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 NFPAs 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 NFPAs 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. NFPAs 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 NFPAs (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 NFPAs 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 NFPAs, 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 $^{123}$I-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 $^{123}$I-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 hypotuituitarism (in 13 patients; Table 2) and basal low to elevated serum luteinizing hormone, follicle-stimulating hormone, or glycoprotein hormone $\alpha$-subunit levels. A slightly elevated serum prolactin ($<100$ μg/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, adrenocorticotropic 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 μg/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 μg/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. Hypotuituitarism 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 $^{123}$I-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%. $^{123}$I-epidepride was obtained from Dr Angelberger, Österreichisches Forschungszentrum Seibersdorf GmbH, Seibersdorf, Austria. The synthesis of $^{123}$I-epidepride has been previously described (29). $^{123}$I-epidepride (31.1–185 MBq) was administered intravenously and images were obtained after 3 h. Acquisition parameters were 1 scan, 36 s/frame, 120 projections, 360 degrees, 64 × 64 matrix (29). Before reconstruction, a Metz filter was applied. Scintigrams were assessed by two investigators (WW de Herder and DJ Kwekkeboom) without previous knowledge of clinical features. All patients were 18 years of age or older.

<table>
<thead>
<tr>
<th>Tumor</th>
<th>$^{123}$I-epidepride scintigraphy uptake grade</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>0</td>
</tr>
<tr>
<td>Microprolactinoma</td>
<td>3</td>
</tr>
<tr>
<td>Macroprolactinoma</td>
<td>–</td>
</tr>
<tr>
<td>Somatotroph macroadenoma</td>
<td>1</td>
</tr>
<tr>
<td>NFPA</td>
<td>17</td>
</tr>
<tr>
<td>Silent corticotroph macroadenoma</td>
<td>–</td>
</tr>
<tr>
<td>Rathke’s cleft cyst</td>
<td>2</td>
</tr>
<tr>
<td>Craniohypophyongioma</td>
<td>1</td>
</tr>
<tr>
<td>Metastatic prostate carcinoma</td>
<td>1</td>
</tr>
<tr>
<td>Meningioma</td>
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</tr>
<tr>
<td>Chordoma</td>
<td>1</td>
</tr>
<tr>
<td>Scar tissue</td>
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<tr>
<td>Malignant prolactinoma (scan-positive metastases: 1)</td>
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</tr>
<tr>
<td>Malignant corticotroph macroadenoma (scan-positive metastases: 1)</td>
<td>2</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>85</td>
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NEPA, non-functioning pituitary adenoma.

Table 1 $^{123}$I-epidepride scintigraphy in 85 patients with pituitary lesions.
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 $\frac{4}{3}\pi r^3$ 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 $^{123}\text{I}$-epidepride uptake in the 85 patients. In two out of two patients with metastatic malignant macroadenomas (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 $^{123}\text{I}$-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 mg/day)). Grading of pituitary uptake of $^{123}\text{I}$-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](https://www.eje-online.org)

**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 $^{123}\text{I}$-epidepride scintigraphy and have been treated with dopamine agonist therapy. ▲, grade 0 uptake of $^{123}\text{I}$-epidepride; □, grade 1 uptake of $^{123}\text{I}$-epidepride; ●, grade 2 uptake of $^{123}\text{I}$-epidepride; ●, grade 3 uptake of $^{123}\text{I}$-epidepride.
as follows: NFPs with grade 0 uptake; mean ± S.E.M., 31 ± 20%; range, 0–99%; NFPs with grade 1 uptake; mean ± S.E.M., 30 ± 15%; range, 5–58%; NFPs with grade 2 uptake; mean ± S.E.M., 36 ± 9%; range, 0–97%; NFP 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 NFPs with grade 1 uptake, two out of three NFPs with grade 1 uptake, and eight out of ten NFPs with grade 2 uptake showed.

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).
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 NFP 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 NFPAs. The present study shows that 123I-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 NFPAs with grade 2 uptake demonstrated tumor shrinkage. However, \textsuperscript{125}I-epidepride scintigraphy might also 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 μg/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 \textsuperscript{125}I-epidepride dopamine D2 receptor imaging for predicting the clinical efficacy of dopamine agonists in selected patients with NFPA is limited.

References


