Assessment of disease activity in Graves' ophthalmopathy

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Publication date
1999

Citation for published version (APA):
Octreotide scintigraphy in thyroidal and orbital Graves’ disease

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Thyroid 1998; 8: 433-436
Introduction
In 1992 Chang and co-workers reported a favourable effect of octreotide treatment on the signs and symptoms of Graves’ ophthalmopathy. They hypothesized that octreotide, a potent long-acting somatostatin analogue, may inhibit local synthesis of insulin-like growth factor-1 (IGF-1) by orbital fibroblasts, thereby reducing glycosaminoglycan production. The hypothesis is theoretically supported by the presence of immunoreactivity to IGF-1 in extraocular muscles and fat cells, and by the suppression of IGF-1 in serum by octreotide. Krenning and co-workers used radiolabeled octreotide in patients with Graves’ disease. By radiolabelling octreotide, tissues which express somatostatin receptors can be visualized. Applying \[^{113}\text{In-DTPA-D-Phel}] octreotide scintigraphy specific uptake of the radiolabel was observed in the thyroid and orbit of some but not all patients with Graves’ disease. In this review we will discuss the determinants of thyroidal and orbital uptake of radiolabeled octreotide and the clinical relevance of octreotide scintigraphy in patients with Graves’ disease.

\[^{113}\text{In}] octreotide scintigraphy in thyroidal Graves’ disease
Postema et al. injected 220 MBq \[^{113}\text{In-DTPA-D-Phel}] octreotide iv as a bolus, and obtained planar anterior \(\gamma\)-camera images of the neck 5 and 24 h after injection. Thyroidal radiolabeled octreotide accumulation was expressed as percentage of the injected dose by the region of interest method on planar anterior images corrected for background (region adjacent to the thyroid on the same image). The results are summarized in Table 1. If thyroidal uptake of radiolabeled octreotide was set at 100% at 5h postinjection, the uptake at 24h postinjection decreased to 68±19% in patients with Graves’ disease, similar to that in controls (58±12%). This decrease was significantly less than the decrease in blood pool radioactivity (from 100% to 15±4%), indicating specific uptake in the thyroid gland.
### Table 1. Thyroidal radiolabeled octreotide accumulation *

<table>
<thead>
<tr>
<th>Subjects</th>
<th>Treatment</th>
<th>Thyroid function</th>
<th>TBII</th>
<th>24h Thyroidal octreotide uptake*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Controls</td>
<td>none</td>
<td>euthyroid</td>
<td>absent</td>
<td>0.03%</td>
</tr>
<tr>
<td>Graves' hyperthyroidism</td>
<td>none</td>
<td>hyperthyroid</td>
<td>present</td>
<td>0.17%</td>
</tr>
<tr>
<td>Graves' hyperthyroidism</td>
<td>methimazole</td>
<td>euthyroid</td>
<td>present</td>
<td>0.14%</td>
</tr>
<tr>
<td>Graves' hyperthyroidism</td>
<td>$^{131}$I, thyroxine</td>
<td>euthyroid</td>
<td>present</td>
<td>0%</td>
</tr>
<tr>
<td>Primary hypothyroidism</td>
<td>thyroxine</td>
<td>euthyroid</td>
<td>absent</td>
<td>0.003%</td>
</tr>
</tbody>
</table>

* figures are median values expressed as percentage of injected dose
‡ data reproduced with permission of Postema et al.3

Thyroidal octreotide uptake is low in controls and relatively high in untreated Graves' hyperthyroidism. The octreoscan thus provides no or a very faint image of the thyroid gland in the absence of thyroid disease, but a nice thyroidal image can be obtained in Graves' disease which cannot be fully explained by the large thyroid gland in Graves' disease. In untreated Graves' hyperthyroidism the thyroidal octreotide uptake is positively related to serum FT4, T3 and TBII (TSH binding inhibitory immunoglobulins), suggesting a relationship with the severity of Graves' hyperthyroidism.3 The correlation is, however, no longer observed in Graves' hyperthyroid patients who have been rendered euthyroid by methimazole treatment; they still have a relatively high thyroidal octreotide uptake3,4,5 and clearly demonstrable concentrations of TBII in serum. It has therefore been speculated that the octreoscan visualizes the lymphocytic infiltrate in the thyroid of patients with Graves' disease, reflecting the activity rather than the severity of the disease. This assumption is supported by the finding that cultured human lymphocytes express distinct subsets of somatostatin receptors6: human T-cells
and myeloma cells had an average of 144 and 1295 high affinity somatostatin receptors per cell respectively, with corresponding Kd values of 3pM and 5pM. The presence of somatostatin receptors on activated T-lymphocytes is also evident from the visualization of pathological lesions by somatostatin receptor scintigraphy in patients with malignant lymphoma, granulomatous inflammation, and rheumatoid arthritis. It might thus well be that visualization of the thyroid gland in Graves’ disease is due to the expression of somatostatin receptors on infiltrating lymphocytes. One argument against this explanation could be that almost no thyroidal octreotide uptake was observed in four patients with autoimmune hypothyroidism, in whom a lymphocytic infiltrate of the thyroid gland is a hallmark of the disease; however, they already had been treated with thyroxine for a long time, and probably had passed the stage of active auto-immune destruction of thyroid epithelial cells. The negative octreoscan in the Graves’ patients rendered hypothyroid by I (in whom TBII was still present), also does not necessarily falsify the given explanation as TBII can be produced extrathyroidally in the lymphatic system.

Of much interest are recent findings suggesting expression of somatostatin receptors on thyroid follicular epithelial cells themselves. This might explain the thyroidal [\(^{111}\)In]octreotide uptake observed in patients with a TSH-producing pituitary adenoma, thyroid adenoma, endemic goiter, or differentiated nonmedullary thyroid cancer (own unpublished observations). The common denominator of these conditions is thyroid growth, either autonomous in thyroid adenomas and cancer or mediated via the TSH receptor in TSH-producing pituitary adenoma and Graves’ disease. It is tempting to speculate that thyroid growth itself is associated with an increased expression of somatostatin receptors on thyrocytes, explaining the visualization with octreotide scintigraphy. In this respect it is of interest to note a direct inhibitory effect of somatostatin on growth (but not on differentiation) of human thyroid follicular cells in vitro, probably by a mechanism not entirely cAMP dependent.
In summary, upregulation of somatostatin receptors on thyrocytes and/or thyroidal lymphocytes are presumably responsible for a positive octreoscan in Graves' disease. The present limited data suggest that thyroidal octreotide uptake in Graves' disease might be related at least partly to the activity of the auto-immune disease rather than to the hyperthyroid state itself. Persistent thyroidal octreotide uptake as observed in Graves' patients taking methimazole would then indicate still active autoimmune thyroid disease; the implication is that a positive thyroidal octreoscan increases the chance of recurrent hyperthyroidism after discontinuation of methimazole treatment. It remains doubtful, however, if this predictive value of thyroidal octreotide scintigraphy (assuming it is proven in a controlled trial) will find clinical application in view of its expense.

**Octreotide scintigraphy in orbital Graves' disease**

The first orbital octreotide scans in Graves' disease have been reported by Postema et al.\(^3\) If peak activity in the orbit 5h after injection of radiolabeled octreotide is set at 100%, a decrease to 40±4% is found at 24h, significantly different from the decrease in blood pool radioactivity (from 100% at 5h to 15±4% at 24 h). The cause of specific orbital uptake is unknown. An attractive hypothesis is that orbital uptake in Graves' disease is caused by the expression of somatostatin receptors on activated T-lymphocytes, thus visualizing the lymphocytic infiltrate in retrobulbar tissues. Alternative explanations cannot, however, be excluded like binding to receptors on other cell types (e.g. eye muscle cells, fibroblasts, endothelial cells) or local blood pooling due to venous stasis by the auto-immune orbital inflammation. Systemic hypercirculation seems only partly responsible, as evident from the rather low orbital uptake in Graves' hyperthyroid patients without clinical signs of ophthalmopathy.\(^3\)

Some studies report a relationship between orbital octreotide accumulation and the severity of Graves' ophthalmopathy, with higher uptake values in more severe eye disease\(^3,8\); severity in these studies is indicated by a higher class or grade in the NO
Octreotide scintigraphy in thyroidal and orbital Graves’ disease

SPECS classification of eye signs in Graves’ ophthalmopathy. Other authors, however, do not find a relationship with severity.\textsuperscript{9,10,11} In contrast, the activity of the eye disease is always found to be related to orbital octreotide uptake whenever studied. This is evident from a direct relationship between orbital uptake and various parameters of disease activity in Graves’ ophthalmopathy like the clinical activity score\textsuperscript{3,11} and the T2 relaxation time of the inferior rectus muscle on MRI.\textsuperscript{4} Orbital octreotide accumulation is greater in patients with active eye disease than in patients with inactive eye disease\textsuperscript{8,9}; the uptake in the inactive group is close to that in control subjects in whom no specific uptake is observed.\textsuperscript{8,10} These data strongly suggest the notion that a positive orbital octreoscan in Graves’ ophthalmopathy indicates active eye disease in which - in contrast to the inactive end-stage of the disease with fibrosis - immunosuppressive treatment might be of therapeutic benefit. Indeed, successful immunosuppression (be it with prednisone, orbital irradiation or intravenous immunoglobulin) is associated with a fall in orbital octreotide uptake.\textsuperscript{8,11}

Orbital octreotide scintigraphy could thus be applied in clinical practice to select patients with Graves’ ophthalmopathy who will benefit from immunosuppression. To this end one must know the predictive value of orbital octreotide uptake for the outcome of immunosuppressive treatment; such data are, however, scarce, as are data about the precision and accuracy of the technique. There are wide differences between various studies in the administered dose of \textsuperscript{[\textsuperscript{111}In-DTPA-d-Phe]}octreotide, the time interval after injection for determining the orbital uptake, the selection of orbital slices for quantification of the orbital uptake, and the method of correction for background radioactivity (Table 2). The earlier studies used rather large doses of radiolabeled octreotide (as usual in the visualization of neuroendocrine tumors), and preferred to determine orbital uptake 24h post injection.\textsuperscript{3,10,12} Moncayo et al.\textsuperscript{11}, however, applied a low dose and measured orbital uptake after a time interval of only 2 hours, arguing that 1) the low dose decreases the radiation burden and the cost of the examination, 2) a short time interval is optimal in view of the kinetics of somatostatin binding to lymphocytic receptors (showing maximal binding after
120 min in vitro) and of the radioactive decay of the octreotide tracer starting 4h after iv application.

Table 2. Orbital radiolabeled octreotide accumulation as determined in various studies.

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Octreo. dose Mbq</th>
<th>Time interval post injection</th>
<th>Orbital region of interest (ROI)</th>
<th>Correction for background</th>
<th>Quantification of uptake</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>220</td>
<td>5-24 h</td>
<td>rim of the skull</td>
<td>semiquantitative grading 0-3</td>
<td></td>
</tr>
<tr>
<td>12</td>
<td>244</td>
<td>4-24 h</td>
<td>rectangular ROI 5 SPECT slices</td>
<td>left temporal skull</td>
<td>orbit to skull uptake ratio</td>
</tr>
<tr>
<td>10</td>
<td>200</td>
<td>24-48h</td>
<td>circular ROI ant. projection</td>
<td>brain</td>
<td>orbit to brain uptake ratio</td>
</tr>
<tr>
<td>9</td>
<td>148</td>
<td>4-24-48h</td>
<td>not specified</td>
<td>brain</td>
<td>semiquantitative grading 0-4</td>
</tr>
<tr>
<td>8</td>
<td>110</td>
<td>4-24 h</td>
<td>irregular ROI 2 SPECT slices</td>
<td>brain</td>
<td>orbit to brain uptake ratio</td>
</tr>
<tr>
<td>11</td>
<td>111</td>
<td>2 h</td>
<td>retrobulbar ROI SPECT slices</td>
<td>scan negative or positive (=uptake in ≥2 SPECT slices)</td>
<td></td>
</tr>
</tbody>
</table>

In disagreement, Krassas and Dumas\textsuperscript{13} state that a low dose might cause problems in count statistics, and that 2h after injection 12% of the dose is still in the blood pool causing high background uptake; furthermore they indicate that the radiation burden received from a high dose of 222 MBq is 16 mSv, in the same order as that from chest computed tomography or angiography. It must be admitted that the difference in orbital octreotide uptake between patients with active and inactive
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eye disease is smaller at 24h than at 4h after injection of a low dose (own unpublished observations). The inference is that for discrimination purposes a 4h time interval is preferred when a low dose is chosen. On the other hand, any remaining orbital radioactivity at 24h after administering a high dose might represent to a greater degree specific tissue binding, possibly enhancing the predictive value of the octreoscan. Future studies should take into account this specific point. Another technical bias is the selection of orbital regions of interest, which may result in considerable intra- and inter-observer variation. SPECT images are obviously required, and measuring uptake in a number of orbital slices from SPECT images is of great advantage in the quantification of results. Correction for background activity has originally been performed by using the left temporal skull area. Uptake in this area is considerable, ascribed to radioactivity in the intracranial venous sinuses. We have recently obtained evidence that at least part of this radioactivity is due to uptake in the parotid gland; consequently we now prefer background measurements in the occipital skull area. Brain itself is used to measure background, but seems less suitable to correct for blood pool radioactivity.

Patients with very active eye disease are bound to respond favourably to immunosuppression; the activity of the eye disease in such cases is clinically evident at first glance, and would not require further assessment with octreotide scintigraphy. In many patients with moderately severe ophthalmopathy, however, it is not at all clear whether or not the eye disease is still in the active stage and whether or not the patient will benefit from immunosuppression. Under these circumstances orbital octreotide scintigraphy might be used as a predictor for outcome of immunosuppression. This will require calculation of the orbital to skull uptake ratio using quantitative measurements in well-defined regions of interest of SPECT slices. The only study in this respect is that of Krassas and coworkers who observed the following orbital to skull uptake ratio's 24h after 244 MBq octreotide: controls, 1.00±0.003; Graves' disease without eye disease 1.25±0.003; Graves' ophthalmopathy responding or not responding to
immunosuppression with sc octreotide, 1.85±0.09 and 1.45±0.05 respectively (pre-treatment values). In all 13 eyes improving with treatment the ratio was ≥1.65, whereas 9 of 11 ‘nonresponding eyes’ had a ratio of <1.65.

It remains to be seen if orbital octreotide scintigraphy will become a widely applied tool in the management of Graves’ ophthalmopathy patients. First, its technique is demanding in terms of accuracy required for prediction. Each institution should develop its own cut-off values in this respect. Second, it is an expensive method with a not negligible radiation burden. Third, it is nonspecific, i.e. positive orbital octreotide scans may also be obtained in patients with orbital meningioma, malignant lymphoma, pseudotumor orbitae, orbital myositis, sarcoidosis Wegener’s granulomatosis, necrotising scleritis, sinusitis and infections of the nasal mucosa. Fourth, orbital octreotide scintigraphy does not allow precise orbital imaging, i.e. evaluation of eye muscle swelling and apical crowding still requires imaging with CT- or MRI-scans. If MRI-scans are as accurate as octreotide scintigraphy in assessing disease activity and thereby in predicting outcome of immunosuppression in Graves’ ophthalmopathy, orbital octreotide scintigraphy would no longer be needed.

References


13. Krassas, Dumas A; and Moncayo R. Octreoscan in Graves’ ophthalmopathy (Letters to the Editor) *Thyroid* 1997;7:805-806.
