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Pergolide As Primary Therapy for Macroprolactinomas

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Abstract. **The objective of this study is to determine whether pergolide therapy is an effective modality for the de novo treatment of patients with macroprolactinomas. Twenty-two consecutive patients with macroprolactinomas were included in the study and followed prospectively. These included 16 men and 6 women in whom pregnancy was not of concern. Pergolide was administered once or twice a day depending on the patient's preference. Ten patients received 0.1 mg daily as a maintenance regimen and in the others the daily dose ranged from 0.05 to 0.5 mg. Eight patients reported minor but tolerable side effects. One patient had to be switched to cabergoline because of intolerable nausea. After a mean of 12 months (range, 3–36), mean PRL levels declined from 3,135 ng/ml (range, 126–31,513) to 50 ng/ml (3–573), representing a mean PRL suppression of 88% (range, 0–99). PRL levels became normal in 15 patients and decreased to 25–40 ng/ml in 3 others. The mean tumor volume shrinkage was 25% or greater in 19 patients (86%), 50% or greater in 17 patients (77%), and 75% or greater in 10 patients (45%). Visual abnormalities were reversible after pergolide therapy in all but 1 of 12 patients with initially abnormal formal visual testing. Two out of 4 premenopausal women did not normalize PRL levels and had persistent oligomenorrhea. Testosterone was low in 14 men at presentation and normalized in 3 with pergolide therapy. We conclude that pergolide is a safe, inexpensive, and generally well-tolerated dopamine agonist for the treatment of macroprolactinomas in men and women in whom pregnancy is not of concern. In these specific populations, pergolide may become the first-line therapy for treatment of macroprolactinomas.**

Key Words. **macroprolactinoma, prolactin-secreting pituitary tumor, pergolide, dopamine agonists**

Introduction

PRL-secreting pituitary adenomas account for 60% of all functioning-pituitary tumors. Patients with macroprolactinomas (≥10 mm) are often men or postmenopausal women who come to medical attention with manifestations of tumor mass effect such as visual field defects, headaches, or hypopituitarism. Patients with macroprolactinomas require therapy to achieve PRL normalization, tumor shrinkage, and reversal of visual abnormalities or pituitary dysfunction. These objectives are usually effectively accomplished medically by using dopamine agonists. Transsphenoidal adenomectomy is currently recommended only when patients are intolerant of or resistant to these medications. Bromocriptine and cabergoline are the only dopamine agonists approved in the United States for the treatment of prolactinomas [1].

Bromocriptine normalizes PRL levels in 70–80% and significantly decreases adenoma size and restores gonadal function in 60–80% of patients with macroprolactinomas [2,3]. Almost 40% of the patients, however, are either resistant or intolerant to bromocriptine [4]. Likewise, because of its very short half-life, bromocriptine needs to be administered up to three times per day, reducing patient's compliance.

Cabergoline is a selective, potent and long-lasting dopamine agonist that is at least as effective as bromocriptine in lowering PRL levels and shrinking tumor size but with significantly less side effects [5]. Cabergoline, with a once or twice weekly dosing, normalizes PRL levels in 61–100%, significantly decreases adenoma size in 65–100%, and restores gonadal function in 80–90% of patients with macroprolactinomas [6–9]. Pergolide is a long-acting, less expensive, ergot derivative that effectively suppresses PRL secretion for more than 24 hours [10], allowing control of hyperprolactinemia with only one daily dose [11], therefore, facilitating patients' compliance. Pergolide is currently approved for the treatment of Parkinson's disease where it is administered at much higher doses than those used for prolactinomas. There is a paucity of data

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in the literature concerning tumor shrinkage with pergolide therapy in patients with macroprolactinomas. The majority of reports have included very few patients, reduction in adenoma size has not been adequately evaluated, and most patients have previously received other dopamine agonists, radiotherapy, or have had pituitary surgery [12–17] confounding the interpretation of the results. A recent paper with adequate clinical, hormonal, and radiological follow up, including 18 patients who received pergolide as first-line therapy, showed excellent results after a mean of 27.4 months of therapy [18]. We report our experience in 22 macroprolactinoma patients who received pergolide as primary therapy and confirm its effectiveness in normalizing PRL levels, reducing tumor size, and improving visual abnormalities with only minor and tolerable side effects.

Patients and Methods

Selection of patients

Thirty-seven patients attending our Pituitary and Neuroendocrine Center because of PRL-secreting pituitary tumors have been treated with pergolide. Patients with macroprolactinomas (≥10 mm) in whom pergolide was used as primary therapy were included in this report (n = 22). Patients who did not meet the above inclusion criteria (n = 13) or were lost to follow up (n = 2) were excluded from the study.

Study design

Complete clinical history, physical and ophthalmologic examination, PRL, testosterone (in men), and FT4 levels were obtained during the first visit. These were repeated one to three months later and at least yearly thereafter. Cortisol and IGF-1 levels were measured at baseline. Plasma gonadotropins were measured in postmenopausal women. Dedicated pituitary MRI was done at baseline, between 2 and 6 months after initiation of pergolide therapy and annually thereafter. The MRI protocol included coronal, sagittal, and axial scans centered at the pituitary region performed before and after administration of gadolinium DPTA. Formal visual testing was carried out in all patients who presented with clinically-apparent visual abnormalities (n = 6) and in 6 other patients without visual complaints but in whom the pituitary adenoma was too close to the optic chiasm to rule out its subclinical compromise. In patients with no distortion of the optic chiasm on the MRI, who had no visual complaints and whose clinical assessment of visual fields was normal, no formal visual field study was performed. Pergolide was started at a dose of 0.025 mg at night, and the dose was increased gradually as tolerated with the goal of achieving a PRL level as close to the normal range as possible. Pergolide was administered as either one or two daily doses, depending on patients' preference. Tumor volume was calculated as $4/3\pi r_1 r_2 r_3$, where r_1, r_2, and r_3 were maximal vertical, lateral and anteroposterior radii, respectively.

All hormone measurements were performed in the Ligand laboratory at the University of Michigan Medical Center, using commercially available kits.

Results

Patient characteristics

Table 1 shows demographic data of 16 men and 6 women included in the study. Mean age in men was 41 yr (range, 16–68) and in women was 48 yr (range, 39–64). The symptom that led to the diagnosis of macroprolactinoma in men was visual loss in 5, headache in 3, short stature in 1, and erectile dysfunction in 1. In 6 men the tumor was incidentally found in CT or MRI scans performed for other reasons. All premenopausal women (n = 4) presented with oligo/amenorrhea and/or galactorrhea. One each of the postmenopausal women presented with visual loss and headache.

Pergolide therapy

The initial treatment dose of pergolide ranged from 0.1 to 0.75 mg per day. Patient 14 was admitted to the hospital for initiation of pergolide, 0.25 mg three times per day because of the severity of his symptoms related to a giant prolactinoma. The most common pergolide maintenance dose was 0.1 mg per day (n = 10), with others ranging between 0.05 and 0.5 mg daily. The median dose of pergolide was also 0.1 mg per day. Nine patients reported side effects related to pergolide theraphy. Side effects were minor and easily tolerable and included stuffy nose (n = 5), postural lightheadness (n = 2), nausea (n = 2), emotional lability (n = 1), headache (n = 1), mood changes (n = 1), and tremor (n = 1). In the vast majority of cases, these side effects tended to decrease in intensity or to vanish altogether with time. Only patient 13 developed intolerable nausea after increasing pergolide to 0.4 mg per day, requiring a switch to cabergoline. MRI scans and hormonal evaluations in this patient were done while on pergolide. No patient experienced apparent cerebrospinal fluid leak during treatment.

PRL normalization

Mean initial PRL level for all patients was 3,135 ng/ml (range, 126–31,513). Three patients had initial PRL levels lower than 200 ng/ml but their tumors shrank by 40% or greater with pergolide therapy, arguing against these tumors being non-secreting pituitary adenomas with stalk compression. PRL levels became lower than 50 ng/ml within 6 months in 11 patients and within 12 months in 15 patients. After a mean of 12 months (range, 3–36), mean PRL level declined to 50 ng/ml (range, 3–573), representing a mean PRL suppression of 88% (range, 0–99). PRL levels became normal (3–25 ng/ml) in 15 patients and decreased to 25–40 ng/ml in 3 others. PRL suppression was 90% or greater in 17 of

Table 1.

Patient #	Gender	Age	PRL Initial ng/ml	PRL Final ng/ml	PRL Supp. %	Pergolide Duration months	Pergolide Dose mg/day	T Initial ng/ml	T Final ng/ml
1	F	64	3,894	13.4	99	12	0.1		
2	F	40	523	7.7	99	9	0.1		
3	F	44	156	103	34	36	0.05		
4	F	39	549	573	0	19	0.1		
5	F	63	2,178	10	99	20	0.1		
6	F	39	360	4	99	13	0.05		
7	M	36	1,834	2.5	99	23	0.1	1.52	2.16
8	M	38	247	33	87	5	0.25	1.71	4.51
9	M	56	126	11.4	90	3	0.1	0.31	1.45
10	M	36	1,617	6.1	90	7	0.5	0.97	0.96
11	M	44	5,245	2.5	99	26	0.05	0.1	on T
12	M	68	799	3.8	99	23	0.1	3.42	7.33
13	M	46	179	33	82	5	0.4	1.64	on T
14	M	32	31,513	4.3	99	6	0.25	0.77	on T
15	M	54	555	101	78	23	0.3	0.1	on T
16	M	26	5,796	15	99	3	0.2	1.89	5.41
17	M	41	2,397	71	93	7	0.25	0.91	on T
18	M	16	595	22	96	5	0.2	0.14	0.49
19	M	39	2,355	40	98	3	0.1	1.08	1.06
20	M	53	1,519	8	99	4	0.2	1.15	2.5
21	M	24	3,249	19	99	3	0.1	2.7	2.57
22	M	49	3,290	25	99	3	0.1	0.01	on T

PRL supp = prolactin suppression. T = testosterone

22 patients. Patients 3 and 4 had tumor shrinkages of 42 and 36%, respectively, despite the fact that PRL levels were almost unchanged. Patient 17 had an almost complete disappearance of the tumor with 93%-PRL suppression, although PRL was still mildly elevated 7 months after initiation of pergolide. Only patient 15 can be considered a therapeutic failure in terms of both PRL suppression and tumor shrinkage.

Tumor shrinkage

Table 2 shows tumor characteristics. The mean initial maximal tumor diameter was 2.9 cm (range, 1.2–5.5). All the tumors but 3 were greater than 2 cm in maximal diameter and 11 tumors were 3 cm or greater. Eleven and 15 patients had tumor size reductions greater than 50% within 6 and 12 months after initiation of pergolide, respectively. The mean final maximal tumor diameter was 1.8 cm (range, 0–4.2). Eleven tumors were smaller than 2 cm and 20 were 3 cm or smaller after pergolide therapy. Overall, the mean tumor volume shrinkage was 67% (range, 9–100). Tumor shrinkage was 25% or greater in 19 patients, 50% or greater in 17 patients, and 75% or greater in 10 patients. Although patient 10 had only 9%-tumor shrinkage with pergolide therapy, his PRL level became normal suggesting adequate response to pergolide. Likewise, patient 24 normalized PRL levels with 99%-PRL suppression, although tumor size reduction was 24% after 4 months of

Table 2.

Patient #	First MRI (V×L×AP) cm	Last MRI (V×L×AP) cm	Shrinkage %
1	3.0×3.1×3.0	1.2×1.2×2.1	89
2	2.3×2.3×1.8	0.7×0.7×1.2	94
3	0.8×1.2×0.9	0.8×0.9×0.7	42
4	1.1×1.8×1.0	1.0×1.4×0.9	36
5	2.5×2.5×2.5	0*	100
6	2.5×3.0×2.8	2.0×2.0×2.2	59
7	1.9×2.1×1.7	0.4×1.0×0.4	97
8	1.6×1.8×1.5	0.6×0.9×1.5	81
9	2.2×2.0×1.8	1.4×1.5×1.6	58
10	2.0×2.3×1.8	1.9×2.2×1.8	9
11	4.3×4.4×4.3	2.3×3.7×2.6	73
12	1.5×2.1×1.8	1.1×0.9×0.9	84
13	2.7×2.9×2.8	2.0×2.0×2.4	56
14	5.5×5.2×4.2	2.1×4.2×3.1	77
15	2.0×3.0×1.5	2.0×2.5×1.5	17
16	3.0×3.8×2.4	0.8×0.8×1.0	98
17	3.0×2.7×2.2	0.8×1.0×0.8	96
18	2.7×2.7×1.9	1.8×2.2×1.5	57
19	3.2×2.2×1.8	2.2×1.6×1.2	68
20	2.6×3.1×2.2	2.2×2.9×2.1	24
21	3.0×2.1×3.1	1.9×2.0×2.2	57
22	4.1×3.5×4.1	0*	100

V = maximal vertical diameter.
L = maximal lateral diameter.
AP = maximal antero-posterior diameter.
* = no tumor identified.

pergolide therapy. Figure 1 shows the MRI scans from patient 22.

Visual fields

Six patients came to medical attention because of visual field defects. These and 6 other patients (n = 12) underwent formal visual testing, which was abnormal in all patients who presented with visual loss and in 4 of the patients who did not. Visual abnormalities were completely reversible in all patients except patient 17 who had a residual left superior temporal quadrant defect.

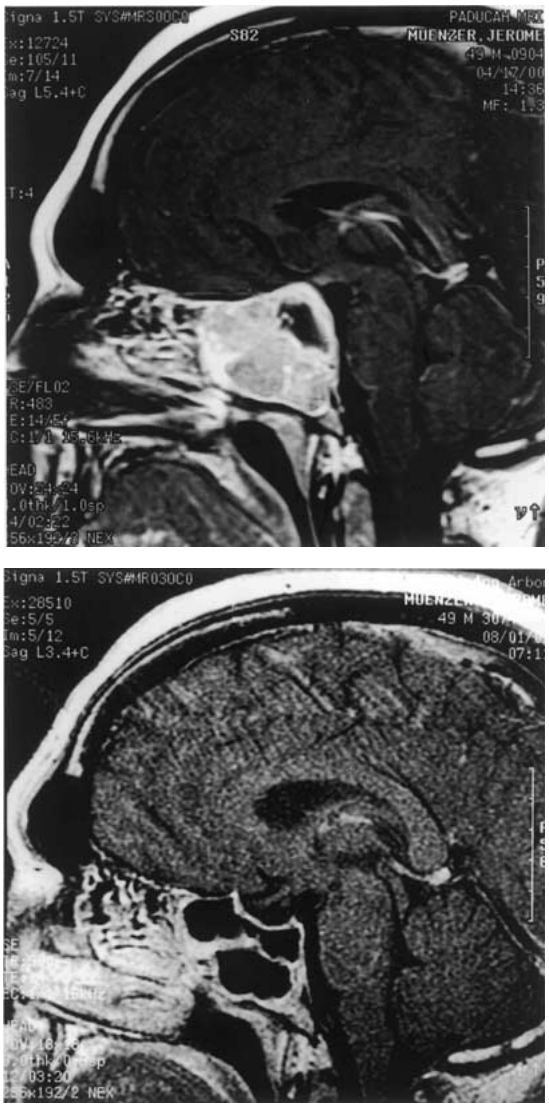

Fig. 1. *Sagittal gadolinium-enhanced T1 weighted pituitary magnetic resonance image before (a) and 3 months after (b) pergolide therapy (patient 22). Figure 1a shows a 4.1 × 3.5 × 4.1-cm sellar mass with suprasellar and sphenoidal sinus extension with cystic and hemorrhagic components. Fig. 1b shows complete disappearance of the mass with normal appearance of the pituitary gland.*

Gonadal function

All premenopausal women (n = 4) presented with oligo/amenorrhea and/ or galactorrhea. Patients 2 and 6 normalized PRL levels with resumption of normal menses. Patients 3 and 4 did not normalize PRL levels, and irregular menstrual periods persisted. Patient 1 was postmenopausal but gonadotropins remained inappropriately low after one year of pergolide therapy, despite normalization of PRL. Patient 5 had physiological elevation of gonadotropins to the postmenopausal range within 6 months of pergolide treatment. By history 10 of 16 men had decreased libido and/or erectile dysfunction for months to years before the diagnosis of macroprolactinoma was established, included two patients with normal testosterone at presentation. Initial testosterone levels were low in 14 men and normalized in only 3 patients with pergolide therapy. Testosterone levels were transiently lower in 6 men after starting pergolide therapy, including patient 21 whose baseline testosterone was normal but came down temporarily below the normal range. None had a final testosterone lower than the initial testosterone levels. Six men received testosterone replacement therapy.

Discussion

We have confirmed in this open label study that pergolide is a very effective primary therapy for the treatment of macroprolactinomas in men and women. This finding along with the excellent tolerance of pergolide, its lower cost, and the once-a-day-dosing schedule suggest that this medication may be considered first line therapy in patients with macroprolactinomas.

In this study, PRL normalization after pergolide therapy was achieved in 15 patients (68%) and PRL levels between 25–40 ng/ml in 3 others. Previous studies have suggested that bromocriptine and pergolide are equally effective in lowering PRL levels in patients with hyperprolactinemia [13,15,17], although only a few patients with macroprolactinomas were included. Although direct comparison between cabergoline and pergolide has not been performed, cabergoline has been found to normalize PRL levels in 61–100% of patients with macroprolactinomas [6,7,9,19] similar to the 68% success rate with pergolide [18] and this study.

We found that a mean of 12 months of pergolide therapy caused a mean tumor shrinkage of 67%. All patients but 3 (86%) had tumor volume reductions greater than 25%. A previous study of tumor shrinkage in patients with macroprolactinomas has shown that 4 of 6 patients on pergolide and 1 of 6 patients on bromocriptine had 25% or greater reductions in adenoma size [17]. Overall, bromocriptine significantly decreases adenoma size in almost 80% of patients with macroprolactinomas [3]. Similarly, cabergoline has been found to significantly reduce tumor volume in 65–100% of patients with macroprolactinomas [6,7,9,19], compared to 67–95% of patients on pergolide [14,17,18]. In only one report that

included 3 patients with macroprolactinomas, tumor size did not change with pergolide administration, but those patients had been previously resistant to other dopamine agonists [16].

Visual field defect amelioration usually precedes or parallels the radiological tumor shrinkage. If visual fields remain compromised after tumor shrinkage despite adequate optic chiasm decompression, subsequent surgical tumor debulking will not add any benefit [20]. In our series, of 10 patients with visual disturbances at presentation, all but 1 (90%) had visual field defects improvement. This figure is similar to that reported with bromocriptine [21] and cabergoline [6,9].

Hypogonadism in patients with macroprolactinomas may be secondary to hyperprolactinemia per se or to gonadotrope dysfunction due to compression or destruction by the tumor. It is difficult to determine before treatment whether gonadal dysfunction is temporary or permanent, and only the response to therapy provides a final answer. If PRL normalization is not accompanied by resumption of normal menstrual periods or elevation of gonadotropin levels in pre and postmenopausal women, respectively, or by testosterone normalization in men, permanent gonadotrope damage is probably present. Three out of 6 women in our series recovered their gonadotrope function. On the other hand, bromocriptine restores ovulatory menses in 80–90% of women with hyperprolactinemia, although most of them have microprolactinomas; and cabergoline restores normal menses in 75–80% of women with macroprolactinomas [6,7]. Fourteen men had low testosterone levels at presentation (87%). Patients who normalized testosterone levels with pergolide therapy (n = 3) or who were placed on testosterone replacement therapy (n = 6) had marked improvement in energy level, sexual function, libido, and body hair growth. A previous study suggested that cabergoline was initially more effective than bromocriptine in improving gonadal and sexual function and fertility in men with macroprolactinomas, although by 6 months there was no difference in those parameters [22]. Freda et al [18] found that pergolide therapy improved symptoms of hypogonadism in 83% of men with macroprolactinomas, although testosterone levels were normalized in only 6 of 15 of them. The low rate of testosterone normalization in our series may be related to the shorter period of follow up in our report compared to that study [18], because initial tumor size and tumor shrinkage is similar in both studies. Six of the men in this study had a transient fall in testosterone levels shortly after pergolide initiation, which has been previously reported [14,18], although their final testosterone levels were either unchanged or higher. This fall in testosterone levels despite PRL suppression and tumor shrinkage may be related to the fact that dopamine agonists may inhibit gonadotropin release [23,24].

Both bromocriptine and cabergoline are expensive. Contacts with several local pharmacies revealed that the average monthly cost of these drugs is approximately $210 and $300 for bromocriptine and cabergoline at customarily recommended doses of 7.5 mg daily and 1 mg weekly, respectively. In contrast, monthly cost of pergolide 0.1 mg daily is about $80. Also pergolide has significantly less side effects than bromocriptine, allowing us to switch successfully 9 patients (not included in this study) to pergolide because of bromocriptine intolerance. Similar to a previous report [18], only one patient in our series had to be switched from pergolide to cabergoline because of side effects. Even though the teratogenic potentials of bromocriptine and cabergoline are exceedingly low [25,26], the current recommendations mandate interruption of these drugs in young women as soon as the diagnosis of pregnancy is established. Since the formal analysis of teratogenicity of pergolide has not been performed, we do not prescribe this medication to young women with reproductive potential. The premenopausal women in this study were either surgically sterilized or sexually inactive and warned against the possibility of pregnancy.

In conclusion, pergolide is a safe, effective, and usually well tolerated dopamine agonist that can be used as primary therapy for the treatment of macroprolactinomas in men and women in whom pregnancy is not of concern. In addition, pergolide is less expensive than the other two dopamine agonists available in the United States and, unlike bromocriptine, can be administered once daily. Therefore, pergolide may be the first line therapy for patients with macroprolactinomas in these specific populations.

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