A comparative study of danazol and norethisterone in dysfunctional uterine bleeding presenting as menorrhagia

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Summary: This randomized open study compared the efficacy and safety of norethisterone, 5 mg three times a day from day 19 to 26, and danazol, 200 mg daily, in the treatment of dysfunctional uterine bleeding presenting as menorrhagia. Clinical criteria were employed to confirm the diagnosis, and subjective assessment of the condition was performed during one pre-treatment and three treatment cycles. Fourteen patients commenced norethisterone and 10 danazol.

Bleeding intensity scores were significantly lower with danazol than with norethisterone, and patients assessed their blood loss to be significantly less with danazol than with norethisterone. Associated symptoms of backache and abdominal pain were improved to a similar degree by both treatments. Adverse reactions were reported with similar frequency and were of a similar nature in both treatment groups.

Introduction

Menorrhagia is a common complaint resulting in annual general practitioner consultation rates of 20.4 per 1,000 women.¹ In those patients in whom no underlying pathology is apparent and menorrhagia is attributable to dysfunctional uterine bleeding (often termed primary menorrhagia), it has been reported that as many as 62% would be found by objective measurement to have a mean menstrual loss within the normal range.² Since the majority of gynaecology clinics do not have facilities to assess menorrhagia objectively, a trial of medical treatment prior to surgical intervention such as hysterectomy, with its attendant morbidity and expense, is generally appropriate.

Various medical regimes have been used in the treatment of primary menorrhagia. Progestational agents, most commonly norethisterone, are widely employed for this complaint, despite the lack of published evidence that they are effective, since they are considered to induce secretory changes in the endometrium, preventing endometrial hyperplasia and regulating the menstrual cycle. Danazol, a synthetic steroid, in contrast, has been shown to

be an effective treatment for primary menorrhagia, substantially reducing menstrual blood loss³ as well as its perceived intensity.⁴ Danazol acts at the pituitary,⁵ ovarian⁶ and endometrial level⁷ and induces endometrial atrophy.⁸

In the absence of previously published comparisons, a pilot study was undertaken to compare the efficacy, tolerability and safety of danazol and norethisterone in treating this condition.

Materials and methods

Study design

Thirty patients diagnosed as having dysfunctional uterine bleeding presenting as menorrhagia (primary menorrhagia) were recruited from the Menstrual Disorders Clinic at the Royal Infirmary, Glasgow. Selection was based on clinical criteria: complaint of menstrual loss requiring more than 5 pads/tampons per day for longer than 6 days cycle; presence of flooding or clots on any day of the cycle; presence of secondary anaemia; excessive menstrual loss proving socially and domestically disruptive. Underlying pathology was excluded by means of history, examination and dilatation and curettage within the preceding 3 to 12 months.

All patients provided written, informed consent prior to commencing the study, which had hospital ethics committee approval.

Initial screening included menstrual, obstetric and general medical histories, general and vaginal

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examinations together with haematological and liver function tests.

Patients were reviewed after 1 cycle without treatment having maintained a daily record of the duration and heaviness of menstrual loss, use of sanitary material and intensity of any abdominal pain or backache. Reports relating to possible adverse events were also noted and laboratory tests repeated if abnormal. If the diagnosis of primary menorrhagia was confirmed, the patient was recruited into the study and randomly assigned to three cycles of treatment with either danazol, 200 mg daily, or norethisterone, 5 mg three times a day from day 19 to 26.

Daily diaries were required throughout treatment and reviewed after each menstrual period, as above. Heaviness of bleeding was rated on a descriptive scale, and scored for each day of bleeding from 1 to 7 (where 1 = spotting and 7 = flooding). Daily scores were combined to yield a bleeding intensity score for each menstrual period. Scores for abdominal pain and backache were derived similarly from a descriptive scale, scored from 1 to 3 (where 1 = mild and 3 = severe).

At each hospital visit the patients' assessment of their condition in relation to baseline (greatly improved to much worse), the efficacy of treatment (completely effective to ineffective), the severity of blood loss (spotting to flooding) and dysmenorrhoea (absent to severe), during the most recent menstrual period were recorded.

Statistical analysis

Comparisons between the two treatment groups were made using the Wilcoxon two sample test, and those within, using the Wilcoxon matched pairs test. Results relating to the first menstrual loss after the start of treatment were not used for comparison since the two groups were not at a comparable stage of treatment. Danazol patients had commenced treatment only at the start of that period whereas those taking norethisterone had completed one cycle of treatment by this stage.

Results

Study population

Thirty patients were recruited into the study; of these 15 were randomized to receive danazol and 15 norethisterone. Six patients were excluded from the analysis (5 from the danazol group, 1 from the norethisterone group), 4 because they did not return and, hence provided no data, following randomization, and 2 because selection criteria had not been met (1 – Wolf Parkinson White syndrome; 1 – epileptic).

There were no significant differences between the two treatment groups in age, number of pregnancies, duration of menorrhagia or menstrual history (Table I).

The variables used to assess efficacy were also comparable at baseline except for abdominal pain score, which was higher in those receiving danazol (Table II).

Withdrawals

Eight patients withdrew during the course of the study, 4 from each treatment group. All data for these patients were included in the analyses up to the point of withdrawal. Of those withdrawing during danazol treatment, 2 did so because of events thought to be related to medication (allergic rash; weight gain, hypertension, musculoskeletal pains) and 2 because of events considered possibly related to medication (vomiting; mood changes with suicidal thoughts). In the norethisterone group, one patient withdrew because of events related to medication (headaches) and three as a consequence of events possibly related to medication (depression, light headedness, sickness; musculoskeletal pain; mood changes, lack of concentration).

Efficacy

Daily assessments (Table II) Bleeding intensity scores were significantly lower with danazol than with norethisterone for the third menses. This score was also significantly improved with danazol, but not with norethisterone, by the 2nd and 3rd menses in comparison with baseline ($P < 0.02$) as were the number of pads/tampons used ($P < 0.05$). Some reduction in the symptoms of backache and abdominal pain accompanied both treatments although between treatment comparisons were not significant.

Clinic assessments The patients' overall assessments of their condition and the efficacy of treatment demonstrated no significant differences

Table I Admission characteristics

	Danazol (<i>n</i> = 10)		Norethisterone (<i>n</i> = 14)	
	Mean	s.d.	Mean	s.d.
Age (yrs)	36.1	5.9	39.2	5.3
No. live births	2.1	1.0	2.9	1.1
No. of terminations	0.1	0.3	0.4	0.8
Duration menorrhagia (yrs)	4.8	5.3	3.8	5.2
Length of cycle (days)	26.2	3.3	28.0	4.6
Days of bleeding	7.1	1.9	7.9	2.5
Average no. pads/cycle	32.2	15.6	34.4	15.7
Average no. tampons/cycle	7.4	15.7	7.4	16.7

Table II Daily assessments (mean ± s.d.)

	Danazol			Norethisterone		
	Baseline (n = 10)	2nd menses (n = 7)	3rd menses (n = 6)	Baseline (n = 14)	2nd menses (n = 11)	3rd menses (n = 10)
Bleeding intensity score	31.9 ± 12.4	14.1 ± 11.3 [‡]	15.0 ± 9.4* [‡]	32.9 ± 15.2	23.7 ± 6.5	23.6 ± 9.6
No. of pads/tampons used	46.9 ± 37.2	13.4 ± 12.2 [†]	14.0 ± 12.2 [†]	37.6 ± 27.9	23.4 ± 11.6	25.1 ± 12.6
No. days bleeding	7.3 ± 2.7	4.3 ± 2.6	5.2 ± 2.6	7.6 ± 3.3	5.8 ± 1.5	5.8 ± 2.2
No. days backache	4.8 ± 2.6	2.4 ± 3.1	3.7 ± 3.4	4.6 ± 2.5	3.2 ± 2.4	2.4 ± 2.8 [‡]
Backache score	10.9 ± 7.2	4.7 ± 6.1 [‡]	6.5 ± 7.1	10.5 ± 6.2	5.7 ± 6.8	5.0 ± 7.0 [†]
No. days abdominal pain	4.8 ± 2.8	2.9 ± 2.9	1.8 ± 2.2 [†]	2.8 ± 2.2	2.8 ± 1.8	1.9 ± 2.5
Abdominal pain score	10.3 ± 5.9*	5.7 ± 6.2	3.0 ± 4.0	5.6 ± 4.6	5.4 ± 3.0	4.2 ± 6.7

* $P < 0.05$ vs norethisterone; [†] $P < 0.05$ vs baseline; [‡] $P < 0.02$ vs baseline.

between the two treatments. However, by the second visit during treatment the patients assessed their blood loss to be significantly less with danazol than with norethisterone (none to moderate, 5 of 7 with danazol vs 3 of 10 with norethisterone, $P < 0.02$). Dysmenorrhoea improved to a significant degree with norethisterone ($P < 0.05$) but not with danazol, although this may reflect the small numbers available for analysis.

Safety

Minor adverse reactions were common and reported with similar frequency in both groups (Table III). Two patients reported voice changes during norethisterone which resolved either during treatment or after discontinuation of treatment. Although the cause of these voice changes is unknown, it is possible that a concurrent upper respiratory-tract infection was responsible.

Although weight gain was complained of by 8 patients on danazol and 7 on norethisterone, during treatment, only 4 patients recorded an increase of greater than 3 kg (3 on danazol, 1 on

norethisterone). Three patients were recorded as having diastolic blood pressures > 90 mmHg, in association with systolic pressures > 140 mmHg for the first time during treatment with danazol, although this resulted in withdrawal from the study in only one patient. However, since the conditions under which blood pressure was measured were not standardized these findings are of doubtful significance.

There were no clinically significant changes in blood count, or liver function tests associated with either treatment, nor were there any clinically serious adverse reactions during the study.

There were no unexpected side effects seen in patients treated with danazol. However, norethisterone was associated with a higher than expected incidence of side effects not widely documented during such treatment.

Discussion

Primary menorrhagia is normally managed symptomatically, and although patients are poor at assessing absolute blood loss, they are more able to assess change.² In keeping with ordinary clinical practice, then, this pilot study employed subjective assessments of the principal variables.

Danazol was employed at a dose of 200 mg daily, a regime which has been demonstrated previously^{3,4} to provide effective treatment for primary menorrhagia. The regimen used for norethisterone therapy is that recommended by the manufacturers, since no objective data were available to indicate the most suitable dose.

Whilst conclusions from this study are limited by the small number of subjects, the findings confirm the clinical efficacy of danazol in controlling menorrhagia, significant improvements being seen in both the prospective daily and clinic assessments of this symptom. The findings also suggest that danazol is more effective than norethisterone, the efficacy of which, in controlling menorrhagia,

Table III Patient reported adverse reactions to treatment

	No. of events	
	Danazol	Norethisterone
Voice changes	0	2
Loss concentration/depression/ tiredness/irritability/strange feelings	5	7
Headache	4	1
Skin changes/rashes	6	3
Gastro-intestinal symptoms	7	5
Weight gain	8	7
Bloatedness	6	3
Total no. patients reporting adverse reactions	10	14

remains in doubt, although it may, like danazol, benefit associated symptoms. Poorer compliance associated with the three times a day norethisterone regimen in comparison with the once daily danazol regimen may have contributed to the differences in efficacy demonstrated in this study.

The high level of adverse events reported probably reflects the particular attention given to this aspect of the study in the baseline as well as the treatment phase. None was clinically serious, but it is notable that the spectrum of complaints and also the frequency of discontinuation of treatment, was

comparable for the two medications.

Since this study was undertaken, a report of objective measurement of blood loss in small groups of patients⁹ casts further doubt on the efficacy of norethisterone, although it confirms that of danazol. Since norethisterone is very widely used, a detailed assessment of its efficacy and safety in comparison to danazol is overdue. Should such a study confirm the findings discussed here then danazol could usefully be employed as first line therapy in the management of dysfunctional uterine bleeding presenting as menorrhagia.

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