# PHARMACOKINETICS OF ETHYNYLOESTRADIOL IN WOMEN FROM DIFFERENT POPULATIONS

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## ABSTRACT

The pharmacokinetics of a dose of 50ug ethynyloestradiol administered orally was studied in fourteen centres. Absorption was rapid and the highest serum concentrations of total ethynyloestradiol were found in most subjects at 1 h and by 24 h concentrations were less than 250 pg/ml. Calculation of the half-lives for absorption, distribution and elimination showed wide variations between subjects, the half-life of elimination varying from 2.5 h to more than 30 h. Bioavailability as measured by the area under the serum ethynyloestradiol concentration-time curve also showed more than a ten-fold variation. Intra-centre differences in the various parameters measured were as large as the inter-centre differences.

**Submitted for publication November 28, 1980**

**Accepted for publication April 24, 1981**

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# CONTRACEPTION

## INTRODUCTION

Previously (1) the rate of metabolism of the gestagen norethisterone was compared in women enrolled in fourteen different World Health Organization Collaborating Centres for Clinical Research. In that study the subjects took a tablet containing both norethisterone and ethynyloestradiol and the present communication presents the results in respect of the rate of metabolism of the oestrogen.

## DESIGN OF INVESTIGATION

The design of the investigation was described in detail previously (1). Each centre was requested to enrol six women who were studied on days 5 or 6 of the menstrual cycle. The subjects were not taking other medication. Blood samples were obtained from each woman enrolled in the trial prior to and at 0.5, 1, 2, 4, 8, 12 and 24 h after taking a pill containing 1 mg norethisterone and 50 µg ethynyloestradiol. All the pills used were from the same batch. The pill was taken between 0700 h and 0900 h and the subjects were allowed a light breakfast. The concentration of total (i.e. unconjugated plus sulphate and glucuronide conjugates) ethynyloestradiol in each sample was estimated as described previously (2). In this method, a methanol extract of plasma is hydrolysed with an enzyme preparation containing an active β-glucuronidase and phenolsulphatase and the free steroid chromatographed on Sephadex LH20 prior to radioimmunoassay of the ethynyloestradiol fraction. The cross-reaction of norethisterone with the antiserum at 50% binding is less than 0.005% and at 80% binding, less than 0.2%. Interference from norethisterone is further reduced by the chromatographic separation. Interference from oestradiol-17β is usually less than 25 pg/ml and is unlikely to be important except in the case of some of the 24 h values. Quetelet's index (weight in kilograms divided by the square of the height in metres) was calculated (3).

## RESULTS

Mean values for the serum total ethynyloestradiol concentration obtained on the samples from each centre are shown in Table I. Absorption was rapid as shown by the fact that in most of the centres the highest values for ethynyloestradiol were obtained in the 1-h sample. Absorption was apparently particularly rapid in Bangkok where similar concentrations were observed at 0.5 h and at 1 h and was considerably slower in Chandigarh, Singapore and Seoul where peak values were obtained in the 2-h sample. As shown by the large standard deviations for the mean values, there was a considerable inter-subject variation in each centre in the steroid concentrations achieved. After the peak there was a marked decrease in the serum levels up to 8 h followed by a slower decrease between 8 and 24 h. By 8 h after administration, there was much less difference between the centres in the mean values achieved, although there was still a considerable inter-subject variation within each centre. At 24 h the mean concentration ranged from 56 pg/ml in Alexandria up to 135 pg/ml in Bangkok. In the 24-h samples, 3 of the subjects in Seoul, 2 of those in Canada and 4 of those in Alexandria had values below the limit of sensitivity of the method (50 pg/ml) and in Alexandria 2 of the subjects had values lower than

Table I. Serum ethynyloestradiol concentrations after oral administration of 50μg ethynyloestradiol

(Values are mean ± SD in pg/ml, number of subjects per centre in parentheses)

| Centre | Time (h) after administration of dose | | | | | | |
|---|---|---|---|---|---|---|---|
| | 0.5 | 1 | 2 | 4 | 8 | 12 | 24 |
| Alexandria (6) | 345 ± 278 | 603 ± 504 | 537 ± 189 | 335 ± 189 | 209 ± 174 | 109 ± 73 | 56 ± 25 |
| Bahia (6) | - | 1350 ± 1077 | 1393 ± 1871 | 545 ± 335 | 249 ± 136 | 192 ± 136 | 100 ± 59 |
| Bangkok (6) | 1432 ± 766 | 1442 ± 736 | 918 ± 498 | 678 ± 411 | 330 ± 224 | 201 ± 134 | 135 ± 57 |
| Bombay (6) | 998 ± 768 | 1508 ± 1058 | 1230 ± 533 | 797 ± 292 | 326 ± 161 | 276 ± 148 | 126 ± 70 |
| Chandigarh (7) | 734 ± 589 | 1187 ± 577 | 1203 ± 375 | 815 ± 334 | 366 ± 122 | 241 ± 62 | 117 ± 50 |
| London, Canada (6) | 968 ± 440 | 1648 ± 497 | 1133 ± 493 | 649 ± 257 | 341 ± 296 | 244 ± 212 | 96 ± 51 |
| Los Angeles (6) | 1037 ± 579 | 1148 ± 378 | 833 ± 350 | 433 ± 222 | 214 ± 72 | 182 ± 72 | 127 ± 70 |
| Lusaka (4) | 759 ± 453 | 1289 ± 477 | 930 ± 331 | 530 ± 314 | 300 ± 97 | 208 ± 116 | 125 ± 97 |
| Mexico (6) | 1341 ± 731 | 1346 ± 625 | 1211 ± 305 | 684 ± 266 | 271 ± 111 | 162 ± 70 | 97 ± 48 |
| Santiago (6) | 496 ± 359 | 875 ± 301 | 942 ± 296 | 504 ± 171 | 369 ± 171 | 212 ± 91 | 92 ± 51 |
| Seoul (6) | 425 ± 270 | 955 ± 781 | 1053 ± 485 | 808 ± 320 | 355 ± 103 | 222 ± 87 | 114 ± 87 |
| Singapore (5) | 629 ± 715 | 742 ± 370 | 1197 ± 519 | 752 ± 210 | 353 ± 123 | 199 ± 105 | 112 ± 69 |
| Stockholm (6) | 1634 ± 758 | 1717 ± 558 | 1112 ± 190 | 548 ± 100 | 311 ± 111 | 213 ± 77 | 107 ± 44 |
| Sydney (6) | 405 ± 315 | 813 ± 376 | 965 ± 563 | 501 ± 317 | 269 ± 194 | 170 ± 70 | 129 ± 57 |

this in the 12-h samples. None of the subjects had a concentration exceeding 250 pg/ml in the 24-h sample.

Judging by the peak levels obtained, absorption of the steroid in Alexandria was poor, since the mean value obtained 1 h after administration of the pill was much lower than that in the other centres. The difference was not, however, significant, due to high values found in one Egyptian subject but the reduced bioavailability in the Egyptian subjects was indicated by the fact that 5 of the 6 women did not show a value of 1 h exceeding 500 pg/ml, whereas in the other 13 centres only 8 of the 78 subjects studied did not achieve this level at 1 h. This poor absorption appeared to be specific for ethynyloestradiol since studies of the norethisterone levels in these subjects at various times after administration of the tablet showed that the values obtained in Alexandria were not lower than those obtained in the other centres.

In contrast with norethisterone, where a straight line was obtained when the logarithms of the serum concentrations were plotted against time, for ethynyloestradiol an exponential curve was obtained and it was not possible to analyse the data for ethynyloestradiol in the same way as for norethisterone. The mean values for each centre were, therefore, analysed by fitting them to a two-compartment model (4), the integrated equation for the model being $C_t = Ae^{-\alpha t} + Be^{-\beta t} - C0e^{-Kat}$ where

$C_t$ = plasma concentration at time t,
A = plasma concentration at time 0 for rapid disposition curve,
B = plasma concentration at time 0 for slow disposition curve,
$\alpha$ = first order rate constant for disposition from the central compartment to the peripheral compartment,
$\beta$ = apparent elimination rate constant,
K = overall elimination rate constant,
$K_{12}$ and $K_{21}$ = first order distribution constants between the central compartment 1 and the peripheral compartment 2,
$K_a$ = first order rate constant of absorption,
C0 = extrapolated value for the concentration at time 0 from the slope of the elimination phase.

The calculated pharmacokinetic parameters for each centre are shown in Table II. Calculation of the absorption half-life confirmed the conclusions from a consideration of the plasma levels that there was a wide variation in the rate of uptake. The uptake was particularly quick in the case of Bangkok, Bombay, Los Angeles, Mexico and Stockholm and it was particularly slow in Singapore. There was less variation in the half-life of distribution ($\alpha$) between the various centres; ten of the 14 centres had a value from 1.4 to 2.0, two centres had a more rapid distribution (Bahia and Canada) and two others (Alexandria and Santiago) had slower rates of distribution. In all except one centre (Santiago), $K_{12}$ was greater than, or approximately equal to, $K_{21}$.

Most of the centres had mean values for the half-life of elimination ($\beta$) between 10 and 22 h, except for Canada, where the half-life of elimination was rapid (8.9 h) and Sydney, where it was extremely slow (30.8 h). However, there was a large inter-subject variation, individual half-lives varying from 2.5 h to more than 30 h (Fig. 1). In 68.7% of

Table II. Pharmacokinetic parameters for ethynyloestradiol after administration of a 50μg dose (Values are mean with SD for AUC 0-24 h values)

| Centre | Intercepts (pg/ml) | | | Slopes ($h^{-1}$) | | | Peripheral Rate Constants ($h^{-1}$) | | Eliminiation Rate Constant ($h^{-1}$) | Half-lives (h) | | | | AUC (ng/ml/h) | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| Centre | A | B | Co | α | β | Ka | $K_{12}$ | $K_{21}$ | | α | β | Ka | F | 0-∞ | 0-24 h |
| Alexandria | 541 | 192 | 990 | 0.248 | 0.047 | 2.254 | 0.08 | 0.09 | 0.12 | 2.8 | 14.7 | 0.31 | 0.40 | 5.8 | 4.6 ± 1.6 |
| Bahia | 4944 | 361 | 9279 | 0.753 | 0.053 | 1.950 | 0.31 | 0.10 | 0.39 | 0.9 | 13.0 | 0.35 | 0.13 | 8.6 | 8.1 ± 6.5 |
| Bangkok | 1413 | 298 | 1661 | 0.328 | 0.033 | 0.752 | 0.15 | 0.08 | 0.13 | 2.1 | 20.8 | 0.09 | 0.26 | 11.1 | 9.9 ± 4.4 |
| Bombay | 1402 | 562 | 3685 | 0.339 | 0.062 | 3.234 | 0.11 | 0.14 | 0.15 | 2.0 | 11.2 | 0.21 | 0.42 | 12.1 | 10.2 ± 4.5 |
| Chandigarh | 2040 | 500 | 3281 | 0.437 | 0.061 | 1.698 | 0.16 | 0.13 | 0.19 | 1.5 | 11.4 | 0.41 | 0.31 | 10.9 | 9.6 ± 1.7 |
| London, Canada | 2493 | 620 | 4440 | 0.704 | 0.078 | 2.332 | 0.31 | 0.20 | 0.27 | 0.9 | 8.9 | 0.29 | 0.28 | 9.6 | 9.9 ± 3.9 |
| Los Angeles | 1525 | 265 | 4834 | 0.505 | 0.031 | 4.937 | 0.27 | 0.10 | 0.15 | 1.4 | 22.4 | 0.14 | 0.20 | 10.6 | 6.1 ± 1.3 |
| Lusaka | 1365 | 349 | 2803 | 0.410 | 0.043 | 2.788 | 0.18 | 0.11 | 0.15 | 1.7 | 16.1 | 0.24 | 0.28 | 10.4 | 7.9 ± 3.7 |
| Mexico | 1884 | 271 | 6310 | 0.388 | 0.043 | 5.170 | 0.15 | 0.08 | 0.19 | 1.8 | 16.2 | 0.13 | 0.22 | 10.0 | 8.7 ± 1.9 |
| Santiago | 635 | 488 | 7608 | 0.266 | 0.070 | 3.591 | 0.06 | 0.15 | 0.12 | 2.6 | 9.9 | 0.19 | 0.58 | 8.7 | 7.5 ± 2.6 |
| Scoul | 1654 | 428 | 2729 | 0.371 | 0.055 | 1.507 | 0.13 | 0.12 | 0.17 | 1.8 | 12.5 | 0.46 | 0.32 | 10.4 | 9.3 ± 3.4 |
| Singapore | 1790 | 353 | 2173 | 0.344 | 0.048 | 0.953 | 0.12 | 0.09 | 0.17 | 2.0 | 14.3 | 0.72 | 0.28 | 10.2 | 8.6 ± 2.8 |
| Stockholm | 1907 | 424 | 11990 | 0.489 | 0.057 | 7.571 | 0.20 | 0.14 | 0.21 | 1.4 | 12.1 | 0.09 | 0.28 | 9.7 | 7.4 ± 3.4 |
| Sydney | 1424 | 291 | 2174 | 0.360 | 0.023 | 1.679 | 0.20 | 0.07 | 0.12 | 1.9 | 30.8 | 0.41 | 0.19 | 12.5 | 7.3 ± 3.6 |

the subjects, the half-life was within the range 6 to 16 h and the overall mean half-life ($\pm$ SD) was 13.1 $\pm$ 7.8 h.

Bioavailability as measured by the area under the concentration-time curve (AUC) was, as expected, greater when derived from the computer analysis, which measured bioavailability from zero to infinity, than when measured from 0 to 24 h by the 'cut and weigh' method. There was a two-fold variation in the mean values for the centres whether calculated on a zero to infinity time basis or on a 0 to 24 h basis. The AUC 0 to 24 h, calculated for each subject, showed a large variation, the lowest value recorded being 2.25 ng/ml/h in an Australian woman and the highest, 29.4 ng/ml/h, in a Brazilian woman. The distribution of the 0-24 h AUC values is shown in Fig. 2. The values for the AUC in Egyptian women were significantly lower ($P < 0.05$) than the values recorded in Bangkok, Bombay, Chandigarh, London (Canada), Mexico, Santiago, Seoul and Singapore.

There was a significant correlation between the 0-24 h AUC values (y pg/ml/h) and the peak serum ethynyloestradiol concentrations (x pg/ml) for each subject ($R = 0.73$, regression equation: $y = 7.69x - 2285$).

## DISCUSSION

The results show that ethynyloestradiol was rapidly absorbed, the mean value for the half-life of absorption in all centres being less than one hour. However, in spite of this rapid absorption, the amount of the steroid available to the systemic circulation, as indicated by the plasma levels, showed a large variation. This would suggest a variability in the magnitude of the first pass effect between subjects (5) or in the amount absorbed from the intestine. It is known that substantial amounts of orally administered ethynyloestradiol are excreted in the faeces (6) but most of this probably arises as a result of the entero-hepatic circulation of the oestrogen.

With the exception of London (Canada), the peripheral rate constants and the elimination constant were low and of a similar order of magnitude. Similar values have been reported previously (4). The mean half-life of the elimination phase showed a wide variation between centres from 9 h in London (Canada) to 31 h in Sydney. The large difference between centres in values for the elimination constant were also noticeable in the range of values within each centre. Thus the values in Alexandria varied from 4 to 36 h, in Bahia from 4 to 22 h and in Bangkok from 10 to 36 h. Large variations of this type were apparent in all centres except Seoul, where the range was from 7 to 11 h. Values quoted by other workers for the elimination half-life are 6 to 14 h (4), 6.9 h (5) and 30 h (7).

A comparison of orally and intravenously administered ethynyl-oestradiol (5) suggested that bioavailability after oral administration was about 50%. The present findings show clearly a large inter-subject variation in bioavailability. The large variation between subjects in the bioavailability and in the elimination half-life could have important clinical implications particularly with the low doses of ethynyloestradiol now being used. When larger doses were used, such variations in the pharmacokinetics of the steroid may not have been important but, with the lower doses, the relationship of the variation in bioavailability and half-life to possible effects of the steroid need to be investigated.

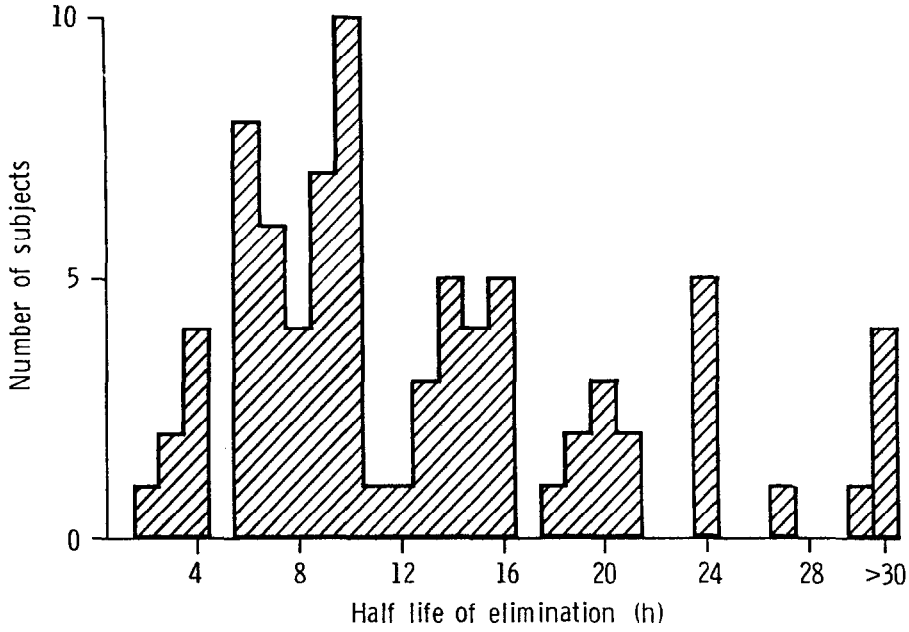


Figure 1. Range of elimination half-lives in women receiving 50µg ethnyloestradiol orally.

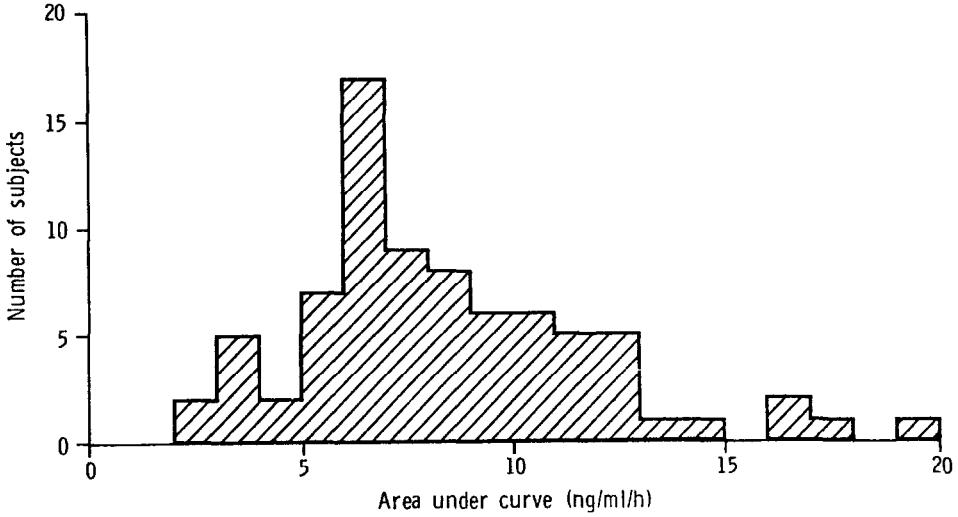


Figure 2. Variations in bioavailability (area under the serum ethynyloestradiol concentration-time curve) in women receiving 50µg ethynyloestradiol orally.

In women where the bioavailability is low and the half-life of elimination is short, there may be some loss of efficacy or the occurrence of spotting or break-through bleeding whereas in women where the half-life is unduly long, there may well be an accumulation of the steroid within the tissues and consequently an increased biological effect. These wide variations also mean that the results of studies employing only a small number of subjects should be interpreted with caution. Apart from the present study, only one other investigation (4) has used a sufficiently large number of subjects to give an overall view of the pharmacokinetics.

Based upon the analysis of the values for the serum ethynyloestradiol concentration in a small number of subjects, Warren and Fotherby suggested that when the values were plotted semi-logarithmically, there was an approximately straight-line relationship between 2 and 8 hours and between 8 and 24 h and half-lives could be calculated based or these assumptions. These assumptions were validated in the present study where sampling occurred more frequently than in the earlier study. When the mean values were plotted semi-logarithmically against time, only two centres (Santiago and Bahia) did not show a straight-line relationship over the period 2 to 8 h and 9 out of the 14 centres gave an approximately straight line for the period 8 to 24 h. In two centres little error would have been caused by assuming a straight-line relationship and in only three centres (Alexandria, Bangkok and Mexico) would the assumption have caused an appreciable error. The results of the present study, therefore, provide some validation for those studies in which less frequent sampling occurred(8). Thus samples taken at 2, 8 and approximately 24 hours after administration of the dose would be sufficient to characterise the distribution and elimination phases for orally administered ethynyloestradiol.

It is known that many factors affect drug disposition and metabolism. Apart from the general health of the subject and body mass, other factors include environmental ones (9), nutritional factors (10, 11) and genetic factors (12). It might be expected, therefore, that subjects from different ethnic groups would show differences in the rate at which they metabolise any particular compound and that these would lead in the different ethnic groups to differences in the responses to, and the toxicity of, the compound. It was, therefore, surprising that there was no marked difference between the metabolism of ethynyloestradiol in the women in the different centres involved in this study. However, all subjects were in good health and in good nutritional status as indicated by the value for Quetelet's index. The centres in which the subjects were enrolled in the present trial were urban ones and therefore, in some countries, the women enrolled may not have been representative of the total population. Another possibility for the lack of any significant difference between the different centres may be that in this pilot study only six women were recruited in each centre. However, the intra-centre differences appeared to be as large as the inter-centre ones, so that large numbers of women would have needed to have been enrolled in each centre to show any significant differences which did exist. A large variation between subjects in serum total ethynyloestradiol was also found in a previous study (8).

A recent report (4) suggests that there are differences in the pharmacokinetics of ethynyloestradiol in women in different populations; plasma ethynyloestradiol levels were lower in Nigerian women than in Thai women after administration of a 50 µg dose. However, in this study there were also considerable variations between subjects. It should be emphasised that the results in this communication pertain to total (unconjugated plus conjugated) ethynyloestradiol. Previous studies have shown that after administration of ethynyloestradiol, conversion of this steroid to the sulphate is rapid and that the levels of conjugated ethynyloestradiol in blood are about ten times higher than those of unconjugated ethynyloestradiol. Almost all of the papers published so far have been concerned with the estimation of unconjugated ethynyloestradiol. The values reported in this paper for the plasma concentration and half-lives of total ethynyloestradiol are in agreement with those published previously (8, 13). Our previous investigations have shown a parallel relationship between the levels of unconjugated and conjugated ethynyloestradiol in plasma suggesting that the conjugated steroid serves as a reservoir for the unconjugated steroid. This suggestion receives some support from the findings that the pharmacokinetic parameters for unconjugated ethynyloestradiol in plasma previously reported (4) agree closely with the values for conjugated ethynyloestradiol found in the present investigation.

ACKNOWLEDGEMENTS

This investigation received financial support from the Special Programme of Research in Human Reproduction, World Health Organisation. J. Akpoviroro was in receipt of a scholarship from the Ministry of Education, Bendel State, Nigeria.

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