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Intranasal treatment with luteinising hormone releasing hormone agonist in women with endometriosis

R W SHAW, H M FRASER, H BOYLE

Abstract

An agonist analogue of luteinising hormone releasing hormone (buserelin) was successfully used to treat women with endometriosis. A dose of 200 µg administered intranasally thrice daily was found to be effective in five patients, in whom the endometriotic lesions resolved after six months' treatment. Failure occurred in a sixth patient, who received only 400 µg once daily. Anovulation was induced in all subjects together with suppression of menstruation after the first month of treatment. Symptoms of abdominal pain, dysmenorrhoea, and dyspareunia were relieved during treatment, and one previously infertile patient conceived within two months of stopping treatment.

No side effects were reported with this dosage, and the results suggest a new form of treatment for patients with endometriosis.

Introduction

Endometriosis presents many problems with regard to aetiology, diagnosis, treatment, and management. Medical management of endometriosis has undergone important evolution during the past four decades, from the initial approaches of high dose diethylstilboestrol treatment¹ and progestin only and pseudo-pregnancy regimens² to the more recent use of the antigonado-

trophic agent danazol.^{3,4} These treatments are often effective, but considerable numbers of patients experience side effects severe enough to cause treatment to be stopped.

During the past few years long term studies of the effects of chronic treatment with agonist analogues of luteinising hormone releasing hormone in women and primates have shown that the pituitary cells secreting gonadotrophin become insensitive to stimulation by endogenous luteinising hormone releasing hormone with resultant suppression of ovarian secretion of steroid and anovulation.⁵⁻⁸ We report the results of a six month trial of the effect of such treatment on six patients with endometriosis and describe their hormonal and symptomatic response to treatment.

Patients and methods

The six patients studied were recruited from the infertility and gynaecology clinics of one of us. Endometriosis was diagnosed at laparoscopy or laparotomy in all patients while they were undergoing investigation for infertility or abdominal or pelvic pain. The format of the study was explained to each patient, and after giving their informed consent they were entered into the trial, which had been approved by the hospital ethical committee.

The first complete menstrual cycle after diagnosis served as a control cycle, during which no treatment was given but early morning urine samples were collected three times a week. On the second day of their next menstrual period the patients started treatment with the luteinising hormone releasing hormone agonist buserelin (D-ser (but)⁶ desgly¹⁰—luteinising hormone releasing hormone ethylamide) (Hoechst Pharmaceuticals). This was administered intranasally with a spray giving a measured dose of 100 µg. One patient (case 1) received 400 µg buserelin once daily; the five other patients received 200 µg buserelin intranasally three times daily.

Treatment was continued for 26-28 weeks except in the patient taking the analogue once daily, in whom it was stopped after 13 weeks (see below). At the end of this period laparoscopy was performed to assess the response to treatment and an endometrial biopsy specimen was taken. Buserelin was then stopped, and the patients were monitored until their first menstrual period.

Throughout the study the patients collected early morning urine

Centre for Reproductive Biology, Edinburgh EH3 9EW

R W SHAW, MD, FRCS, senior lecturer, department of obstetrics and gynaecology

H M FRASER, PHD, research scientist, Medical Research Council reproductive biology unit

H BOYLE, HNC, chief technician, National Health Service reproductive endocrine laboratory

Correspondence to: Professor R W Shaw, Academic Department of Obstetrics and Gynaecology, Royal Free Hospital, London NW3 2QG.

samples three times weekly, and these were analysed for ratios of oestrogen to creatinine and pregnanediol to creatinine concentrations, as previously described,⁹ to establish ovarian steroidogenic function. Patients were reviewed every four weeks to assess the development of other symptoms or side effects. Blood samples were screened at three months and at the end of treatment for the development of antibodies to the luteinising hormone releasing hormone agonist, as previously described.¹⁰

Results

The table summarises the relevant clinical details of the patients, the extent of endometriosis (using the classification suggested by Kistner *et al.*¹¹) and the response to treatment.

The first patient recruited to the trial received only 400 µg buserelin once daily, which is the dose that was previously used to suppress ovulation in contraceptive trials with this agent. This patient continued to have episodes of abdominal pain, and the endometrioma appeared to increase in size. For this reason, after 13 weeks of treatment she underwent laparotomy. The size of her endometrioma had been such that any form of medical treatment was unlikely to succeed, but she had originally refused surgery.

In view of this failure with the first patient subsequent recruits were started on a larger dose of buserelin. During the first month of treatment with buserelin 200 µg thrice daily three of the five patients experienced some vaginal bleeding between the first and fifth days, but it was not as heavy as normal menstruation. Thereafter, they remained amenorrhoeic while being treated, although one patient had occasional episodes of scant vaginal bleeding, with no set pattern, lasting one to two days.

Ovulation was suppressed in all six patients while they were taking the analogue, as indicated by the urinary pregnanediol concentrations, but the pattern of oestrogen secretion fell into two broad categories. Three patients showed a pattern of persistently suppressed oestrogen secretion with values in the range found in the early follicular phase. The other three patients showed a pattern of intermittent surges of oestrogen, though not to midcycle peak concentrations, which suggested waves of follicular development with failure to proceed to ovulation. No regular pattern was discernible, but any episodes of bleeding coincided with falls in oestrogen concentrations. The figure shows urinary steroid profiles in two patients, one from each category.

Laparoscopy at the end of treatment with the analogue showed an excellent response in five patients (cases 2-6) with scarring and resolution of all endometriotic areas. One patient (case 2) conceived within two months of stopping treatment.

The histology of the endometrial biopsy specimens obtained just before the end of analogue treatment corresponded well with the type of oestrogen secretory pattern observed during treatment. The three patients with suppressed flat patterns had proliferative atrophic, poorly developed endometria, and those who had maintained higher oestrogen output had endometria consistent with days 10-13 of a normal menstrual cycle. There was no evidence of cystic glandular hyper-

Pattern of urinary oestrogen and pregnanediol excretion in two patients receiving buserelin 200 µg intranasally thrice daily for six months, showing the patterns of ovarian secretion of steroid observed. Shaded blocks indicate periods of bleeding.

Conversion: SI to traditional units—Creatinine: 1 mol ≈ 113 g. Oestrogen: 1 µmol ≈ 288 µg. Pregnanediol: 1 nmol ≈ 320 mg.

plasia or atypia developing. The histological assessments were all done by the same person.

Although one patient noted reduced vaginal secretion during treatment, this did not cause any coital problems, and the other patients did not develop any side effects or symptoms of oestrogen deficiency. No antibodies to buserelin were found in the blood samples analysed. The symptoms of pain and dyspareunia resolved completely during treatment.

The first spontaneous menstruation in the five patients who completed treatment began 18-27 days after analogue treatment was stopped. In three patients the ovulatory cycles were normal; the two others had shortened luteal phases with low excretion of pregnanediol.

Discussion

Our results establish that long term treatment with luteinising hormone releasing hormone agonist, leading to suppression of ovarian steroid production, can result in the resolution of endometriotic tissue in women. This confirms a recent study on the effects of a luteinising hormone releasing hormone agonist in monkeys with experimentally induced endometriosis, which was

Clinical details and duration and outcome of treatment in six women

Case No	Age (years)	Symptoms at presentation	Classification of endometriosis treated	Dosage of buserelin	Duration of treatment	History	Follow up laparoscopy
1	33	Abdominal pain, dysmenorrhoea	IIA ₂	400 µg once daily	19 September-7 December 1981	Laparoscopy, April 1981. Endometrioma of left ovary 7 cm, numerous other deposits 2 mm. Started danazol, but stopped in July 1981. Pain persisted. Laparotomy in December 1981. Hysterectomy and left salpingo-oophorectomy.	All resolved. Pregnant September 1982
2	22	Primary infertility for 24 months, dyspareunia	IIA	200 µg thrice daily	2 January-7 July 1982	Laparotomy in November 1981. Right oophorectomy. Endometrioma 20 cm; numerous other deposits noted 2-5 mm.	All resolved except one lesion 2 mm in diameter
3	29	Primary infertility for 36 months, abdominal pain	IIA	200 µg thrice daily	17 August 1982-22 February 1983	Laparoscopy in July 1982. Confirmed endometriosis; numerous deposits 5 mm in diameter on ovaries and cul de sac.	All areas resolved
4	27	Primary infertility for 28 months, dysmenorrhoea	I	200 µg thrice daily	13 September 1982-29 March 1983	Laparoscopy in August 1982. Numerous endometriotic lesions 2 mm within pelvis.	All areas resolved
5	26	Primary infertility for 48 months	IIA	200 µg thrice daily	11 November 1982-5 May 1983	Laparotomy in October 1982. Left ovarian endometrioma 8 cm excised. Numerous other deposits on bladder, cul de sac, right ovary 2-5 mm.	All areas resolved
6	23	Primary infertility for 30 months	IIA	200 µg thrice daily	9 December 1982-5 May 1983	Laparoscopy in October 1982. Endometriotic deposits on ovaries cul de sac, uterosacra 2-5 mm.	All areas resolved

effective in 12 out of 15 animals when given for three months,¹² and extends previous preliminary results in women with endometriosis.^{13 14}

The one patient who did not respond to the treatment had a particularly severe form of the disease and was treated with agonist only once daily. During the course of this and other studies it became apparent that more frequent administration of the agonist might be more effective in maintaining suppression of follicular oestradiol (J Brancroft, R W Shaw, H M Fraser, unpublished findings).

As reported in other studies on the effects of long term treatment with a luteinising hormone releasing hormone agonist for contraception^{6 8} the return of ovulatory cycles after the end of treatment was not delayed. Indeed, one of the patients who had presented with infertility became pregnant two months after stopping treatment with the agonist.

Although no important side effects of the agonist were reported during the six month treatment regimen, longer term treatment may lead to a degree of oestrogen suppression that results in hot flushes developing in some women, as has been observed in patients receiving agonist treatment for the premenstrual tension syndrome (J Brancroft, R W Shaw, H M Fraser, unpublished findings). It may well be necessary, however, to endeavour to achieve almost total suppression of ovarian function to allow endometriotic lesions to resolve and avoid the problem of prolonged unopposed oestrogen acting on the endometrium.

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Acne and anticonvulsants

R GREENWOOD, P B C FENWICK, W J CUNLIFFE

Abstract

The severity of acne and rate of excretion of sebum were assessed in 243 patients with epilepsy taking various anticonvulsants who were in hospital long term and in matched controls derived from a normal population of 2176 people. Neither the prevalence of acne nor the sebum excretion rate significantly increased in the patients compared with the controls or in patients taking phenytoin compared with those not.

It is concluded that anticonvulsant treatment does not cause acne.

Department of Dermatology, General Infirmary, Leeds LS1 3EX
R GREENWOOD, BM, MRCP, senior registrar
W J CUNLIFFE, MD, FRCP, consultant dermatologist

Maudsley Hospital, London SE5 8AZ

P B C FENWICK, MRCPsych, DPM, consultant neuropsychiatrist

Correspondence to: Dr R Greenwood.

Introduction

Phenytoin was first made available for the treatment of epilepsy in 1938. Since then, despite a lack of clinical and scientific evidence, it has been widely believed and taught that anticonvulsants, and in particular phenytoin, cause or aggravate acne.¹ We report the results of a study of patients with epilepsy who were taking anticonvulsants and were in hospital long term. We set out to ascertain whether acne was more prevalent in patients with epilepsy than in the general population. Seborrhoea is cited as being one of the causative factors in acne,² and we therefore measured the rate of excretion of sebum in a selected number of the patients. We also studied particularly those patients taking phenytoin as this is the drug most commonly linked with acne.

Subjects and methods

We studied 131 men (aged 16-70) and 111 women (aged 17-70). We graded the severity of their acne with a standardised technique with a high degree of interobserver correlation.³ The grades were compared with those assessed in 1077 men (aged 18-69) and 1099 women (aged 18-69) taken from a normal factory population and not receiving any drug.⁴ Statistical analysis for this comparison was by the χ^2 method.