Assessment of disease activity in Graves' ophthalmopathy
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Octreotide-scintigraphy is a disease-activity parameter in Graves’ ophthalmopathy

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Summary

Objective. It is thought that immunosuppressive treatment of Graves' ophthalmopathy should be restricted to patients with active eye disease, but assessing disease activity is difficult. Octreotide scintigraphy has been claimed to differentiate active from inactive disease. Here we study the intra-observer variability and diagnostic accuracy of the quantitative measurement of orbital octreotide uptake.

Patients and Design. Twenty-two consecutive patients with moderately severe ophthalmopathy were treated with retrobulbar radiotherapy. Pretreatment octreotide scintigraphic data were related to the response at six months after radiotherapy, using Receiver-Operating-Characteristic curves (ROC-curves).

Measurements. Octreotide uptake was measured at 4 and 24 hours after i.v. injection of approx. 3 mCi (=111 Mbq; range 75-150 Mbq) \(^{111}\)Indium-DTPA-Octreotide with a neuro-SPECT camera. Counts were measured in fixed regions-of-interest in 4 transversal slices of the orbit, the temporal and the occipital area. Measurements were done twice and intra-observer variability was analyzed by coefficients of variations (CV). Uptake is expressed as orbital/background ratio. The nature of the temporal uptake was studied by matching an octreoscan with a technetium scan and MRI.

Results. Intra-observer variability of measuring octreotide uptake is rather good, and the coefficient of variation is slightly better using the orbital/occipital ratio (11%), than the orbital/temporal ratio (16%). From matching studies it appears that the temporal uptake takes place, in part, in the parotid gland. The orbital/occipital ratio was used to predict the outcome of radiotherapy. Mean (±SD) uptake on the 4 hours scan was higher in responders (2.2 ±0.66) than in non-responders (1.7 ±0.39; p= 0.04). From the Receiving-Operator-Characteristics curve we determined a cut-off value of 1.85, which yielded a positive predictive value of 92% and a negative predictive value of 70%. The 24 hours scan could not predict a response.
Conclusions. Quantitative measurement of orbital octreotide uptake is possible. Using the orbital/occipital ratio on the 4 hours scan, the octreoscan seems useful in predicting response to subsequent radiotherapy. The 24 hours scan seems not useful in predicting therapeutic outcome.

Introduction

On the premise that Graves’ ophthalmopathy (GO) is an autoimmune disorder, patients with moderate-severe eye disease are usually treated with immunosuppressive therapies. However, corticosteroids or retrobulbar radiotherapy ameliorate the signs and symptoms in only ~65% of the patients and thus one-third is treated without benefit.¹ ² The reason for this is probably the fact that these therapies are also given to patients with severe, but inactive ophthalmopathy. This is because it is difficult to distinguish active from inactive disease, whereas only the former condition will improve upon immunosuppressive treatment.²

Differentiating active from inactive Graves’ ophthalmopathy has become an important goal. Histologic evidence for lymphocytic infiltration would be the gold standard, but is difficult to obtain. Therefore other parameters for assessing disease activity have been sought. In the absence of histology, an acceptable working definition would be that such an activity parameter should be able to predict a response to immunosuppression.

In addition to the Clinical Activity Score³ and Magnetic Resonance Imaging (MRI)⁴, octreotide scintigraphy has been claimed to be able to assess disease activity.⁵,⁶,⁷,⁸,⁹ Indeed, several studies have shown an increased orbital uptake of ¹¹¹Indium labeled octreotide in the orbits of patients with Graves’ ophthalmopathy. A reliable and objective measurement of this increased orbital uptake might thus help in defining which patients would benefit from immunosuppression. So far different qualitative⁷,⁶ and quantitative¹¹ measurements of orbital uptake have been
Octreotide-scintigraphy is a disease-activity parameter in graves' ophthalmopathy reported, but there are no data on their reproducibility and the best way to correct for non-specific background uptake is currently unknown.

The aim of the present study was to evaluate the intra-observer variability of measuring octreotide uptake in the orbits of patients with Graves' ophthalmopathy and to determine how to correct for non-specific background uptake. Also, most authors perform two scintigraphic measurements, e.g. at 4 hours and 24 hours after injection, and it is unknown whether this is useful. In addition, we studied the clinical usefulness of octreotide scintigraphy in predicting the response to retrobulbar radiotherapy in 22 unselected consecutive patients with Graves' ophthalmopathy.

Patients and methods

Methods.

The orbital uptake of $^{111}$Indium labeled octreotide was measured using a high resolution, multidetector neuro-SPECT (Single Photon Emission Computerized Tomography) camera (Strichman Medical Equipment, SME 900). Uptake was analyzed at 4 and 24 hours after i.v. injection of approx. 3 mCi (=111MBq; range 75-150 MBq) of $^{111}$Indium-DTPA-Octreotide (Mallinkrodt Medical BV, Petten, The Netherlands). A total of ten images (5 mm apart) in the transverse plane were obtained and from these ten, the four slices with maximal orbital uptake were selected, using the pituitary gland as anatomical reference. Thus, per patient eight orbital images were analyzed. The measurement of orbital uptake was done using a fixed (1154 pixels) rectangular region of interest (ROI; see Fig. 1). The number of counts in the eight orbital images were averaged. In each of the four slices the non-specific, background uptake was determined in two anatomical areas: a temporal area and an occipital area (Fig. 1). Per area, the counts in the four slices were measured using the same fixed ROIs and the means of the four slices were calculated. To correct orbital uptake for non-specific background uptake, we calculated the ratio of orbital to temporal, and orbital to occipital uptake.
Figure 1. Placing of the fixed rectangular regions of interest (ROIs) on one of the transverse images obtained by SPECT camera 4 hours after injection with $^{111}$In-DTPA-octreotide in a patient with Graves' ophthalmopathy. Counts are measured in both orbital ROIs, and in the temporal and occipital ROIs to correct for background uptake by determining an orbital/temporal and an orbital/occipital ratio.

To establish the intra-observer variability of measuring orbital, temporal, and occipital uptake, the $^{111}$In-octreotide-scintigraphies performed in 22 patients with Graves' ophthalmopathy (for patient characteristics see below) were analyzed twice. These analyses were done in random order by the same observer, who was blinded for the identity of the patient.

To elucidate the origin of the rather marked uptake in the temporal area, scintigraphic SPECT images were coregistered with a MRI study. Firstly a dual isotope study employing both $^{111}$Indium-octreotide (120 MBq i.v.), as well as $^{99m}$Tc-pertechnetate (200 MBq i.v.) was performed at 4 hours, resp. 15 minutes, after injection on a triple head camera (MultiSPECT 3, Siemens). The energy windows were chosen experimentally in order for the downscatter of the $^{111}$In to be less than 5% in the $^{99m}$Tc window. Subtraction of both images was done after
normalization for the maximum counts per pixel in each study in order to correct for scatter. Both scintigraphies were three dimensionally coregistered with the MRI on a sun workstation (HermesR, Nuclear Diagnostics, Stockholm, Sweden), employing a chamfer method.\textsuperscript{11}

\textbf{Patients.}

Twenty-two patients with moderately severe Graves' ophthalmopathy were studied. We included untreated, consecutive patients with $\geq 25$ mm proptosis or evident restriction of eye movements,\textsuperscript{12} who were euthyroid for more than two months. The patients were treated with retrobulbar irradiation (10 fractions of 2 Gy) and the response to this therapy was assessed at six months after start of treatment. We defined the response according to minor and major criteria. The major criteria were 1. An improvement in diplopia: intermittent (i.e., present only occasionally), inconstant (i.e., present but not in primary gaze), or constant (i.e., present in primary gaze); 2. Improvement in eye muscle motility of $\geq 8$ degrees elevation.\textsuperscript{13} Minor criteria were variations of 2 mm or more in lid width, exophthalmometer readings, and variations in soft-tissue involvement (i.e., mild, moderate or severe as judged from colour slides).\textsuperscript{14} We defined a response as very good if a patient improved in at least 2 major criteria; a good response meant improvement in 1 major and/or 2 minor criteria; no changes occurred, or if only a change in one minor criterium was found, this was classified as no change. Activity of Graves' ophthalmopathy was measured using the clinical activity score.\textsuperscript{3}

\textbf{Statistical analysis.}

Intra-observer variability of measuring orbital, temporal, and occipital uptake was analyzed by calculating the coefficient of variation (CV).

Differences in uptake ratio's between responders and non-responders were analyzed using the Mann Whitney U test.
**Results**

*Table 1. Mean of the absolute number of counts, and the coefficients of variability (CV) for the three different regions of interest (ROI) and the ratio’s on the 4 hours and the 24 hours octreotide scans.*

<table>
<thead>
<tr>
<th></th>
<th>Uptake mean</th>
<th>CV (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>4 hours Octreotide uptake</strong></td>
<td></td>
<td></td>
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<tr>
<td>Orbit</td>
<td>8558</td>
<td>8%</td>
</tr>
<tr>
<td>Temporal ROI</td>
<td>7787</td>
<td>15%</td>
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<td>Occipital ROI</td>
<td>4992</td>
<td>6%</td>
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<tr>
<td>orbit/temporal ratio</td>
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<td>16%</td>
</tr>
<tr>
<td>orbital/occipital ratio</td>
<td>1.70</td>
<td>11%</td>
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<tr>
<td><strong>24 hours Octreotide uptake</strong></td>
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<td></td>
</tr>
<tr>
<td>Orbit</td>
<td>1825</td>
<td>7%</td>
</tr>
<tr>
<td>Temporal ROI</td>
<td>1129</td>
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<tr>
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<td>orbit/temporal ratio</td>
<td>1.92</td>
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</tr>
<tr>
<td>orbital/occipital ratio</td>
<td>2.19</td>
<td>12%</td>
</tr>
</tbody>
</table>

**Intra-observer variability of measuring octreotide uptake**

The CV’s of the measurements on the 4 hour and 24 hour In-octreotide scintigraphies in the different areas are given in Table 1. From these results it can be concluded that the intra-observer variation in measuring orbital In-octreotide uptake was rather good. Because determining occipital background uptake
Octreotide-scintigraphy is a disease-activity parameter in graves' ophthalmopathy. Appeared to show less variability, correcting the orbital uptake for non-specific background in the occipital area is more reliable than using the temporal area.

**Anatomical origin of temporal octreotide uptake**

There was a quite marked octreotide uptake in the temporal area, especially on the 4 hour scan (see Table 1; Figure 1). The reason for this is unknown, but this marked uptake suggests that this area might not be representative of non-specific, background uptake. We performed a SPECT study including the whole skull in one patient. From these images we concluded that this temporal uptake occurred in the region of the parotid gland. Therefore, a dual isotope scan with octreotide and technetium pertechnetate was performed (Fig. 2). In addition, an $^{111}$In-octreotide scintigraphy was matched with an MRI scan of the same patient. From the images in Fig. 2 it was apparent that a major part of this temporal octreotide uptake actually corresponded to the parotid gland.

**Clinical usefulness of octreotide scanning in Graves' ophthalmopathy.**

The patients characteristics of 22 patients with moderately severe Graves' ophthalmopathy were: (mean(sd)) age 52 (10) years, sex (F/M) 15/7, duration of Graves' ophthalmopathy was 25 (20) months and 11/22 (50%) smoked. Fourteen (64%) responded to retrobulbar radiotherapy (5 very good responders, 9 good responders); eight did not change after radiotherapy. We compared the 14 responders and the 8 non-responders in terms of orbital $^{111}$In-octreotide uptake before start of treatment, using the orbital/occipital ratio (Fig. 3). On the 4-hours $^{111}$In-octreotide scintigraphy, responders indeed had a higher mean ±SD orbital/occipital uptake ratio: 2.2 ±0.66 versus 1.7 ±0.39 ($P=0.04$). Using the orbital/occipital uptake ratio on the 24-hours scan, no difference between responders and non-responders was found: 1.8 ±0.50 versus 1.4 ±0.50 ($P=0.20$). There was no significant correlation between octreotide uptake and severity of the disease, nor with smoking status. Also there was no significant correlation between smoking status and response to treatment.
Figure 2. Dual isotope imaging of the same patient with Graves' ophthalmopathy, using a triple head MultiSPECT camera.

A. Octreotide scintigraphy, 4 hours after injection of $^{111}$In-DTPA-octreotide.
B. Technetium scintigraphy, 15 minutes after injection of 99mTc-pertechnetate.
C. Octreotide scintigraphy with subtraction of the technetium images. The temporal uptake on the octreotide scintigram is markedly reduced after subtraction of the uptake on the technetium scan (arrows in B), yielding black punched-out holes on the subtraction scan (arrows in C).
Octreotide-scintigraphy is a disease-activity parameter in graves' ophthalmopathy

To evaluate whether the 4-hour orbital/occipital uptake ratio could predict a response to radiotherapy, we plotted a Receiving Operator Characteristic (ROC) curve. The area under the curve (AUC) was 0.767. A value of ~1.85 yielded the best cut-off level: positive predictive value 92%, negative predictive value 70%. The ROC curve derived from the 24 hours scan yielded no cut-off value (AUC 0.51), nor did the clinical activity score (AUC 0.51).

Figure 3. The orbital/occipital ratio on the 4 hours and 24 hours p.i scans in 14 Graves' ophthalmopathy patients who had responded to radiotherapy (responders), compared to 8 non-responders. Mean values are indicated. The dotted line represents the cut-off level (1.85) as calculated from a ROC curve.
Discussion

This study shows that quantitative measurement of orbital octreotide uptake might be of use in predicting the outcome of immunosuppressive treatment of patients with Graves' ophthalmopathy. This was already suggested by earlier studies, which however did not correlate octreotide scintigraphy to the clinical outcome of immunosuppression. Postema et al.\textsuperscript{6} and Moncayo et al.\textsuperscript{7} used a qualitative assessment of orbital octreotide uptake and found a good correlation with the Clinical Activity Score, whereas Kahaly et al.\textsuperscript{10} showed that octreotide uptake measured quantitatively correlated with the T2 relaxation time on MRI. In the present study we performed pre-treatment octreoscans in 22 consecutive patients with moderately severe ophthalmopathy, who were not selected for clinically apparent active eye disease. They thus represent patients that will be seen routinely at clinics specialized in the treatment of this thyroid related eye disease. In this group, \textsuperscript{111}In-octreotide scintigraphy could predict a subsequent positive response to retrobulbar radiotherapy in 92\% of the cases. This is in agreement with a small study with 12 patients, finding a positive predictive value of 84\%\textsuperscript{10}, and with a recent study in selected (active) patients with Graves' ophthalmopathy (positive predictive value: 90\%).\textsuperscript{9} Therefore, it appears that in the absence of histology (the gold standard for disease activity), increased orbital uptake of \textsuperscript{111}In-octreotide probably represents active ophthalmopathy amenable to immunosuppression.

However, our study also shows that octreotide scintigraphy should be interpreted with caution. Although quantitative (rather than qualitative) measurement of orbital uptake is possible, it has a rather limited accuracy. To our knowledge, ours is the first study to evaluate the reliability of measuring orbital uptake in ophthalmopathy patients. When examining 22 patients, the intra-observer variation is 6-16\%, and further depends on the methodology to correct for non-specific, background uptake. Our results show that the uptake in the occipital area is best used for this purpose. The variability of the orbital/occipital uptake ratio is better than that of the orbital/temporal ratio, which has been advocated in
Octreotide-scintigraphy is a disease-activity parameter in Graves' ophthalmopathy earlier studies. The reason for this might be that the marked uptake in the temporal area does not represent exclusively a non-specific uptake in a venous bloodpool. From our studies in which scintigraphy was matched with MRI, it appears that a major part of the temporal octreotide uptake occurs in the parotid gland. It thus might represent specific, rather than background uptake.

Orbital octreoscans are usually performed twice, e.g. at 4 hours and at 24 hours post injection. From the present study we conclude that using a relatively low dose $^{111}$In-DTPA-octreotide, the second 24 hours postinjection scan, is not useful in predicting a response to immunosuppression. This is in agreement with other studies. Although the reason for the low 24 hours uptake is unknown, it might be due to the fact that the breakdown of $^{111}$In-octreotide already starts at 4 hours after injection. However, this finding raises also the question whether or not the observed uptake is mediated by specific receptor binding.

How does the octreoscan compare to other parameters for disease activity in Graves' ophthalmopathy? In our patients we found a positive predictive value of 92%, which is higher than the non-invasive Clinical Activity Score. The negative predictive value is only 70%, comparing unfavorably to other measurements of disease activity like the T2 relaxation time on MRI (86%). It might be that we need a combination of activity parameters to accurately predict response to treatment. For this we would need a larger study in which several parameters for disease activity are compared.

In conclusion, we found that $^{111}$In-DTPA-octreotide scintigraphy seems useful to predict a positive response to immunosuppressive treatment in Graves' ophthalmopathy. For this, best images are obtained only 4 hours after injection. The best correction for aspecific background uptake appeared to be the occipital skull uptake.
Acknowledgements

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References

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