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PHARMACOKINETICS OF NORETHISTERONE FROM TWO DIFFERENT COMBINATION CONTRACEPTIVE PILLS IN INDIAN WOMEN

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Summary : In view of our previous studies that the plasma elimination of norethisterone (NET) from minipill is faster in low socio-economic group Indian women, the present studies were contemplated to find the least effective dosage of NET from combination pills. Pharmacokinetics of NET were evaluated in a total of twenty women of low socio-economic group taking pills containing NET-acetate (500 μg or 1 mg) and ethinyl estradiol (30 or 50 μg respectively) on empty stomach. Blood samples were drawn at different time intervals from 0.5 to 24 hr and plasma NET was estimated by a specific radio-immunoassay.

In the women taking 1 mg NET-acetate containing pills peak plasma levels ranging from 6.2 to 20.8 ng/ml were observed at 1 hr whereas with 500 μg pill they ranged from 2.0 to 6.5 ng/ml and the peak was noted at 4 hr. Pharmacokinetic parameters of NET were more or less comparable between the two pills. The results suggest that pills containing 500 μg NET-acetate and 30 μg ethinyl estradiol provide adequate levels of NET even in low-socio-economic group women.

Key words : pharmacokinetics norethisterone contraceptives combination pills

INTRODUCTION

The synthetic steroid, norethisterone (NET), is one of the contraceptive progestational steriods either used singly or in combination with other estrogens. In our earlier study with NET mini pill (0.35 mg) it was found that plasma elimination half life of NET was faster in women from low socio-economic group as compared to high socio-economic group (1). Because of this there is the possibility that malnutrition may cause increased drug failures. Since combination pills are more commonly used, the pharmacokinetics of NET were evaluated in women of low socio economic group from two different combination pills.

MATERIALS AND METHODS

The subjects belonged to a group of low socio-economic group attending a contraceptive testing centre. The details of selection of volunteers for this study are same as in our earlier study (1). The subjects were administered orally a pill containing either 1 mg or 500 μg NET-acetate along with 50 or 30 μg ethinylestradiol (EE_2), respectively, on empty stomach. The tablets were prepared and supplied by IDPL, Hyderabad. Blood samples were drawn at 0.5, 1, 2, 4, 6, 8, 12 and 24 hr after administration

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of the pill into heparinised tubes, plasma was separated and stored at −20°C until analysis. Anthropometric measurements such as skin fold thickness at triceps, height, weight and mid-arm circumference were recorded.

Plasma levels of NET were estimated by a specific radioimmunoassay according to the method given in our earlier report (1) using the antiserm raised at IRR, Bombay (2). Pharmacokinetic parameters were evaluated graphically for each individual using a two compartment open model as described previously (1).

RESULTS

Mean plasma levels of NET over 24 hr in women who ingested 1 mg and 500 μg pills are given in Table I. Except for one subject in each case the peak concentrations were noticed within 1 to 2 hr with 1 mg pill and the peak was much delayed (appeared at 4 hr) in the case of 500 μg pill. The peak levels of NET ranged from 6.08 to 20.8 ng/ml with the higher dose as compared to 2.03 to 6.8 ng/ml with low dose. The corresponding range of plasma levels at 24 hr were 0.33-1.75 ng/ml and 0.12 to 0.87 ng/ml respectively.

The pharmacokinetic parameters of NET obtained with both oral pills are compared in Table II. There were no differences in the half lives of distribution rate constants ($t_{\frac{1}{2}}\alpha$) between the two pills. The overall area under the plasma concentration curve (AUC) and 24 hr values are in proportion to the dose given. The plasma elimination half life ($t_{\frac{1}{2}}\beta$) was significantly lower in the subjects receiving lower dose as compared to those receiving higher dose.

TABLE I : Mean plasma NET values (ng/ml) at different time points from two contraceptive preparations.

Dose	*Time in hr*							
	0.5	1	2	4	6	8	12	24
1 mg NET-acetate+	5.9±	10.5±	9.6+	4.6±	3.4±	2.1±	1.6±	0.86±
50 μg EE_2 (n=9)	2.06	1.82	0.91	0.75	0.43	0.32	0.24	0.17
500 μg NET-acetate+	0.18±	0.53±	1.08±	4.75±	—	2.27±	1.31±	0.43±
30 μg EE_2 (n=11)	0.023	0.193	0.421	0.484		0.358	0.225	0.072

Values are mean±S. E. M.

TABLE II : Comparison of three different oral contraceptive preparations for pharmacokinetic parameters of NET.

Dose	$t_{\frac{1}{2}}\alpha$	$t_{\frac{1}{2}}\beta$	$Kat_{\frac{1}{2}}$	Wt/Ht_2%	*SFT (mm)*	*AUC ng/ml-1*	*hr of peak (range)*	*Peak values ng/ml (range)*	*24 hr values ng/ml (range)*
	Mean±S. E.								
1 mg NET-acetate + 50 μg Ethinyl estradiol (8)	1.01± 0.09	10.75±* 0.72	0.43± 0.082	0.202± 0.007	16.2± 2.1	64.8± 7.6	0.5 to 2.0 hr	6.08 to 20.8	0.33 to 1.75
500 μg NET-acetate+30 μg EE_2 (10)	1.11± 0.14	8.02± 0.697	$	0.183± 0.007	12.3± 1.8	41.9± 4.6	4 hr	2.03 to 6.82	0.12 to 0.87
350 μg NET only mini pill (previous study) (11)	1.0± 0.14	5.9± 1.06	0.57± 0.007	0.188± 0.006	13.7± 1.6	33.5± 5.8	1 to 2 hr	4.7 to 14.8	ND

*P <0.05 as compared to other groups

$ — Ka could not be calculated as there was a shift in the absorption phase or the number of points were inadequate.

ND — Not detectable. No. in parentheses indicates sample size

SFT — Skin fold thickness (triceps)

Though Wt/Ht²% and skin fold thickness at triceps (SFT) of the subjects investigated for 1 mg pill tends to be higher, the differences were not statistically significant. One of the striking differences noted here is the difference in time to attain peak levels. The time to reach peak levels is longer with 500 μg NET-acetate than with 1 mg NET-acetate. The reasons for this delayed absorption are not known. The tablets were made by the same supplier using similar components. It is unlikely that a small increment in estrogen to progestagen ratio of the pill is responsible for causing the delay in achieving peak levels with 500 μg pills.

DISCUSSION

The pharmacokinetics of NET from contraceptive pills containing NET-acetate and EE_2 have indicated a longer half life as compared to the values we reported earlier from pills containing NET alone (1). Statistically, the difference was significant only between NET-acetate 1 mg and NET mini pill (Table II).

The longer half life with higher dose could be due either to the comparatively better anthropometry of the women (1 mg pill) (1) or the dose dependent characteristics of NET as was reported earlier (3). Since dose dependent alterations in half life are known to occur only at very large intakes of the drug, the observed longer half life may be a result of the better anthropometry of the corresponding group.

A comparative account of all the available data on pharmacokinetics of NET and combination pills containing NET-acetate (along with those from the present study) is depicted in Table III. The data are consistent with the previous reports, suggesting that even in low socio-economic group users, a dose of 500 μg NET-acetate + 30 μg EE_2 seems to provide adequate plasma levels of NET.

TABLE III : Comparison of NET pharmacokinetics with literature values

Details of the dose administered	T_{max} *(hr)*	*Peak value ng/ml*	$t_{\frac{1}{2}}\alpha$ *(hr)*	$t_{\frac{1}{2}}\beta$ *(hr)*	*Kat* $\frac{1}{2}$ *(hr)*	*References*
1 mg NET-acetate+ 50 μg EE_2	1 to 2	—	1.17	4.8 to 12.8	—	(6,7,8)
1 mg NET+50 μg EE_2 or 1 mg NET+120μg EE_2	0.5 to 2	14.3 to 15.7	0.6 to 6.8	5.2 to 12.9	0.21	(7,9,10,11,12)
500 μg NET+35 μg EE_2	—	—	—	11 5±2.4	—	(13)
2 mg NET+70 μg EE_2	1.2 to 2.4	—	—	6.2 to 6.4	—	(14)
1 mg NET-acetate+ 50 μg EE_2	0.5 to 2.0	6.0 to 20.8	1.01±0.09	10.75±0.72	0.43+0.082	Present study
500 μg NET-acetate+ 30 μg EE_2	4 hr	2.03 to 6.82	1.11±0.14	8.02±0.69	—	Present study

Values are mean (± S.E.M.) or range

From clinical evaluation, it was reported that irregular bleeding is a major cause of poorer follow-up with 500 μg as compared to 1 mg NET pills (4, 5). The plasma levels of NET attained after ingestion of both the pills are reasonably high from the present acute studies and therefore cannot explain the difference in the incidence of breakthrough bleeding noted by previous workers. However, the steady state plasma levels of NET achieved after multiple doses are to be evaluated before a firm conclusion is drawn as to the suitability of 500 μg dose of NET-acetate pharmacokinetically.

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