

# Oral Dehydroepiandrosterone for Adrenal Androgen Replacement: Pharmacokinetics and Peripheral Conversion to Androgens and Estrogens in Young Healthy Females after Dexamethasone Suppression

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## ABSTRACT

Women with adrenal insufficiency suffer from chronic dehydroepiandrosterone (sulfate) [DHEA(S)] deficiency. To define a suitable dose for DHEA replacement, we studied the pharmacokinetics and biotransformation of orally administered DHEA in nine healthy female volunteers (mean age  $23.3 \pm 4.1$  yr, mean body mass index  $22.5 \pm 1.8$  kg/m<sup>2</sup>) with transient suppression of adrenal androgen secretion because of dexamethasone (dex) administration ( $4 \times 0.5$  mg/day for 4 days). Diurnal blood sampling was performed during the early follicular phase of four subsequent menstrual cycles (study period 1: baseline; study periods 2–4: dex + placebo, dex + 50 mg DHEA or dex + 100 mg DHEA in a randomized cross-over design). Dex induced not only a significant suppression of serum cortisol (to 8% of baseline) but also of DHEA (18%), DHEA(S) (16%), and androstenedione (26%), as well as of testosterone (28%), dihydrotestoster-

one (43%), and estrone (54%). Oral administration of 50 mg DHEA led to restoration of DHEA(S) baseline levels, whereas 100 mg induced supraphysiological concentrations [baseline vs. 50 mg DHEA vs. 100 mg DHEA: area under the concentration-time curve (AUC) 0–12 h DHEA:  $280 \pm 85$  vs.  $241 \pm 73$  vs.  $383 \pm 106$  nmol/L  $\times$  h; AUC 0–12 h DHEA(S):  $89.1 \pm 48.4$  vs.  $139.6 \pm 43.5$  vs.  $213.3 \pm 21.6$   $\mu$ mol/L  $\times$  h). Serum concentrations of dihydrotestosterone and estrone were restored to baseline after 50 mg DHEA, whereas baseline testosterone and androstenedione levels were only achieved by administration of 100 mg DHEA. In conclusion, 50 mg DHEA seems to be a suitable replacement dose in females with adrenal insufficiency. Furthermore, the rapid and lasting conversion to potent androgens demonstrates a potential role of DHEA for androgen replacement in females in general. (*J Clin Endocrinol Metab* 83: 1928–1934, 1998)

DEHYDROEPIANDROSTERONE (DHEA) and its sulfated ester DHEA(S) are the most abundant steroids in the human circulation, but their physiological role remains to be elucidated. DHEA(S) concentrations show a strong age-associated decline in both males and females with a broad, probably genetically determined variation (1–4). Recent research has indicated that DHEA(S) may have a variety of beneficial effects. These results led to speculations about a possible role of DHEA as an antiaging hormone or even a fountain of youth (5, 6).

Cross-sectional studies revealed a significant positive correlation between serum DHEA(S) concentrations and functional status in elderly people (7, 8) as well as to psychometric parameters of well-being in 40- to 60-yr-old women (9). In a recent study in age-advanced men and women, 50 mg DHEA restored adrenal androgen levels to youthful levels, whereas 100 mg induced supraphysiological levels in women but not in men (5). Moreover, administration of DHEA (50 mg/day) to elderly men and women led to an increase in self-reported well-being (10). As a neuroactive steroid DHEA may influ-

ence processes of cognition and memory as well as sleep architecture (11, 12). Furthermore, DHEA may have an important role in the regulation of the immune response and in the control of cell proliferation (13–15).

Patients with adrenal insufficiency suffer from chronic DHEA(S) deficiency, because routine replacement therapy with glucocorticoids and mineralocorticoids fails to restore adrenal androgen concentrations. It has been shown that DHEA(S) is transformed into potent androgens in a variety of tissues (16). Therefore, DHEA replacement therapy may be of special importance for female patients with adrenal insufficiency, because androgen deficiency in these patients is frequently neglected (17). Accordingly, it has been shown that despite an otherwise adequate replacement therapy in Addison's disease, quality of life may be inferior to that of normal subjects (18). Thus, DHEA replacement in female patients with adrenal insufficiency may hold the potential to improve their functional status and well-being. Moreover, DHEA administration to these patients is well suited to gain further insight into the physiological role of DHEA, because a true deficit is replaced.

The aim of this study was, therefore, to define the optimum DHEA dose necessary to restore hormone concentrations in DHEA-deficient women to the normal range. To this end we studied the pharmacokinetics and biotransformation of

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orally administered DHEA in young females after suppression of adrenal steroid synthesis by dexamethasone (dex) and compared the results with baseline hormone secretion in these women.

## Subjects and Methods

### Subjects

Nine healthy female volunteers (age 19–30 yr, mean age  $23.3 \pm 4.1$  yr; eight nonsmoking, one smoking) were included in the study. All subjects were nonobese with a body mass index of 19.5 to 25.1 kg/m<sup>2</sup> (mean  $22.5 \pm 1.8$  kg/m<sup>2</sup>) and were regularly menstruating. None of the women had baseline serum concentrations of DHEA(S), androstenedione and/or testosterone (T) above the normal range. No participant was using oral contraceptives or other medications. Further inclusion criteria were normal blood cell counts and normal hepatic and renal function parameters. Before the initiation of the study, the protocol had been approved by the Ethics Committee of the University of Wuerzburg and written informed consent was obtained from all volunteers.

### Protocol

The study was performed in a single-dose, randomized, cross-over design. All subjects were studied during the early follicular phase of four subsequent cycles. Cycle 1 served as baseline. Preceding the study days during the cycles 2–4 all subjects were pretreated with oral dex ( $4 \times 0.5$  mg daily for 4 days). On the study days 2–4, either placebo or 50 or 100 mg DHEA were administered orally at 0900 h in a randomized order. On all four study days, 24-h frequent blood sampling was performed, starting after an overnight fast at 0830 h and ending at 0900 h the following day [–30 (0830 h), 0, 30, 60, 90, 120, and 150 min, and 3, 4, 5, 6, 7, 8, 10, 12, and 24 h]. Standardized meals were served at 1030, 1500, and 2100 h.

### DHEA preparation

The capsules containing 50 mg DHEA as well as the placebo capsules were both provided by Jenapharm (Jena, Germany). As determined by high performance liquid chromatography (HPLC), the mean DHEA content of the capsules was  $49.3 \pm 0.20$  mg. To assess the liberation rate, DHEA capsules ( $n = 20$ ) were given in 1000 mL water with 0.4% SDS. DHEA was measured by HPLC at 10, 20, 30, and 45 min, respectively, giving an *in vitro* liberation rate of 82.8% within 45 min.

### Hormone assays

All serum hormones were determined by established specific direct RIAs. Cortisol: Diagnostic Systems Laboratories (Sinsheim, Germany), cross-reactivities: DHEA 0.02%, T 0.14%, and 17 $\beta$ -estradiol ( $E_2$ ) 0.02%; DHEA: Diagnostic Systems Laboratories, cross-reactivities: DHEA(S) 0.04%, 4-androstene-3,17-dione 0.46%, and T 0.03%; DHEA(S): DPC Biermann (Bad Nauheim, Germany), cross-reactivity to DHEA 0.08%, androstenedione 0.12%, T 0.10%,  $E_2$  0.03%, estriol 0.03%; 4-androstene-3,17-dione (A' dione): Diagnostic Systems Laboratories, cross-reactivities: DHEA 0.04%, 5 $\alpha$ -dihydrotestosterone (DHT) 0.05%, estrone ( $E_1$ )

0.08%, estriol 0.03%; 5 $\alpha$ -androstane-3 $\alpha$ ,17 $\beta$ -diol-17-glucuronide (ADG): Diagnostic Systems Laboratories, cross-reactivity to DHT-glucuronide 1.2%, no cross-reactivity to 5 $\alpha$ -androstane-3 $\beta$ ,17 $\beta$ -diol or 5 $\alpha$ -androstane-3 $\alpha$ ,17 $\beta$ -diol-3-glucuronide; T: DPC Biermann, cross-reactivities: A' dione 0.5%, DHT 3.1%,  $E_2$  0.02%; DHT: Diagnostics Biochem Canada (London, Canada), cross-reactivities: 5 $\beta$ -DHT 4.1%, DHEA 5.5%;  $E_2$ : Biochem Immunosystems (Freiburg, Germany), cross-reactivities:  $E_1$  1.77%, estriol 0.47%;  $E_1$ : Diagnostic Systems Laboratories, cross-reactivities:  $E_2$  1.25%,  $E_1$  sulfate 2.02%, and estriol 0.22%. Cross-reactivities to other steroids relevant to this study were <0.01%. For all assays the intra- and interassay coefficients of variation were <8% and <12%, respectively.

### Statistical analyses

All data are reported as mean  $\pm$  SEM. The maximum serum concentration measured during a study period of a volunteer was reported as  $c_{\max}$ . The time at which  $c_{\max}$  occurred was reported as  $t_{\max}$ . The terminal elimination rate constant  $\lambda$  was calculated by means of log-linear regression. The area under the concentration-time curve (AUC) was calculated by means of trapezoidal integration. Because the suppressive effect of dex on the measured serum concentrations was markedly diminished after 12 h, we used AUC 0–12 h instead of AUC 0–24 h for data comparison. The mean concentrations of the various hormones, AUC 0–12 h as well as  $t_{\max}$  and  $c_{\max}$  were calculated and compared by ANOVA with repeated measurements,  $t$  tests, and Wilcoxon signed rank tests for paired samples. Significance was defined as  $P < 0.05$ .

## Results

### Dex suppression

The effect of dex suppression is shown in Table 1. Pretreatment with dex led to a lasting and pronounced suppression of cortisol, DHEA, DHEA(S), A' dione, ADG, T, DHT, and  $E_1$ . In contrast,  $E_2$  varied within a wide range at baseline and remained unchanged after dex (Table 1). Twenty-four hours after the end of dex treatment, the cortisol concentrations rose to 60% of baseline levels (Fig. 1A), whereas the other steroids (except  $E_2$ ) exhibited a prolonged suppressive effect (Table 1).

### DHEA and DHEA(S)

After the administration of 50 and 100 mg DHEA, respectively, DHEA serum concentrations increased in a dose-dependent manner to peak between 60–480 min ( $t_{\max}$  for 50 and 100 mg DHEA,  $2.5 \pm 2.1$  h and  $2.4 \pm 0.4$  h, respectively) followed by a slow decrease (Fig. 1B). Also, DHEA(S) increased rapidly peaking between 120–300 min ( $t_{\max}$  for 50 and 100 mg DHEA,  $2.9 \pm 0.9$  h and  $2.8 \pm 0.5$  h, respectively) followed by a decrease to levels found at baseline at 12 h (50 mg DHEA) and at approximately 18 h (100 mg DHEA) (Fig.

**TABLE 1.** Mean serum concentrations ( $\pm$ SEM) of measured hormones in female volunteers ( $n = 9$ ) at baseline (0 min) compared with concentrations after preceding dex treatment ( $4 \times 0.5$  mg/day for 4 days; placebo + dex, 0 min) and 1 day after end of dex treatment (placebo + dex, 24 h)

Hormones	Serum concentration at baseline	Serum concentration after dex	% of baseline (median, min–max)	Serum concentration after dex + 1 day	% of baseline (median, min–max)
Cortisol (nmol/L)	$360.1 \pm 23.6$	$19.3 \pm 2.4$	5.8 (2.9–8.7)	$232.6 \pm 30.1$	59.7 (37.9–118.8)
DHEA (nmol/L)	$33.9 \pm 4.7$	$5.8 \pm 0.9$	21.3 (8.7–38.9)	$20.1 \pm 3.1$	59.9 (24.5–109.2)
DHEA(S) ( $\mu$ mol/L)	$8.92 \pm 1.38$	$1.44 \pm 0.27$	12.9 (7.4–47.2)	$2.54 \pm 0.48$	31.2 (15.5–52.0)
Androstenedione (nmol/L)	$9.26 \pm 1.21$	$2.49 \pm 0.69$	16.1 (10.6–77.3)	$5.10 \pm 0.50$	62.0 (29.2–91.1)
ADG (nmol/L)	$1.59 \pm 0.35$	$0.32 \pm 0.07$	18.3 (7.4–45.7)	$0.45 \pm 0.07$	42.4 (8.8–55.0)
Testosterone (nmol/L)	$1.46 \pm 0.19$	$0.52 \pm 0.23$	18.7 (10.0–107.7)	$0.55 \pm 0.16$	33.3 (10.9–77.3)
DHT (nmol/L)	$0.61 \pm 0.08$	$0.27 \pm 0.08$	38.0 (16.0–79.9)	$0.30 \pm 0.08$	53.4 (33.2–96.6)
$E_2$ (pmol/L)	$149 \pm 31$	$310 \pm 172$	105.4 (25.8–830.1)	$127 \pm 47$	60.5 (13.0–257.6)
$E_1$ (pmol/L)	$190 \pm 19$	$106 \pm 19$	52.4 (25.2–104.7)	$99 \pm 15$	64.6 (18.1–72.0)

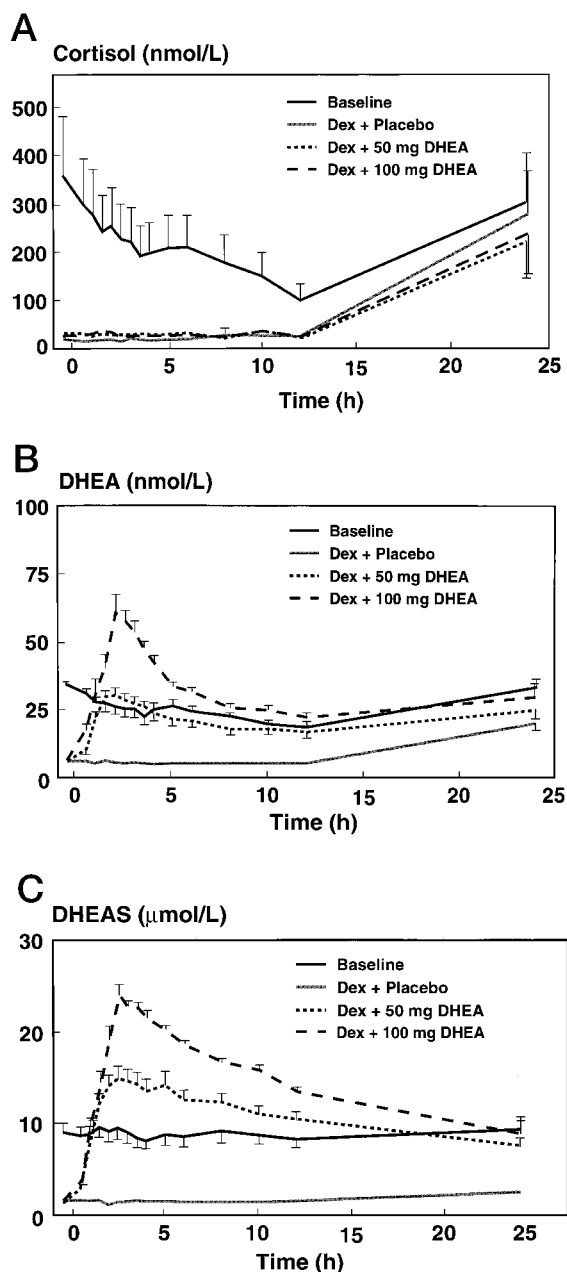


FIG. 1. A–C, Serum concentrations of cortisol (A), DHEA (B), and DHEA(S) (C) (mean  $\pm$  SEM) in nine female volunteers at baseline and following pretreatment with dex ( $4 \times 0.5$  mg/day for 4 days) after ingestion of placebo, 50 mg DHEA, or 100 mg DHEA.

1C). Comparing the AUC 0–12 h, the administration of 50 mg DHEA led to a restoration of baseline serum DHEA and DHEA(S), whereas 100 mg induced supraphysiological concentrations (Table 2). Detailed data concerning the pharmacokinetics of the two different DHEA doses are given in Table 3.

#### Other androgens

The administration of 50 mg DHEA induced an increase in serum androstenedione concentrations to levels around 60% of baseline, and 100 mg DHEA induced a further increase ( $t_{\max}$

for 50 and 100 mg DHEA,  $2.6 \pm 1.5$  h and  $2.6 \pm 0.7$  h, respectively) followed by a decrease to levels paralleling baseline concentrations from 6–24 h (Fig. 2A).

Fifty milligrams DHEA induced a 2-fold increase in serum T to levels significantly lower than baseline day concentrations, which were achieved after administration of 100 mg DHEA. Peak concentrations of T were measured after 60–480 min ( $t_{\max}$  for 50 and 100 mg DHEA,  $3.6 \pm 2.2$  h and  $2.6 \pm 0.6$  h, respectively) (Fig. 2B). DHT serum concentrations peaked between 30–240 min after 50 mg DHEA ( $t_{\max}$   $1.8 \pm 0.7$  h) to levels comparable with baseline, whereas 100 mg DHEA induced a lasting increase in DHT to levels above baseline ( $t_{\max}$   $2.6 \pm 0.8$  h) (Fig. 2C).

The administration of 50 mg DHEA was followed by a sharp increase in serum ADG concentrations to levels around baseline during the whole sampling period, whereas 100 mg DHEA led to elevated ADG concentrations around 200% of baseline levels ( $t_{\max}$  for 50 and 100 mg DHEA,  $2.7 \pm 1.1$  h and  $3.0 \pm 1.2$  h, respectively) (Fig. 2D).

#### Estrogens

After 50 mg DHEA, serum  $E_1$  increased to levels equivalent to baseline for at least 12 h. In a dose-dependent manner, 100 mg DHEA led to an increase in serum  $E_1$  to levels significantly above baseline (Fig. 3A). Peak concentrations were achieved after 180–480 min ( $t_{\max}$  for 50 and 100 mg DHEA,  $4.0 \pm 2.2$  h and  $2.8 \pm 0.6$  h, respectively). Serum  $E_2$  concentrations varied within a wide range on all 4 study days with neither a significant influence of dex nor of DHEA administration (Fig. 3B). The AUC 0–12 h after 100 mg DHEA was significantly higher than during baseline but not higher than after placebo (Table 2).

#### Discussion

Replacement of adrenal androgens in patients with Addison's disease or hypopituitarism should ideally restore DHEA(S) concentrations to levels equivalent to those before the onset of adrenal insufficiency. In our study we used dex administration as a tool to reproducibly suppress DHEA(S) concentrations to levels found in Addison's disease. We studied the effect of two different orally administered DHEA doses on circulating hormone concentrations in dex-suppressed young women and compared the results with the levels measured during a placebo cycle with dex and to a baseline cycle without preceding dex suppression. Thus, a detailed analysis of the optimum DHEA replacement dose became possible. In our study the restoration of DHEA(S) baseline levels was achieved by oral administration of a single dose of 50 mg DHEA. This supports the recently published results of Young *et al.* (19) who studied the pharmacokinetics of oral DHEA in 10 patients with hypopituitarism and observed an increase in DHEA(S) concentrations to the normal range of young females following the administration of 50 mg DHEA. Similar data were given by Casson *et al.* (13, 20) and Morales *et al.* (10) who used 50 mg DHEA for replacement in postmenopausal women and elderly males. However, the normal range of DHEA(S) shows a broad, mainly genetically determined variation. Our study is the first to compare the incremental levels after oral DHEA not

**TABLE 2.** AUCs of first 12 sampling hours (AUC 0–12) (mean  $\pm$  SEM) for measured hormones in female volunteers (n = 9). Comparison of baseline vs. placebo, 50 mg DHEA, and 100 mg DHEA, respectively, by *t* test after logarithmic transformation of measured values

AUC 0–12	Baseline	Placebo	DHEA (50 mg)	DHEA (100 mg)
DHEA (nmol/L $\times$ h)	280 $\pm$ 28	65 $\pm$ 8 <i>P</i> < 0.0001	241 $\pm$ 24 NS ( <i>P</i> = 0.38)	383 $\pm$ 35 NS ( <i>P</i> = 0.089)
DHEA(S) ( $\mu$ mol/L $\times$ h)	89.1 $\pm$ 16.1	17.5 $\pm$ 3.1 <i>P</i> < 0.001	139.6 $\pm$ 14.5 NS ( <i>P</i> = 0.067)	213.3 $\pm$ 7.2 <i>P</i> < 0.01
Androstenedione (nmol/L $\times$ h)	81.2 $\pm$ 9.0	22.4 $\pm$ 5.6 <i>P</i> < 0.001	47.1 $\pm$ 4.6 <i>P</i> < 0.05	86.3 $\pm$ 7.9 NS ( <i>P</i> = 0.62)
ADG (nmol/L $\times$ h)	15.1 $\pm$ 3.6	4.2 $\pm$ 1.4 <i>P</i> < 0.001	15.6 $\pm$ 2.1 NS ( <i>P</i> = 0.50)	32.6 $\pm$ 4.8 <i>P</i> < 0.001
T (nmol/L $\times$ h)	15.2 $\pm$ 2.3	4.4 $\pm$ 1.4 <i>P</i> < 0.001	7.0 $\pm$ 1.0 <i>P</i> < 0.01	15.1 $\pm$ 2.7 NS ( <i>P</i> = 0.98)
DHT (nmol/L $\times$ h)	5.71 $\pm$ 0.83	2.64 $\pm$ 0.56 <i>P</i> < 0.001	4.23 $\pm$ 0.63 <i>P</i> < 0.05	7.47 $\pm$ 0.90 NS ( <i>P</i> = 0.05)
E <sub>2</sub> (pmol/L $\times$ h)	1677 $\pm$ 518	3329 $\pm$ 1150 NS ( <i>P</i> = 0.26)	2723 $\pm$ 865 NS ( <i>P</i> = 0.14)	4166 $\pm$ 1682 <i>P</i> < 0.05
E <sub>1</sub> (pmol/L $\times$ h)	2050 $\pm$ 336	1255 $\pm$ 192 <i>P</i> < 0.01	2312 $\pm$ 319 NS ( <i>P</i> < 0.22)	3386 $\pm$ 247 <i>P</i> < 0.01

NS, Not significant.

**TABLE 3.** Pharmacokinetic data (calculated after baseline correction) of DHEA and DHEA(S) after oral administration of 50 mg DHEA and 100 mg DHEA, respectively

	Serum DHEA (after 50 mg DHEA)	Serum DHEA (after 100 mg DHEA)	Serum DHEA(S) (after 50 mg DHEA)	Serum DHEA(S) (after 100 mg DHEA)
AUC 0–12 h (DHEA: nmol/L $\times$ h; DHEA(S): $\mu$ mol/L $\times$ h)	176.1 $\pm$ 21.2 <i>P</i> < 0.001 <sup>a</sup>	317.6 $\pm$ 35.3 <i>P</i> < 0.001 <sup>a</sup> <i>P</i> < 0.001 <sup>b</sup>	121.6 $\pm$ 12.3 <i>P</i> < 0.001 <sup>a</sup>	195.4 $\pm$ 8.9 <i>P</i> < 0.001 <sup>a</sup> <i>P</i> < 0.001 <sup>b</sup>
C <sub>max</sub> (DHEA: nmol/L; DHEA(S): $\mu$ mol/L)	26.4 $\pm$ 3.8 <i>P</i> < 0.001 <sup>a</sup>	62.1 $\pm$ 11.4 <i>P</i> < 0.001 <sup>a</sup> <i>P</i> < 0.001 <sup>b</sup>	14.9 $\pm$ 1.4 <i>P</i> < 0.001 <sup>a</sup>	25.2 $\pm$ 1.5 <i>P</i> < 0.01 <sup>a</sup> NS ( <i>P</i> = 0.5) <sup>b</sup>
T <sub>max</sub> (h)	2.5 $\pm$ 2.1 NS ( <i>P</i> = 0.07) <sup>c</sup>	2.4 $\pm$ 0.4 NS ( <i>P</i> = 0.05) <sup>c</sup> NS ( <i>P</i> = 0.21) <sup>c</sup>	2.9 $\pm$ 0.9 NS ( <i>P</i> = 0.09) <sup>c</sup>	2.8 $\pm$ 0.5 NS ( <i>P</i> = 0.07) <sup>c</sup> NS ( <i>P</i> = 0.57) <sup>c</sup>
$\lambda$ (1/h)	0.09 $\pm$ 0.03	0.10 $\pm$ 0.03	0.05 $\pm$ 0.01	0.06 $\pm$ 0.02
t <sub>1/2</sub> (h)	8.9 $\pm$ 3.6	7.6 $\pm$ 2.7	13.2 $\pm$ 2.7	12.1 $\pm$ 2.8

<sup>a</sup> Comparison of placebo vs. 50 mg DHEA or 100 mg DHEA by means of ANOVA.<sup>b</sup> Comparison of 50 mg DHEA vs. 100 mg DHEA by means of ANOVA.<sup>c</sup> Comparison by Wilcoxon signed rank test.

with a reference range, but with the individual baseline levels of the volunteers and thereby allows a closer look on dose-response relationships. Looking at the daily production rate of DHEA (20–30 mg) (10) and the *in vitro* liberation rate of our DHEA capsule (83%), the administration of a 50-mg dose for DHEA replacement seems plausible. Buster *et al.* (21) studied the pharmacokinetics of 150 and 300 mg DHEA in eight postmenopausal women and concluded from their data that a dose of 50–75 mg may be suitable to approximate the premenopausal adrenal androgen milieu (21). Accordingly, the administration of 100 mg DHEA to our volunteers induced an increase in DHEA(S) levels to the supraphysiological range. In previous studies, high doses of DHEA up to 1600 mg (22–24) or even 2250 mg (25) have been used, but only few pharmacokinetic data have been reported. In most of these studies a dose-dependent, 3- to 10-fold increase in DHEA(S) baseline levels to persistent supraphysiological concentrations has been described. In our study a lasting, dose-dependent increase in DHEA(S) concentrations was noted after both DHEA doses, with DHEA(S) levels comparable with baseline following the administration of 50 mg DHEA. However, at 24 h after DHEA administration DHEA(S) concentrations had not fully returned to levels observed after placebo. Thus, chronic treatment with a daily dose of 50 mg

DHEA may induce slightly supraphysiological DHEA(S) concentrations. Long-term studies of our DHEA preparation are required to clarify whether for chronic replacement in females an even lower dose (*e.g.* 30–40 mg) may be sufficient.

The increase in DHEA(S) shortly after oral ingestion of DHEA indicates an important contribution of extraadrenal sulfotransferases. The liver most likely plays a predominant role in this activity, because transdermal and transvaginal administration of DHEA avoiding the first-pass effect induces a higher DHEA/DHEA(S) ratio (26, 27). This was also observed during the early phase after sublingual DHEA administration (5). Moreover, the preparation of DHEA may also affect the pharmacokinetics, because Casson *et al.* (26) described a decrease of the DHEA/DHEA(S) ratio after oral administration of micronized DHEA in comparison with a crystalline preparation. However, despite the high sulfotransferase activity in the liver, a multitude of tissues contain sulfotransferases and may also contribute to the conversion of DHEA to DHEA(S) (28, 29). After peaking, serum DHEA concentrations showed a slow decline, although the reported half-life of endogenous DHEA is only around 50 min (30). This suggests that DHEA(S), with its much longer half-life, is continuously converted back to DHEA via widespread tissue sulfatase activity (31–34).



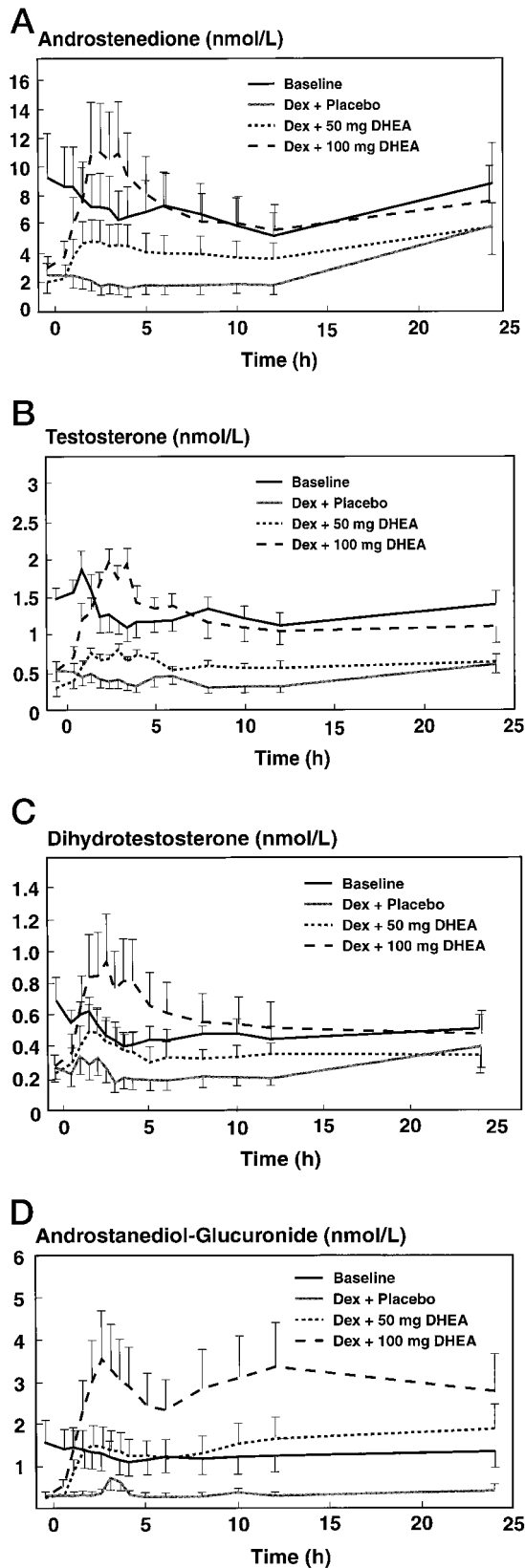


FIG. 2. A–D, Serum concentrations of androstenedione (A), T (B), DHT (C), and ADG (D) (mean  $\pm$  SEM) in nine female volunteers at baseline and following pretreatment with dex ( $4 \times 0.5$  mg/day for 4 days) after ingestion of placebo, 50 mg DHEA, or 100 mg DHEA.

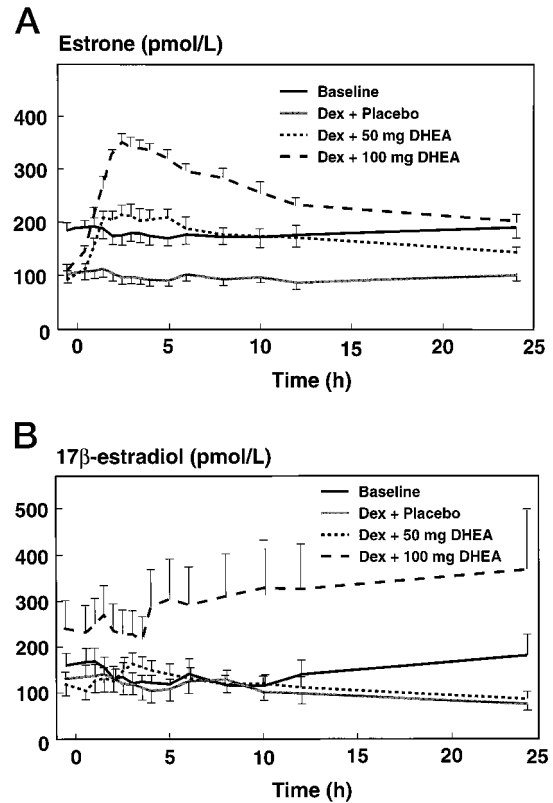


FIG. 3. A and B, Serum concentrations of  $E_1$  (A) and  $E_2$  (B) (mean  $\pm$  SEM) in nine female volunteers at baseline and following pretreatment with dex ( $4 \times 0.5$  mg/day for 4 days) after ingestion of placebo, 50 mg DHEA, or 100 mg DHEA.

Administration of 50 mg DHEA was sufficient to restore the serum concentrations of DHT and ADG to nonsuppressed baseline levels, whereas 100 mg DHEA was required to fully restore A'dione and T concentrations to baseline. This could be explained by high  $5\alpha$ -reductase activity with rapid conversion of T to DHT at a dose of 50 mg DHEA, whereas at 100 mg DHEA saturation of  $5\alpha$ -reductase may be reached. However, 24 h after 100 mg DHEA, A'dione and T levels had not returned to the mean levels seen after placebo, indicating that chronic administration of 100 mg DHEA may bear the risk of supraphysiological androgen concentrations. Our findings are in agreement with the study of Young *et al.* (19) in patients with hypopituitarism. They described an increase in T and A'dione to the lower normal range and of DHT and ADG into the higher normal range of women after 50 mg DHEA, whereas 200 mg DHEA induced supraphysiological androgen concentrations (19). Labrie *et al.* (27) studied pharmacokinetics and bioconversion during percutaneous administration of a 20% DHEA solution in a daily dose of 20 mL for 2 weeks in elderly men and women. In the female volunteers A'dione increased by 80% and T by 50%, with DHT concentrations remaining unchanged, whereas ADG increased by 120% (27). Therefore, transdermal administration of DHEA also increases circulating androgens, but possibly to a lesser degree than oral DHEA. In contrast, it has been reported that after transvaginal administration of 150 mg DHEA serum T remained unaffected (26), also indicating that

biotransformation of DHEA may be modified by the route of administration.

DHEA is generally assumed to exert its effects mainly via bioconversion to androgens (or estrogens) rather than by direct action (5). Recently published results on a DHEA-specific binding site on human T-lymphocytes (35) have not yet been reconfirmed. However, serum concentrations of androgenic and estrogenic steroids may not correctly reflect the bioconversion of DHEA, because a considerable amount of DHEA is converted into active androgens (or estrogens) directly in the cells of peripheral target tissues thereby exerting an intracrine action (36). In a variety of tissues steroidogenic enzymes responsible for DHEA conversion to androgens (and estrogens) have been demonstrated including  $3\beta$ -hydroxysteroid dehydrogenase,  $17\beta$ -hydroxysteroid dehydrogenase,  $5\alpha$ -reductase, and aromatase (16). ADG is a major metabolite of DHT as well as of A'dione (37) and has been suggested to be a marker of T metabolism in peripheral tissue (38). Therefore, the proportionally higher increase of ADG observed in our volunteers as well as in the studies of Young *et al.* (19) and Labrie *et al.* (27) may be because of enhanced bioconversion of DHEA to potent androgens inside the peripheral target cells. This may indicate that local hormone concentrations are not adequately reflected by the androgen concentrations measured in the circulation but rather by the level of their metabolite ADG.

Interestingly, following ingestion of DHEA a dose-dependent increase in circulating estrone also was observed. This supports the recent report by Young *et al.* (19) in patients with hypopituitarism describing a dose-dependent increase in  $E_1$  as well as in  $E_2$  levels. Unfortunately, no gender-specific analysis of estrogen increases was given (19). Serum  $E_2$  concentrations in our female volunteers with intact ovarian function were unaffected by DHEA administration. Mortola and Yen (24) saw no change in serum  $E_1$  or  $E_2$  within 4 h after administration of 400 mg DHEA to six postmenopausal women, but a 3-fold increase in  $E_1$  and  $E_2$  after 14 days of treatment with a daily dose of 1600 mg. Buster *et al.* (21) found no change in  $E_1$  and  $E_2$  concentrations during 12 h following oral intake of 150 and 300 mg DHEA. In a study of 17 females treated with 50 mg DHEA for 12 weeks no effect on estrogens was seen, but this may have been because of the heterogeneity of the volunteers, because 2 of the 17 women were premenopausal and 8 of the 15 postmenopausal women were current users of estrogen replacement therapy (10).

In our study the role of DHEA as an androgen precursor is not only reflected by the increase in androgens after oral administration of DHEA, but also by the dex-induced suppression of androgens. Only a few studies have analyzed the effect of dex on circulating androgens in healthy, nonhyperandrogenemic young females (39, 40). During the early follicular phase, the adrenal contribution to serum T and A'dione has been calculated as 66% and 55%, respectively (39). However, from our results an even higher adrenal contribution can be calculated, because after dex pretreatment the serum concentrations of both steroids fell below 30% of baseline levels. Additionally, it has to be taken into account that a significant proportion of the ovarian contribution to peripheral androgens may derive from DHEA(S), which has been suggested as a precursor of ovarian steroidogenesis (41,

42). Thus, our study highlights the importance of adrenal steroid secretion for female androgen physiology. Moreover, dex pretreatment also induced a significant suppression of serum  $E_1$  to 50–60% of baseline levels thereby supporting the view that DHEA(S) serves as a prohormone for some 30% of serum  $E_1$  in normal young women (42).

In conclusion, our results suggest a daily dose of 50 mg DHEA as suitable for replacement therapy in females with adrenal androgen deficiency. According to cross-sectional studies (7, 8, 9), as well as to the first clinical experiences with DHEA replacement (10) in elderly people, DHEA(S) seems to have a positive influence on well-being. An even more pronounced effect of DHEA has to be expected in patients with adrenal insufficiency, especially females. Moreover, the observed kinetics of DHEA biotransformation with a lasting androgen increase after a single oral dose make DHEA a promising tool for any kind of androgen replacement in females (*e.g.* postmenopausal women). On the other hand, the generation of highly active circulating steroids after DHEA ingestion suggests that DHEA may possibly have unfavorable effects in a variety of clinical settings, *e.g.* hormone-dependent cancer (28). Therefore, the widespread uncontrolled use of DHEA should be discouraged until more data concerning adverse effects have become available. Long-term studies in patients with adrenal insufficiency are now needed.

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