A CLINICAL TRIAL OF A NEW TOTALLY SYNTHETIC LOW DOSE PROGESTAGEN

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Summary. The new totally synthetic progestational steroid norgestrel has been subjected to a clinical trial in gynaecological and endocrine cases and for oral contraception, and its toxicity and side-effects have been investigated. The effect of norgestrel alone and in combination with ethinyl oestradiol in various dosage/time schedules on the endometrium has been studied. The previous reports of its effectiveness in low dosage combinations with oestrogen with absence of significant side-effects or toxicity have been confirmed. These findings, together with its very high potency, make it an important addition to progestational therapy in gynaecological practice and for oral contraception.

INTRODUCTION

Recently a very potent progestagen Wy-3707, norgestrel, was derived by a method of total synthesis from bench chemicals (Smith and his colleagues, 1963). The compound (DL-13 β -ethyl-17 α -ethynyl-17 β -hydroxygon-4-en-3-one) resembles norethisterone in certain structural characteristics, but possesses a unique angular ethyl group in position 13 of the steroid nucleus. Norgestrel is a racemate, the D form being active biologically, whereas the L form is inert (Edgren, Smith, Hughes, Smith & Greenspan, 1963).

The formula and its comparison to norethisterone are as follows:

Norgestrel
(DL-13 β -ethyl-17 α -ethynyl-
17 β -hydroxygon-4-en-3-one)

Norethisterone
(17 α -ethynyl-17 β -hydroxyoestr-
4-en-3-one)

Much animal experimental work on this progestagen has been carried out, and this is well summarized by Edgren, Peterson & Jones (1966).

When compared with other oral progestagens in the human, by the Greenblatt/Swyer postponement of menstruation assay, norgestrel appeared over ten times more potent than any other compound so far tested (Mears, 1965). Reports on its use in gynaecology (Greenblatt & Junck, 1966), as a contraceptive with added oestrogen (Roland, 1966; O'Roark, Lock, Smith Foushee & Burt, 1966; McBride, 1967) and for the treatment of threatened abortion (Swyer & Little, 1965a, b) have made claims for its efficiency and low incidence of side effects.

METHODS AND MATERIALS

For 3 years this progestagen has been investigated in Bristol to determine the effective doses for induction of cyclical withdrawal bleeding, the control of irregular or heavy bleeding and the suppression of menstruation. It has also been given to patients as an oral contraceptive. Studies have been made on its effect on the endometrium in various combinations of dosage, alone or in combination with ethinyl oestradiol (EO). Careful record was made of any side-effects and a group of patients was investigated by serial liver function tests to determine possible toxic effects of various doses. Experience has been limited to the study of 125 patients for over 1100 treated cycles. Detailed records were made when patients were seen at 1- or 2-monthly intervals.

Sections of endometrium were obtained after various dosage regimens and were obtained either by biopsy or at hysterectomy. The endometrium was fixed in Bouin's solution, and sections were stained with haematoxylin and eosin. Liver function tests were carried out before and at intervals during treatment. These included serum bilirubin, alkaline phosphatase, serum proteins and electrophoresis, and either serum glutamic oxalo-acetic transaminase (SGOT), or serum glutamic pyruvic transaminase (SGPT). Blood urea and blood counts and urine analyses were also made. Blood samples were collected at the end of a course of treatment or cycle.

Cervical smears were done in married women after several months' treatment.

The doses of norgestrel used at the start of the trial were based on those used by Greenblatt & Junck (1966), but it soon became apparent that they were too high, and, as experience accumulated with norgestrel (and particularly from previous experience with norethisterone; Foss, 1960), adjustments were made.

RESULTS

Induction of regular cyclical bleeding

Nine patients aged 17 to 20 years with primary amenorrhoea and ten patients, aged 20 to 43 years, with long-standing secondary amenorrhoea have been treated for over 300 cycles. Satisfactory induction of withdrawal bleeding with good cycle control was achieved with a combination of norgestrel 0.5 mg and EO 0.05 mg given daily for 21 days each month. The onset of bleeding occurred within 6 days of finishing a course of treatment.

Menometrorrhagia

The control of heavy, irregular or regular bleeding with norgestrel alone was unsatisfactory, as its effect was not immediate and the dose required, 4 to 8 mg, was too near the limit of tolerance. When EO was added, its action was accentuated and flooding was stopped within 48 hr on norgestrel 0.5 mg and EO 0.05 mg four times per day. Menstruation was then suppressed for long intervals quite readily. This was a useful therapeutic measure for nine patients until the day of hysterectomy and the patient with the longest suppression was on the waiting list for 273 days.

If hysterectomy was not indicated, patients were then given cyclical treatment for 21 days each month with norgestrel 0.5 to 1.5 mg and EO 0.05 to 0.1 mg daily. In this manner bleeding was normal or scanty and regular in sixty-three out of seventy-five treated cycles.

TABLE 1
SUPPRESSION OF MENSTRUATION

<i>Continuous daily dose Norgestrel + Ethinyl oestradiol (mg) (mg)</i>		<i>Days of suppression</i>
3.5	0.05	65
2.0	0.2	29, 235
2.0	0.1	48, 49, 56, 63
2.0	0.05	63, 108
1.0	0.1	56, 68, 112, 115, 162, 166, 273, 364
1.0	0.05	77, 93, 106
0.5	0.05	51, 53, 54, 67, 92, 216, 224

Oral contraception

A small pilot trial with fifty-eight patients was carried out. Four of these were newly married and the rest had had one to six children. Cyclical treatment was given for 21 days each month. A combination of norgestrel 1.0 mg plus EO 0.05 mg was first given for 210 cycles and then the dose of norgestrel was reduced to 0.5 mg together with EO 0.05 mg for 277 cycles. None of these patients became pregnant. In this small series of 487 cycles, break-through bleeding or spotting for 1 or more days occurred in 3.2% of cycles. One patient on the 1.0-mg dose of norgestrel and one patient on 0.5 mg had amenorrhoea, in each case for 2 months.

Endometrial studies

These were made in sixteen patients on nineteen occasions (Table 2).

Side-effects

An assessment of side-effects was made when norgestrel had been given to eighty-eight patients, with ages ranging from 17 to 51 years, for 764 cycle-months (Table 3), and were analysed separately for forty-seven patients who had, at that time, been given this compound for oral contraception. The side-effects were minimal, except when the larger doses of norgestrel were used alone

TABLE 2
ENDOMETRIAL STUDIES WITH NORGESTREL

<i>Name</i>	<i>Age</i>	<i>Dose and time</i>	<i>Last period onset</i>	<i>Glands</i>	<i>Stroma</i>	<i>Vessels</i>
NORGESTREL ALONE						
Wo O.C.	31	0.05 mg × 28 continuous	28 days before	Small glands, secretory, round nuclei	Slight peripheral pseudo- decidua	No spiral arterioles
Row O.C.	35	0.05 mg × 20 continuous	20 days before	Small glands; columnar cells; nuclei linear to ovoid	Dense; no decidua cells	No venous ectasia; some spiral arterioles
Tyl Endometriosis, hysterectomy	29	0.05 mg × 31 continuous	31 days before	Normal secretory	No pseudodecidua	
Sta O.C.	32	0.1 mg × 27 continuous	27 days before	Infrequent small glands; low columnar cells; ovoid nuclei	Loose oedema	
Rhy (Pl. 1, Fig. 1) Hysterectomy, metrorrhagia	51	0.25 mg × 31 continuous	31 days before	Small glands; columnar cells; linear nuclei	Dense; few decidua cells	Few spiral arterioles
Wra Oligomenorrhoea	38	1.5 mg × 14	77 days before	Tortuous secretory; cuboid cells; round nuclei	Loose focal oedema; pseudo- decidua cells at periphery	Spiral arterioles
Bed Menorrhagia	45	3.0 mg × 14	29 days before	Secretory, cuboidal cells; round nuclei	Mostly dense with patchy oedema	Spiral arterioles
Bo Metrorrhagia	42	3.0 mg × 28	41 days before	Small atrophic glands; columnar cells; linear nuclei	Mostly dense; pseudodecidual cells	Venous ectasia
Dun Oligomenorrhoea	37	4.0 mg × 22	41 days before	Small glands, columnar or low cuboid, round nuclei	Pale pseudodecidual cells +	Few spiral arterioles
Rh Metrorrhagia	51	8.0 mg × 20	20 days before	Small glands; polyps; cuboidal cells, round nuclei; empty cells	Areas of oedema and denser stroma; pseudodecidua	

Name	Age	Dose and time	Glands	Stroma	Vessels
OESTROGEN PRIMING FOLLOWED BY NORGESTREL					
Ba Primary amenorrhoea	26	EO 0.1 mg × 21 then norg. 3 mg × 7	Round large glands, columnar cells, subnuclear vacuolation, ovoid or round nuclei, intra-luminal polyps	Dense; small areas of pseudodecidua	
Sul Secondary amenorrhoea	37	EO 0.1 mg × 25 then norg. 3 mg × 8	Large glands, mixed secretory, early subnuclear vacuolation, columnar cells, ovoid nuclei; some intraluminal polyps	Loose, some oedema; early pseudodecidua cells in periphery	
At Primary amenorrhoea	30	Implant oestradiol 200 mg 40 months before norg. 3 mg × 13	Tortuous secretory, cuboidal cells, round nuclei	Peripheral pseudodecidua	Spiral arterioles
Chil (Pl. 1, Fig. 2) Secondary amenorrhoea	41	EO 0.1 mg × 21 then norg. 4 mg × 8	Tortuous secretory, subnuclear vacuolation, columnar to cuboid, ovoid or linear nuclei	Mostly dense, focal pseudodecidua	
OESTROGEN + NORGESTREL					
Ba (Pl. 2, Fig. 3) Primary amenorrhoea	27	EO 0.05 mg + norg. 1 mg × 21	Small atrophic, columnar cells, linear nuclei	Variable, dense to oedematous; pseudodecidua at periphery	Venous ectasia
Sul Secondary amenorrhoea	39	EO 0.05 mg + norg. 1 mg × 21	Small infrequent, columnar cells, linear nuclei	Dense	
Wal Metrorrhagia	44	EO 0.1 mg + norg. 1 mg × 21	Small infrequent, atrophic cuboidal cells, round nuclei	Pseudodecidua	Venous ectasia, Spiral arterioles
Ris Metrorrhagia	49	EO 0.1 mg + norg. 2 mg × 56	Infrequent, some cystic, mixed columnar and cuboid, linear or round nuclei	Dense, and small areas of pseudodecidua cells	
Mi (Pl. 2, Fig. 4) Metrorrhagia, hysterectomy	38	EO 0.05 mg + norg. 2 mg × 92	Small glands away from periphery; mixed columnar and cuboidal cells with linear or round nuclei; intra-luminal polyps	Thick peripheral pseudodecidua	Spiral arterioles

for long periods. With the low dosage 0.5 to 1.0 mg norgestrel plus EO 0.05 mg used cyclically for oral contraception or amenorrhoea, the incidence was highest in the first treated cycles—tiredness, weakness, headache and nausea being the most common complaints.

TABLE 3
SIDE-EFFECTS

<i>Side-effect</i>	<i>Percentage*</i>
Nausea	8.4
Tiredness	6.2
Headache	5.2
Breast tenderness	3.6
Depression or irritability	3.2
Bloated feeling	0.7
Abdominal discomfort	0.5
Vomiting	0.4
Oedema	0.3
Blurred vision	0.1

* Expressed as a percentage of 764 cycle-months.

Investigation of toxicity

Blood samples were collected from eighty-seven patients on 355 occasions. No abnormalities were found in full blood counts, blood urea estimations or serum proteins. Urine analysis completed on all these occasions was normal.

Cervical smears were examined in thirty-six married women, and all were assessed by the pathologist as Grade I or II.

Fifty-four patients had serial transaminases done. Six patients had raised SGPT in the first cycle of treatment when the control value had been normal. They reverted to normal limits thereafter in succeeding months. Four patients with no control value had a raised SGPT for the first estimation and these reverted to normal with treatment. One of these was ill at the time of examination with a salmonella infection.

In one case of menorrhagia treated by suppressing menstruation with 4 mg norgestrel alone for 6 weeks, there was a high level of 540 units/ml at 1 month, but no control cycle was done. High levels were seen in this same patient on three other occasions, when she had been given doses of 1.5 to 3.5 mg daily alone, in an attempt to suppress menstruation.

However, in another patient, 8 mg daily for 14 days produced severe nausea, tiredness and a bloated feeling, necessitating withdrawal of treatment, but the SGOT was not above 23 units. A level of SGOT above 30 units (the normal upper limit) was only seen on two occasions in two out of thirty patients, one after suppression with norgestrel 2 mg plus EO 0.05 mg for 32 days, and the other after suppression with norgestrel 3 mg plus EO 0.15 mg for 28 days. These were both the first assessment at 1 month and reverted to normal limits thereafter with continued treatment.

FIG. 1. Rhy. Small glands; columnar cells; linear nuclei; dense stroma; few decidual cells; few spiral arterioles (see Table 2). H & E, $\times 100$.

FIG. 2. Chil. Glands secretory with subnuclear vacuolation; stroma mostly dense; focal pseudodecidual cells (see Table 2). H & E. $\times 100$.

(Facing p. 64)

FIG. 3. Ba. Glands small and atrophic; stroma dense to oedematous; pseudodecidual cells at periphery; venous ectasia (see Table 2). H & E, $\times 100$.

FIG. 4. Mi. Glands small; mixed columnar and cuboid cells; thick peripheral pseudo-decidua; spiral arterioles evident (see Table 2). H & E, $\times 100$.

(Facing p. 65)

Alkaline phosphatase was only above the normal range (15 units/ml) on three occasions, at which time the SGOT figures were normal.

Serum bilirubin was above normal in two patients, on one occasion each. One patient had obstructive jaundice due to gallstones which were removed.

DISCUSSION

Greenblatt & Junck (1966) reported on a series of 288 assorted gynaecological patients who received 1000 courses of medication with norgestrel 1.25 to 30 mg daily. They showed that dysfunctional uterine bleeding could be controlled by norgestrel alone, in a dose of 2.5 to 30 mg, within 48 hr in 92% of cases. In the present series, 4 mg sometimes failed to stop flooding in 48 hr, whereas 8 mg daily produced unacceptable side-effects. Norgestrel given for 7 to 10 days (i.e. starting either from the 21st or 18th day of the cycle respectively) controlled menstrual loss, but some break-through bleeding occurred. When EO 0.05 to 0.1 mg was added to norgestrel, good suppression of bleeding or control of cycles was obtained.

The combination of 0.5 mg of norgestrel with EO 0.05 mg given four times daily is a valuable method of treatment for controlling and suppressing heavy bleeding even in the presence of large fibroids, and amenorrhoea can be continued until a patient is admitted for elective hysterectomy, allowing haemoglobin levels to be made up so that transfusion is not necessary, after admission, in preparation for operation. The gynaecologists assured me that this suppressive treatment did not make the operation technically more difficult. Such measures can also be used temporarily to postpone menstruation for a honeymoon, or other important social or sporting occasion.

As norgestrel has little intrinsic oestrogenic activity its use in practice in low dosage is undoubtedly enhanced when combined with ethinyl oestradiol. The combination of norgestrel 0.5 mg with EO 0.05 mg would appear to be satisfactory for the induction of cyclical withdrawal bleeding in cases of primary or secondary amenorrhoea and as an oral contraceptive.

Richards (1967) has reported the results of the combined trials in the British Family Planning Clinics and in America. There have been no pregnancies in this moderately large series of 4637 patients during 27,055 cycles. Their results of success rate and side-effects are similar to my findings in a very much smaller series.

The endometrial changes were similar to those described by Ober (1966) and Roland, Clyman, Decker & Ober (1966).

Investigation of serial liver function tests, blood counts, blood urea and urine analyses on 355 occasions did not show any evidence of toxicity, except in one case given large doses, in which definite side-effects were associated with elevation of SGPT.

Norgestrel is an effective progestational steroid, when in combination with added EO, at a much smaller dosage than any other progestagen. Side-effects, break-through bleedings and amenorrhoea are of minimal concern. In view of its high potency and its synthetic production, it offers advantages over other preparations in current use.

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