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Norethisterone oenanthate as an injectable contraceptive: use of a modified dose schedule

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Summary and conclusions

Norethisterone oenanthate (NET-OEN) was given as an injectable contraceptive to 295 healthy women over 1606 woman-months. A modified injection schedule was used. There were no pregnancies, and the 12-month, life-table, use-related discontinuation rate was 39.1/100 users. Menstrual disturbance (10.8/100 women), minor side effects (13.5/100 women), and personal reasons (12.0/100 women) were the main causes of use-related discontinuation. There was no difference in use-related discontinuation rates between women receiving their first injection during a normal menstrual period and those receiving it immediately after a pregnancy. There were no serious side effects.

The use of NET-OEN in certain groups of women is recommended, particularly in those in need of highly effective contraception, who cannot or do not wish to take oral contraceptives, who are lactating, or who are awaiting hospital admission for sterilisation.

Introduction

The discovery by Junkman that the esterification of a progestogen alcohol produced a systematically active long-acting progesten led to the synthesis of a series of long-acting fertility-regulating agents.¹ During the past 15 years several of these drugs have been investigated,^{2,3} although only two of them—depot-medroxyprogesterone acetate (DMPA) and norethisterone oenanthate (NET-OEN)—have reached large-scale human trials.⁴⁻⁶ In the United Kingdom experience with injectable contraceptives is limited and DMPA is the only such preparation currently licensed by the Committee on Safety of Medicines,

and that only for short-term use.⁷ DMPA is effective in preventing pregnancy, with quoted failure rates of 0.1-2/100 woman-years and over 77 000 woman-years of experience reported worldwide. It may not be the drug of choice for long-term use owing to a high incidence of amenorrhoea and irregular bleeding patterns. In a multinational study⁸ comparing DMPA with NET-OEN given at 12-weekly intervals, patients using NET-OEN were found to have less amenorrhoea but significantly more pregnancies.

NET-OEN has been the subject of clinical trials in England for the past two and a half years. We report our experience with the drug given on a modified injection schedule.

Patients and methods

Patients were recruited from the family planning clinics, gynaecology wards, and postnatal wards of King's College Hospital. Informed consent was obtained from all. Only healthy women aged 18-45 years were admitted to the study. Unless they had recently delivered or been pregnant they were required to have a history of regular menstrual cycles, with a variation of not more than 10 days between the longest and the shortest menstrual cycles in the last three months. Patients who normally used hormonal contraceptives stopped using them for at least four weeks before the study.

Injection schedule—NET-OEN was supplied in ampoules containing 200 mg of the steroid in 1 ml of an oily solution. The ampoule was warmed in hot tap water and the drug given as an intramuscular injection into the gluteal muscles. A modified injection schedule was used. The first injection was given during days 1-5 of a normal menstrual period or before discharge from hospital after confinement or termination of pregnancy. The second, third, and fourth injections were given at eight-week intervals. Subsequent injections were given at 12-week intervals.

Follow-up—At each visit weight and blood pressure were recorded and menstrual details obtained. Complaints and any possible adverse effects were noted. All injections were given within seven days of the scheduled day. Patients who did not attend for injection on schedule were sent written reminders or contacted by telephone or home visit. If no response was obtained or the patient did not attend within seven days of a scheduled visit she was recorded as lost to follow-up. Patients who discontinued treatment were asked the reason for doing so. When a doctor discontinued treatment the reason for doing so was also recorded. The absence of periods for 90 days or more was recorded as "amenorrhoea," while continuous vaginal bleeding for more than 10 days was recorded as "prolonged bleeding." Patients discontinuing treatment because of the absence of regular vaginal bleeding, including those who discontinued because of vaginal bleeding requiring no sanitary protection (spotting), were recorded as having "irregular bleeding."

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Statistical methods—Life-table analysis by the methods of Tietze and Lewit⁹ and Potter¹⁰ was applied to the data, producing net and gross event rates. Student's *t* test was used for comparison of ages and parity between groups. The χ^2 test was used to determine the probability of discontinuing treatment.

Results

From 1 December 1975 to 31 August 1977, 295 women agreed to accept NET-OEN. Their mean age was $26.8 \pm \text{SD } 6.1$ years, and mean parity $2.0 \pm \text{SD } 1.5$. Table I lists their previous methods of contraception. Ninety-one of the women (30.8%) received their first injection after a pregnancy (hospital confinement or termination) and 204 (69.2%) during a normal menstrual period (table II). There was no significant difference in age ($P = 0.025$) or parity ($P = 0.10$) between the two groups.

TABLE I—Previous methods of contraception used by the 295 acceptors of NET-OEN

	No of patients		No of patients
Oral contraception ..	127	Coitus interruptus ..	6
Intrauterine device ..	100	No contraception ..	26
Barrier method ..	36		

TABLE II—Mean age and parity of women having their first injection of NET-OEN after pregnancy and during normal menstruation

	After pregnancy (n = 91*; 30.8%)	During normal menstruation (n = 204; 69.2%)
Mean age (years) : SD ..	25.5 ± 6.0	27.0 ± 6.0
Mean parity : SD ..	1.9 ± 1.3	2.1 ± 1.7

*Confinement, 60; termination, 31.

Tables III and IV give the results of life-table analysis by time of use. All rates are for use-related withdrawal from treatment. With use of the modified injection schedule the life-table pregnancy rate was zero. The main reasons for use-related withdrawal at 18 months were menstrual disturbance (22 patients), personal reasons (22 patients), and minor side effects (23 patients), the net discontinuation rates being 14.7, 14.2, and 13.5/100 women respectively. Amenorrhoea accounted for discontinuation by only 1.4/100 women. Discontinuations for personal reasons included 13 patients who were sterilised or no longer required contraception. Discontinuations for minor side effects included 10 patients who gained over 3 kg, three who had various aches and pains, and two who felt bloated. The two patients discontinuing because of major side effects had raised blood pressure during treatment, the diastolic pressure being 105 mm Hg or more. The overall use-related discontinuation rates were 39.1/100 women at 12 months and 49.2/100 women at 18 months.

Thirty patients failed to attend for injection within seven days of the scheduled date and were recorded as lost to follow-up. The χ^2 test comparison of those who started treatment during a menstrual period (204 patients) with those who began after a pregnancy (91 patients) showed no difference in the probability of discontinuing treatment ($P > 0.10$).

TABLE III—Life-table analysis of reasons for discontinuing NET-OEN expressed as net rates $\pm 1 \text{ SE}/100$ women. (Actual numbers of women given in parentheses)

Months of use:	6	12	18
Accidental pregnancy ..	0	0	0
Menstrual disturbance:			
Amenorrhoea ..	0.5 ± 0.5 (1)	1.4 ± 1.0 (2)	1.4 ± 1.0 (2)
Irregular bleeding ..	2.6 ± 1.0 (6)	3.4 ± 1.3 (7)	3.4 ± 1.3 (7)
Prolonged bleeding ..	4.3 ± 1.4 (9)	5.5 ± 1.7 (10)	9.4 ± 2.6 (12)
Other ..	0.5 ± 0.5 (1)	0.5 ± 0.5 (1)	0.5 ± 0.5 (1)
Minor side effects ..	9.2 ± 2.0 (19)	13.5 ± 2.6 (23)	13.5 ± 2.6 (23)
Major side effects ..	0.4 ± 0.4 (1)	1.6 ± 1.1 (2)	1.6 ± 1.1 (2)
Planned pregnancy ..	1.2 ± 0.8 (2)	1.2 ± 0.8 (2)	5.2 ± 2.9 (3)
Other personal reasons ..	7.2 ± 1.7 (16)	12.0 ± 2.5 (21)	14.2 ± 2.8 (22)
Women-months of use	1134.0	1504.0	1606.0

TABLE IV—Life-table analysis of reasons for discontinuing NET-OEN expressed as gross rates $\pm \text{SE}/100$ women. (Actual numbers of women given in parentheses)

Months of use:	6	12	18
Accidental pregnancy ..	0	0	0
Menstrual disturbance:			
Amenorrhoea ..	0.6 ± 0.6 (1)	1.9 ± 1.4 (2)	1.9 ± 1.4 (2)
Irregular bleeding ..	2.8 ± 1.1 (6)	3.9 ± 1.5 (7)	3.9 ± 1.5 (7)
Prolonged bleeding ..	4.9 ± 1.6 (9)	6.6 ± 2.2 (10)	12.6 ± 3.4 (12)
Other ..	0.6 ± 0.6 (1)	0.6 ± 0.6 (1)	0.6 ± 0.6 (1)
Minor side effects ..	10.1 ± 2.2 (19)	15.9 ± 3.0 (23)	15.9 ± 3.0 (23)
Major side effects ..	0.4 ± 0.4 (1)	2.2 ± 1.5 (2)	2.2 ± 1.5 (2)
Planned pregnancy ..	1.5 ± 1.0 (2)	1.5 ± 1.0 (2)	8.8 ± 4.8 (3)
Other personal reasons ..	7.8 ± 1.9 (16)	14.1 ± 2.8 (21)	17.3 ± 3.4 (22)
Women-months of use	1134.0	1504.0	1606.0

Discussion

Injectable contraceptives have several advantages: they are simple to administer, require minimum patient compliance with the administration schedule and so reduce the user's error, are independent of coitus, cannot be detected, do not interfere with lactation,¹¹ and are highly effective. Experience with DMPA in several countries confirmed these advantages; there were low pregnancy rates and typical 12-month continuation rates of 49–80/100 woman-years.^{5 12 13} Wilson¹⁴ found DMPA useful in high-risk patients in Glasgow. Experience with NET-OEN is more limited, and there are no other reports of its use for contraception in the United Kingdom. Although El-Mahgoub and Karim⁶ found no pregnancies in women given NET-OEN every 90 days, reported pregnancy rates for NET-OEN given every 84–90 days have tended to be higher than those for DMPA. Kessuru-Koos *et al*¹⁵ reported a pregnancy rate of 1.49/100 woman-years among 1844 women given NET-OEN every 12 weeks, while in a recent multinational study in which NET-OEN or DMPA was given every 12 weeks, a 12-month gross pregnancy rate of 3.6/100 woman-years was found for NET-OEN compared with 0.6/100 woman-years for DMPA.⁸ Seventy-five per cent of the pregnancies with NET-OEN occurred in the first injection interval, mostly in the last four weeks.

Studies of the return of ovulation in patients given a single injection of NET-OEN showed that ovulation may be restored in most cases by day 80.^{16 17} In one study¹⁷ two out of eight patients ovulated by day 55 and another three ovulated between days 55 and 80. By using a modified injection schedule no pregnancies occurred in our series. Hormone profiles¹⁸ showed that when using this modified injection schedule ovulation does not occur. This consistent suppression of ovulation and the recognised effects of NET-OEN on cervical mucus probably account for the improved contraceptive efficacy of NET-OEN when given on a modified injection schedule. Giving the first injection during a menstrual period or before discharge from hospital after confinement or termination of pregnancy ensures that no patient is injected in the presence of an early unrecognised pregnancy.

Unpredictable vaginal bleeding is a major disadvantage of injectable progestogen contraception. A recent study^{8 19} showed that the discontinuation rates for bleeding irregularities were similar for NET-OEN and DMPA but that the incidence of amenorrhoea was at least three times higher in DMPA users, and that there were more discontinuations for amenorrhoea in DMPA users (11.5/100 women) than in NET-OEN users (1.8/100 women). In our study, using a NET-OEN injection schedule which is more likely to produce anovulation and amenorrhoea, the 12-month discontinuation rate for amenorrhoea was 1.4/100 women, which is similar to the rate reported in the multinational study.⁸ We also found that menstrual irregularity was more common in the first two injection intervals and that discontinuations were more likely to occur in the first four months of treatment. Other investigators¹⁵ have reported regular cycles in 58.6% of patients and amenorrhoea in 23.6% during the first year of treatment. They also reported that regular cycles

increased while the incidence of amenorrhoea decreased in patients who continued for three years. Although we cannot confirm these findings, as the duration of our study was comparatively short, if patients are more likely to discontinue because of menstrual abnormality early in treatment, probably the proportion of those discontinuing because of amenorrhoea later on will decrease.

Howard *et al*²⁰ found that NET-OEN did not adversely affect blood clotting factors or glucose tolerance, while in the multinational study⁸ no change was detected in blood pressure. Few patients on NET-OEN have an appreciable increase in weight. These added advantages permit the use of NET-OEN in some patients in whom oral contraceptives are contraindicated. In our study two patients were withdrawn because of raised blood pressure, while 10 discontinued because of weight gain.

Unlike Wilson,¹⁴ who used DMPA in patients at high risk of pregnancy in Glasgow, we studied NET-OEN as part of a comprehensive family-planning programme. We have found NET-OEN to be highly effective and to have few serious side effects. The continuation rate is similar to that for oral contraceptives and less than that for an intrauterine device.²¹ In addition to short-term contraceptive use, for which DMPA has been approved by the Committee on Safety of Medicines, we feel that NET-OEN may be used for any woman who desires or needs highly effective contraception, particularly if she does not mind having menstrual irregularity; women who do not wish to use oral contraceptives or for whom they are contraindicated because of the risk of thromboembolism or cardiovascular disease; lactating women; and any woman awaiting hospital admission for sterilisation.

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ceuticals, for supplying NET-OEN and for financial support; the doctors and staff of the family planning clinics at King's College Hospital for their help; and Mrs L Back for typing the manuscript.

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Variation in rates of hospital admission for appendicitis in Wales

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Summary and conclusions

In a study designed to investigate the variations in rates of admission to hospital for appendicitis in Wales Hospital Activity Analysis listings were analysed according to the sex and age of the patients and the month and day of the week of admission. The incidence of hospitalisation was greatest among boys aged 10-14 and girls aged 15-19. The number of admissions was higher on weekdays than at weekends, but there were no seasonal variations. Durations of stay differed between the 17 health districts.

We conclude that admission rates vary mainly because of differing hospital admission policies. Admission is not wholly governed by the sudden onset of abdominal pain;

other factors include the threshold of consultation of each patient, the referral habits of general practitioners, the availability of hospital beds, and the degree to which doctors and patients expect admission.

Introduction

Appendicitis is one of the most common acute surgical conditions in the UK, particularly among young people. Emergency admission to hospital and emergency appendicectomy are the common sequelae. A study of all hospital admissions for appendicitis in Wales in 1971 identified 5018 first admissions, which is equivalent to a yearly first-admission rate of about 1.9/1000 population.¹ There are wide variations, however, both between countries²—for example, the yearly admission rate in West Germany in 1966 was about 5.7/1000³—and between hospital regions in England—2.1/1000 yearly in the South-east London region and 1.4/1000 in Sheffield in 1972.⁴ We report briefly a study of the rates of admission to hospital for appendicitis in Wales in 1976, in which we examined the rates for each of the 17 health districts by age and sex of the patients and by the season and day of the week of admission, and in which we calculated the mean length of stay in the major hospitals serving the districts.

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