Oral Medroxyprogesterone in the Treatment of Dysfunctional Uterine Bleeding : A Preliminary Report

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Abstract : *The preliminary study of the effectiveness of oral medroxyprogesterone acetate was conducted among seventeen women with dysfunctional uterine bleeding at Songklanagarind Hospital from September 1988 to August 1989. The patients were treated with a dosage of 10 mg (one tablet) daily for ten days as initial hormonal hemostasis. After the first withdrawal bleeding, the menstrual blood flow was regulated for the next three cycles at a dosage of 10 mg daily from day 15 to day 24 of the cycle. The patients were evaluated by subjective description (menstrual calendar) for continuous observation (3 cycles after therapy).*

Twelve of the seventeen women (70.5 per cent) who had partial follow-up were satisfactory during treatment, and ten of the seventeen women (58.8 per cent) were satisfactory during treatment and post treatment. There were no adverse drug reactions. (Thai J Obstet Gynaecol 1989 ; 1 : 91-6.)

Key words : medroxyprogesterone acetate, dysfunctional uterine bleeding

Dysfunctional uterine bleeding (DUB) is abnormal bleeding that has no organic causes such as neoplasia, inflammation, or complication of pregnancy. Dysfunctional uterine bleeding results from a disturbance in hormonal secretory activity. Although the term has frequently been used to signify anovulatory forms of bleeding, it also describes disturbances in ovulatory forms of bleeding. While it has a nonorganic aetiology by definition, it can coexist with organic pathology, such as malignant and benign neoplasms[1].

Menorrhagia is usually a clinical diagnosis based entirely on the women's perception, and in many cases cannot be confirmed by objective measurement[2]. Oral medroxyprogesterone has been used for many years as one of the standard treatments for both ovulatory and anovulatory dysfunctional uterine bleeding[3-6]. In women with anovulatory cycles it seems reasonable to replace

progesterone in the cycle to make the periods regular and to offset the unopposed action of estradiol on the endometrium[7]. Because the bleeding results from an excess of unopposed estrogen, it is unnecessary to treat these patients with estrogen, either alone or in the form of oral contraceptives[8]. Medroxyprogesterone acetate (Provera) is an orally active synthetic progestin available in 5 and 10 mg tablets, that can be used instead of estrogen-progesterone combination cyclic therapy because of low adverse drug reactions. So, the aim of this study is to evaluate the efficacy of medroxyprogesterone acetate in the treatment of DUB.

Materials and Methods

Patients

The clinical trial included 27 patients with DUB treated with medroxyprogesterone acetate at Songklanagarind Hospital from September, 1988 to August, 1989. The patients' age varied from 18 to 39 years (mean 28.1 ± 5.8), parity was 0 to 3 (average 1), and 8 of 17 women were nulliparous. The common presentation was metrorrhagia and menorrhagia. Apart from history taking and routine pelvic examination, blood samples were drawn from all patients for serum prolactin determination. Endometrial biopsy with Novak's curette was performed on all but the nulliparous patients. The tissue was sent to the pathological department for an official report.

Treatment

The planned treatment was divided into 3 Phases. In Phase I, oral medroxyprogesterone acetate 10 mg daily was prescribed for initial hormonal hemostasis. After 10 days of treatment the drug was discontinued for progestational withdrawal bleeding to occur. The menstrual blood flow was regulated for the next three cycles (Phase II) by oral medroxyprogesterone acetate in a dosage of 10 mg daily from day 15 to day 24 of the cycle (the first day of bleeding was the first day of the cycle). And after that, in Phase III, bleeding was recorded on the menstrual calendar by the patients for the next 3 cycles to observe the regularity of the menstruation.

Hormonal assay

Serum prolactin measured by a radioimmunoassay method (Amersham, U.K.), depends on the competition for a limited number of binding sites on a prolactin-specific antibody between ^{125}I-labeled prolactin and prolactin in serum.

Patients' evaluation

The menstrual blood loss was evaluated by the menstrual calendar, which was designed for a subjective record of menstrual blood loss through the study by all women. In practice, the amount of bleeding expressed in terms of "light", "moderate", or "heavy" flow, so the record in each day of the calen-

dar was painted with red color, and corresponded with one, two, or three subsegments in each column respectively.

The criteria for satisfactory result was defined as after initial hemostasis and progestational withdrawal bleeding (phase II) the menstrual pattern returned to normal uterine bleeding, except the withdrawal bleeding which was occasionally delayed after discontinuing the medication.

Results

Among 27 patients, 10 were lost to follow-up. Data from 17 women were analysed by description, as shown in Table 1. The follow-up rate was 17 of the 27 women (62.9 per cent; 5 menorrhagia, 10 metrorrhagia, 1 metromenorrhagia and 1 oligomenorrhea) ; 12 women (number 1 to 12) had complete follow-up (Phase I + Phase II + Phase III), and 5 women (number 13-17) had partial follow-up (Phase I + Phase II). Of twelve women with complete follow-up, ten of them had satisfactory result, and of this satisfactory group, three of ten (number 1, 2, 7) had one cycle of oligomenorrhea due to delay of withdrawal bleeding.

Table 1 Subjective description in 17 women with a complaint of abnormal bleeding who were treated with oral medroxyprogesterone acetate

Subject number	Pretreatment complaint	**Phase I** Withdrawal bleeding before (-) or after (+) complete medication (days)	**Phase II** Cyclic regulation for 3 cycles 1st 2nd 3rd (Interval/duration)	**Phase III** Continous observation for 3 cycles
1	menorrhagia	+ 8	37*/4 25/7 29/7	satisfactory
2	menorrhagia	+ 7	37*/4 24/7 28/4	satisfactory
3	menorrhagia	+ 4	28/4 28/4 29/5	satisfactory
4	metrorrhagia	+ 4	27/4 28/4 27/4	satisfactory
5	metrorrhagia	+ 4	27/6 29/6 27/5	satisfactory
6	menorrhagia	+ 7	28/4 27/3 28/4	satisfactory
7	metrorrhagia	- 1	26/3 37*/4 29/4	satisfactory
8	metrorrhagia	+ 8	28/2 29/4 30/5	satisfactory
9	metrorrhagia	+ 1	23/5 32/1 31/6	satisfactory
10	oligomenorrhea	+ 2	27/5 28/4 27/4	satisfactory
11	metrorrhagia	+ 4	23/3 MTR MTR	unsatisfactory
12	metrorrhagia	+ 6	17*/4 MTR MTR	unsatisfactory
13	menorrhagia	+ 2	31/5 31/2 21/4	partial FU
14	metrorrhagia	+ 1	27/5 31/5 25/6	partial FU
15	metrorrhagia	+ 8	MTR MTR MTR	partial FU
16	metrorrhagia	MTR	MTR MTR MTR	partial FU
17	metromenorrhagia	MTN	MTN MTN MTN	partial FU

* = oligomenorrhea ; MTR = metrorrhagia, MTN = metromenorrhagia, FU= follow-up

Of five women with partial follow-up (only Phase I + Phase II), two of them (number 13, 14) had satisfactory result. Overall, 12 of the 17 women (70.5 per cent) were satisfactory during treatment, and 10 of the 17 women (58.8 per cent) were satisfactory (among these, case numbers 13, 14, 15, 16, 17, had partial follow-up) during treatment and posttreatment.

The efficacy of medroxyprogesterone acetate in the treatment of dysfunctional uterine bleeding was 88.2 per cent in Phase I (15 of the 17 women), 70.5 per cent in Phase II (12 of the 17 women), and 28.8 per cent (10 of the 17 women, in Phase III.

Three of the seventeen patients (17.7 per cent ; case numbers 2, 4, 11) had elevated serum PRL level (> 20.0 ng/ml), as shown in Table 2.

Table 2 Screen PRL level in dysfunctional uterine bleeding

Screen PRL level	Number	per cent
Elevated (> 20.0 ng/ml)	3	17.7
Normal	14	82.3

Table 3 shows the microscopic examination of the endometrium, and among these 4 of the 17 women (23.5 per cent) were virgin cases so that they had no sampling endometrial biopsy. There were proliferative endometrium in 8 of the 13 (61.5 per cent), secretory endometrium in 3 of the 13 (23.1 per cent), and atrophic endometrium in 2 of the 13 (15.4 per cent).

Table 3 Endometrial biopsy in dysfunctional uterine bleeding

Microscopic examination	Number	per cent
Proliferative	8	61.5
Secretory	3	23.1
Atrophic	2	15.4

There were no side effects of the drug among the patients treated with oral medroxyprogesterone acetate.

Discussion

The basis of hormonal hemostasis in the treatment of dysfunctional uterine bleeding is the administration of a large dose of synthetic progestin (progesterone). In a usual case of DUB, progesterone is lacking, and theoretically that is all that is required. The main problem of exogenous estrogen combined with progesterone in the treatment of DUB is that the medication may cause nausea and vomiting because of the estrogen content[9]. So the patient should be treated with progestin that will cause spiral artery constriction and result in normal progesterone-withdrawal menses. Since progesterone is not well absorbed orally, a progestin-like medroxyprogesterone in the form of Provera should be used. Studies of the morphology of the endometrium under the influence of progestins suggest that long term therapy (10-13 days) is needed to regress the proliferation[10]. Thus, medroxyprogesterone acetate 10 mg/day for 10-13 days per month is recommended.

In this study we used medroxyprogesterone at a dosage of 10 mg daily for ten days as the initial hormonal hemostasis and withdrawal bleeding, and

10 mg daily from day 15 to day 24 of the cycle as regulation for the next three cycles. The patient assessments by subjective description were satisfactory 10 of the 17 women (58.8 per cent) during treatment and posttreatment, and 12 of the 17 women (70.5 per cent) during treatment alone. Whereas the management should be medical in the first instance, if the problems recurred during therapy or during the subsequent follow-up period organic lesion shold be suspected. So the effectiveness of the treatment depends on the accurate investigation for pathologic DUB. Oral medroxyprogesterone is another drug as well as norethisterone which can be used in the treatment of DUB due to some advantages to exogenous estrogen. The so-called "post-pill amenorrhea syndrome" does not have any relation to estrogen therapy. Use of estrogen does not appear to increase the risk of myocardial infarction. On the contrary, its use increases HDL-cholesterol level and should be beneficial in this aspect.

It is now apparent that the only logical management of uterine bleeding caused by endocrine imbalance is hormonal. If a bleeding episode is caused by progesterone insufficiency, exogenous progestin will also be able to control it. The ideal hormonal agent to arrest and control an acute episode of dysfunctional bleeding, should have strong progestational, potent estrogenic, and mild androgenic properties. Of course, no single steroid compound has such activities. Pria et al[1] recommended a combination of ethinylestradiol 0.05 mg and norethindrone acetate 2.5 mg, given several times a day according to a decreasing dose schedule. Four tablets a day result in arrest of bleeding in most cases. The dose was then gradually decreased to 1 tablet a day for a total length of treatment of 10-16 days. The bleeding was arrested in over 75 per cent of patients within the first 48 hours. Withdrawal bleeding generally took place 1-4 days after termination of treatment, and the duration of flow was 4-5 days. A similar regimen employing other types of estrogen-progesterone preparations has been recommended[9]. Arrest of bleeding was usually observed within the first 48 hours in over 75 per cent of patients. In this study the arrest of bleeding was 88.2 per cent.

We had a preliminary evaluation to show that serum prolactin level may be valued in correlation with DUB. In normal adult women the range of serum prolactin concentration is 3-30 ng/ml[11], but our laboratory has set the the standard at less than 20.0 ng/ml. We found 3 of the 17 women (17.7 per cent) to have elevated serum PRL of more than 20.0 ng/ml, and that needs further study. Pepperell[12] found elevated prolactin levels in 7.6 per cent of women with oligomenorrhea. Hyperprolactinemia may also be associated with menstrual irregularities from defective corpus luteum function. So the prolactin and menstrual disorders are an interesting topic for further study.

Most of the patients (61.5 per cent) revealed proliferative endometrium compatible with some degree of estrogen stimulation. The progestin in the treatment of DUB is sufficient to change

the endometrium to secretory phase and followed by progesterone (progestin) withdrawal bleeding.

This study had some pitfalls; the amount of menstrual blood flow which was recorded by menstrual calendar is subjective data, and because the loss of patients follow-up was rather high. However, the results of the study did conclude that progestin was the alternative therapy to induce stabilizing predecidual stromal changes, followed by a withdrawal flow, the socalled "medical curettage". Some authors have suggested that in the treatment of dysfunctional metromenorrhagia or menorrhagia the duration of therapy may be increased to 10-14 days[3].

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