at 0800 h each day, for 10 consecutive days. They were asked to eat breakfast and brush their teeth before applying BATT, and to avoid drinking for 30 min afterwards.

Subjects were resident from 12 h before to 24 h after dosing, during the baseline phase, and on days 1 and 10 of each period. On days 5–9, subjects attended each morning for pre-dose blood samples, then applied BATT.

Hormone assays

We measured testosterone, free testosterone and DHT in serum samples taken at the following times: before dosing and 1·5, 3, 4, 5, 6, 8, 12, 15, 18 and 24 h after dosing on day −1 (baseline phase) and on days 1 and 10 of each period, before dosing on days 5–9 of each period.

Serum was separated and stored at −20 °C or below until assayed. Hormone concentrations were measured by validated, radioimmunological assays (RIA) using kits from Diagnostic Systems Laboratories, Inc. (Webster, TX, USA). Lower limits of quantitation were 0·35 nmol/l (testosterone), 0·001 nmol/l (free testosterone) and 0·09 nmol/l (DHT). Intra-assay and interassay coefficients of variation for all assays were <9% and <12% respectively.

RIA is not as good as equilibrium dialysis for measuring absolute concentrations of free testosterone. However, with respect to free testosterone, we were mainly concerned with relative concentrations on different doses of BATT, so we believe the method to be adequate for our purposes.

Pharmacokinetic analyses

For all BATT doses, we determined the following pharmacokinetic parameters of each hormone: maximum concentration (C_{max}), minimum concentration (C_{min}), time of maximum concentration (t_{max}), area under the concentration curve from 0 to 24 h ($AUC_{0–24}$), and time-average concentration (C_{avg}, equal to $AUC_{0–24}/24$).

In addition, we calculated baseline-adjusted pharmacokinetic parameters for each hormone, by subtracting the subject's baseline (day −1) serum concentrations from the corresponding concentrations on days 1 and 10. We obtained baseline-adjusted $AUC_{0–24}$ by deducting the subject's baseline $AUC_{0–24}$ from the observed $AUC_{0–24}$.

Lastly, we calculated free testosterone/testosterone and testosterone/DHT ratios, using the baseline-adjusted concentrations of each hormone.

Safety and tolerability assessments

We assessed BATT safety and tolerability by: dental assessment, ECG, vital signs, physical examination and laboratory safety tests before and after dosing, and by adverse events.

In addition, we examined the subject's gingiva and lip mucosa before and 12 h after BATT application, at baseline (day −1), and on days 1 and 10 of each treatment period. Subjects were also asked to assess tablet acceptability and tolerability.

Statistical analyses

Baseline-adjusted pharmacokinetic parameters of each hormone were used in all statistical analyses; C_{max} and $AUC_{0–24}$ were log transformed. Significance was evaluated at the level of $P<0·05$.

To test for dose proportionality, we did an analysis of variance (ANOVA) of the dose-normalised pharmacokinetic parameters of each hormone, using PROC GLM (SAS version 6·12; SAS Institute, Cary, NC, USA). To test for BATT accumulation, we compared t_{max}, C_{max} and $AUC_{0–24}$ of each hormone between days 1 and 10, by a linear mixed effect analysis using PROC MIXED (SAS Institute). Initial models contained fixed effects for sequence, period and dose, and carryover from the dose of the preceding period, and random effects for subject nested within sequence. If carryover effects were not significant, they were dropped from the model. The morning pre-dose concentrations of each hormone (C_{min}) were analysed in the same manner, to assess when steady state had been reached.

To investigate the possibility of an age effect on the pharmacokinetic parameters of each hormone, we did an additional ANOVA on the mean of each parameter for all three treatment periods, with fixed effects for age, body weight and sequence.

Safety and tolerability data were summarised by frequency counts or summary statistics, as appropriate; no formal statistical testing was done.

Results

Suppression of subjects with leuprorelin acetate

During the screening phase, subjects received 7·25–11·25 mg leuprorelin acetate over 4–6 weeks. Morning serum testosterone was suppressed to $\leq$5·38 nmol/l (mean=2·34; S.D.=1·60). During the follow-up phase, serum testosterone returned to the normal range in all subjects (10·41–34·70 nmol/l).

Pharmacokinetics of BATT

Mean serum testosterone, free testosterone and DHT concentrations over 24 h were similar on the three doses of BATT (Fig. 1). At steady state, all BATT doses produced an early increase in mean testosterone and free testosterone, with maximum concentrations about 8–9 h after tablet application, and a slow decline thereafter. DHT concentrations peaked about 2 h later, and declined more gradually, than those of testosterone and free testosterone.

Summary statistics of the baseline-adjusted pharmacokinetic parameters of each hormone are shown in Table 1. Mean pre-dose testosterone, free testosterone and DHT did not differ significantly between successive days, on days 5–9, indicating that steady state had been reached by day 5. At steady state, mean C_{max} and $AUC_{0–24}$ of each hormone increased with dose. However, dose-normalised, mean C_{max} and $AUC_{0–24}$ of each hormone were significantly lower in the 30 mg than in the 10 mg dose group, on both day 1 and day 10 ($P<0·001$). Thus, the increase in testosterone, free testosterone and DHT was less than dose-proportional.

In the 20 and 30 mg dose groups, mean C_{max} and $AUC_{0–24}$ of each hormone were higher on day 1 than on day 10, indicating that none of the hormones accumulated. Furthermore, mean t_{max} and dose-normalised $AUC_{0–24}$ of testosterone and free testosterone, and t_{max} of DHT, were significantly lower on day 10 than on day 1 ($P=0·02$ to $<0·001$). Age had no statistically significant effect on mean baseline-adjusted pharmacokinetic parameters of testosterone, free testosterone or DHT ($P=0·06$ to 0·96). Carryover effects were not significant in most of the statistical analyses.

C_{avg} of testosterone, free testosterone and DHT are shown in Fig. 2, with the associated normal ranges. Hormone concentrations were within the normal range in most subjects on all BATT doses. Free testosterone/testosterone ratios averaged about 0·02, on all BATT doses, and on placebo. On the 10 and 20 mg tablets, average testosterone/DHT ratios were between 4 and 14 during the 24 h after dosing, compared with 4 to 8 on placebo. However, on BATT (30 mg), average testosterone/DHT ratios fluctuated more widely with time, ranging between 3 and 23.

Although C_{avg} of testosterone was <34·70 nmol/l in all subjects, concentrations in some blood samples were supraphysiological. Testosterone concentrations were >41·64 nmol/l in at least one blood sample in three subjects on BATT (20 mg), and in five subjects on BATT (30 mg). DHT concentrations were >3·45 nmol/l in at least one blood sample in six, eleven and thirteen subjects on BATT (10, 20 and 30 mg) respectively. In most

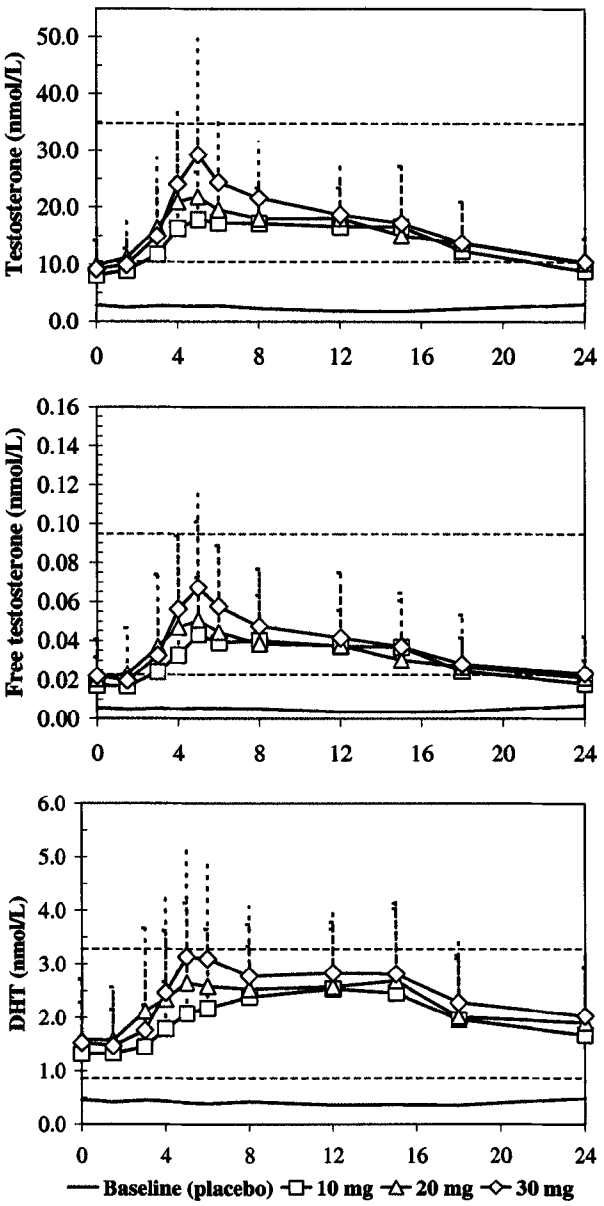

Figure 1 Mean, baseline-adjusted serum concentrations of testosterone, free testosterone and DHT on the three dose regimens of BATT over 24 h, at steady state (day 10 of dosing). Time (h) is on the x axis. Vertical broken lines are S.D. and horizontal broken lines represent normal ranges for eugonadal men (testosterone: 10·41–34·70 nmol/l; free testosterone: 0·023–0·095 nmol/l; DHT: 0·86–3·28 nmol/l).

subjects, such high hormone concentrations were observed at about two to four sampling times.

Safety and tolerability

There were no clinically significant changes in vital signs, physical examination, ECG or laboratory safety values. Minor adverse events were experienced by several subjects; however, none was considered to be related to treatment.

Localised hyperaemia at the BATT application site was noted in two subjects on day 10 of the last treatment period. Thirteen and twelve subjects reported local discomfort on BATT and placebo respectively; most subjects experienced that discomfort in the first treatment period.

Discussion

Leuprorelin successfully minimised fluctuations of endogenous testosterone and suppressed concentrations to $\leq$5·38 nmol/l in all subjects, so that exogenous hormone concentrations could be reliably measured with little interference from endogenous testosterone. A similar method has been used successfully to study transdermal testosterone (Rolf *et al.* 1999). However, endogenous testosterone secretion might have recovered partially before the end of the study. We minimised that possibility by giving an additional injection of leuprorelin, which suppresses testosterone for 4 weeks (Physician's Desk Reference 2000), at the end of the first treatment period. Morning testosterone was still below the lower limit of normal at first follow-up, although it returned to normal subsequently. Thus, we believe there was little interference from endogenous testosterone in our assessment of the performance of BATT.

The pharmacokinetic data showed that substantial testosterone absorption occurred after BATT administration in all twenty-four subjects. On all three dosage regimens, testosterone, free testosterone and DHT increased soon after tablet application, and remained above baseline for at least 24 h. By day 5, the first sampling day after the initial 24-h blood collection on day 1, steady state had already been reached. Therefore, it is likely that steady state was achieved soon after BATT was started. In contrast, testosterone replacement therapy with intramuscular injections or some transdermal patches may require several weeks of use before steady state is reached (Place & Nichols 1991, Yu *et al.* 1997).

Androgen replacement therapy in hypogonadal men seeks to provide near-physiological circulating concentrations of testosterone and its active metabolites, and to mimic the diurnal pattern seen in healthy men (Bhasin 1992, Snyder *et al.* 2000). On all three doses of BATT, 24-h average concentrations of testosterone, free testosterone and DHT were in the normal range in most subjects. Supraphysiological concentrations of testosterone occurred in only a few blood samples (<3% above 38·17 nmol/l, maximum=74·61 nmol/l) in some subjects on the 20 and 30 mg doses, and never reached the concentrations reported after intramuscular testosterone (Cunningham *et al.* 1989, Dobs *et al.* 1999). In addition, testosterone/DHT ratios were generally within the normal range

Table 1 Mean (S.D.) baseline-adjusted pharmacokinetic parameters for each hormone on 10, 20 and 30 mg BATT at steady state (day 10 of dosing)

	10 mg	20 mg	30 mg
Parameter			
Testosterone (nmol/l)			
AUC_{0-24}	279·96 (125·06)	315·60 (96·88)	349·81 (147·72)
C_{max}	23·28 (7·98)	27·62 (11·94)	32·20 (17·94)
C_{min}	3·57 (4·37)	3·33 (3·19)	3·33 (4·58)
t_{max}	9·5 (5·3)	9·1 (6·3)	8·2 (5·3)
Free testosterone (nmol/l)			
AUC_{0-24}	0·615 (0·347)	0·668 (0·254)	0·779 (0·396)
C_{max}	0·057 (0·029)	0·064 (0·035)	0·077 (0·045)
C_{min}	0·007 (0·009)	0·006 (0·006)	0·007 (0·009)
t_{max}	8·6 (4·7)	8·7 (5·9)	7·8 (4·9)
DHT (nmol/l)			
AUC_{0-24}	39·80 (21·17)	45·72 (20·32)	48·78 (21·17)
C_{max}	2·95 (1·30)	3·55 (1·50)	3·93 (1·71)
C_{min}	0·60 (0·71)	0·62 (0·51)	0·59 (0·70)
t_{max}	12·4 (6·4)	9·8 (6·9)	9·7 (5·9)

(Meikle *et al.* 1992), and fluctuated only modestly over 24 h on BATT (10 and 20 mg).

Hormone concentrations on BATT showed diurnal fluctuation, with steady-state testosterone and free testosterone concentrations peaking about 9 h after tablet application, and declining slowly thereafter. DHT concentrations peaked several hours later than did testosterone, and declined more slowly. Our results indicate that release and absorption of testosterone from BATT must continue for some hours after the tablet is applied. The later peak and slower decline of DHT concentrations have been reported with other testosterone replacement systems (Meikle *et al.* 1996, Dobs *et al.* 1998), and can be attributed to continued metabolite formation as testosterone declines, and to the somewhat longer half-life of DHT.

The mean concentrations of all three hormones increased with BATT dose, although that increase was less than dose-proportional. No accumulation of testosterone was noted with repeated doses of BATT. In fact, on all three doses, mean testosterone and free testosterone were lower at steady state than on day 1, suggesting that the rate of testosterone elimination might have increased, or bioavailability decreased, at steady state. There was large intersubject variability in the serum concentrations of each hormone, even after steady state had been reached and, in some subjects, hormone concentrations decreased with BATT dose. Studies of transdermal patches (Brocks *et al.* 1996) and of testosterone gel (Wang *et al.* 2000*a*) in hypogonadal men also show high variability among subjects, and failure of serum testosterone concentrations to increase with dose in some subjects.

Dobs *et al.* (1998), in their study of a different buccal testosterone preparation in thirteen hypogonadal men, noted diurnal fluctuations of testosterone, free testosterone and DHT concentrations, and found no evidence of hormone accumulation over time. However, although testosterone/DHT ratios were in the normal range, the authors observed much higher testosterone (mean C_{max}=96·81 vs 23·28 nmol/l) and DHT concentrations (mean C_{max}=3·79 vs 2·95 nmol/l) on a 10 mg dose than we did. Thus, BATT seems to yield more physiological concentrations of those hormones.

Studies of 100 mg testosterone gel report average 24-h testosterone concentrations at steady state that are roughly double those that we observed on the three BATT dosages (Wang *et al.* 2000*a*,*b*), and mean C_{min} that is much higher on gel than on BATT. Also, the ratio of mean peak:trough testosterone concentrations on gel was about 2, whereas on BATT it was about 10. However, it remains to be studied whether those differences have any clinical consequences.

Our results suggested that there is an upper limit to the rate of absorption of testosterone from BATT, across a given area of gingival mucosa: a smaller proportion of the testosterone content was absorbed from the higher doses of BATT than from the 10 mg tablet. Furthermore, there was no appreciable difference between the 20 mg and 30 mg dose groups with respect to C_{avg} of any hormone. If our results are indeed explained by rate-limited absorption across the gingival mucosa, then the proportion of dose that is absorbed might be improved by applying BATT over a wider area. Two × 10 mg tablets or two × 20 mg tablets, for example, might yield higher bioavailability than would single tablets containing the same dose.

BATT was well tolerated. As many subjects experienced discomfort from placebo as from BATT. Most subjects who reported discomfort did so during the first

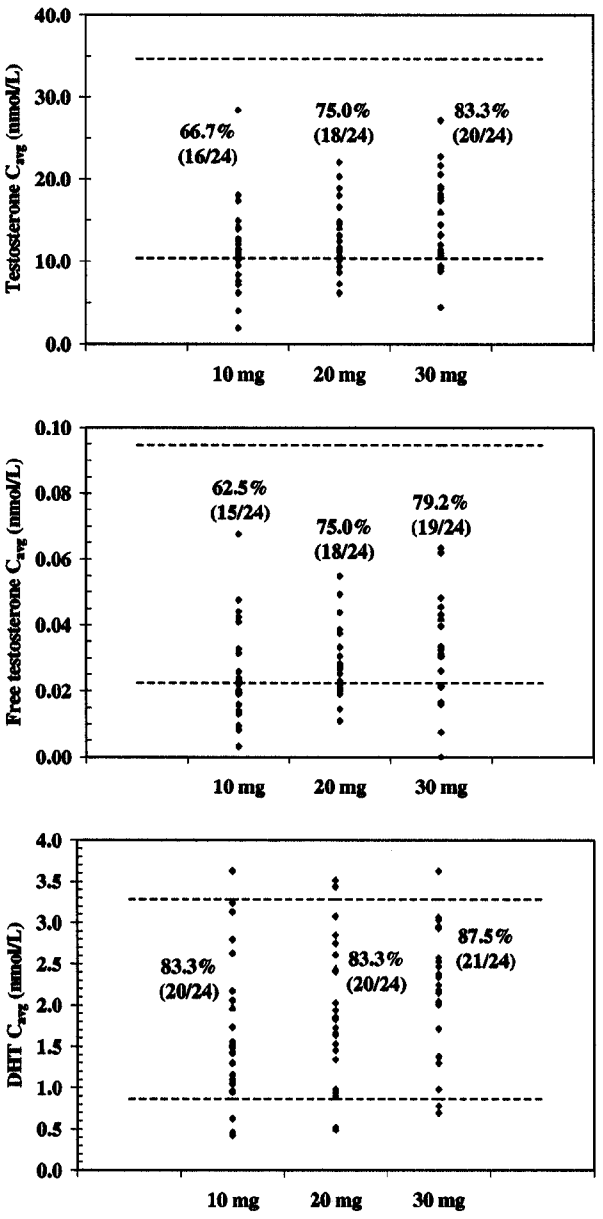

Figure 2 Baseline-adjusted 24 h average concentrations (C_{avg}) of each hormone on the three dose regimens of BATT (x axis), with the number and percentage of subjects in the normal range. All hormone concentrations are at steady state (day 10 of dosing). Broken lines represent normal ranges for eugonadal men.

treatment period only, suggesting that discomfort was due to unfamiliarity with the tablet.

In summary, physiological concentrations of testosterone, free testosterone and DHT were reached on all three doses of BATT, and a circadian rhythm in hormone concentrations was produced. Steady state was rapidly attained, and hormone levels quickly returned to baseline after tablet removal. Furthermore, BATT was well tolerated. Studies in hypogonadal men are warranted.

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