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# Absorption and metabolism of oral progesterone

M I WHITEHEAD, P T TOWNSEND, D K GILL, W P COLLINS, S CAMPBELL


## Summary and conclusions

**The absorption, metabolism, and clearance of progesterone from the peripheral circulation were investigated in five postmenopausal women after oral administration of 100 mg daily for five consecutive days. Maximal plasma concentrations of progesterone were observed within four hours after ingestion of the last dose, when the range (22·11-34·18 nmol/l; 696-1077 ng/100 ml) was comparable with that observed during the mid-luteal phase of the ovarian cycle. The surge in values lasted six hours, and progesterone concentrations remained raised for at least 96 hours. Of the three metabolites studied, the plasma concentrations of pregnanediol-3α-glucuronide were most raised by treatment, the peak values ranging from 1097 nmol/l (54·9 μg/100 ml) to over 2000 nmol/l (100 μg/100 ml), which was the upper limit of the assay used. Concentrations of 17-hydroxyprogesterone were least raised, and the peak values ranged from 4·32 to 9·68 nmol/l (143-319 ng/100 ml). The plasma profile of 20α-dihydroprogesterone most closely approximated that of progesterone, although the range of maximal values was lower (7·11-16·06 nmol/l; 228-514 ng/100 ml). Plasma concentrations of oestradiol were unchanged by giving progesterone.**

**It is concluded that the increases in circulating concentrations of progesterone and the biologically active metabolite 20α-dihydroprogesterone, and the duration of these increases, were sufficient to modulate the biochemistry of responsive tissues. Oral progesterone may thus have a therapeutic role, and this route of administration merits further investigation.**


## Introduction

Synthetic progestogens have been used with benefit to manage dysfunctional uterine bleeding, endometrial hyperplasia and carcinoma, premenstrual tension, and endometriosis. In addition, they have been combined with oestrogens in oral contraceptive preparations and to treat menopausal symptoms. These synthetic steroids possess chemical configurations based on either 19 or 21 carbon atoms. The structural differences lead to variations in biological effects. Certain progestogens possess androgenic effects while others have antiandrogenic and some even oestrogenic properties. Adverse reactions owing to excessive androgenic or oestrogenic activity are well recognised.[1-3] Naturally occurring progesterone has rarely been used in clinical practice. Doses of 1000 mg/day have been administered by mouth to pregnant women with a history of habitual abortion and low pregnanediol concentrations: in 60% of pregnancies a viable baby was delivered.[4] Doses of 300 mg daily inhibit ovulation.[5] In men 100 mg produced a plasma surge lasting less than six hours.[6] Until now, no information has been available on the pharmacodynamics of progesterone after oral administration in women.

We designed the present study to assess the rate of absorption of progesterone from the gastrointestinal tract and to determine the concentration appearing in the peripheral circulation. We studied the hormone's metabolism by determining its conversion to pregnanediol-3α-glucuronide, 20α-dihydroprogesterone, and 17-hydroxyprogesterone. Finally, we evaluated the importance of oral progesterone as a precursor of oestradiol.

## Patients and methods

Five asymptomatic postmenopausal women volunteered to participate in the study. All were parous, had intact ovaries, and had experienced a natural menopause between two and eight years previously. Their ages ranged from 51 to 57 years and their weights from 61·5 to 92·4 kg. Four had never received any hormonal medication, but the fifth had been prescribed an oestrogen and progestogen preparation for 36 months to alleviate menopausal symptoms. This treatment had been stopped 12 months previously.

The study lasted 11 days. To obtain baseline values venepuncture was performed between 0900 and 1000 on days 1 and 2. For the next five consecutive days (days 3-7) one progesterone capsule containing 100 mg pure steroid was given by mouth at 0800.

On day 7 venepuncture was performed hourly from 0900 to 1600 and again at 2000. Additional blood samples were taken at 0800 on days 8, 9, 10, and 11—that is, 24, 48, 72, and 96 hours after the last capsule was administered. Each 20 ml blood sample was collected into lithium heparin tubes and centrifuged immediately, and the plasma stored at −20°C.

All concentrations of steroid hormones were measured by radioimmunoassay. The method for progesterone was that described by Youssefnejadian *et al*,[7] except that we used a more specific antiserum to progesterone-11α-succinyl-bovine thyroglobulin, which reduced the cross-reaction with 5α-dihydroprogesterone to less than 15%. We measured 20α-dihydroprogesterone and 17-hydroxyprogesterone concentrations by the methods of Florensa *et al*[8] and Youssefnejadian *et al*[9] respectively. The concentration of pregnanediol-3α-glucuronide was measured in a 50 μl plasma aliquot by adapting the method for estimating the concentration in urine.[10] Oestradiol was assayed by the method of Emment *et al*,[11] except that we used a more specific antiserum to oestradiol-6-carboxymethyl oxime-BSA, which reduced the cross-reaction with oestrone to less than 2%.

For each steroid we examined the distribution of values by calculating the arithmetic mean, geometric mean, median, degree of skewness, and kurtosis. The results obtained between 0900 and 1600 on day 7 were examined similarly after adjusting the time relative to the peak value for progesterone. As all values approximated to a normal distribution we compared the concentrations before and after ingestion of progesterone by using Student's *t* test.

## Results

Figure 1 shows the concentration of plasma progesterone in all samples from the five patients. All pretreatment concentrations (days 1 and 2) were within the postmenopausal range for our laboratory. Interpatient differences in absorption of progesterone are shown by the variation in the time taken to achieve maximal plasma concentrations after administration of the last capsule. Thus in three patients maximal concentrations occurred one hour after the last capsule had been taken. In the two other patients, however, absorption was slower and peak values were reached three hours later at 1200. Similar patterns were observed for pregnanediol-3α-glucuronide, 20α-dihydroprogesterone, and 17-hydroxyprogesterone.

To establish the temporal relation in plasma between concentrations of progesterone and those of pregnanediol-3α-glucuronide, 20α-dihydroprogesterone, 17-hydroxyprogesterone, and oestradiol we

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standardised the values obtained between 0900 and 1600 on day 7 by using the maximal plasma concentration of progesterone as a reference point P. Figure 2 shows the means of the results, the baseline values on days 1 and 2, and the values obtained between 24 and 96 hours after the last capsule was taken. All pretreatment values were within the postmenopausal range for our laboratory.

The plasma concentrations of progesterone, pregnanediol-3α-glucuronide, 20α-dihydroprogesterone, and 17-hydroxyprogesterone reached a peak simultaneously. Progesterone concentrations fell most rapidly, and four hours after they were maximal approximated to concentrations of 20α-dihydroprogesterone. Thereafter, the concentrations of these two hormones fell similarly, those of 20α-dihydroprogesterone just exceeding those of the parent compound. Concentrations of pregnanediol-3α-glucuronide on days 7-11 greatly exceeded those of 20α-dihydroprogesterone and 17-hydroxyprogesterone; those of 17-hydroxyprogesterone were the least raised. Oestradiol concentrations were not changed by administration of progesterone and remained within the pretreatment range.

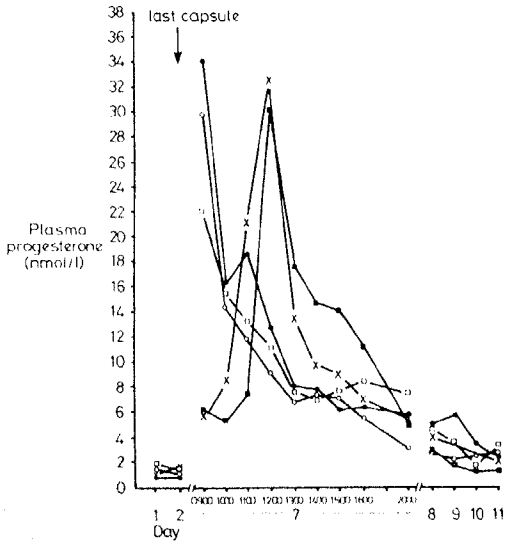


FIG 1—Concentrations of progesterone in peripheral plasma before and after oral administration of progesterone in the five patients studied.

*Conversion: SI to traditional units*—Plasma progesterone: 1 nmol/l ≈ 32 ng/100 ml.

For each hormone the peak values obtained on day 7 and the values observed 12, 24, and 96 hours after the last progesterone capsule was taken were compared with the pretreatment values (table). Concentrations of progesterone were significantly raised when maximal ($p < 0.0005$) and 96 hours after the end of treatment ($p < 0.01$). Concentrations of pregnanediol-3α-glucuronide and 20α-dihydroprogesterone were significantly raised when maximal and for up to 24 hours after the end of treatment ($p < 0.0005$). The concentration of 17-hydroxyprogesterone was significantly raised only when maximal ($p < 0.0025$), and had returned to within the pretreatment range within 12 hours after the end of treatment. Oestradiol concentrations did not change significantly during the study.

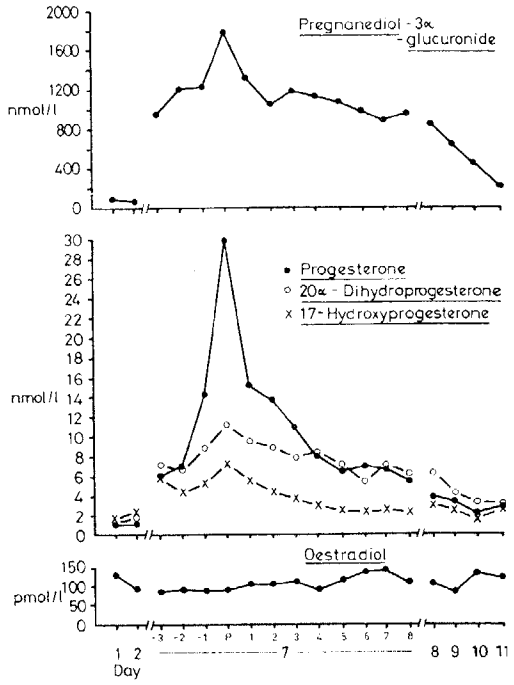


FIG 2—Mean concentrations in peripheral plasma of pregnanediol-3α-glucuronide, progesterone, 20α-dihydroprogesterone, 17-hydroxyprogesterone, and oestradiol before and after oral administration of progesterone. The concentrations on day 7 were standardised by taking the peak plasma concentration of progesterone as the reference point P.

*Conversion: SI to traditional units*—Pregnanediol-3α-glucuronide: 1 nmol/l ≈ 50 ng/100 ml. Progesterone: 1 nmol/l ≈ 32 ng/100 ml. 20α-Dihydroprogesterone: 1 nmol/l ≈ 32 ng/100 ml. 17-Hydroxyprogesterone: 1 nmol/l ≈ 33 ng/100 ml. Oestradiol: 1 pmol/l ≈ 27 pg/100 ml.

## Discussion

The mass of progesterone administered daily in this study (100 mg) is about four times the mean mass produced daily by the ovary during the mid-luteal phase of the ovarian cycle.[12] The peak progesterone concentrations, however, were within the range found in the luteal phase, indicating that about 25% of the progesterone taken by mouth appeared in peripheral plasma.

This study has shown that the absorption, further metabolism, and clearance of oral progesterone are rapid. Within four hours after ingestion maximal plasma concentrations of progesterone had been achieved in all five patients, and peak concentrations of the parent steroid and its three major metabolites occurred simultaneously. Plasma concentrations of progesterone were raised to within the range found in the mid-luteal phase for about six hours, although the values at 24 and 96 hours after the end of treatment were still significantly raised above the baseline. Similar rapid absorption and clearance of progesterone have been reported after rectal and vaginal administration[13] and oral ingestion by men.[6]

*Mean (± SD) concentrations of various steroids in peripheral plasma of five postmenopausal women before and after oral administration of progesterone*

| | Before treatment | Peak values on day 7 | Time after last capsule taken | | |
|---|---|---|---|---|---|
| | | | 12 hours | 24 hours | 96 hours |
| Progesterone (nmol/l) | 1·30 ± 0·14 | 29·81 ± 4·67*** | 5·43 ± 2·29** | 3·89 ± 1·06*** | 2·41 ± 0·73* |
| 20α-Dihydroprogesterone (nmol/l) | 1·67 ± 0·82 | 11·05 ± 3·38*** | 6·14 ± 1·63*** | 6·23 ± 1·38*** | 2·91 ± 1·25 |
| 17-Hydroxyprogesterone (nmol/l) | 1·98 ± 1·03 | 7·35 ± 2·49** | 2·41 ± 1·40 | 3·18 ± 1·80 | 2·27 ± 0·86 |
| Pregnanediol-3α-glucuronide (nmol/l) | 85 ± 59 | 1774 ± 452*** | 967 ± 84*** | 873 ± 151*** | 202 ± 130 |
| Oestradiol (pmol/l) | 114 ± 60 | 94 ± 32 | 113 ± 30 | 112 ± 89 | 123 ± 91 |

Significance of difference from concentrations before treatment: *$p < 0.01$; **$p < 0.0025$; ***$p < 0.0005$.

*Conversion: SI to traditional units*—Progesterone: 1 nmol/l ≈ 32 ng/100 ml. 20α-Dihydroprogesterone: 1 nmol/l ≈ 32 ng/100 ml. 17-Hydroxyprogesterone: 1 nmol/l ≈ 33 ng/100 ml. Pregnanediol-3α-glucuronide: 1 nmol/l ≈ 50 ng/100 ml. Oestradiol: 1 pmol/l ≈ 27 pg/100 ml.

The greatest and most prolonged increase in the concentrations of the major metabolites occurred with pregnanediol-3α-glucuronide. The peak mean factorial increase was 20·9, and the mean 24 hours after the end of treatment was 10·3. Concentrations of 17-hydroxyprogesterone were least raised: the peak factorial increase was only 3·7, and within 12 hours after the end of treatment the concentrations had returned to within the pretreatment range.

Unlike the two other metabolites, 20α-dihydroprogesterone is not only biologically effective in its own right[14] but is also formed from progesterone in target tissues such as the endometrium.[15] Therefore, raised plasma concentrations of this hormone are important in terms of biological activity. In our opinion the plasma concentrations of progesterone and 20α-dihydroprogesterone observed in this study are sufficient to suggest that progesterone given by mouth may affect target tissues. Further studies are needed to determine the end-organ response and therapeutic efficacy. Plasma concentrations that are sustained within the range found in the luteal phase for longer periods may be necessary to achieve the optimal therapeutic response. Logically, administering progesterone either twice daily or in combination with cholesterol pivalate, which increases the bioavailability,[6] will produce this effect.

Progestins are prescribed primarily for their anti-oestrogenic effects. Physiologically progesterone is a precursor of oestrogen, and extensive conversion of administered progesterone to oestradiol would be undesirable. The absence of any significant change in oestradiol values during this study is thus reassuring. Clinically, oral progesterone may be of value when synthetic progestogens have caused adverse symptoms that necessitate stopping treatment. These symptoms include acne, breast tenderness, and depression and have been observed during treatment with oral contraceptives[3 16 17] and with oestrogen and progestogen preparations used during the menopause (M I Whitehead, P T Townsend, and J McQueen, unpublished observations). No such side effects were reported in this study. In addition, the synthetic progestogen component of the oral contraceptive pill has been linked with more serious hazards such as hypertension,[18] and this effect is possibly mediated through adverse changes in high-density lipoprotein cholesterol.[19] Naturally occurring progesterone may not alter blood lipids, and as it is stable for two years and cheap it may possibly be usefully combined with oestrogen as a contraceptive and in treating the menopause.

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ONE HUNDRED YEARS AGO Professor Flower, FRS, lately delivered a very interesting lecture at the Royal Institution, before a crowded audience, on Fashion in Deformity. He passed in review the various methods adopted by different nations and at different ages of deforming or altering the natural form of some portion of the body, in obedience to the dictates of fashion. The various practices of shaving, cutting, and dressing the hair and beard, and tattooing the skin, were alluded to by him; but more attention was given to the disfigurement of the nose, lips, and ears, by cutting holes and inserting various substances through them—almost identical customs being described among people living in most remote regions of the world. The fantastic methods of filing and chipping the front teeth into different patterns, practised by the Malays and some African Negroes, were then noticed. An account of the mode of altering the form of the head, which prevailed once extensively in Europe, and was almost universally adopted in Peru and on the western coast of North America, was followed by a description of the effects produced upon the feet of civilised races by the unnatural form of the boots commonly worn; the evils of pointed toes and high heels being exemplified by diagrams and specimens. The construction of the waist was next noticed, the figure of the Venus of Milo and one taken from the last Paris fashion-book being compared and contrasted. All these customs were shown to arise from a similar propensity, which manifested itself in the human mind under all conditions of civilisation, to tamper with a form which good sense as well as good taste ought to teach was the most perfect that could be designed. The origin of these fashions was mostly lost in obscurity, all attempts to solve them being little more than guesses. Some of them have become associated with superstitious observances, and have been spread and perpetuated; some have been vaguely thought to be hygienic; most have some relation to conventional standards of improved personal appearance; but, whatever their origin, the desire to conform to common usage, and not to appear singular, is the prevailing motive which leads to their continuance. The vitiation of taste produced by these conventional standards, which shows itself in the Malay in the preference of black teeth to those of the most pearly whiteness; in the Bougs, Negro, and American Botocudos, in liking lips and ears which are enormously and to our eyes hideously enlarged by huge wooden plugs inserted through them; in the Chinook Indian, by contempt of any head which is not flattened like a pancake or elongated like a sugar-loaf—is displayed among ourselves by the admiration of unnaturally pointed toes and contracted waists. (*British Medical Journal*, 1880.)