TREATMENT OF FUNCTIONAL MENSTRUAL DISORDERS WITH NORETHISTERONE

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The introduction of 19-nortestosterone derivatives (Djerassi *et al.*, 1954) has put a series of powerful oral progestogens at the disposal of the clinician, whereas previously the only orally active progestogen available was ethinyltestosterone (ethisterone). The corresponding nor-compound, ethinyl-nortestosterone (see Formulae), was found by Hertz *et al.* (1954) to be five times as active by the Clauberg (1930) test, when given by the oral route to rabbits.

Greenblatt (1956) studied the progestogenic properties of norethisterone. He found that in doses of 10 mg. daily for five days it would induce withdrawal bleeding in women complaining of amenorrhoea, provided the endometrium was adequately primed with oestrogens, and that it raised the basal body temperature significantly in doses of 10 to 30 mg. daily. Pots (1957) was able to transform the endometrium of an oestrogen-primed castrate and of amenorrhoeic women into a fully secretory type with doses of 10 to 20 mg. daily for 10 days and to induce luteal changes in the vaginal smears as well as to demonstrate a marked thermogenic effect. He also induced a withdrawal bleeding in oestrogen-primed amenorrhoeic patients with a total dose of 40 mg. given over a period of two to four days.

The 19-nortestosterone compounds are not only powerful progestogenic agents but also potent inhibitors of pituitary gonadotrophic activity (McGinty and Djerassi, 1958), and the most publicized use to which they have been put in this connexion is to act as oral contraceptives by suppressing ovulation (Pincus *et al.*, 1958). It is, nevertheless, difficult to demonstrate the inhibition of ovulation objectively in women treated with these compounds because they exert their progestational properties shortly after the administration is begun. It is, however, generally agreed that spasmodic dysmenorrhoea occurs only in an ovulatory cycle and can be prevented from ensuing in a cycle in which ovulation has been inhibited (Sturgis and Albright, 1940). If the 19-nortestosterone compounds suppress ovulation dysmenorrhoea should not occur provided they are administered from an early date in the cycle.

With these properties in mind we set out to study the following effects of norethisterone ("primolut N"). (1) The ability to induce withdrawal bleedings in cases of metropathia haemorrhagica when given once a month, thereby forestalling the otherwise inevitable metropathic bleeding phase. (2) The ability to arrest haemorrhage when given during the course of a metropathic bleeding episode. (3) The ability to induce normal menstrual loss in cases of ovulatory menorrhagia. (4) The ability to prevent dysmenorrhoea.

Norethisterone was administered to 75 women during the course of 349 menstrual cycles in doses varying between 5 and 25 mg. daily.

Production of Withdrawal Bleeding

Albright (1938) suggested the device of inducing a "medical curettage" once a month in cases of anovulatory metropathic bleeding so that the endometrium should not be given the opportunity of building itself up to the histological picture of cystic glandular hyperplasia from which another episode of prolonged and sometimes heavy metropathic bleeding could be expected to occur. Before the introduction of the 19-nortestosteroids it had been our custom to give either progesterone 25 mg. daily by injection for four days or ethisterone 25 mg. daily by mouth for 10 days to achieve the withdrawal bleeding.

A total of 35 patients suffering from metropathia haemorrhagica were given norethisterone to produce withdrawal bleeding. The diagnosis was either confirmed by finding the condition of cystic glandular hyperplasia on histological examination of the curettings, or assumed from the previous pattern of the menstrual bleeding. In all, 182 courses were administered, each course lasting for four days, except for four of three days' duration and another in which the tablets were given for 10 days. The daily dose was 25 mg. in 62 courses and 20 mg. in 45, 15 mg. in 38, 10 mg. in 34, and 5 mg. in 3. On every occasion except two, withdrawal bleeding duly occurred within a few days of the last dose. The failures took place once when the daily dose was 20 mg., though this patient responded on four other occasions to a similar dose; and once when 5-mg. doses were administered. Three patients complained of nausea. In one of these a 25-mg. daily dose was associated with nausea, but when the dose was lowered to 20 mg. the symptom disappeared, though it reappeared later on 10-mg. doses. A second patient complained of nausea only with the sixth and seventh course of treatment using 20-mg. doses. One patient complained of feeling bloated when taking 20 mg. daily.

Haemostasis

There were only eight opportunities to use norethisterone in an attempt to arrest bleeding during a metropathic episode. Pots (1957) found that 10 or 20 mg. daily checked the bleeding significantly within 24 or 48 hours. He continued the treatment for up to 5, 6, or 10 days, withdrawal bleeding taking place on the third or fourth day after treatment was discontinued. Endometrial biopsy revealed secretory changes after a total dose of 100–200 mg. had been given.

Our regime was to give 20 mg. daily for four days and then to "taper off" by giving 10 mg. daily for a subsequent seven days, so that a total dose of 150 mg. was administered. This proved successful on five out of the eight occasions, though in one of these five cases the

tapering-off dose was 15 mg. In the other three cases the treatment failed to arrest the haemorrhage.

Induction of Normal Bleeding in Cases of "Menorrhagia"

There are two main types of bleeding pattern in cases of functional uterine haemorrhage. The first is metrorrhagic, in which periods of amenorrhoea of variable duration alternate with bleeding episodes. Ovulation does not take place and the endometrium hypertrophies under the unopposed influence of oestrogen and gives rise to the histological picture of cystic glandular hyperplasia and the clinical pattern of prolonged bleeding varying in amount from a mere trickle to a flooding when the endometrium eventually breaks down.

In contrast, there is the picture of ovulatory menorrhagia, in which bleeding recurs at fairly regular intervals, though the cycles may be shorter than usual. The bleeding is heavy and may last for seven days or more. Basal temperature records often indicate that ovulation has taken place. Tyler (1957) has studied a number of such short cycles by means of basal temperature records, pregnanediol estimations, cervical and vaginal smears, and endometrial biopsy, and concludes that the luteal phase is curtailed and that this may be a cause of infertility. It may also lead to excessive bleeding owing to inadequate progesterone influence on the endometrium. Administration of 19-nortestosterone compounds might be expected to induce full secretory changes and therefore give rise to normal shedding and normal menstrual loss.

Norethisterone was administered from the 15th to 25th days in a total of 52 cycles in 13 patients suffering from menorrhagia. The subsequent menstrual bleeding was normal in amount, instead of being heavy, in 34 of these cycles (13 out of 20 on a daily dose of 20 mg., in all 8 cycles on 15 mg., in 13 out of 22 on 10 mg., and in neither of the 2 cycles on 5 mg.), "break-through" bleeding occurred on one occasion with the 20-mg. dose and on another with the 10-mg. dose. Dysmenorrhoea was complained of, however, in 8 and possibly 10 of the 20 cycles treated with 20 mg. daily, in 5 of the 8 cycles treated with 15 mg., and in 5 and possibly 6 of the 22 cycles treated with 10 mg. In only one of the patients involved was dysmenorrhoea a prominent feature of the menstrual pattern before treatment. In this case two and possibly four cycles on a 20 mg. dose were associated with dysmenorrhoea, though one period on the 10 mg. dose was painless but heavy.

Painless Periods after Norethisterone Therapy in Cases of Dysmenorrhoea

Twenty-seven patients suffering from incapacitating spasmodic dysmenorrhoea accompanying every period were treated with norethisterone in a total of 107 cycles.

Results of Norethisterone Treatment of Spasmodic Dysmenorrhoea

Daily Dosage	Painless	Painful	Break-through Bleeding
25 mg.	2	2	
20 "	21	7	1 Also with pain
15 "	10	2	2 One cycle also with pain
10 "	26	7	3 " "
7.5 "	5	2	
5 "	1		1
	65	20	7

The usual course consisted in giving norethisterone daily for 20 days from the 5th to the 25th day of the cycle in doses varying from 5 to 25 mg. This regime was adopted in 91 cycles (85%), though in one case the treatment was administered from the 4th to the 24th day, and in two others from the 6th to the 26th day. The dosage, number of cycles, and the results are given in the Table.

Case 1.—This patient had been under our care for many years. It took over a year to explain the importance of paying attention to the "timing" of hormone administration, and we were beginning to despair of ever training her, when she suddenly conformed to the necessary discipline, and from then on for three years stilboestrol 2 mg. daily for 14 days, starting within the first five days of the cycle, kept her painless and content. With the advent of the new progestogens she was given "enavid" with disastrous results, which were repeated when norethisterone was substituted. She accounts for one of the two painful cycles listed under 25 mg. in the Table and for two of the painful cycles under 20 mg. and for the break-through bleeding on the 20-mg. dose.

The number of cycles treated was not sufficient to reach a conclusion concerning the minimal or optimal daily dose, though if the two painful cycles experienced on the 20 mg. dose in Case 1 are subtracted there would be 5 painful as opposed to 21 painless cycles on that dose (80% success), as compared with 7 painful as against 26 painless cycles on the 10-mg. dose (about 79% success). This suggests that the 10-mg. dose is as effective as the 20-mg. dose. Individual patients of course vary in their response to the hormone. This is shown in Case 2.

Case 2.—In two out of three cycles this patient experienced pain when treated with the 10-mg. daily dose, whereas in eight cycles on a 15-mg. daily dose painless bleeding ensued.

On 13 occasions the treatment was continued for less than 20 days: three times on 15-mg. doses for 10 days with painful results; twice on 10-mg. doses for 14 days, the subsequent periods being painless; on three occasions when only 5-mg. doses were given for 14 days pain occurred; in three cycles 10-mg. doses were given for 10 days and pain ensued; in one cycle break-through bleeding occurred after seven days with a daily dose of 10 mg.; and in another cycle break-through bleeding occurred on the 10th day of a 5-mg. daily course. Thus, though it may sometimes be possible to induce a pain-free period after a 14-day course, it seems that a 20-day course is more likely to give good results.

On five occasions the treatment was begun later than the sixth day of the cycle, with the result that the ensuing period was painful. The daily dose in three of these cycles was 15 mg. and in the other two 10 mg.

Side-effects were not a conspicuous feature. One patient took norethisterone in 15-mg. daily doses for one cycle only, and said it made her feel "peculiar," and another patient developed severe acne after she had been taking 10 mg. daily for 20 days in 12 consecutive cycles.

Discussion

These studies of the effects of norethisterone have been carried out in a routine gynaecological endocrine clinic. On the one hand, it is difficult to persuade patients attending such a clinic to submit to a battery of investigations such as pre- and post-treatment endometrial biopsies: indeed, in many cases it is impossible to train the patients to record their basal body temperatures accurately. On the other hand, in a busy clinic

of this kind it is difficult to provide the facilities and assistance to carry out such investigations. Our object, therefore, was to determine the therapeutic efficacy on a relatively large number of cases submitted to the ordinary routine of hospital out-patient treatment, rather than to study a small and carefully selected number of patients who would be willing to submit to the inconvenience of time-consuming controls and investigations. Basal temperature records, vaginal cytological studies, and endometrial biopsies have been performed in some of these cases, but the results of these studies have not been included, because they are inadequate to affect the overall clinical impression. This is not a carefully controlled double-blind trial; it is an attempt to evaluate the behaviour of a new therapeutic compound in a routine clinic.

From the results obtained it seems clear that a four-day course of norethisterone in daily doses of 10 mg. or more will consistently induce withdrawal bleeding, simulating a normal period, when given monthly in cases of metropathia haemorrhagica. It may even be capable of doing so in lower doses. From the evidence available in the literature these withdrawal bleedings are brought about by converting the proliferative endometrium which has been under the constant and sole influence of oestrogen into a secretory type which sheds like that of a normal ovulatory cycle when the progestogen influence is withdrawn. This represents a valuable method of tiding a patient over a phase of non-ovulatory ovarian activity in the hope that spontaneous ovulatory cycles will eventually be re-established.

Only eight opportunities occurred to test the haemostatic efficacy of a regime which consisted of four daily doses of 20 mg. of norethisterone followed by a week's tapering off on 10 mg. daily. This regime was effective on five occasions. Perhaps the higher doses should have been continued for longer than four days or that even higher doses than 20 mg. should have been given initially.

The treatment of ovulatory menorrhagia with progestogens probably calls for more intensive studies than were possible here. Basal temperature records and vaginal cytology might be employed to pin-point the day of ovulation and endometrial biopsies, on the first day of the period, to demonstrate that bleeding is taking place from an inadequately luteinized endometrium. A further endometrial biopsy after treatment might establish the fact that the progestogen had in fact induced full maturation of the endometrium, though it might prejudice the evaluation of the effect of the progestogen on the volume of bleeding. Single- or double-blind trials with progestogen might help to elucidate the extent of relief of this predominantly subjective end-result—namely, the amount of blood actually lost at each menstrual haemorrhage. These would be formidable studies, and would occupy the resources of even the best-stocked endocrine clinic for many months, if not years. Our results suggest that when norethisterone is administered in 10-mg. doses and upwards daily from the 15th to the 25th day of the cycle the subsequent bleeding is "normal" instead of "incapacitating" in amount in two-thirds of the cycles treated. These results are much better than those obtained, in our experience, with androgens or with ethisterone.

An interesting side-effect, however, appears as the result of giving the progestogen in the second half of the cycle—dysmenorrhoea. Patients volunteered the infor-

mation that their periods were painful in 16 and possibly 19 of the 50 cycles treated. The progestogen therefore produced pain in 33% to almost 40% of the cycles treated. In no case was the dysmenorrhoea so severe as to make the patient unwilling to continue with the treatment, though in some cases the failure to modify the bleeding, combined with the fact that treated cycles were painful, led to the treatment being abandoned. Sturgis and Albright (1940) drew attention to the fact that spasmodic dysmenorrhoea occurs only in ovulatory cycles, and it would seem to be due to progesterone. Administration of a highly potent progestogen in the second half of the cycle might therefore be expected to induce dysmenorrhoea in some cases.

On the other hand, if this powerful progestogen is also a suppressant of pituitary gonadotrophic activity when given early in the cycle one would expect that it would lead to painless periods in cases of dysmenorrhoea. This was the result achieved in 75% of 107 cycles treated.

Summary

Norethisterone ("primolut N") was given to 75 women suffering from functional menstrual disorders, during the course of 349 cycles, the doses varying from 5 to 25 mg. daily.

It succeeded in inducing withdrawal bleeding in 180 out of 182 occasions in cases of metropathia haemorrhagica. It seems likely that the dose need not exceed 10 mg. daily for four days, and may even be lower.

On five out of eight occasions a dosage of 20 mg. daily for four days, then 10 mg. daily for seven days, arrested a phase of metropathic bleeding and was followed by a normal withdrawal bleeding.

When administered from the 15th to the 25th day of the cycle in 13 cases of ovulatory menorrhagia, normal bleeding was substituted for the heavy loss in 34 out of 52 cycles. Dysmenorrhoea was complained of, however, in 18 and possibly 21 of the 52 cycles.

Painless periods followed administration of norethisterone on 65 out of 91 occasions in 27 patients complaining of dysmenorrhoea. When the treatment was begun after the sixth day of the cycle the ensuing period was always painful.

Side-effects were not conspicuous. One patient developed acne after taking 10 mg. daily for 20 days in 12 consecutive cycles, and 3 of the 35 patients being treated with metropathia complained occasionally of nausea.

We are grateful to Dr. Jürgen Friebel, of Schering A.G., Berlin, for placing unlimited supplies of primolut N at our disposal in order to enable us to undertake this clinical study. We are also grateful to Mr. G. S. Blackie, of Pharmethicals, London, for arranging for the supplies to be delivered to us.

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