A novel delivery system has been developed for testosterone replacement. This formulation, COL-1621 (Striant), a testosterone-containing buccal mucoadhesive system, has been shown in preliminary studies to replace testosterone at physiological levels when used twice daily. Therefore, the current study compared the steady-state pharmacokinetics and tolerability of the buccal system with a testosterone-containing skin patch (Andropatch or Androderm) in an international multicenter study of a group of hypogonadal men.

Sixty-six patients were randomized into two groups; one applied the buccal system twice daily, whereas the other applied the transdermal patch daily, in each case for 7 d. Serum total testosterone and dihydrotestosterone concentrations were measured at d 1, 3 or 4, and 6, and serially over the last 24 h of the study. Pharmacokinetic parameters for each formulation were calculated, and the two groups were compared. The tolerability of both formulations was also evaluated.

Thirty-three patients were treated with the buccal preparation, and 34 were treated with the transdermal patch. The average serum testosterone concentration over 24 h showed a mean of 18.74 nmol/liter (SD = 5.90) in the buccal system group and 12.15 nmol/liter (SD = 5.55) in the transdermal patch group (P < 0.01). Of the patients treated with the buccal system, 97% had average steady-state testosterone concentrations within the physiological range (10.41–36.44 nmol/liter), whereas only 56% of the transdermal patch patients achieved physiological total testosterone concentrations (P < 0.001 between groups). Testosterone concentrations were within the physiological range in the buccal system group for a significantly greater portion of the 24-h treatment period than in the transdermal patch group (mean, 84.9% vs. 54.9%; P < 0.001). Testosterone/dihydrotestosterone ratios were physiological and similar in both groups. Few patients experienced major adverse effects from either treatment. No significant local tolerability problems were noted with the buccal system, other than a single patient withdrawal. We conclude that this buccal system is superior to the transdermal patch in achieving testosterone concentrations within the normal range. It may, therefore, be a valuable addition to the range of choices for testosterone replacement therapy. (J Clin Endocrinol Metab 89: 2039–2043, 2004)
disorders. Patient characteristics are shown in Table 1. Testosterone-deficient men with a morning (0900 h) serum testosterone less than 6.94 nmol/liter, normal age-related prostate-specific antigen levels, and hematocrit less than 50 were included in the study. Patients with an American Urological Association System Index for Prostatism score greater than 7 were excluded. After an appropriate washout period of their previous testosterone replacement (>6 months for implants, >4 wk for injections, and >1 wk for skin patches), patients had a baseline series of blood investigations performed (including alanine aminotransferase, γ-glutamyl transpeptidase, sodium, potassium, creatinine, total cholesterol, high-density lipoprotein, triglycerides, and glucose), a 12-lead electrocardiogram, blood count (including hemoglobin, hematocrit, white blood cell and differential count, and red blood cell count) and physical examination. If eligible for the study, they formally consented and then received either the buccal system (30 mg twice daily at 0800 and 2000 h) or the transdermal patch (5 mg once a day at 2200 h) in a randomized manner. Twice-daily blood samples were taken on d 3, 4, and 6, and multiple 24-h blood samples were taken on d 7 and 8. A follow-up visit with blood sampling occurred at 2–14 d after treatment was discontinued.

Twenty-nine of 33 patients in the buccal system group and 28 of 34 patients in the transdermal patch group completed the protocol without any protocol violations and were included in the efficacy analysis. Exclusion of these subjects did not influence the baseline population parameters. Four patients (12.1%) in the buccal system group and six patients (17.6%) in the transdermal patch group had a major protocol violation leading to exclusion of their data from the analysis. The most common violation was patients taking a disallowed medication (testosterone product) during the study (three patients in the buccal system group and five patients in the transdermal patch group). One patient in the buccal system group withdrew from the study after receiving 2 d of treatment and so did not provide any efficacy data for the primary endpoint, and one patient in the transdermal patch group violated the exclusion criterion regarding hematocrit (>50). No additional violations occurred that could potentially influence the interpretation of the efficacy data. Analysis on the basis of intention-to-treat analysis produced small changes in actual numbers but did not influence the overall significance of the data.

Serum was assayed for total testosterone [IMMULITE, Diagnostic Products Corp., Los Angeles, CA (11); normal range, 10.41–36.44 nmol/liter], dihydrotestosterone (DHT) (RIA with extraction, Esoterix, San Diego, CA; normal range, 1.03–2.92 nmol/liter), estradiol [IMMULITE, Diagnostic Products Corp.; normal range (male) <0.21 nmol/liter], FSH, LH, SHBG, full blood count, and liver function tests (Nova-Medical, Diego, CA; normal range, 1.03–2.92 nmol/liter), estradiol [IMMULITE, Diagnostic Products Corp.; normal range (male) <0.21 nmol/liter], FSH, LH, SHBG, full blood count, and liver function tests (Nova-Medical, Medi-Lab, Copenhagen, Denmark).

In each center, the appropriate ethical committee approval was sought and obtained before any patient was initiated into the trial, and all patients provided written informed consent.

**Table 1. Patient characteristics**

<table>
<thead>
<tr>
<th></th>
<th>Buccal system</th>
<th>Transdermal patch</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>33</td>
<td>34</td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>48.2 (12.1)</td>
<td>50.3 (14.8)</td>
</tr>
<tr>
<td>Body mass index [mean (SD)]</td>
<td>27.4 (2.4)</td>
<td>27.0 (3.7)</td>
</tr>
<tr>
<td>Etiology of testosterone deficiency</td>
<td>5 (15.2%)</td>
<td>9 (26.5%)</td>
</tr>
<tr>
<td>Primary</td>
<td>Secondary</td>
<td>26 (78.8%)</td>
</tr>
<tr>
<td>Percentage of time that serum concentrations were within the physiological range of 10.41–36.44 nmol/liter over the 24-h sampling period (%T24dur)</td>
<td>5 (15.2%)</td>
<td>26 (78.8%)</td>
</tr>
<tr>
<td>Percentage of time that serum concentrations were above 10.41 nmol/liter over the 24-h sampling period (%T24above)</td>
<td>26 (78.8%)</td>
<td>26 (78.8%)</td>
</tr>
<tr>
<td>Percentage of reportable total testosterone serum concentrations within the physiological range over the 24-h sampling period (%T24phys)</td>
<td>5 (15.2%)</td>
<td>26 (78.8%)</td>
</tr>
</tbody>
</table>

**Pharmacokinetic analysis**

Concentration vs. time data were summarized by noncompartmental estimation methods using the PK software program WinNonlin Professional (versions 3.1 and 3.2) (Pharsight, Mountain View, CA). The following pharmacokinetic parameters were analyzed:

- Maximum observed serum concentration (Cmax0–24h)
- Time-averaged steady-state serum concentration (Cavg0–24h)
- Minimum observed serum concentration (Cmin0–24h)
- Area under the serum concentration-time curve (AUC0–24h)
- Area under the curve (AUC0–24h). The area under the curve (AUC) was calculated by the trapezoidal method. Missing data were calculated by interpolation. For the AUC calculations only, missing values were calculated by interpolation; otherwise, if blood samples were missing, concentrations were not reported. If a serum concentration was less than the lower limit of quantification of the assay, it was deleted from the AUC calculation, except for the predose concentration at time 0 (t0) where a value of zero was assigned. Average concentration over a particular sampling interval for the buccal system and for the transdermal patch was calculated as: Cavg (t1 – t2) = AUCHt1 – t2/(t2 – t1), where t2 = 12 h and t1 = 0 h for the first 12-h sampling period, t2 = 24 h and t1 = 12 h for the second 12-h sampling period, and t2 = 24 h and t1 = 0 h for the 24-h sampling period.

**Statistical analysis**

Sample size estimation was performed on the basis of the following assumptions on the mean testosterone levels in steady state: average control mean total testosterone level was assumed to be 17.35 nmol/liter (sd = 34%) and of the buccal system 19.09 nmol/liter (sd = 12%). Because mean serum concentrations less than 10.41 nmol/liter define testosterone deficiency, the effect size (d) of the control treatment vs. no treatment was estimated to be 6.94 nmol/liter. The noninferiority margin δ = d was set to 2/3d(δ) = 4.65 nmol/liter. According to appropriate guidelines on statistics in clinical trials, the α-level for this one-sided comparison was set to 0.025. The power of the test (1 – β) was required to be 80%.

Sample size N per group was estimated using the following formula:

\[
N = 2 \left[\frac{z_{\alpha} + z_{1–\beta}}{sd} \right]^2 = 2 \left[\frac{z_{0.025} + z_{0.0}}{sd/4.65} \right]^2
\]

where \(z_{0.025} \) and \(z_{0.0} \) denote the 100 × (1 – α) % and the 100 × (1 – 0.8) % points of the standard normal distribution, respectively. Because the sd of difference is not known a priori, calculations were made for different values of sd varying from 0.69 to 5.90 nmol/liter. As a conservative assumption, it is assumed that sd will not exceed 5.90 nmol/liter; therefore, a sample size of 26 patients per group would be required.

The noninferiority lower limit has been set to be above 80% for the ratio of least-squares geometric means, rather than above 4.65 nmol/liter for the difference between means. Ninety percent confidence intervals (CIs) for the originally planned difference between nontransformed means and the protocol-specified 95% CIs were also calculated.

The primary analysis, noninferiority, and the secondary analysis, superiority of the buccal system vs. the transdermal patch was calculated on the same endpoint by ANOVA using 95% CIs. Fisher’s exact test, mean and sd, or median and minima and maxima were used as appropriate.
An analysis was performed to assess the homogeneity of the treatment effects across centers by the inclusion of a treatment by center interaction term in the ANOVA model for the primary analysis. This term was not statistically significant and was therefore not included in the model. Hence, conclusions can be made consistently across all centers. The statistical package SAS (version 8.2; SAS Institute, Cary, NC) was used. Significance was taken at $P < 0.05$.

**Results**

Since the primary analysis, noninferiority, was met, these results focus on the secondary analysis, superiority. Use of the buccal system resulted in a steady maintained level of serum total testosterone in subjects that was generally in the normal range throughout (Fig. 1). Mean testosterone levels on d 7 and 8 are shown in Fig. 2. In the buccal system group, the mean concentrations at all time points were within the physiological range. By contrast, in the transdermal patch group, mean concentrations at five timepoints were outside of the physiological range. For both mean (0–24 h) and minimum testosterone levels, the proportion of patients with values outside the physiological range was lower in the buccal system group than in the transdermal patch group, the differences being statistically significant ($P < 0.001$ for both). For peak testosterone levels, the proportion of patients with values outside the physiological range was higher in the buccal system group, although this was not statistically significant. The serum testosterone concentrations over the 24-h period were higher for patients receiving the buccal system than for patients in the transdermal patch group (mean AUC ± SD, 451.31 ± 140.71 h*nmol/liter vs. 304.63 ± 134.46 h*nmol/liter; 95% CI 1.25, 1.91; $P < 0.00001$). For the buccal system group, the mean maximum 24-h testosterone (31.58 nmol/liter) and the mean minimum 24-h testosterone (11.10 nmol/liter) values were within the physiological range. For the transdermal patch group, the mean maximum 24-h testosterone levels (20.68 nmol/liter) were within the physiological range, but the mean minimum 24-h testosterone levels (5.76 nmol/liter) were below the physiological range. The concentration ratios for the buccal system group were relatively constant over the 24-h sampling period, and were within the expected normal physiological range (13).

The median estradiol concentrations increased from baseline to d 7, and returned to baseline values at the follow-up visit. The median increase from baseline to d 7 was significantly greater in the buccal system group (55.07 pmol/liter) than in the transdermal patch group (34.87 pmol/liter; $P < 0.001$). After discontinuation of treatment, the levels rapidly returned to baseline values.

The percentage of patients reporting adverse events (AEs) in all body systems were similar between the two groups, with 17 patients (51.5%) in the buccal system group reporting

**Fig. 1.** Predose morning testosterone levels after 12-h buccal system administration in 29 patients and morning testosterone levels after 24-h (at 2200 h) transdermal patch application in 28 patients (mean ± SD). The dotted lines show the normal range for testosterone.

**Fig. 2.** Serum testosterone levels on d 7 and 8 of treatment (mean ± SD). The dotted lines show the normal range for testosterone. The black arrows represent the application times for the buccal system, whereas the open arrow represents that for the transdermal patch.
a total of 28 AEs, and 16 patients (47.1%) in the transdermal patch group reporting a total of 37 AEs. A single patient was discontinued from the buccal system group due to tenderness and blistering of the gum. The most common AEs reported for both treatment groups were application-site disorders [reported by six patients (18.2%) in the buccal system group and six patients (17.6%) in the transdermal patch group]. Patients in both groups experienced application-site erythema [reported by two patients (6.1%) in the buccal system group and five patients (14.7%) in the transdermal patch group] and application-site irritation [two patients (6.1%) in the buccal system group and one patient (2.9%) in the transdermal patch group].

There were no clinically significant changes in mean or median hematology or clinical chemistry parameters from baseline to follow-up in either treatment group.

Discussion

Our study investigated the effect of a buccal testosterone preparation in hypogonadal men and compared its effects to a conventional testosterone skin patch. The data presented here demonstrate that the buccal system causes a steady mean testosterone level within the normal range and that the patients using the buccal system had testosterone levels in the normal range in a higher percentage of the day when compared with patients using the conventional patch. Patients taking the buccal system also had higher DHT levels than those on the patch, but the values were within the normal range. Slightly higher DHT levels were observed after a testosterone gel preparation (AndroGel) in a recent study (7). Serum estradiol levels rose appropriately after both treatments in the present study. The buccal system appeared to be safe and well tolerated. The most common AE reported was an application-site reaction, but when this occurred it was generally mild and rarely caused interruption of treatment (other than in a single patient).

Current forms of injectable testosterone include the long-established depot injections and implants. The depot injections currently consist of a mix of one or more oily esters, and are extremely cheap, but need to be repeated every 1–4 wk. They can also be painful by IM injection. However, the most unacceptable aspect of these formulations is the grossly non-physiological pharmacokinetic profiles of testosterone that they produce (6, 14). This can be improved by giving smaller doses more frequently, e.g., 100 mg weekly, but clearly at the expense of comfort and convenience (14). The recently introduced longer-acting injectable testosterone undecanoate needs injections every 10–12 wk, and wider experience will establish its place in testosterone replacement therapy (10). Implants are generally more acceptable to patients, but the actual implantation requires a surgical procedure, albeit a small one, and unless they are being performed in a center with considerable experience in their use, there can be unacceptably high extrusion rates. Oral testosterone undecanoate rarely produces physiological levels of testosterone and must be administered several times a day (15).

The newer testosterone patches were thought originally to offer a superior form of replacement therapy, but due to the requirement for a high dose of testosterone to be delivered transdermally, the current patches are relatively large and can be cosmetically unsightly. The high rate of dermatological AEs experienced with some of these formulations has also limited their use (16). The scrotal patch, although providing physiological levels of testosterone, results in supra-physiological levels of DHT as a consequence of the high rate of testosterone metabolism in scrotal skin compared with that at other dermal application sites (17). There are increasing amounts of available data on the dermal gel formulation, suggesting it to be effective and without any application-site side effects and negligible interpersonal testosterone transfer (7–9, 11, 12, 18–20). A preliminary study of the use of a different, noncontrolled/sustained release buccal testosterone preparation has been reported earlier, where six subjects were taking one or two 10-mg buccal systems applied to the lower gum (21). Testosterone levels rose to within the normal range and improved scores in sexual function were achieved, although the duration of the increased testosterone level after the application of the system was rather short (2–4 h) (21). A sublingual preparation, cycloextrin testosterone, has also been tested in the past, but limited experience is available with this preparation (22). More recently, three doses of a buccal preparation were tested on healthy volunteers pretreated with gonadotropin agonist, and favorable hormone profiles were achieved (23).

Our results show that this testosterone buccal system mucoadhesive produces physiological testosterone levels in hypogonadal men, and is superior to the transdermal patch in achieving testosterone concentrations within the normal range. It represents a promising new agent that requires further longer-term study.

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