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Pharmacokinetics of estradiol, progesterone, testosterone and dehydroepiandrosterone after transbuccal administration to postmenopausal women

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Key words: SEX HORMONES, TROCHE, BUCCAL DELIVERY, POSTMENOPAUSAL SYMPTOMS

ABSTRACT

Objective To evaluate the pharmacokinetic profiles of estradiol, progesterone, testosterone and dehydroepiandrosterone in postmenopausal women following single and multiple dosing using a troche and the transbuccal route of administration.

Methods Each troche contained estradiol (0.5 mg), progesterone (200 mg), testosterone (2.0 mg) and dehydroepiandrosterone (10 mg). A half troche was administered to each of six women and the plasma concentration–time profiles determined over 24 h. Thereafter, a one-half troche was taken twice daily for 2 weeks and concentrations determined over a dosage interval (12 h). Blood and saliva samples were collected at specified time intervals on the first day and again after 2 weeks.

Results Each of the hormones was readily absorbed via the buccal mucous membrane. Peak plasma concentrations of estradiol and progesterone were comparable to those found normally in young menstruating women.

Conclusion The transbuccal route is a novel approach to provide therapy for the management of menopause-related symptoms of postmenopausal women without the need to resort to conjugated or synthesized hormones, and may overcome the poor or erratic systemic availability associated with other routes of administration.

INTRODUCTION

Hormone replacement therapy (HRT) for women has increased in popularity during the past 50 years. It is estimated that about 30% of Australian women over the age of 50 are now using hormones to relieve postmenopausal symptoms, or to reduce the risk of problems such as osteoporosis, genitourinary changes or neurological disorders[1]. However, some reassessment is likely in view of the recently published Women's Health Initiative study[2].

A number of HRT regimens have been devised for the management of symptoms of the

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postmenopause, with variable success. Most treatments have been based on the use of natural 17β-estradiol, conjugated equine estrogen or other conjugated estrogens, in combination with a group of synthesized progestogens such as norethisterone, levonorgestrel, medroxyprogesterone acetate and dydrogesterone. While these combination regimens have been successful in controlling symptoms, a number of side-effects or complications may occur, which have variously been attributed to the type or dose of estrogen used, or to the type or dose of synthetic progestogen administered. Some physicians have noted that progestogens are often associated with an increased rate of mastalgia, bloating, weight gain, irritability, mood swings, depression and loss of libido, while others have suggested that sequential progestogens increase the risk of developing breast cancer[3–5].

Lee has proposed that the use of natural progesterone instead of synthesized progestogens may avoid the unwanted progestogenic side-effects, and the above problems would be avoided[6,7]. However, oral administration of natural progesterone has not been well accepted in clinical practice. This may reflect the lack of readily available commercial preparations of micronized progesterone, or the difficulty in maintaining circulating blood concentrations of progesterone needed to achieve biological activity in the endometrium or the breast[8]. Progesterone has been administered in creams and gels for transdermal absorption and as a paste for transvaginal use[9–11], in part to avoid the high first-pass metabolism associated with oral administration. Transdermal delivery of progesterone has demonstrated that this hormone can be absorbed through the skin, but circulating concentrations of progesterone achieved by this route of administration have proved to be insufficient to achieve a biological effect in the endometrium[12].

Over the past decade, the use of androgens has become a useful therapeutic tool for postmenopausal women who complain of loss of drive, energy and libido. While the issue is still controversial, there is evidence to suggest that administration of testosterone to women does improve sexual desire and enjoyment for some[13,14]. As a consequence, a number of delivery systems for testosterone have been employed, including subdermal implants, oral formulations and transdermal creams, each of which has provided clinical benefits to postmenopausal women.

Dehydroepiandrosterone (DHEA) is an adrenal hormone that can be metabolized to either estrone or testosterone. Some physicians have begun to prescribe DHEA to treat postmenopausal symptoms based on concepts propounded by a number of authors[15–19], and in this context it is now touted as an alternative therapy for the postmenopause.

Research continues into optimizing the delivery of HRT, with an emphasis on achieving optimal clinical response while also maintaining patient acceptability. Recently, the mucous membranes of the nose and the mouth have been employed as a route of administration for the delivery of hormones[20–22].

Administration of progesterone via the buccal route may be favored because delivery by other routes is limited by erratic absorption (e.g. transdermal delivery), or by poor bioavailability (e.g. oral administration) owing to degradation in the gut or as a result of first-pass metabolism[23].

The aim of this study was to investigate the pharmacokinetic profile of several sex hormones following single and multiple doses of a transbuccal troche (lozenge) to postmenopausal women. The troche investigated in this study contained 17β-estradiol, progesterone, testosterone and dehydroepiandrosterone. Furthermore, because the use of salivary hormone estimations has been promoted as a means of monitoring the hormonal status of postmenopausal women receiving hormonal therapy[7,23], a secondary aim of this investigation was to compare circulating blood concentrations of each of the hormones with time-paired salivary concentrations.

METHODS

The study was approved by the St. Vincent's Hospital Human Research Ethics Committee.

Study formulation

Each troche (lozenge) contained 17β-estradiol (0.5 mg), progesterone (200 mg), testosterone (2.0 mg) and DHEA (10.0 mg). The excipients in the troche consisted of silica gel, acacia, sevia and polyethyleneglycol, with a wildberry flavor. The troches employed in this trial were formulated as a single batch for the study by Richard Stenlake Compounding Pharmacist (Bondi Junction, Australia).

Study protocol

The study was an open-label investigation in six postmenopausal women. Before entry into the trial, subjects gave informed consent, and

underwent medical and biochemical screening. Subjects ranged in age from 45 to 60 years (mean 56 years), and had a mean weight of 69 kg (range 64–74 kg), mean height of 166 cm (range 157–178 cm) and mean body mass index of 25.2 kg/m^2 (range 23.4–27.6 kg/m^2). Subjects were in good general health, and at least 1 year postmenopausal. Follicle stimulating hormone (FSH) concentrations ranged from 34.2 to 72.3 IU/l (postmenopausal range > 16 IU/l), while baseline (pre-dose) estradiol ranged from 3 to 58 pmol/l (< 100 pmol/l postmenopausal).

Subjects did not have a history of cancer of the breast or uterus, thrombosis, embolism, hypertension, diabetes, hyperlipidemia or obesity, nor were smokers. They also did not have any clinically significant abnormalities on routine biochemical and hematological screening.

Subjects discontinued prescribed HRT therapy as well as any herbal or alternative medicines not less than 4 days prior to the first study day. Subjects presented to the St. Vincent's Clinical Trials Centre on the morning of each study day after an overnight fast. An indwelling cannula was inserted into a forearm vein and a baseline blood specimen collected.

On the first day, a half troche was placed in the buccal cavity (between the cheek and the gum) and allowed to dissolve. Subjects were instructed to allow the troche to dissolve in the oral cavity and not to swallow the dose form. Dissolution of the formulation in the buccal cavity took up to 30 min. Subjects rinsed their mouths with water at 45 min. Blood samples were collected via the cannula at timed intervals over 24 h. Subjects were discharged, but continued to take half a troche, twice daily in the same manner, for the following 2 weeks. Subjects then re-presented to the Clinical Trials Centre where the morning dose was taken, and further blood samples were collected at timed intervals over the dosage interval of 12 h.

Blood samples were scheduled for collection after the single dose at the following times: pre-dose (0), 0.25, 0.5, 0.75, 1.0, 1.5, 2.0, 3.0, 4.0, 6.0, 8.0, 12.0, 16.0, 20.0 and 24.0 h; and at pre-dose (0), 0.25, 0.5, 0.75, 1.0, 2.0, 2.5, 3.0, 4.0, 6.0, 8.0, 10.0 and 12 h after the 2-week dosing interval (steady state). Actual times were recorded, and these were used for the pharmacokinetic calculations.

Saliva was collected according to standardized directions provided by the laboratory, Analytical Reference Laboratories (Melbourne), and stored frozen (–20°C) prior to shipping for hormonal analysis. In brief, subjects rinsed their mouths thoroughly with water and waited 5–10 min before swallowing any saliva in the mouth. Subjects then expressed saliva directly into the collection tubes.

Saliva samples were obtained for single dose estimation at the following times: pre-dose (0), and 1.0, 4.0, 8.0, 12.0, 16.0 and 24 h after dosing. For steady-state analysis, saliva was collected at pre-dose (0), and 1.0, 4.0, 8.0 and 12.0 h after troche administration.

Analytical methods

Plasma and saliva concentrations of hormones were determined using validated radioimmunoassay techniques as routinely conducted by Sydpath (St. Vincent's Hospital Pathology, Sydney) and the Analytical Reference Laboratories (Melbourne), respectively. Both laboratories are accredited pathology providers and participate in national quality-assurance programs for hormonal analysis. Variability (coefficients of variation) of the hormone assays for both plasma and saliva over the ranges of concentrations encountered were, respectively: testosterone < 12.7%, estradiol < 9.7%, progesterone < 16.0% and DHEAS < 16%.

With the exception of DHEAS, the concentrations of hormones achieved in saliva commonly far exceeded the upper limits of the usual standard curves employed for these analytes, and it was necessary subsequently to re-thaw and re-assay the samples after appropriate dilution.

DHEA concentrations were not determined directly, but are reported as the sulfate metabolite (DHEAS).

RESULTS

Concentrations of hormones in plasma

Single and multiple dosing of the troche produced very similar mean concentration–time profiles for estradiol in plasma (Figure 1). Substantial inter-subject variability in concentrations was evident (Tables 1 and 2).

Single and multiple dosing of the troche also produced virtually superimposable mean concentration–time profiles for testosterone in plasma, with markedly increased concentrations for up to 4 h and a return to pretreatment values within approximately 8 h (Figure 2). Absorption of this hormone was more rapid than for the other

hormones, with peak concentrations occurring at a mean of 0.6 h (Tables 1 and 2).

Elimination of progesterone appeared to be biphasic, with a secondary peak evident at approximately 4 h following both single and multiple dosing. In contrast to estrogen and testosterone, there appeared to be some accumulation of progesterone when dosed to steady state, such that concentrations may have been more sustained from 8 h onwards (Figure 3 and Table 1).

Single dose administration of one-half troche (5 mg DHEA) resulted in a doubling of blood concentrations of the sulfate, DHEAS, over 5–10 h (Figure 4), with a subsequent return to pretreatment concentrations within 24 h. Steady-state concentrations of DHEAS exceeded single dose concentrations at all time points. Intersubject variability was high (Tables 1 and 2 and Figure 4).

Concentrations of hormones in saliva

As noted above in the 'Methods', with the exception of DHEAS, the concentrations of hormones achieved in saliva were higher than expected on

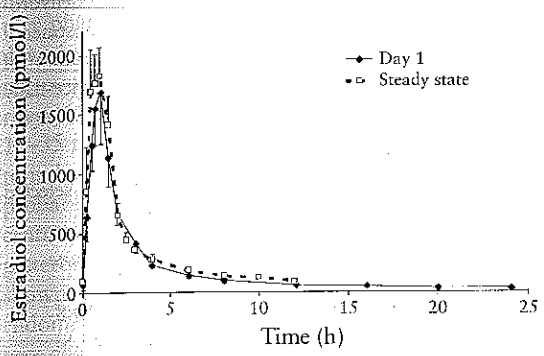

Figure 1 Mean concentration–time profile of estradiol in six postmenopausal women after first buccal administration of troche (day 1) and after 2 weeks of troche twice-daily administration (steady state). Error bars are ± SEM

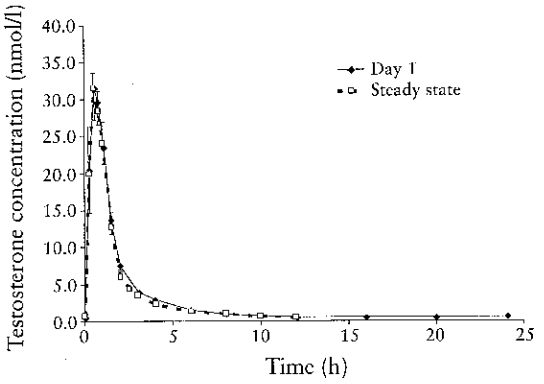

Figure 2 Mean concentration–time profile of testosterone in six postmenopausal women after first buccal administration of troche (day 1) and after 2 weeks of troche twice-daily administration (steady state). Error bars are ± SEM

Table 1 Baseline hormone concentrations (± SD) of six postmenopausal women prior to troche administration ('pre-dose' concentrations) and after 2 weeks of twice daily administration

Hormone	*Pre-dose concentration on day 1*	*Pre-dose concentration at steady state*
Estradiol (pmol/l)	21.7 ± 19.3	96.0 ± 33.8
Testosterone (nmol/l)	0.38 ± 0.08	0.67 ± 0.28
Progesterone (nmol/l)	1.35 ± 0.73	6.35 ± 2.82
DHEA sulfate (μmol/l)	1.50 ± 0.62	3.56 ± 1.99

DHEA, dehydroepiandrosterone

Table 2 Maximum hormone concentrations (C_{max} ± SD) and time they occurred (T_{max} ± SD) after first dose (day 1) and after 2 weeks of treatment (steady state)

	Day 1		*Steady state*	
Hormone	C_{max}	T_{max}	C_{max}	T_{max}
Estradiol (pmol/l)	1836 ± 640	1.0 ± 0.4	2275 ± 633	0.9 ± 0.5
Testosterone (nmol/l)	35.4 ± 11.0	0.6 ± 0.2	34.9 ± 7.0	0.4 ± 0.2
Progesterone (nmol/l)	25.0 ± 7.8	1.3 ± 0.5	29.5 ± 5.8	0.9 ± 0.4
DHEA sulfate (μmol/l)	2.8 ± 0.5	3.0 ± 2.0	4.9 ± 1.0	2.2 ± 1.9

DHEA, dehydroepiandrosterone

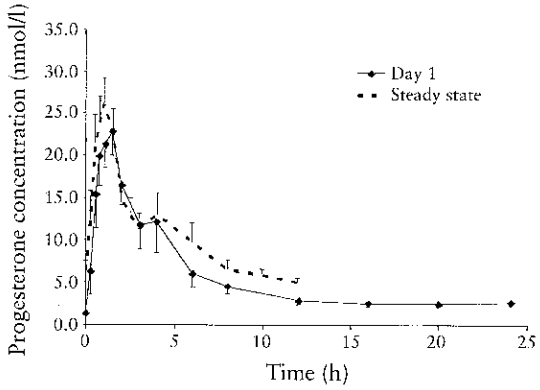

Figure 3 Mean concentration–time profile of progesterone in six postmenopausal women after first buccal administration of troche (day 1) and after 2 weeks of troche twice-daily administration (steady state). Error bars are ± SEM

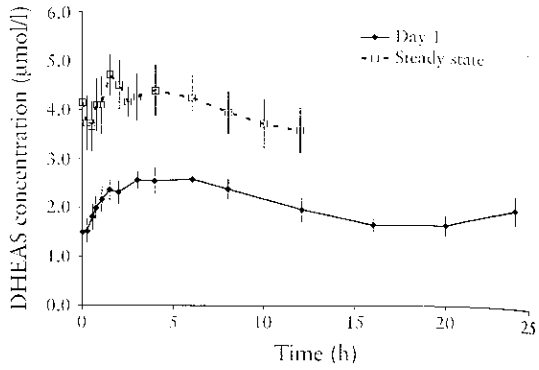

Figure 4 Mean concentration–time profile of dehydroepiandrosterone sulfate (DHEAS) in six postmenopausal women after first buccal administration of troche (day 1) and after 2 weeks of troche twice-daily administration (steady state). Error bars are ± SEM

Table 3 Mean (± SD) ratios (ranges) of saliva/plasma concentrations of hormones after chronic dosing at selected time points

Time	*DHEAS*	*Estradiol*	*Testosterone*	*Progesterone*
Baseline* (pre-dose)	0.010 ± 0.005	27.7 ± 14.4	2.7 ± 1.1	9.4 ± 10.8
	(0.004–0.016)	(11.7–49.6)	(2.2–4.0)	(1.8–27.8)
Post-dose (1 h)	0.015 ± 0.009	209 ± 128	31 ± 34	214 ± 75
	(0.004–0.030)	(65–390)	(4–80)	(94–296)
Post-dose* (12 h)	0.007 ± 0.001	24 ± 19	5.4 ± 2.6	6.2 ± 11.8
	(0.005–0.008)	(9–61)	(2.1–7.7)	(0.1–30.2)

*In each case one outlier was excluded from data set: these represented data for which at least one analyte varied from group mean by more than 20-fold; DHEAS, dehydroepiandrosterone sulfate

first analysis, commonly far exceeding the upper limits of the usual standard curves employed for these analytes in saliva, being: estradiol 600 pmol/l, testosterone 2500 pmol/l and progesterone 22 260 pmol/l. Consequently, while a guide to the actual concentrations, the large dilutions required to bring salivary hormone concentrations within the range of the standards and the possible instability of the analytes during freezing and re-thawing left some uncertainty as to the accuracy of these data.

The baseline salivary concentrations of the hormones were generally much lower than those in plasma. The exception was estradiol, for which ratios of saliva/plasma concentrations at baseline exceeded 1.0 for four of the six subjects (data not reported). Thereafter, however, following the first single dose, ratios of the concentrations in saliva/plasma exceeded unity for each hormone in all subjects except for DHEAS, whose concentrations in saliva remained much lower than in plasma (baseline mean ± standard deviation (SD) ratio of 0.004 ± 0.005). The single dose data were highly variable, and apparent ratios of saliva/plasma concentrations exceeding 1000 (data not shown) were observed at 1.0 h for estradiol, in particular.

The ratios of saliva/plasma concentrations (determined on re-assay and appropriate dilution) at steady state are summarized in Table 3. These demonstrated less intersubject variability. At baseline (pre-dose), i.e. before administration of the day's dosage at the Clinical Trials Centre, the concentrations in saliva far exceeded those in plasma (Table 3), except again for DHEAS.

DISCUSSION

Concentrations of hormones in plasma

Each of the hormones, estradiol, progesterone, testosterone and dehydroepiandrosterone (the latter monitored as the active sulfate metabolite), was readily absorbed after transbuccal administration as a troche. Plasma concentrations of

estradiol and progesterone were comparable to those found in normal young menstruating women[24]. Peak concentrations were achieved relatively rapidly, with a return to baseline between 4 and 8 h after the single dose. The profiles at steady state were very similar for estrogen and testosterone, reflecting their short half-lives with respect to the dosing interval. By contrast, at steady state, there was evidence of accumulation of progesterone, to give concentrations that may be associated with physiological and biological activity in young normal women. Ferenczy and colleagues[25] have shown that the endometrium of normal young women does not change to a secretory phase, nor is mitosis inhibited, until the fifth day after ovulation. During these 5 days following ovulation, the concentration of progesterone rises from about 2 nmol/l to approximately 15–35 nmol/l. However, the critical concentration to induce a change has not been identified, but is probably related to exposure time as well as concentration. If the sustained concentration of progesterone following regular use of the troche is shown to produce inhibition of mitosis in the endometrium, or result in development of secretory change, then this route of delivery of progesterone could be utilized for the management of postmenopausal symptoms.

Progesterone demonstrated secondary peaks at approximately 4 h following both single and multiple doses. There are at least two factors that may have contributed to this observation: enterohepatic recycling of progesterone that had been systemically absorbed, and/or a combination of the effects of both buccal and subsequent intestinal absorption of progesterone. However, the limited number of subjects in this investigation, together with the timing of blood collections, provides insufficient data to allow any reliable explanation for this observation.

DHEAS concentrations increased after dosing to steady state, reflecting the longer elimination half-life of DHEAS (10–20 h) compared with other steroids under investigation. Ongoing formation of DHEAS from DHEA will also tend to increase the apparent elimination half-life of DHEAS[26,27].

Concentrations of testosterone have recently been reported[28] following both buccal (1 mg testosterone propionate) and percutaneous gel (1 mg testosterone) administration to healthy postmenopausal women. Consistent with the present data, high peak concentrations ranging from approximately 11–38 nmol/l were observed following a single dose of the lozenge. The gel provided sustained but much lower plasma concentrations over 24 h. Accumulation of testosterone was evident when the hormone was administered for 14 days as either a lozenge or the gel formulation, an observation not observed in the present study of the troche.

The advantage of the buccal route of delivery is that it allows rapid absorption of the hormones and attainment of physiologically relevant plasma concentrations. This route of delivery avoids the first-pass metabolism which is associated with oral administration, while also obviating the difficulties commonly associated with transdermal application of progesterone, namely erratic or poor absorption. However, further studies are needed to determine the effectiveness of the buccal route of administration in controlling symptoms, modifying side-effects and preventing adverse changes in organs such as the uterus.

Concentrations of hormones in saliva

Concentrations in saliva were highly variable, especially following the first single dose and in particular at the peak time in saliva at 1.0 h post-dose. For example, ratios of saliva/plasma concentrations of estradiol of over 1000 (data not reported) were observed. It is unclear why similar ratios were not seen at steady state (Table 3). Although subjects observed the protocol that required them to rinse their mouths at 45 min post-dose, as well as before saliva collection, on each occasion, contamination by hormones present in undissolved troche or perhaps due to binding of steroids to other cellular material in the saliva is one explanation that cannot be totally discounted.

The need to re-assay samples involving an additional freeze–thaw cycle, together with the large dilutions required to bring concentrations within the range of the standards, leaves some uncertainty as to the exact ratios. Nevertheless, even assessment of the saliva data whereby the highest concentrations in saliva were limited to the upper cut-off for each analyte without dilution (i.e. an underestimate of the size of the ratio) suggested that there was significant accumulation of the hormones in saliva, relative to plasma.

These data suggest that, with the exception of DHEAS, the hormones are concentrated and excreted by the salivary glands. It has been hypothesized that progesterone, in particular, is carried on or in the surface of the membrane of red blood cells, and then delivered to particular end organs in a specific, effective manner with

the hormone diffusing along the concentration gradient[29]. According to this hypothesis, progesterone diffuses from the red cells into the salivary secretions and, therefore, any progesterone found in saliva accurately reflects that available to other target cells. This rationale supports monitoring of salivary hormone concentrations as a more accurate means of determining the potential activity of progesterone than measuring plasma concentrations[7]. However, this hypothesis is not supported by recent data[30] which found that concentrations of progesterone in these cells are negligibly low. The important observation in this latter study in relation to the present findings, however, was that, despite application of progesterone cream to the skin, saliva concentrations greatly exceeded those in plasma. Furthermore, regarding the findings of the present study, there were highly variable concentrations of hormones in saliva. We also conclude, therefore, that there remains insufficient information on the excretion of hormones into saliva to be certain of the value of this mode of analysis for therapeutic monitoring of hormonal therapy.

CONCLUSION

The transbuccal route is a novel approach to administering sex hormones to postmenopausal women. Pharmacokinetic profiles of hormones suggest that physiological patterns of the concentrations of all natural hormones can be readily achieved by this route. Particularly interesting is the finding that delivery of natural progesterone may be facilitated using the troche, an outcome not readily achieved by other means.

This study suggests that troches can be developed to provide therapy for the symptoms of postmenopausal women without the need to resort to conjugated or synthetic hormones, although further safety studies are required to determine the effect on the endometrium and on symptoms.

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Conflict of interest None of the authors have any interest in the development or sale of transbuccal troches, nor did they receive any financial reward for conducting the trial.

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