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Pharmacokinetics of progesterone and its metabolites allopregnanolone and pregnanolone after oral administration of low-dose progesterone

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Abstract

Objectives: To investigate the pharmacokinetics of progesterone, allopregnanolone and pregnanolone after treatment with a low oral dose of progesterone.
Methods: Eight postmenopausal women were given a single oral dose of 20 mg of micronised progesterone on Day 1 and 20 mg twice daily on Days 2–7. Blood samples for the analysis of progesterone, allopregnanolone and pregnanolone were collected, and pharmacokinetic parameters were calculated.
Results: After ingestion of a single dose, areas under the plasma concentration-time curve (AUC) from 0 to 12 h for progesterone, allopregnanolone and pregnanolone were 127%, 196% and 119% higher than the corresponding AUCs estimated to be caused by endogenous production. The maximum plasma concentration (C_{max}) and the AUC values were significantly lower for pregnanolone than for progesterone and allopregnanolone. The trough concentrations at steady state (C_{ss}) were significantly higher than the baseline values, and C_{ss} for pregnanolone was significantly lower than for allopregnanolone and progesterone. C_{ss} for allopregnanolone was in the range of what is normally seen in the menstrual cycle.
Conclusions: After ingestion of a low-dose of progesterone, the concentrations of allopregnanolone were in the same range as those of progesterone. Oral doses of 20 mg of progesterone twice daily to postmenopausal women produced allopregnanolone concentrations comparable to those achieved physiologically in premenopausal women. Low-dose oral progesterone may be used as a prodrug to allopregnanolone when the aim is to investigate low-dose allopregnanolone effects in humans.

Keywords: Oral progesterone; Allopregnanolone; Pregnanolone; Pharmacokinetics

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1. Introduction

Sequential hormone therapy (HT) causes cyclicity in mood symptoms in many women. It appears that the addition of progestagens [1] and vaginal progesterone [2] in sequential HT provokes these negative mood symptoms.

Allopregnanolone and pregnanolone are metabolites of progesterone and act through binding to the $GABA_A$ receptor complex in the brain where they enhance inhibitory neurotransmission [3]. High concentrations of allopregnanolone and pregnanolone have been reported to have anxiolytic, sedative, anaesthetic and antiepileptic effects when administered to animals and humans [4–7]. However, more recent studies show a bimodal effect of $GABA_A$ receptor positive modulators like allopregnanolone, pregnanolone, barbiturates, benzodiazepines and alcohol in certain individuals. High concentrations cause the effects described above, whereas low physiological concentrations appear to exert anxiogenic effects [8–10]. A bimodal effect on negative mood has also been found in postmenopausal women treated with sequential HT with different dosages of medroxyprogesterone acetate (MPA) or natural progesterone. The women felt worse after receiving 10 mg compared with 20 mg of MPA [1] and 400 mg compared with 800 mg of vaginal progesterone [2]. Furthermore, a study of postmenopausal women taking sequential HT with natural progesterone showed a significant association between negative mood and allopregnanolone plasma concentrations similar to those seen during the luteal phase in ovulatory cycles [11].

Physiologically, plasma concentrations of allopregnanolone and pregnanolone follow those of progesterone [12], and increased levels are found in the luteal phase of the menstrual cycle and during pregnancy [13–15]. In women with premenstrual dysphoric disorder, the deterioration of physical and psychological symptoms is related to an increase in progesterone and allopregnanolone concentrations during the late luteal phase of ovulatory cycles [14,16]. $GABA_A$ receptor sensitivity to neurosteroids decreases with extended or repeated exposure [17]. Therefore, pregnanolone and allopregnanolone may have more pronounced effects in postmenopausal women than in women with ovulatory cycles.

Given the qualitative differences in effect between high and low doses and/or plasma concentrations of progesterone, allopregnanolone and pregnanolone, it is of interest to study the pharmacokinetics of allopregnanolone and pregnanolone after administration of different doses of progesterone. Previous studies have all investigated the pharmacokinetics of these steroids after oral administration of high doses of progesterone (200–1200 mg), causing clearly supraphysiological plasma concentrations [18–20]. Only one of these studies included postmenopausal women [18], whereas the other two [19,20] included premenopausal subjects. Moreover, these were all single-dose studies. Thus, no studies have hitherto investigated the pharmacokinetics of progesterone, allopregnanolone and pregnanolone after repeated administration of low-doses of progesterone, assumed to cause allopregnanolone and pregnanolone concentrations close to or within the physiological ranges.

Based on the evidence of bimodal action of allopregnanolone and pregnanolone and the lack of pharmacokinetic studies after administration of low-doses of progesterone, the objective of the present study was to investigate the pharmacokinetics of progesterone and its metabolites allopregnanolone and pregnanolone after treatment with a low-dose of progesterone in postmenopausal women.

2. Methods

2.1. Subjects

Eight women who were more than 6 months postmenopausal participated in the study. Their mean age was 54 years (range 44–65 years old). All women were considered physically healthy, had uterus and ovaries in situ, and had not used any hormone replacement therapy for the last 3 months prior to inclusion in the study. They were not receiving other progestin or steroid treatment and had not been treated with psychotropic drugs within the last 6 months. Their mean body weight was 69 kg (range 60–80 kg), and their body mass index was 25.9 kg/m^2 (range 21.3–30.1 kg/m^2). One woman dropped out during the study course due to palpitations and breast pain, but the first nine blood samples collected were included in the analyses.

2.2. Study design

On the first day of the study 20 mg of micronised progesterone was administered orally at 8 a.m. with 150 ml of tap water. The subject's fasted 8 h prior to and 2 h after administration of progesterone. An intravenous cannula was inserted in one forearm, and blood samples for the analysis of progesterone, allopregnanolone and pregnanolone in the plasma were collected immediately before the initial progesterone dose (C_0; for determination of the baseline hormone levels produced endogenously) and 1, 2, 3, 4, 6, 8, 12 and 24 h after the dosage.

On the following 6 days (Days 2–7), 20 mg of micronised progesterone was administered orally twice a day (at 8 a.m. and 8 p.m.). Blood samples were drawn once daily, immediately before the morning dose. On Day 7, blood samples were also collected 2, 4, 6, 8 and 12 h after dosage. Finally, a sample was collected 60 h after the last dose.

The oral formulation was in the form of soft gelatin capsules containing 20 mg of micronised progesterone in monohydrous lactose. The capsules were prepared by Apoteket AB, Production and Laboratories, Stockholm, Sweden (the Swedish National Pharmacy Company). The Umeå University Ethical Committee and the Swedish Medical Products Agency approved the study.

2.3. Steroid assays

Measurements of plasma progesterone were taken using Delfia progesterone kits (Wallac Oy, Turku, Finland), a fluoroimmunoassay, according to the manufacturer's instructions.

Measurements of plasma allopregnanolone and pregnanolone were taken by extraction, celite chromatography and radioimmunoassay analysis, as described in detail previously [11]. In celite chromatography, the recovery was determined for each assay using tritium-labelled allopregnanolone and pregnanolone (New England Nuclear, Boston, USA). The recovery for allopregnanolone was 78% and for pregnanolone 85%. The allopregnanolone antiserum was raised against 3α-hydroxy-20-oxo-5α-pregnan-11-yl carboxymethyl ether coupled with bovine serum albumin [21]. The pregnanolone antiserum was raised against 3α,21-dihydroxy-5β-pregnan-20-one 21-hemisuccinate coupled with bovine serum albumin [5]. The antisera were kind gifts from Dr. Robert H. Purdy, Department of Psychiatry, College of Medicine, University of California, San Diego, CA, USA. The minimum level of detection in the standard curve was 25 pg with an intraassay coefficient of variation for allopregnanolone and pregnanolone of 6.5% and an interassay coefficient of variation of 8.5%.

2.4. Pharmacokinetic and statistical analyses

Pharmacokinetic parameters were using the software package Kinetica Version 4.3 (InnaPhase Corporation, Philadelphia, PA, USA). After the first progesterone dose, the levels of progesterone, allopregnanolone, and pregnanolone returned to baseline concentrations (C_0) within 12 h after dosage.

Therefore, progesterone was given at 12-h intervals and area under the curve (AUC) values from 0 to 12 h after dosage were calculated. For these calculations, a mixed log-linear method was used. Baseline AUC values during the same period (AUC_0) were calculated as $C_0 \times 12$ h and compared with the total AUC values. Percent increase in AUC during the period of 0–12 h was calculated as $[(AUC - AUC_0)/AUC_0] \times 100\%$. Maximum concentrations (C_{max}) and time to achieve maximum concentrations (t_{max}) were obtained directly from the measured values. Because the C_{max} values were relatively low compared to C_0 and because progesterone and its metabolites are continuously produced via endogenous pathways, reliable elimination half-lives could not be estimated. Consequently, it was not possible to extrapolate AUC to infinity nor to calculate clearance values and volumes of distribution.

Trough concentrations at steady state (C_{ss}) were calculated as the mean concentration from each individual based on the samples obtained 12 h after ingestion of 20 mg of progesterone twice daily on Days 3–7. Samples were obtained after 0, 2, 4, 6, 8, 10 and 12 h after ingestion of the last dose, and AUC values were compared with the corresponding AUC values after the first dose.

Pharmacokinetic parameters were compared with one-way analyses of variance (ANOVA) with repeated measures. Continuous variables are displayed as mean ± standard error of mean (S.E.M.). Least significant difference tests were used as post-hoc method when applicable. For comparisons between two groups

of hormone levels, Wilcoxon matched pairs signed ranks tests were applied. The statistical package SPSS was used for the analyses. P values below 0.05 were considered statistically significant.

3. Results

3.1. Pharmacokinetics after ingestion of the first dose

Key pharmacokinetic variables for progesterone, allopregnanolone and pregnanolone are summarized in Table 1. The corresponding time-concentration curves are displayed in Fig. 1. At baseline (C_0) there was a significant difference in endogenous plasma concentrations of progesterone, allopregnanolone and pregnanolone ($F(2,14) = 8.69$; $P < 0.01$), with significantly higher plasma levels for progesterone than for allopregnanolone and pregnanolone. After ingestion of a single dose of progesterone, a significant variance in maximum plasma concentration (C_{max}) and the AUC between the three steroids was noticed ($F(2,14) = 4.67$; $P < 0.05$ and $F(2,14) = 9.21$; $P < 0.01$, respectively). Pregnanolone had significantly lower C_{max} and AUC than progesterone ($P < 0.05$ and $P < 0.01$, respectively) and allopregnanolone ($P < 0.05$ and $P < 0.01$, respectively) (Table 1).

The plasma concentrations of progesterone and pregnanolone were significantly higher than baseline at 4 and 8 h, respectively, after ingestion of progesterone (Fig. 1). For allopregnanolone, the plasma concentrations were significantly higher than baseline at 12 h after ingestion, although the difference between baseline and the 12-h sample was numerically very low (Fig. 1).

3.2. Steady state pharmacokinetics

The plasma concentrations of progesterone, allopregnanolone and pregnanolone reached a plateau on Day 3 of treatment, that is, after the first day with a dosage of 20 mg twice daily (Fig. 2). Mean trough plasma concentrations at steady state (C_{ss}) were 1.97 ± 0.24 nmol/l for progesterone, 1.77 ± 0.18 nmol/l for allopregnanolone, and 1.26 ± 0.07 nmol/l for pregnanolone. The C_{ss} values were all significantly higher than the C_0 values ($P < 0.05$). There was a significant difference between the C_{ss} values for progesterone, allopregnanolone and pregnanolone ($F(2,12) = 11.40$; $P < 0.01$), with concentrations of pregnanolone significantly lower than those of progesterone and allopregnanolone ($P < 0.01$ and $P < 0.05$, respectively).

The AUC values on Day 7 were significantly higher than the corresponding AUC values after ingestion of the first dose ($P < 0.05$ for all three steroids investigated). The relative increases (mean ± S.E.M.) were $34\% \pm 8$ for progesterone, $66\% \pm 11$ for allopregnanolone, and $48\% \pm 18$ for pregnanolone.

The plasma concentrations of progesterone, allopregnanolone and pregnanolone 60 h after the last dose of progesterone (mean ± S.E.M.) were 1.13 ± 0.22, 1.08 ± 0.06 and 1.17 ± 0.11 nmol/l, respectively. The differences between these concentrations and the baseline concentrations (C_0) were statistically significant

Table 1
Pharmacokinetic parameters of progesterone, allopregnanolone and pregnanolone in eight postmenopausal women after a single oral dose of 20 mg of progesterone

	Progesterone	Allopregnanolone	Pregnanolone	P value
	Mean ± S.E.M. [range]	Mean ± S.E.M. [range]	Mean ± S.E.M. [range]	
C_0 (nmol/l)	1.2 ± 0.12 [0.65–1.9]	0.74 ± 0.06 [0.50–1.0]	0.72 ± 0.06 [0.44–0.94]	<0.01
C_{max} (nmol/l)	9.7 ± 2.0 [3.4–19]	8.8 ± 2.0 [4.9–22]	4.7 ± 0.52 [2.1–7.0]	<0.05
t_{max} (min)	105 ± 25 [60–240]	98 ± 19 [60–180]	60 ± 0.0 [60–60]	n.s.
AUC_0 (nmol/l h)	14 ± 1.5 [7.8–22]	8.9 ± 0.70 [6.0–13]	8.6 ± 0.70 [5.3–11]	<0.01
AUC (nmol/l h)	30 ± 2.6 [21–41]	26 ± 2.7 [18–42]	18 ± 1.5 [13–24]	<0.01
Percent increase in AUC	127 ± 24 [27–243]	196 ± 35 [138–436]	119 ± 32 [29–311]	n.s.

C_0 = baseline (endogenous) plasma concentration; C_{max} = maximum plasma concentration; t_{max} = time in minutes (min) to achieve maximum plasma concentration; AUC_0 = estimated area under the plasma concentration-time curve from 0 to 12 h, assumed to be caused by endogenous production; AUC = area under the plasma concentration-time curve from 0 to 12 h, based on the observed concentrations. The P values presented are the values found when the same pharmacokinetic variable is compared for the three steroids; n.s. = not significant.

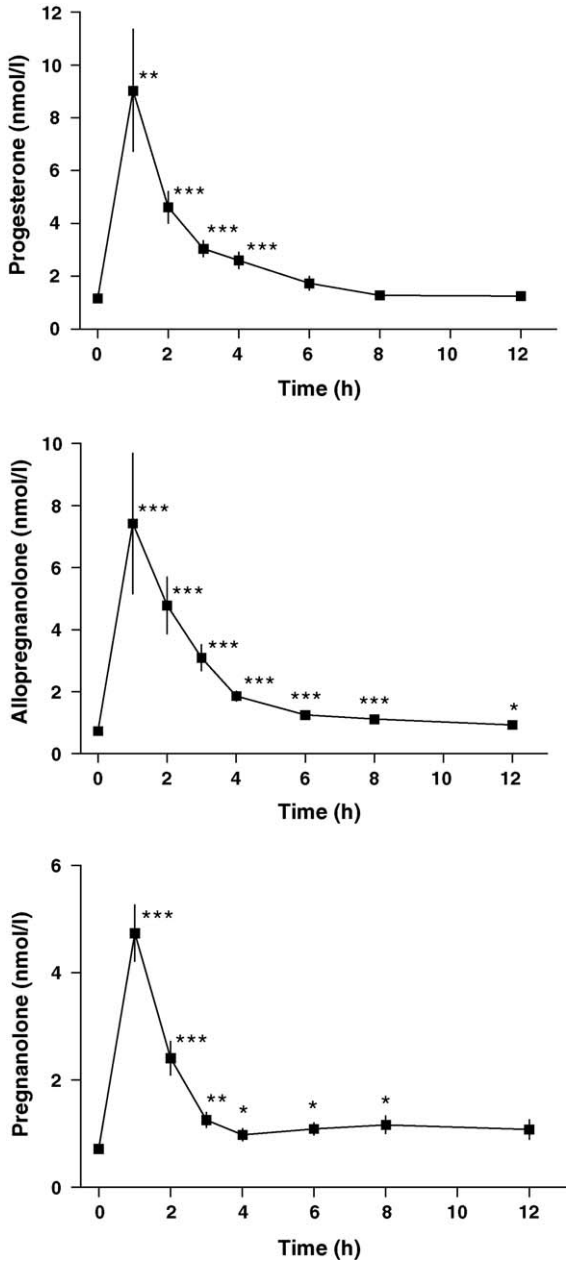

Fig. 1. Mean (±S.E.M.) plasma concentrations of progesterone (top panel), allopregnanolone (middle panel) and pregnanolone (bottom panel) in eight postmenopausal women after a single oral dose of 20 mg of micronised progesterone. Significant increases in steroid concentrations compared with the baseline plasma concentrations (time 0) are indicated with stars: * $P<0.05$; ** $P<0.01$; *** $P<0.001$.

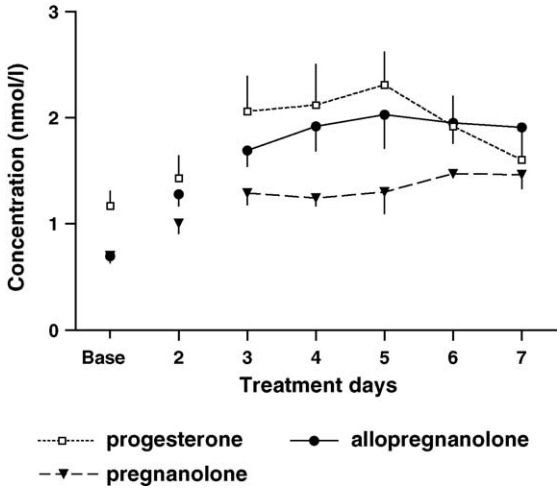

Fig. 2. Mean (±S.E.M.) plasma concentrations of progesterone, allopregnanolone and pregnanolone in seven postmenopausal women. Base = baseline, that is, before start of treatment on Day 1. Day 2 = 24 h after ingestion of a single oral dose of 20 mg progesterone. From Day 3, the samples were obtained as trough samples 12 h after ingestion of 20 mg of progesterone twice daily.

for allopregnanolone and pregnanolone ($P<0.05$ and $P<0.05$, respectively) but not for progesterone.

4. Discussion

This study has evaluated the pharmacokinetics of progesterone, allopregnanolone and pregnanolone in postmenopausal women treated with a low oral dose of micronised progesterone. The results indicate that a high proportion of the exogenous progesterone was rapidly metabolised to allopregnanolone. In fact, the concentrations of allopregnanolone were similar to those of progesterone. On the other hand, the concentrations of pregnanolone were significantly lower. Previous studies have demonstrated that conversion of progesterone to allopregnanolone and pregnanolone through the vaginal route is significantly lower than conversion via the oral route [2]. For example, after vaginal administration of progesterone, allopregnanolone is also the main metabolite although its concentrations amount to only about 10% of those of progesterone [19]. In another study, the allopregnanolone/progesterone C_{max} ratio after vaginal administration of progesterone was 18% [2]. Animal studies

have shown that 5-β reductase is expressed mainly in the liver, whereas 5-α reductase activity is expressed in several tissues including the brain and the skin [22]. Taken together, these findings indicate that the gastrointestinal and/or hepatic first pass metabolism is of importance both for the 5-α conversion to allopregnanolone and the 5-β conversion to pregnanolone, albeit to a higher degree for the metabolism to allopregnanolone. Furthermore, the findings indicate that allopregnanolone might thereafter also be produced in several other tissues.

In the present study the AUC values at Day 7 for progesterone, allopregnanolone and pregnanolone were all significantly higher than at Day 1. Moreover, the concentrations of allopregnanolone and pregnanolone 60 h after the last progesterone dose were still significantly higher than the corresponding baseline concentrations. Although the present study could not be used to calculate exact half-lives due to the relatively high levels of endogenously produced steroids, the increasing concentrations after repeated administration demonstrate that the elimination half-lives are longer than a few hours, at least for progesterone. In contrast, previous studies with single doses of supraphysiological progesterone have found that the elimination half-lives of progesterone and its metabolites are very short [23]. Moreover, after short-term intravenous administration of pregnanolone the half-life of this steroid was only about 30 min [24]. However, it seems reasonable that the true elimination half-lives have not been revealed in these studies [23], most likely because the methodology used did not made it possible to study whether accumulation takes place in the deep compartments. In contrast, the findings in the present study are consistent with the results from an animal study showing that steroid accumulation occurs in fat tissue as well as in other lipid-rich tissues like the brain [22]. The results also compatible with those of a study on pregnanolone in humans, estimating a half-life of 4–6 h due to slow release from deep compartments [25].

In this study, when 20 mg of progesterone is given twice daily, the concentration of allopregnanolone attained at steady state is in the range of what is normally seen during the menstrual cycle [18–20,26]. Thus, this dosage can be used to achieve physiological premenopausal plasma concentrations in postmenopausal women. In contrast, in previous studies employing higher dosages of progesterone, distinctly supraphysiological levels of progesterone and its metabolites have been obtained [18–20,26].

In conclusion, after administration of 20 mg of progesterone orally once or twice daily, the concentrations of allopregnanolone are in the same range as those of progesterone. Thus, low-dose oral progesterone may be used as a prodrug to allopregnanolone when the aim is to investigate low-dose allopregnanolone effects in humans. When the treatment goal is to achieve physiological premenopausal plasma concentrations of allopregnanolone in postmenopausal women, our data suggests that it may be suitable to administer an oral dose of 20 mg of progesterone twice daily.

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The experiments in this study comply with the current laws of Sweden, where the study was performed. The Umeå University Ethical Committee and the Swedish Medical Products Agency approved the study.

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