Rapid regression of macroprolactinomas by the new dopamine partial agonist terguride

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Abstract. Two patients with macroprolactinomas were treated with the partial dopamine agonist, terguride. The prolactin (Prl) levels were lowered very effectively and in both cases the clinical symptoms improved markedly during the first days of treatment. Computerized tomography (CT) and magnetic resonance imaging (MRI) follow-up studies showed distinct tumour shrinkages which were first documented by MRI within 2 weeks of treatment. Tumour residues were, however, still demonstrable by MRI after more than one year respectively 3 months of therapy. In principal, results from both imaging techniques were comparable with the exception of the one year follow-up study of patient 1. In CT no residual tumour mass was visible whereas MRI showed only little reduction when compared to the 30th week scan. Throughout the treatment terguride was well tolerated without any side effects up to a maximal daily dosage of 3 mg given orally. Presumably the partial agonistic features of terguride contributed to the good tolerance of the treatment as compared to that of full dopamine agonists like bromocriptine or lisuride. Thus, these preliminary results indicate that terguride may be a beneficial alternative in the treatment of prolactinomas and other hyperprolactinaemic states.

Dopamine agonists are accepted as the primary therapy for macroprolactinomas (Grossman & Besser 1985). Remarkable reductions of tumour size have been reported during treatment with these substances, e.g. bromocriptine, lisuride and others (Chiodini et al. 1981; Wass et al. 1982; Clayton et al. 1985). Despite the clinical success achieved with these drugs in the suppression of Prl secretion and reduction of the tumour mass, the therapy is not tolerated in some patients because of side effects of which most are attributable to their potent dopaminergic properties (von Werder et al. 1982). We report here the results of long-term terguride treatment in 2 patients with macroprolactinomas. Terguride, the 9,10-dihydrogenated analogue of lisuride (Fig. 1), is a potent, long-acting Prl-inhibiting agent with no or only minor side effects in humans (Dorow et al. 1983; Wachtel & Dorow 1983; Dallabonzana et al. 1985). Terguride is thought to act as a partial agonist on the dopamine receptor, since it combines dopamine agonistic activities (Prl lowering effect) with, at higher doses, dopamine antagonistic properties (apomorphine antagonism, cataleptogenic effect in rodents), as reported by Wachtel & Dorow (1983). It was therefore assumed that terguride would be beneficial in the treatment of the various forms of hyperprolactinaemia, especially in patients suffering from Prl producing pituitary adenomas.

Materials and Methods

Case 1

A 40 year old woman was referred to the hospital with the following clinical history: for about 15 years, starting shortly after the birth of her last son, the patient had complained of headaches which had increased in frequency and severity during the last few years. The severity of this symptom can be gauged from her weekly use of analgesics (up to about 50 tablets and more per week during the last few months). Furthermore, the patient had had episodes of galactorrhoea for several
years which occurred at about 2–3 times per year, but lasted for only a few days.

Additional symptoms, e.g. nausea, dizziness, orthostatic dysregulations and ophthalmological symptoms described as visual clouding had been noted during the preceding few months. After discontinuation of chronic oral contraceptives 3 years ago (used for 15 years), the patient had been consistently amenorrhoeic.

The diagnostic programme at the time of admission included the usual clinical and laboratory investigations, various endocrine studies and tests – the endocrine analyses were performed using commercial radioimmunoassay kits – ophthalmological examinations and imaging methods, e.g. conventional X-ray, CT and MRI studies with and without enhancement. The CT scans were performed with a Somatom 2 (Siemens) and the MRI studies were done with a 0.35 tesla magnetic resonance scanner (Siemens).

The follow-up studies included clinical and laboratory routine investigations as well as monitoring of basal and TRH-stimulated Prl serum levels 1 to 4 times a month. Throughout the entire treatment period the TRH tests were performed 2 to 3 h after drug intake in the morning. CT and MRI studies were performed prior to, 2, 4, 15, 30 and 54, respectively 58 weeks after start of the treatment. After written informed consent had been obtained, the patient was treated with terguride increasing from 0.125 to 1.5 mg/day. From the end of the 26th week she received additionally increasing oral doses of lisuride up to a maximum of 0.6 mg (0.2 mg t.i.d.) for 3 weeks.

Thereafter lisuride was withdrawn and the treatment continued with increasing dosages of terguride up to 3 mg daily (see Fig. 2). The total treatment period with terguride to date is more than one year.

Case 2
A 23 year old woman attended the clinic because of increasing daily headaches, oedematous swelling of her extremities, tiredness and weakness. All these symptoms had occurred within the last 4 to 5 months prior to admission. The patient had been amenorrhoeic (secondary) for about 6 years. Furthermore she complained of a weight gain of 15 to 20 kg during this period. Galactorrhoea or ophthalmological disturbances were not reported. With the exception of obesity and tibial oedema the physical examination was unre-
markable. The endocrinological and radiological examinations were similar to those described in case 1. CT and MRI scans were performed prior to, 2 and 14 weeks after start of the treatment. Increasing doses of terguride with 0.25 mg t.i.d. were given from the third day onwards (see Fig. 4).

Results
Case 1
The initial endocrine studies revealed excessively elevated Prl levels (basal Prl: 2136–2292 ng/ml). Cortisol levels were relatively low (between 145 and 226 nmol/l) on repeated measurements at 09.00 a.m., as were also LH (2.4–2.7 mIU/ml) and oestradiol (15 pg/ml) levels. Parameters of thyroid function such as T₃, FT₃, T₄, FT₄ and basal TSH as well as GH levels were in the normal range. Following TRH stimulation (400 µg iv), the TSH response was adequate (0 min: 0.4 mU/l, 30 min: 13.7 mU/l), while the Prl level increased only slightly from 2292 to 2490 ng/ml. In response to 250 µg synthetic 1-24ACTH iv cortisol levels rose from 226 to 669 nmol/l within 30 min. Ophthalmological investigations revealed no pathological findings. Imaging studies (skull X-ray, CT and MRI) confirmed the presumed diagnosis of a large pituitary adenoma. The sella turcica was enlarged, the dorsum displaced and the bottom eroded. According to CT and MRI studies, the tumour exceeded the sella in the supra-, infra-, and partly, also in the parasellar region. The tumour size as estimated from the CT and MRI scans was 19 x 18 x 24 mm and 19 x 18 x 25 mm, respectively (maximum fronto-occipital, latero-lateral, and cranio-caudal extensions) (Fig. 3).

Under increasing dosages of terguride, the Prl levels deceased very rapidly from 2292 to 1350 ng/ml within the first week, and to 326 ng/ml after 4 weeks of treatment. The follow-up data for the basal and TRH-stimulated Prl concentrations are summarized in Fig. 2. They indicate a further constant decrease from the 4th week onwards throughout the entire treatment period of more than 12 months. However, during the combined treatment with terguride and lisuride, the basal Prl levels tended to decrease even more, from 170 to a minimum of 90 ng/ml, when compared with the effect of terguride alone. That this observation was due to lisuride is substantiated by the fact that the basal Prl levels were found to increase within one week from 90 to 136 ng/ml after withdrawal of lisuride, while terguride treatment continued at the same dose.

Increments of Prl secretion after TRH stimulation roughly parallel the course of basal Prl levels during the treatment. Interestingly, the TRH stimulatory effect on Prl was enhanced during the first 2 weeks of terguride treatment as compared to the pretreatment increase. Thereafter, apart from some minor variations which might be attributable to different test times in relation to the intake of terguride, the stimulatory potency of TRH decreased constantly in relation to the duration of treatment and its suppressive effect on basal Prl levels.

The first MRI control, which was performed 2 weeks after start of the terguride therapy, showed a marked reduction in tumour size. At the end of the 4th week of treatment this improvement was confirmed by both MRI and CT. The MRI findings revealed no or only minor further tumour shrinkage, but showed a major change in its signal intensity, the significance of which is unknown. The CT results confirmed the MRI finding that the size of the tumour had decreased. The tumour mass was now reduced to 17 x 13 x 20 mm as estimated by CT, and 21 x 14 x 19 mm by MRI scan, mainly due to shrinkage of the suprasellar portion (Fig. 3). The CT and MRI studies after 14 and 29 weeks of treatment showed no further significant reduction in the tumour size. Whereas the latest MRI performed in the 58th week of treatment showed a tumour residue of about the same size as had been visualized in the 15th and 30th week, CT scans from the 54th week showed no intra- or extrasellar tumour mass (data not shown).

Subjective clinical symptoms improved markedly and parallel with the suppression of Prl secretion and shrinkage of the tumour. The frequency and severity of headaches, nausea and dizziness decreased very distinctly during the first 2 weeks of treatment, enabling the patient to reduce her weekly consumption of analgesics from the previous level of more than 50 to less than 20 tablets. Only minor headaches were reported by the end of the 7th week of treatment and in the following weeks subjective complaints disappeared completely. Apart from a feeling of tiredness from the 3rd week of treatment onwards which tended to improve within 2 h after ingestion, no side effects occurred throughout the
therapy with terguride. However, even this symptom subsided when the dosage was reduced for a short time from 1.5 to 0.75 mg daily from the 5th week onwards, and did not recur when the dosage was increased again to 1.5 mg daily (Fig. 2). Interestingly, the patient complained about tiredness, dizziness, headaches and nausea during the combined treatment of terguride and lisuride.
These complaints which resemble typical side effects known to be induced by full dopamine agonists, disappeared after lisuride treatment had been discontinued. During the following terguride treatment period with unchanged doses no side effects were apparent. Furthermore, no unwanted effects occurred even when the dosage was increased from 1.5 to 3 mg daily from the 31st week onwards. This increase enhanced the Prl suppressive effect of terguride to a very similar extent as was observed before under the combined treatment with terguride and lisuride. After 58 weeks of treatment Prl levels were still slightly above normal (55 ng/ml).

**Case 2**

Before treatment the basal Prl concentration was elevated to 318 ng/ml. The basal cortisol level (measured at 11.30 a.m.) was found to be lowered to 154 nmol/l and increased due to $^{1-24}$ACTH-stimulation up to a maximal level of 678 nmol/l. Basal LH was 6 mIU/ml with a surge up to 70 mIU/ml after LRH stimulation and the oestradiol level was found to be lowered to 8 pg/ml. Normal results were estimated for GH, T3, FT3, T4, FT4, TSH (basal and TRH stimulated) and testosterone concentrations. Despite elevated free fatty acid concentrations (346 mg/dl) all routine laboratory parameters were found to be within the normal range. Both, by CT and MRI studies an intrasellar pituitary adenoma with a diameter of 12 mm and slight suprasellar extension was shown.

During the treatment period with terguride the Prl levels were normalized within 4 days (from 318 to 16.5 ng/ml) (Fig. 4). Two weeks after start of the treatment the adenoma size was found to be reduced to about one third and the headaches had improved distinctly within the first day. During a total treatment period of more than 13 weeks the Prl levels remained to be in the normal range, headaches disappeared totally within 2 weeks and the menstruation re-occurred during the 11th week of treatment. MRI control studies performed in the 14th week after onset of the treatment showed an intrasellar tumour residue of 8 mm in diameter. The basal cortisol levels, measured repeatedly during the morning hours, remained to be lowered (between 176 and 56 nmol/l) throughout the early treatment period with terguride. Clinical symptoms such as weakness, tiredness as well as the oedema improved only when the patient was treated additionally with hydrocortisone (20 mg po daily). Throughout the treatment period of more than 3 months, terguride was tolerated without any side effects.

**Fig. 4.**

Effect of terguride on basal (●) and TRH stimulated (*) serum Prl levels in a patient with a macroprolactinoma (case 2) throughout a total treatment period of more than 3 months.
Discussion

The present case reports show that terguride, a dopamine partial agonist, very effectively lowers excessive Prl secretion due to macroprolactinomas. Both, this finding and the observed reduction in tumour size are in agreement with results previously reported for treatment with full dopamine agonists (see Introduction). Apart from preliminary reports on the use of the diastereomeric mixture of cis-transdihydrolisuride (Dironyl®) by Marek et al. (1982, 1984) and the Prl lowering effect of terguride after acute treatment in hyperprolactinaemic patients (Dallabonzana et al. 1985), these are the first case reports of macroprolactinomas treated with the terguride to document a reduction in tumour size as demonstrated by MRI and CT long-term follow-up studies. The very good tolerance of terguride in our patients is in agreement with the findings of various human pharmacological studies (Dorow et al. 1983; Wachtel & Dorow 1983) and with preliminary results in the use of terguride in patients with Parkinson's disease (Corsini et al. 1984). In our experience terguride given acutely to healthy volunteers (Dorow et al. 1983; Wachtel & Dorow 1983) and patients (Dallabonzana et al. 1985), is generally better tolerated than e.g. bromocriptine and lisuride. This finding is corroborated in the two cases presented here and furthermore, by the fact that during the treatment period of terguride combined with lisuride various subjective side effects occurred which were not observed under terguride alone. We assume that the absence of major side effects may be directly related to the partial dopamine antagonistic potency of terguride.

Whereas, in human pharmacological studies, terguride was found to suppress Prl secretion dose-dependently even in very low dose ranges for a period of 8 to 24 h (Dorow et al. 1983), the first clinical findings do not indicate that terguride is superior to classical dopamine agonists as regards its Prl inhibitory potency in general. However, it is most likely that, compared with the findings in human pharmacological studies dosages between 0.75 and 1.5 mg are submaximal in the treatment of macroprolactinomas, which is in contrast to other clinic findings (Dallabonzana et al. 1985). We suggest that, at least in patients with macroprolactinomas, terguride should be applied in dosages between 1.5 and 3 mg daily to exert a maximal Prl inhibitory effect. Based on our limited clinical experience and in agreement with the pharmacological findings, no or only minor side effects are to be expected up to this dose range.

Good tolerance and the Prl lowering effect of up to 1.5 mg/day terguride given for 1 to 3 months was also found in 5 acromegalic patients in whom GH levels were not sufficiently suppressed (Gräf, unpublished results).

We conclude that terguride suppresses Prl secretion very effectively, presumably due to a direct dopaminergic action at the level of the pituitary Prl cell based on its high dopamine receptor affinity (Suchy et al. 1983), as in the case of lisuride (Cronin et al. 1981). Because of its very good tolerance, terguride may be of benefit in the treatment of prolactinomas and possibly also of other hyperprolactinaemic states as well as in Parkinson's disease.

Acknowledgments

We gratefully acknowledge the help of I. Kürt for determination of hormone levels and E. Kaps and A. Dahrmann for preparation of the manuscript.

References


Received on June 28th, 1985.