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Pharmacokinetics of norethindrone oenanthate in 5 women after a single dose of norethindrone oenanthate and estradiol valerate

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ABSTRACT The pharmacokinetics of norethindrone oenanthate (NET-OEN) and norethindrone (NET) were studied in 5 healthy Chinese women after a single im injection of NET-OEN 50 mg + estradiol valerate (EV) 5 mg in 1 ml peanut oil: benzyl benzoate 6 : 4 v/v. Peak levels of NET and NET-OEN in all women reached within 5 d, the mean peak values for NET and NET-OEN were 4.6 and 1.2 ng/ml, respectively. The apparent elimination rate constants (K) were calculated as 0.15 d^{-1} and 0.25 d^{-1} for NET and NET-OEN. The apparent elimination half-lives were 4.6

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and 3.1 d for NET and NET-OEN, respectively. There was a significant correlation between the elimination half-life and peak values for NET. The time required for the serum steroid concentration to decrease below 100 pg/ml were 32±4 d for NET, and 14±6 d for NET-OEN. There was a $1^1/_2$ fold variation among the women in the bioavailability of NET. After im injection, 96.5% of bioavailable NET was released within 30 d.

KEY WORDS norethindrone oenanthate; norethindrone; estradiol valerate; female contraceptive agents; intramuscular injections; pharmacokinetics; radioimmunoassay

One of the major side-effects of progestogen-only long-acting injectable contraceptives is the disruption of normal endometrial function[1]. Monthly injections of progesterone/estrogen combination have a high efficacy and a good cycle control and are highly acceptable[2]. We have compared monthly injections of NET-OEN 80 mg + EV 5 mg and NET-OEN 50 mg + EV 5 mg with NET-OEN 200 mg given every 60 d in clinical study. The formulation of NET-OEN 50 mg + EV 5 mg has been shown to be a very promising monthly injectable contraceptive.

However, few studies of the pharmacokinetics have been published on monthly injectables. The present study deals with the serum levels of NET and NET-OEN after a single im injection of NET-OEN 50 mg + EV 5 mg.

MATERIALS AND METHODS

Five healthy women who had not used any form of steroidal contraceptives in the preceding 3 months, aged 30±6 yr with a normal menstrual history were chosen for this study. Each received 50 mg NET-OEN and 5 mg EV in 1 ml vehicle (peanut oil: benzyl benzoate = 6:4, v/v) by intragluteal injection on d 5 of menstrual cycle. Blood samples were collected every other day during the medication and allowed to clot. The serum was stored at −20℃ until analysis. The concentrations of NET[3] and NET-OEN[4] were determined by radioimmunoassay.

NET-OEN and [15,16-^{3}H] NET-OEN (720 GBq/mmol) were obtained from Schering AG, Berlin. NET and [6, 7-^{3}H]NET (2035 GBq/mmol)were purchased from New England Nuclear and Sigma Co, UK.

Sensitivity of assays were 10 and 25 pg/tube for NET and NET-OEN, respectively. The variations of inter- and intraassays were 6.0-8.0% and 9.6-10.3%, respectively.

Quetelet's Index (weight in kg divided by square of height in metres) was calculated[5].

RESULTS

All the 5 women studied had values for Quetelet's Index within the desirable range.

Absorption of NET-OEN The NET and NET-OEN levels in serum are shown in Fig 1. Peak levels of NET and NET-OEN were seen within 5 d. The mean time to reach peak values for NET and NET-OEN were 3.4 and 2.6 d, respectively. In one woman, absorption was very rapid and peak values for NET and NET-OEN were attained within 2 and 1 d, respectively. The peak serum values of NET and NET-OEN ranged 4.6±1.3 and 1.2±0.5 ng/ml. There was a twofold variation in the peak values for NET and a fourfold variation for NET-OEN. However, these variation ranges appeared to be smaller than those observed by giving 200 mg NET-OEN[6]. The peak concentrations of NET were always greater than those of NET-OEN. The serum levels of NET and NET-OEN reached with 50 mg NET-OEN combination were lower than those obtained by injecting 200 mg NET-OEN[6]. The peak

serum concentrations of NET showed a significant negative correlation with the time required to reach these peak values ($r = -0.74$). However, there was no correlation between Quetelet's Index and peak values of NET and NET-OEN, and the time to reach peak values.

Elimination of NET-OEN Following im injection of NET-OEN the serum concentration-time curve showed an initial rising phase and a later decling phase. when the serum concentrations of NET and NET-OEN were plotted semilogarithmically against time in days (Fig 1), the plotted data were fitted to a one-compartment model and the absorption and elimination involved two consecutive apparent first-order processes. The integrated equation is a biexponential:

$$C = C_0(e^{-Kt} - e^{-Kab^t})$$

From the time of the peak values, there was a highly significant decrease in the concentration with time ($r > 0.90$). The regression line equation ($Y = B - AX$) was calculated for both NET and NET-OEN, the values for the constants B and A are shown in Tab 1. Using these regression equations, values for the apparent elimination constant (K) and elimination half-lives were calculated[8]. The elimination half-lives of NET and NET-OEN were 4.6 $\pm$0.7 and 3.1$\pm$1.1 d, respectively. There was a much wider variation in these values for NET-OEN than for NET. The apparent elimination half-lives of NET showed a significant ($p < 0.05$) correlation with the peak values ($r = 0.89$), and the time for serum steroid concentration to reach peak values ($r = 0.96$).

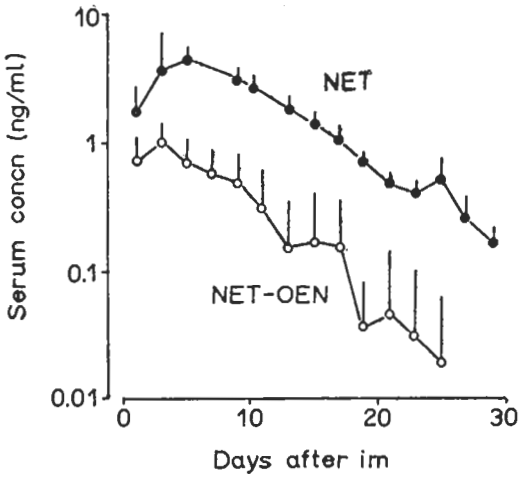

Fig 1. Serum concentrations of norethindrone (NET) and norethindrone oenanthate (NET-OEN) in 5 women after im 50 mg NET-OEN + 5 mg estrdiol valerate (EV). ($\bar{x} \pm SD$)

According to the regression line equations, the number of days required for the serum steroid concentration to decrease below 100 pg/ml was calculated. In all women

Tab 1. Pharmacokinetic parameters for NET-OEN

Subject	Quetelet's index (kg/m²)	Peak values (ng/ml)		TP* (d)		Regression line (Y = B-AX)(NET)		K		Apparent elimination half-life (d)	
		NET	NET-OEN	NET	NET-OEN	B	A	NET	NET-OEN	NET	NET-OEN
S	24.8	4.94	1.03	4	2	1.1734	0.06387	0.147	0.196	4.7	3.5
L	19.5	4.01	1.14	3	3	1.1105	0.06826	0.157	0.211	4.4	3.3
H	20.2	6.65	1.44	2	1	1.2541	0.08207	0.189	0.386	3.7	1.8
W	22.0	4.05	1.92	3	2	1.0282	0.06557	0.151	0.152	4.6	4.6
Y	19.9	3.26	0.58	5	5	0.9448	0.05237	0.121	0.304	5.7	2.3
Mean	21.3	4.6	1.2	3.4	2.6	1.1002	0.06643	0.153	0.25	4.6	3.1
SD	2.2	1.3	0.5	1.1	1.5	0.1209	0.01064	0.024	0.09	0.7	1.1

*TP The time after injection to reach peak values.

NET was detectable for a longer time (32±4 d) than was NET-OEN (14±6 d). All women had circulating levels of NET greater than 180 pg/ml on the d 25 after im injection.

The time for NET to be detectable showed a significant correlation with the apparent elimination half-lives ($r = 0.97$) and the peak values attained ($r = 0.99$).

Bioavailability of NET The relative bioavailability of NET was calculated by the trapezoid rule according to the following equation:

$$AUC_{0-\infty} = AUC_{0-T} + C_T/K$$

The $AUC_{0-\infty}$ (53±9 ng/ml·d) of NET varied among the women. Much lower values were obtained for NET-OEN (9±5 ng/ml·d). Since all of NET-OEN probably converted to NET, the values can be disregarded. The rapidity of the uptake of NET-OEN from the injection site was indicated by the fact that 43.7±12.0% of the bioavailable NET was released within 7 d a fter injection. The further47. 7±9.2% became available between d 8 and 21, and 5.1±2.3% from d 22 to 30.

There was a significant correlation between the AUC and the peak values of serum NET ($r = 0.89$) but no correlation with those for NET-OEN. There was no correlation between Quetelet's Index and all elimination pharmacokinetic parameters.

DISCUSSION

Several studies have been undertaken on the pharmacokinetics of NET-OEN at a dosage of 200 mg[3,4,9]. It seems that some of the side effects are related to an initial burst of drug release. In order to obviate these problems, one approach has been made to increase the number of injections, so that one injection is given monthly. The combination contained NET-OEN 50 mg and EV 5 mg has been widely tested as monthly injectable[2]. Therefore, it is interesting to study the pharmacokinetic profile of monthly injectable NET-OEN combination.

The plasma peak levels of NET and NET-OEN in all women were reached within 5 d after injection. In one woman, absorption rate was even more rapid. Similar to the situation of a dose of 200 mg NET-OEN, there was a variation in the peak values and the time required to reach the peak values for NET and NET-OEN, but the variation range was found to be smaller. The peak values of NET-OEN were always less than those of NET in case of injection of 200 mg NET-OEN.

Our previous metabolic study of [6,7-^{3}H] NET in rats proved that the elimination half-life was 3.2 d and the elimination constant (K) was 0.217 d^{-1} after iv injection; while apparent elimination half-life was 12 d and the K_{ab} was 0.0578 d^{-1} after im injection[7]. In such case $K_{ab} < K$, so that changes in absorption kinetics produced changes in the rate of elimination of drug from the body. This is sometimes called a "flip-flop" model. According to the "flip-flop" model, the terminal linear portion of a plot of log C versus time will have a slope of $-K_{ab}/2.303$ (A) rather than $-K/2.303$ and the method of residuals yields a measure of K rather than K_{ab}[8]. However, it still needs detailed pharmacokinetic data from human being to prove if there is same phenomenon in women receiving im injection of NET-OEN.

The estimates of bioavailability of NET showed a $1^1/_2$ fold variation among women and the mean value obtained was 52.8 ng/ml/d. The bioavailability of NET after giving 200 mg NET-OEN was about 150 ng/ml/d. In the present study, 96.5% of the bioavailable NET was released within 30 d after im. In all women the amount of NET becoming bioavailable after d 30 appeared to be about 3.5% of the total. Therefore, a possibility needs to be considered that the total amount of NET in the body will progressively increase with each

subsequent injection, if the rate of absorption of gestagen from im site remains constant and the metabolism of NET by liver is not increased by serial injections.

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单次注射庚炔诺酮和戊酸雌二醇后庚炔诺酮在妇女体内的药物动力学

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提要　5 名健康中国妇女 im 庚炔诺酮（NET-OEN）50 mg 及戊酸雌二醇 5 mg 后，血中炔诺酮（NET）及 NET-OEN 浓度均在 5 d 内达峰值，其平均峰值为 4.6 和 1.2 ng/ml. NET 与 NET-OEN 的表观消除速度常数 k 分别为 0.153 d^{-1} 和 0.25 d^{-1}. 血浆 NET 和 NET-OEN 的表观消除半衰期分别为 4.6 和 3.1 d，与血浆峰值及达峰时间明显相关. im 后 30 d 内，96.5%的 NET 已被释放并吸收.

关键词　庚炔诺酮；　炔诺酮；　戊酸雌二醇；　女用避孕药；　肌肉注射；　药物动力学；　放射免疫测定