CLINICAL STUDY

Dopamine agonist therapy of clinically non-functioning pituitary macroadenomas. Is there a role for ^{123}I -epidepride dopamine D2 receptor imaging?

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Abstract

Objective: Clinically non-functioning pituitary adenomas (NFPAs) can express functional dopamine D2 receptors. Therapy with dopamine (DA) agonists may result in a NFPA size reduction. However, DA agonist-sensitive and -resistant NFPAs are clinically indistinguishable. We have studied the correlation between *in vivo* imaging of D2 receptors using ^{123}I -epidepride and the radiological response of NFPA to DA in 18 patients.

Methods: Patients were treated with either cabergoline (1–2 mg/week) or quinagolide (150–300 µg/day) for a mean period of 89.7 months (range, 34–187 months).

Results: Pituitary uptake of ^{123}I -epidepride varied from slight uptake classified as grade 0 to very high classified as grade 3. Grade 0 uptake was found in four patients; grade 1 in three; grade 2 in ten, and grade 3 in one. NFPA stabilization or shrinkage with DA agonist therapy showed no significant difference between grade 0, 1, and 2 tumors (mean tumor stabilization or shrinkage: 31, 30, and 36% respectively). However, when we considered a decrease in tumor size ranging from 0 to 20% as tumor stabilization and > 20% decrease in tumor size as true shrinkage, one out of four NFPAs with grade 1 uptake, two out of three with grade 1 uptake, and eight out of ten with grade 2 uptake showed tumor shrinkage.

Conclusion: In conclusion, there is limited clinical usefulness of dopamine D2 receptor imaging for predicting the clinical efficacy of DA agonist in selected patients with NFPAs. DA agonist therapy in NFPAs can result in tumor stabilization and shrinkage.

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Introduction

Clinically non-functioning pituitary adenomas (NFPAs) are the most prevalent pituitary macroadenomas (1–3). A specific clinical syndrome related to hormonal hypersecretion is generally absent (1–3). Therefore, most patients present late in the course of their disease, when the tumor causes mass-related signs and symptoms (1–3). Furthermore, some NFPAs present as pituitary incidentalomas (1–3). Pituitary surgery is the first line of treatment, but is generally not curative in majority of the patients (1–6). Radiotherapy is the only modality shown to be effective in the prevention of residual tumor growth (7–9). The use of dopamine (DA) agonists has been previously explored as a treatment alternative for NFPA (10–25). Greenman and co-workers have shown that postoperative DA treatment resulted in a decrease or stabilization of tumor mass in 90% of patients in contrast to 2 and 5 years re-growth rates of 30 and 70% in untreated patients respectively (26). In 61% of patients with tumor remnant growth during the course of routine follow-up, growth

stabilized or decreased with this therapy (26). In contrast, tumor size remained stable only in 38% and increased in the remaining 62% of untreated subjects (26). In another study, Pivonello and co-workers have shown significant tumor shrinkage in five out of nine NFPA patients treated with the DA agonist cabergoline for 12 months (27). The more prominent response was attained in patients whose tumors expressed the dopamine 2 receptor (D2R) short isoform (27). Several groups, including our own, have shown that D2-receptor imaging in pituitary adenomas is possible with single-photon emission computed tomography (SPECT) using ^{123}I -S(-)-N-[(1-ethyl-2-pyrrolidinyl)methyl]-2-hydroxy-3-iodo-6-methoxybenzamide (^{123}I -IBZM) or the substituted benzamide epidepride, (S)-N-[(1-ethyl-2-pyrrolidinyl) methyl]-5-iodo-2,3-dimethoxybenzamide (^{123}I -epidepride) (28–35). We have previously demonstrated the superiority of ^{123}I -epidepride over ^{123}I -IBZM (31). In a series of ten patients with NFPA, the clinical usefulness of ^{123}I -IBZM scintigraphy for predicting tumor response to DA agonists could be demonstrated in two with high tumor uptake of the

radioligand (34). Therefore, we studied the correlation between *in vivo* imaging of D2 receptors using ¹²³I-epidepride and the response of NFPA to long-term DA agonist therapy, as evaluated by magnetic resonance imaging (MRI).

Design, materials and methods

Subjects

A total of 85 selected patients (34 women, 51 men) underwent scintigraphy with ¹²³I-epidepride in our center (see Table 1). Eighteen patients (6 women, 12 men; mean age, 66 years; range, 32–86 years) with NFPA were treated with DA agonists (Table 2). These patients had neither visual field defects nor decrease of visual acuity and ophtalmoplegia. A subgroup of these patients had significant co-morbidity, relative contraindications for anesthesia, or refused surgery. The remaining 36 NFPA patients had visual field defects or decreased visual acuity necessitating surgery or refused to participate in a trial with a dopamine agonist. The diagnosis of NFPA was based on the detection of a pituitary macroadenoma (remnant) on MRI, the absence of a characteristic clinical syndrome apart from hypopituitarism (in 13 patients; Table 2) and basal low to elevated serum luteinizing hormone, follicle-stimulating hormone, or glycoprotein hormone α -subunit levels. A slightly elevated serum prolactin (PRL) (<100 μ g/l; 3000 mU/l), which was not in agreement with tumor size was interpreted as resulting from pituitary–hypothalamic disconnection. In these patients, no elevations of serum thyroid-stimulating hormone, free thyroxine, adrenocorticotrophic hormone, morning cortisol, insulin-like growth factor-I (IGF-I), or IGF-binding protein (IGFBP)-3 levels were found. None of the patients had signs or symptoms of compression of optic chiasm, nor ophtalmoplegia. Five patients had undergone transsphenoidal surgery prior to the start of therapy

(patients 6, 10, 11, 14, and 18 in Table 2) and one was operated after initiation of DA agonist therapy (patient 5 in Table 2, see later). As a result, the diagnosis of NFPA could be confirmed by immunohistology on tumor specimen obtained during surgery in six patients. None of the patients underwent external pituitary radiotherapy. Patients were treated with quinagolide (150–300 μ g/day) and cabergoline (1–2 mg/week) was preferentially used after it became registered in The Netherlands. Both drugs were titrated up to a maximum dose of 300 μ g/day quinagolide, or 2 mg/week cabergoline, but some patients had to be treated with lower doses because of dose-dependent side effects (like orthostasis and nausea). There was no placebo arm. Hypopituitarism was appropriately treated. No subject was receiving medications known to interfere with dopamine metabolism or uptake. All patients gave informed consent to participate in the study, which was approved by the hospital ethics committee (Figs 1–3).

Imaging

Pituitary SPECT studies with ¹²³I-epidepride were performed as previously described (31). SPECT images of the head were obtained using a three-headed camera (Prism 3000 XP, Picker Int., Cleveland, Ohio, USA), equipped with a medium energy collimator. The pulse height analyzer window was centered over the energy peak (159 keV) with a window width of 20%. ¹²³I-epidepride was obtained from Dr Angelberger, Österreichisches Forschungszentrum Seibersdorf GmbH, Seibersdorf, Austria. The synthesis of ¹²³I-epidepride has been previously described (29). ¹²³I-epidepride (111–185 MBq) was administered intravenously and images were obtained after 3 h. Acquisition parameters were 1 scan, 36 s/frame, 120 projections, 360 degrees, 64 $\times$ 64 matrix (29). Before reconstruction, a Metz filter was applied. Scintigrams were assessed by two investigators (WW de Herder and DJ Kwekkeboom) without previous

Table 1 ¹²³I-epidepride scintigraphy in 85 patients with pituitary lesions.

Tumor	¹²³ I-epidepride scintigraphy uptake grade				n
	0	1	2	3	
Microprolactinoma	3	–	–	–	3
Macroprolactinoma	–	6	2	2	10
Somatotroph macroadenoma	1	3	0	0	4
NFPA	17	12	18	7	54
Silent corticotroph macroadenoma	–	1	2	–	3
Rathke’s cleft cyst	2	–	–	–	2
Craniopharyngioma	1	–	–	–	1
Metastatic prostate carcinoma	1	–	–	–	1
Meningioma	1	–	–	–	1
Chordoma	1	–	–	–	1
Scar tissue	1	–	–	–	1
Malignant prolactinoma (scan-positive metastases: 1)					2
Malignant corticotroph macroadenoma (scan-positive metastases: 1)					2
Total					85

NEPA, non-functioning pituitary adenoma.

Table 2 Dopamine agonist therapy in 18 patients with clinically nonfunctioning pituitary macroadenomas who have also undergone ^{123}I -epidepride scintigraphy.

Patient no.	Sex	Age at baseline	^{123}I -epidepride scan	Hypo-pituitarism	Drug	Dose	Duration of therapy (months)	Tumor volume (mm^3)	% shrinkage
1	M	68	0	Yes	Quinagolide	300 $\mu\text{g/day}$	163	23 085	6
2	M	62	0	Yes	Quinagolide	300 $\mu\text{g/day}$	158	46 637	99
3	M	71	0	Yes	Quinagolide	150 $\mu\text{g/day}$	84	17 149	18
4	F	52	0	No	Quinagolide	150 $\mu\text{g/day}$	68	5081	0
5	M	79	1	No	Cabergoline	1 mg/week	57	24 417	5
6	F	65	1	Yes	Quinagolide	300 $\mu\text{g/day}$	110	27 231	58
7	F	66	1	Yes	Quinagolide	300 $\mu\text{g/day}$	84	904 320	27
8	M	75	2	Yes	Quinagolide	300 $\mu\text{g/day}$	34	76 451	27
9	F	86	2	Yes	Quinagolide	300 $\mu\text{g/day}$	48	73 585	25
10	M	54	2	Yes	Cabergoline	1 mg/week	34	91 906	32
11	M	32	2	No	Quinagolide	300 $\mu\text{g/day}$	96	407 513	74
12	M	75	2	Yes	Quinagolide	150 $\mu\text{g/day}$	39	19 383	27
13	M	59	2	Yes	Cabergoline	1 mg/week	84	31 846	5
14	F	77	2		Quinagolide	150 $\mu\text{g/day}$	68	137 189	35
15	M	50	2	Yes	Quinagolide	300 $\mu\text{g/day}$	101	31 846	97
16	M	67	2	No	Quinagolide	300 $\mu\text{g/day}$	115	588 679	42
17	M	78	2	Yes	Quinagolide	300 $\mu\text{g/day}$	187	95 227	0
18	F	76	3	Yes	Cabergoline	2 mg/week	72	164 553	0

knowledge on MRI results. The uptake of radioactivity in the pituitary area was compared with that in the left and right basal ganglia and the cerebral cortex. Absence of pituitary uptake was classified as grade 0. Uptake in this region, which was higher than or equal to that observed for the basal ganglia, was classified as grade 3. Uptake in the pituitary region, which was less than in the basal ganglia but higher than in the cerebral cortex, was classified as grade 2. Slight uptake, which was equal to or less than in the cerebral cortex, was classified as grade 1. Examples of grade 0–3 scans can be found in a previous publication (31). All the treated subjects underwent pituitary MRI at baseline, and 3–6 and 12 months following initiation of medical therapy and yearly thereafter. The method of volume calculation was based on the three axes of the tumor as previously described (20). In this method, the x , y , and z radii were measured in the frontal, sagittal, and coronal planes respectively. Assuming a spherical volume, the formula $4/3 \pi r^3$ was used for volume calculation, r being the mean of the x , y , and z radii (20). Visual field examinations were performed at the same time points.

Results

Table 1 shows the distribution of ^{123}I -epidepride uptake in the 85 patients. In two out of two patients with metastatic malignant macroprolactinomas (one of these patients was published as a case report, (36)) and in one out of two patients with metastatic malignant corticotrope tumors uptake in metastatic lesions could be demonstrated. Out of these 85 patients, 54 had NFPA. Of these 54 NFPA, 17 showed grade 0 uptake, 12 showed grade 1 uptake, 18 showed grade 2 uptake, and

7 showed grade 3 uptake of ^{123}I -epidepride (Table 1). For a mean period of 89.7 months (range, 34–187 months), 18 patients (6 women, 12 men; mean age, 66 years; range, 32–86 years) with NFPA were treated with DA agonists (either cabergoline (1–2 mg/week) or quinagolide (150–300 $\mu\text{g/day}$)). Grading of pituitary uptake of ^{123}I -epidepride in these patients was as follows: grade 0, four patients; grade 1, three patients; grade 2, ten patients; and grade 3, one patient (Table 2). Patients were treated for 34–187 months with DA agonists (mean, 89.7 months; Table 2). In five patients, DA agonist therapy was started after pituitary surgery, one (patient 5 in Table 2) underwent surgery after medical therapy was initiated, because of the lack of significant tumor regression and a clinical significant threat of damage to neighboring structures. Tumor stabilization or shrinkage with DA agonist therapy was

Figure 1 Change of tumor size, expressed as percentage of baseline size in 18 patients with clinically non-functioning pituitary macroadenomas (NFPA) who have also undergone ^{123}I -epidepride scintigraphy and have been treated with dopamine agonist therapy. $\blacktriangle$, grade 0 uptake of ^{123}I -epidepride; $\blacksquare$, grade 1 uptake of ^{123}I -epidepride; $\bullet$, grade 2 uptake of ^{123}I -epidepride; $\blacklozenge$, grade 3 uptake of ^{123}I -epidepride.

Figure 2 Magnetic resonance image in the coronal plane after administration of Gd-DTPA (top panels) and sagittal plane (bottom panels) of a histologically confirmed NFPA (in patient 10, Table 2) at baseline (left panels), and after 33 months (right panels) showing 32% tumor shrinkage with dopamine agonist therapy (cabergoline 1 mg/week).

as follows: NFPA with grade 0 uptake; mean $\pm$ S.E.M., $31 \pm 20\%$; range, 0–99%; NFPA with grade 1 uptake; mean $\pm$ S.E.M., $30 \pm 15\%$; range, 5–58%; NFPA with grade 2 uptake; mean $\pm$ S.E.M., $36 \pm 9\%$; range, 0–97%; NFPA with grade 3 uptake, only one patient, 0%; Table 2, Figs 1–3. One patient with a grade 0 tumor showed complete disappearance of the tumor (patient 2, Table 2), one patient with grade 1 tumor showed 58% shrinkage

(patient 6, Table 2) and two patients with grade 2 tumors showed 74% and complete shrinkage respectively (patients 11 and 15 respectively, Table 2). When we considered a decrease in tumor size ranging from 0 to 20% as tumor stabilization and $> 20\%$ decrease in tumor size as true shrinkage, one out of four NFPA with grade 1 uptake, two out of three NFPA with grade 1 uptake, and eight out of ten NFPA with grade 2 uptake showed

Figure 3 Magnetic resonance image in the coronal plane after administration of Gd-DTPA (top panels) and sagittal plane (bottom panels) of a NFPA (in patient 15, Table 2) at baseline (left panels), and after 100 months (right panels) showing 97% tumor shrinkage with dopamine agonist therapy (quinagolide 300 µg/day).

tumor shrinkage. Despite differences in their affinities for the dopamine D2 and D4 receptor subtypes, there was no significant difference between cabergoline- and quinagolide-treated patients. DA agonist therapy resulted in a complete suppression of serum PRL levels to values below the detection limit in all patients (data not shown).

Discussion

NFPAs express functional membrane-bound dopamine receptors (10, 11, 13, 14, 27, 37, 38). However, the effects of the DA agonist bromocriptine on reducing NFPA size has been disappointing, as most studies have shown only modest size reduction in a minority of treated tumors (12, 14, 17, 21, 25). Therefore, bromocriptine therapy has not been advocated on a routine basis. Better, but still variable, results have been reported on the treatment with the non-ergot DA agonist quinagolide and the specific DA agonist cabergoline (20, 23, 26, 27, 34, 35, 39). The heterogeneity of responses to treatment has been attributed to the different pattern and level of expression of dopamine receptor subtypes in the individual tumors, as well as to

possible alterations in the receptor-related signal transduction pathway (10, 27, 38). In the present study, we were unable to demonstrate superiority of cabergoline over quinagolide or *vice versa* in the therapy of NFPAs. Greenman and co-workers have shown that tumor mass decreased or remained stable in 90% of patients in whom DA treatment was initiated upon detection of residual tumor on postoperative MRI (26). In 61% of patients with tumor remnant growth during the course of routine follow-up growth stabilized or decreased with this therapy (26). In contrast, tumor size remained stable in only 38% and increased in the remaining 62% of untreated subjects (26). Pivonello and co-workers have shown significant tumor shrinkage in five out of nine patients treated with the DA agonist cabergoline for 12 months (27). The more prominent response was attained in patients whose tumors expressed the D2R short isoform (27). No useful clinical test presently exists that can predict the response to long-term dopaminergic treatment in NFPA patients. The present study shows that ^{123}I -epidepride scintigraphy is generally not useful in this respect. However, using a 20% tumor decrease as cut-off for defining tumor shrinkage versus tumor stabilization a trend could be

observed, especially NFPA with grade 2 uptake demonstrated tumor shrinkage. However, ^{123}I -epidepride scintigraphy might also still be useful in specific situations like those given in Table 1, for example, for discrimination of scar tissue from NFPA recurrence or residual NFPA, or the differential diagnosis between pituitary tumors and metastases. The present study reconfirms previous studies and shows that long-term (in this study, a mean follow-up of 7.5 years) tumor stabilization and shrinkage (in this study, a mean shrinkage of 30%) can be attained using cabergoline or quinagolide therapy. In four patients, dramatic (58–100%) tumor reduction, as can be seen in patients with macroprolactinomas (40–43) and some patients with Nelson's syndrome (44–46), could be observed. However, as pathology was lacking in two of these patients, it cannot be excluded that these patients had poorly functioning prolactinomas. This study reconfirms that quinagolide or cabergoline therapy can reduce the need for preventive postoperative radiotherapy, at least in some NFPA patients in whom there is evidence for remnant tumor growth, or they can either postpone or prevent pituitary surgery by preventing tumor enlargement. In patients with considerable co-morbidity or contraindications for operation, this therapy might also be tried. In the present series, we chose a maximum dose of 300 $\mu\text{g}/\text{day}$ quinagolide, or 2 mg/week cabergoline, but it cannot be excluded that higher doses might have been (even) more effective. The clinical usefulness of ^{123}I -epidepride dopamine D2 receptor imaging for predicting the clinical efficacy of dopamine agonists in selected patients with NFPA is limited.

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