Effectiveness of pergolide mesylate in long term treatment of hyperprolactinaemia

S FRANKS, P M HORROCKS, S S LYNCH, W R BUTT, D R LONDON

Abstract

Twenty five patients with hyperprolactinaemia were treated with pergolide mesylate, a new dopamine receptor agonist. Twenty three received treatment for six to 20 months, and in all serum prolactin concentrations were considerably reduced. In most patients prolactin concentrations were maintained in the normal range by a low, once daily dose of pergolide and reversal of associated reproductive disorders was observed. Tumour volume as assessed by computed tomography decreased considerably during treatment in three out of four patients with a pituitary tumour. The drug was well tolerated. Side effects were similar to those of bromocriptine, but four out of eight patients who had been forced to stop taking bromocriptine because of untoward effects were subsequently able to tolerate treatment with pergolide.

Pergolide mesylate promises to be a useful addition to the currently available long acting dopamine agonists in the management of hyperprolactinaemia.

Introduction

Pergolide mesylate (Lilly) is a synthetic ergoline derivative that suppresses secretion of prolactin in both subjects with hyperprolactinaemia and those with normal prolactin concentrations.[1-4] It is a potent dopamine receptor agonist that effectively lowers serum prolactin concentrations in patients with hyperprolactinaemia for at least 24 hours after a single dose.[3] Preliminary results of chronic administration of the drug to men and women with hypersecretion of prolactin suggested that pergolide would be a safe and successful means of treatment for such patients.[3] Two patients who had been unable to tolerate treatment with bromocriptine were later maintained with pergolide. We now present the results of long term treatment in 25 patients, 22 of whom received treatment for six to 20 months.

Patients

WOMEN (table)

Seventeen women (age 14-42) entered the study. Seven had radiological evidence of a pituitary tumour. Sixteen presented with amenorrhoea and one with irregular periods. Two wished to become pregnant. Eight of the amenorrhoeic patients had galactorrhoea and four also complained of vaginal dryness on intercourse. Two women suffered hot flushes. Eight patients had previously received bromocriptine, which had proved unsuccessful either because of unacceptable side effects or because the serum prolactin concentration was not adequately suppressed (as in one patient (case 6) with a large prolactinoma and a serum prolactin concentration of 22 100 mU/l). Three women were forced to stop taking pergolide within two weeks after starting treatment because of persistent nausea; the remaining 14 were treated for six to 20 months.

Departments of Medicine and Endocrinology, Queen Elizabeth Hospital, and Birmingham and Midland Hospital for Women, Birmingham

S FRANKS, MD, MRCP, lecturer in medicine
P M HORROCKS, MB, MRCP, lecturer in medicine
S S LYNCH, PHD, biochemist
W R BUTT, DSC, PHD, professor of biochemical endocrinology
D R LONDON, DM, FRCP, consultant endocrinologist

Correspondence to: Dr S Franks, Department of Obstetrics and Gynaecology, St Mary's Hospital Medical School, London W2 1PG.

MEN (table)

Eight men were included in the study; pituitary tumours had been diagnosed in seven. Five of these seven had previously undergone pituitary surgery but still had high serum prolactin concentrations; these five had remained hypogonadal after surgery but had evidence of gonadotrophin deficiency in addition to hyperprolactinaemia. They had all received testosterone replacement but despite normal serum concentrations of testosterone four of the five were not satisfied with their lack of response to treatment and complained, in particular, of lack of growth of facial hair. Two men (cases 18 and 20) presented with infertility and oligospermia. Sexual function in these two patients was otherwise normal, and we considered that the hyperprolactinaemia was probably a coincidental finding. Nevertheless, we thought it worth while to give them a trial of pergolide. One patient (case 25) had a visual field defect associated with a recurrent chromophobe adenoma of the pituitary. His serum prolactin concentration was only twice the upper limit of normal, and he almost certainly had a large "functionless" tumour rather than a prolactinoma, but we elected to give him a course of pergolide before considering more radical treatment. Two of the men with hypogonadism (cases 21 and 22) had considerable residual tumour tissue on computed tomography, and we were interested to see whether, in these patients too, pergolide would reduce the volume of the tumour. One man (case 24) had previously been treated with bromocriptine, which he had had to stop because of side effects.

METHODS

The once daily dosage schedule and the programme of investigation of patients receiving chronic treatment that we used were essentially those described previously[4] and included regular measurement of serum concentrations of prolactin and gonadotrophins. We made one modification as a 25 μg capsule had become available. In the light of our preliminary assessment of the drug[4] patients were given 25 μg initially and the dosage was increased at intervals of two weeks until effective suppression of prolactin was obtained. A biochemical profile for assessment of the results of liver function tests was monitored monthly. Ovulation was assessed by measurement of serum progesterone concentration in the mid-luteal phase of the menstrual cycle.

Results

Prolactin concentrations in the 17 women before treatment ranged from 880 to 24 100 mU/l (upper limit of normal 480 mU/l) (table, fig 1). The mean maintenance dose of pergolide was 108 μg/day (range 25-600 μg). In the eight men prolactin concentrations ranged from 700 to 57 300 mU/l (upper limit of normal 360 mU/l) and the mean maintenance dose of pergolide was 156 μg/day (range 50-500 μg) (table).

SERUM PROLACTIN CONCENTRATIONS

Serum prolactin concentrations were measured before and during treatment in 24 patients (fig 1). In the other patient (case 7), who stopped taking the drug within a few days, no concentration after treatment was recorded. Prolactin concentrations were greatly reduced in all patients, to below 1000 mU/l in 21 of the 24 and to within the normal range in 16. In one woman (case 6) the serum prolactin concentration fell from 22 100 to 7500 mU/l but could not be

Details of patients treated with pergolide mesylate

Case No	Sex	Age (years)	Clinical features	Abnormal fossa	Serum prolactin (mU/l)		Dose (μg/day)	Duration (months)	Outcome
					Before treatment	During treatment			
1	F	42	Amenorrhoea, flushes	+	4500	80	50	6	Ovulation*
2	F	19	Amenorrhoea, galactorrhoea	+	4500	150	150	20	Ovulation, galactorrhoea abolished
3	F	32	Amenorrhoea, greasy skin	+	900	90	100	14	Ovulation, skin improved
4†	F	27	Amenorrhoea	−	2470	100	25	17	Ovulation
5	F	31	Amenorrhoea, galactorrhoea, vaginal dryness	+	2080	650	50	11	Ovulation, galactorrhoea abolished
6†	F	30	Amenorrhoea	+	22100	7500	600	20	No change
7†	F	31	Oligomenorrhoea	−	880	—	50	<1	No change*
8†	F	30	Amenorrhoea	−	1910	450	50	<1	No change*
9	F	28	Amenorrhoea, galactorrhoea, vaginal dryness	−	5500	220	100	14	Ovulation, galactorrhoea abolished
10†	F	32	Amenorrhoea, galactorrhoea	−	2160	1210	100	14	No change
11	F	28	Amenorrhoea, flushes	+	24100	980	150	<1	No change*
12	F	41	Amenorrhoea	+	1260	230	50	14	Ovulation
13†	F	35	Amenorrhoea, galactorrhoea	−	1420	570	50	11	Ovulation, galactorrhoea abolished*
14	F	29	Amenorrhoea, galactorrhoea, vaginal dryness	−	3000	130	50	6	Ovulation, galactorrhoea abolished
15	F	31	Amenorrhoea, vaginal dryness	−	5320	240	50	6	Ovulation
16†	F	25	Amenorrhoea, galactorrhoea	+	6280	790	100	7	Ovulation, galactorrhoea abolished
17†	F	28	Amenorrhoea, galactorrhoea	−	3450	750	150	6	Menstruation
18	M	22	Azoospermia, infertility	+	1620	<80	150	12	No change
19†	M	23	Hypogonadism	+	1470	210	100	20	Increased facial hair
20	M	21	Oligospermia, infertility	−	1070	80	50	12	No change
21	M	45	Hypogonadism, residual tumour	+	18000	1590	500	13	Tumour size decreased
22	M	32	Hypogonadism, residual tumour	+	57300	150	200	14	Increased facial hair, tumour size decreased
23	M	27	Hypogonadism	+	1100	80	50	11	Increased facial hair
24†	M	26	Hypogonadism	+	48000	620	100	6	No change*
25	M	42	Big tumour, visual field defect	+	700	<80	100	6	No change

*Stopped taking pergolide (see text).
†Previously treated with bromocriptine, which was stopped because of side effects or failure to suppress prolactin adequately.

suppressed further despite administration of 600 μg/day pergolide; she had previously proved resistant to treatment with bromocriptine.

The fall in serum prolactin concentrations was related to the dose of pergolide (fig 2). Each dose produced a rapid decline in secretion of prolactin, but the maximum suppression and, in particular the duration of the effect, varied with the dose. Pergolide 50 μg maintained effective suppression of prolactin up to 24 hours after a single dose.

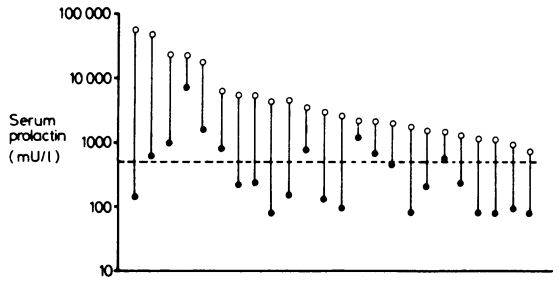

FIG 1—Serum prolactin concentrations before and after treatment with pergolide mesylate in 24 patients with hyperprolactinaemia. ○=Pretreatment concentrations. ●=Lowest recorded concentrations during treatment with pergolide. Horizontal broken line indicates upper limit of normal range (480 mU/l in women).

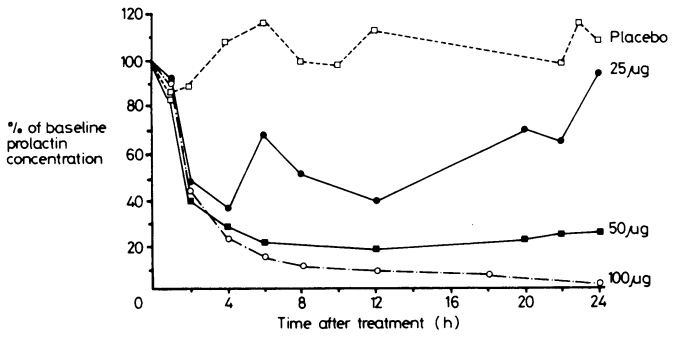

FIG 2—Response of serum prolactin concentrations to various doses of pergolide in patient given single dose of the drug at 0 hours.

CLINICAL RESPONSE

Of the 17 women treated with pergolide, 14 continued taking the drug for at least six months. Menstruation resumed in 12 of these 14 and ovulation was confirmed in 11 of the 12. In the two women who did not menstruate (cases 6 and 10) prolactin concentrations remained above the upper limit of normal. Neither of the two women who wished to conceive (cases 4 and 15) became pregnant. Both were ovulating regularly, but one (case 4) had obstruction of her one remaining Fallopian tube. A computed tomogram showed unequivocal evidence of reduction of tumour volume during treatment in case 6 even though the serum prolactin concentration did not fall below 7000 mU/l.

Clinical response was more difficult to judge in the men, but three out of four volunteered that their beard growth had increased while they were taking pergolide even though their androgen replacement treatment had not been changed.

In two men with prolactinomas (cases 21 and 22) the size of the tumour was reduced as judged by computed tomography during treatment (doses 500 μg and 200 μg a day, respectively). There was no obvious change on radiological assessment or by perimetry in the patient (case 25) with a visual field defect, but subsequent surgical exploration showed that the defect was related to fibrosis in the region of the optic chiasm and not to a direct effect of tumour tissue. Effective suppression of prolactin concentrations in the two men with oligospermia (cases 18 and 20) had no effect on sperm density or fertility.

SIDE EFFECTS

The most common side effects were nausea (12 patients), nasal congestion (eight), and postural dizziness (eight); others were constipation (two), tiredness (two), and depression (one). In most patients the symptoms were mild and transient (particularly when the patients were started on a dose of 25 μg daily) and were minimised by the patients taking the drug during a snack after retiring to bed. In three patients (cases 7, 8, and 11) nausea and postural dizziness were severe enough to force them to stop taking pergolide after only a few days' treatment (two had suffered a similarly severe reaction to bromocriptine), and three further patients stopped taking the drug after six to nine months' treatment: two (cases 1 and 24) complained of persistent nausea and drowsiness and the third (case 13) of depression.

Of the eight patients who had previously been treated with bromocriptine and in whom treatment had been stopped because of side effects, four, including the two described above, suffered the

same adverse symptoms while taking pergolide but the remaining four were able to tolerate long term treatment with pergolide. One of this last group (case 17) had suffered a rash while taking bromocriptine, which did not recur on pergolide. In all, six patients stopped taking pergolide because of side effects; four had suffered the same symptoms during previous treatment with bromocriptine (nausea in two (cases 7 and 8), drowsiness in one (case 24), and depression in one (case 13)), but two (cases 1 and 11), who both complained of nausea and drowsiness, experienced fewer problems when subsequently given bromocriptine and were able to continue long term treatment with this drug. As in our preliminary study, no patient had evidence of disturbed liver function while taking pergolide.

Discussion

Preliminary studies indicated the potential value of pergolide mesylate in treating hyperprolactinaemic states in women and men.[1 2 4] This long term study confirms the efficacy of a single, low, daily dose of pergolide in suppressing serum prolactin concentrations in hyperprolactinaemia. In most patients the effective dose is between 50 μg and 150 μg daily.

As with bromocriptine, and in agreement with the findings of Kleinberg *et al*,[3] we noted a reversal of the reproductive disorders and reduction of tumour size during long term treatment.[5-9] The increase in facial hair during treatment of hyperprolactinaemic men receiving testosterone replacement treatment was an interesting finding. One possible explanation is an increase in serum concentrations of dihydrotestosterone; normal men with experimentally induced hyperprolactinaemia appear to have lower concentrations of dihydrotestosterone than control subjects, and this trend is reversed by bromocriptine treatment.[10] We are currently testing this hypothesis. Pergolide was no more successful than bromocriptine in suppressing secretion of prolactin in a patient with a resistant prolactinoma, though the size of the tumour decreased considerably with pergolide.

Side effects were similar to those experienced during treatment with bromocriptine, but four out of eight patients who had previously been unable to continue taking bromocriptine because of side effects were successfully maintained on pergolide. Conversely, two of the six patients who were forced to stop taking pergolide because of untoward effects were subsequently able to tolerate bromocriptine. It would thus seem reasonable to consider treatment with pergolide when treatment with bromocriptine has failed because of unacceptable side effects. Use of pergolide as first line drug treatment of hyperprolactinaemia will clearly depend on the results of further clinical trials, but most patients who had previously received bromocriptine preferred the convenience of a drug that need be taken only once a day.

We thank Dr Alan Glynne and Dr Janet Scotton of the Lilly Research Centre (Windlesham, Surrey) for providing the pergolide capsules and for their helpful advice. We are grateful to our medical and gynaecological colleagues at Queen Elizabeth Hospital and the Birmingham and Midland Hospital for Women, Birmingham, for allowing us to investigate and treat patients under their care.

References

1 Lemberger L, Crabtree RE. Pharmacologic effects in man of a potent long-acting dopamine receptor agonist. *Science* 1979;**205**:1151-2.
2 Perryman RL, Rogol AD, Kaiser DL, MacLeod RM, Thorner MO. Pergolide mesylate: its effects on circulating anterior pituitary hormones in men. *J Clin Endocrinol Metab* 1981;**53**:772-8.
3 Kleinberg DL, Lieberman A, Todd J, Meddick J, Neophytides A, Kuppersmith M. Twenty-four hour suppression of prolactin by pergolide mesylate [Abstract 679]. *Programme of the 62nd annual meeting of the Endocrine Society, Washington, USA, 1980*. Bethesda, Maryland: Endocrine Society, 1980:242.
4 Franks S, Horrocks PM, Lynch SS, Butt WR, London DR. Treatment of hyperprolactinaemia with pergolide mesylate: acute effects and preliminary evaluation of long-term treatment. *Lancet* 1981;ii:659-61.
5 Thorner MO, McNeilly AS, Hagan C, Besser GM. Long-term treatment of galactorrhoea and hypogonadism with bromocriptine. *Br Med J* 1974;ii:419-22.
6 Franks S, Jacobs HS, Hull MGR, Steele SJ, Nabarro JDN. Management of hyperprolactinaemic amenorrhoea. *Br J Obstet Gynaecol* 1977;**84**:241-51.
7 McGregor AM, Scanlon MF, Hall K, Cook DB, Hall R. Reduction in size of a pituitary tumour by bromocriptine therapy. *N Engl J Med* 1979;**300**:291-3.
8 Wass JAH, Thorner MO, Charlesworth M, *et al*. Reduction of pituitary tumour size in patients with prolactinomas and acromegaly treated with bromocriptine with or without radiotherapy. *Lancet* 1979;ii:66-9.
9 Kendall-Taylor P, Hall K, Johnston DG, Prescott RWG. Reduction in size of prolactin-secreting tumours in men treated with pergolide. *Br Med J* 1982;**285**:465-7.
10 Magrini G, Ebiner JR, Burckhardt P, Felker JP. Study on the relationship between plasma prolactin levels and androgen metabolism in man. *J Clin Endocrinol Metab* 1967;**43**:944-6.

(*Accepted 25 January 1983*)

SHORT REPORTS

Assay of Schwangerschafts protein 1 (SP_1) as test for pregnancy

The standard biochemical test for pregnancy requires the detection of chorionic gonadotrophin, but it is insensitive and cannot be done within a few days of administration of chorionic gonadotrophin. Schwangerschafts protein 1 (SP_1) is a protein produced by the placenta and secreted into the maternal bloodstream. Early work suggested that it might be a useful marker of pregnancy,[1] but this entailed measuring the protein by radioimmunoassay, which put it beyond the range of many laboratories. An easier enzyme immunoassay is now available.[2] We applied this method to determining before the time of the first missed period whether a woman had conceived.

Patients, methods, and results

We took heparinised blood samples from 150 women attending an infertility clinic in Aberdeen. Seventy of the women received no treatment during the cycle under observation; 48 were treated with clomiphene citrate; 14 had ovulation induced with human menopausal gonadotrophin, and 12 were receiving bromocriptine. The remainder had undergone artificial insemination of donor semen. All patients were seen 21-32 days from their last period or, in the case of amenorrhoeic women, from the onset of treatment. All were in the luteal phase as judged by basal body temperature and plasma progesterone assay. In some the date of ovulation was pinpointed by determining the peak concentration of luteinising hormone and by ultrasonic scanning of the ovaries. In all patients the sample was taken, as far as we could determine, six to 14 days after ovulation. Serial samples were taken from patients under close observation. If all samples were negative for the protein they were taken as a single negative; if any were positive the patient was scored as being positive.

SP_1 was measured with an immunoassay kit (Behringwerke AG).[2] The lower limit of sensitivity claimed by the manufacturers is 0·3 μg/l. We operated a cut off point of 0·5 μg/l.

Twenty six women yielded a concentration of the protein above 0·5 μg/l, the lowest value in this group being 1·8 μg/l. All these women were later shown to be pregnant by a standard urinary haemagglutination pregnancy test and by ultrasonography. The table shows the clinical data on the patients.

The remaining 124 of the 150 patients tested yielded negative results. None was subsequently found to have been pregnant.

Comment

Although the number of cases examined was small, our findings suggest that assays of SP_1 are a reliable pregnancy test and comparable with assays of β chorionic gonadotrophin. There were no false positive or false negative results, and the results are available on the