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Short communication

Improved visualization of carcinoid liver metastases by indium-111 pentetreotide scintigraphy following treatment with cold somatostatin analogue

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Abstract. Five patients with hepatic metastases of midgut carcinoid underwent somatostatin receptor scintigraphy with indium-111 pentetreotide before and during treatment with octreotide. Octreotide treatment changed the biodistribution of ^{111}In-pentetreotide significantly. Whereas the radioactivity in liver, spleen and kidney decreased, hepatic metastases showed increased contrast. In one patient, liver metastases could only be detected during octreotide treatment. These data suggest that the diagnostic reliability of somatostatin receptor scintigraphy in carcinoid liver metastases is not necessarily compromised by octreotide therapy. Because of different biodistributions, the detection of liver metastases may even be improved during octreotide therapy.

Key words: Somatostatin receptor scintigraphy – Carcinoid – Octreotide – Indium-111 pentetreotide

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Introduction

Somatostatin receptor scintigraphy (SRS) has shown diagnostic utility in the management of patients with neuroendocrine tumour of the gastrointestinal tract [1–4]. Positive SRS findings seem to predict a favourable response to a therapeutic regimen with unlabelled somatostatin analogues such as octreotide [5]. Whenever SRS is planned in patients during ongoing octreotide treatment, it is generally recommended that this drug be withdrawn to reduce the occupancy of somatostatin receptors. This may be a significant disadvantage in patients with severe carcinoid syndrome.

To investigate this problem further, we have performed SRS in patients with metastatic carcinoid disease both before treatment or after a withdrawal period and during ongoing octreotide therapy. The aim of the study was to find out whether or not the diagnostic reliability of SRS is affected by treatment with unlabelled somatostatin analogues as predicted from some experimental data [6].

We present our SRS findings in five patients with hepatic metastases who have been investigated twice, before and during ongoing octreotide therapy.

Materials and methods

Five patients with functioning midgut carcinoid were investigated. All of them had liver metastases and additional tumour spread in abdominal and/or mediastinal lymph nodes, as demonstrated by computed tomography.

The first SRS study was performed before any treatment with octreotide in two patients; in three patients the scintigraphic procedure was carried out after a 24-h period of octreotide withdrawal. The second SRS study was carried out under an ongoing therapeutic regimen with octreotide at a daily dosage of 600 μg. The interval between the two studies did not exceed 4 weeks.

A mean dose of 137 MBq indium-111 pentetreotide (range 105–237 MBq) (OctreoScan, Mallinckrodt, The Netherlands) was injected intravenously. Scintigraphy comprised planar images (anterior and posterior) 30 min, 4 h and 24 h post injection and was carried out on a Siemens Orbiter 7500 equipped with a medium-energy collimator; data were collected with a Siemens Microdelta computer system. Digital planar images were analysed semiquantitatively by a regions of interest (ROI) technique for activity in liver, spleen, kidney and liver metastases. Average counts/pixel were corrected for data acquisition time and applied dose of ^{111}In-pentetreotide. The calculated values of the respective ROI were compared in each patient as relative tissue activity (see Fig. 2) and liver metastasis-to-liver ratio (Table 1).

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Table 1. Analysis of tumour activity of ^{111}In-pentetreotide (4 h p.i.): target-to-non-target ratio for liver metastases in four patients

	Liver metastasis-to-liver ratio	
	Initial SRS	SRS during octreotide treatment
Pat. 1	1.01	1.14
Pat. 2	1.06	1.41
Pat. 3	0.97	1.27
Pat. 4	1.09	1.32

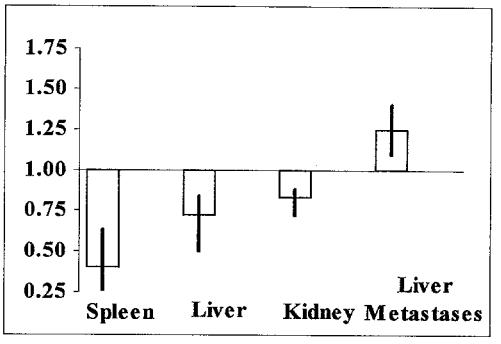

Fig. 2. Analysis of tissue activity of ^{111}In-pentetreotide (4 h p.i.). Relative values of ^{111}In-pentetreotide accumulation during ongoing octreotide treatment. The diagram illustrates the decrease of radioactivity in liver, spleen and kidney and the increase of ^{111}In-pentetreotide accumulation in liver metastases in four patients as mean values (*columns*) and range (*bars*)

Results

Biodistribution

The most striking difference between the two scintigraphic studies in each patient was the markedly reduced accumulation of ^{111}In-pentetreotide in the spleen under ongoing therapy with the somatostatin analogue octreotide (Fig. 1). The semi-quantitative evaluation revealed a decrease of spleen activity to a mean value of 40% (range 25%–63%) when compared with the initial study. Hepatic and renal accumulation of ^{111}In-pentetreotide was also reduced by octreotide treatment to a mean value of 72% (range 50%–84%) and 83% (range 72%–88%) respectively (Fig. 2).

Tumour visualization

In four patients, the hepatic metastases could be delineated by SRS more precisely and in one patient the hepatic tumour masses could only be visualized during octreotide treatment (Fig. 3).

As shown in Fig. 2, tracer accumulation was enhanced in all hepatic metastases under ongoing octreotide therapy. Subsequently the target-to-non-target ratio improved markedly 4 h after injection (Table 1). Late images 24 h after injection did not show any further improvement of this ratio.

Discussion

In experimental studies, Bakker et al. [6] showed that somatostatin receptor-expressing tumours could not be visualized by means of ^{111}In-pentetreotide scintigraphy in rats pretreated with octreotide. These data were interpreted as the result of a complete saturation of somatostatin receptors of the tumour due to a ratio of cold-to-labelled SMS analogue of 1000:1. Furthermore, no significant difference in the concentration of radioactivity measured in liver, spleen and kidney was found between pretreated and control rats.

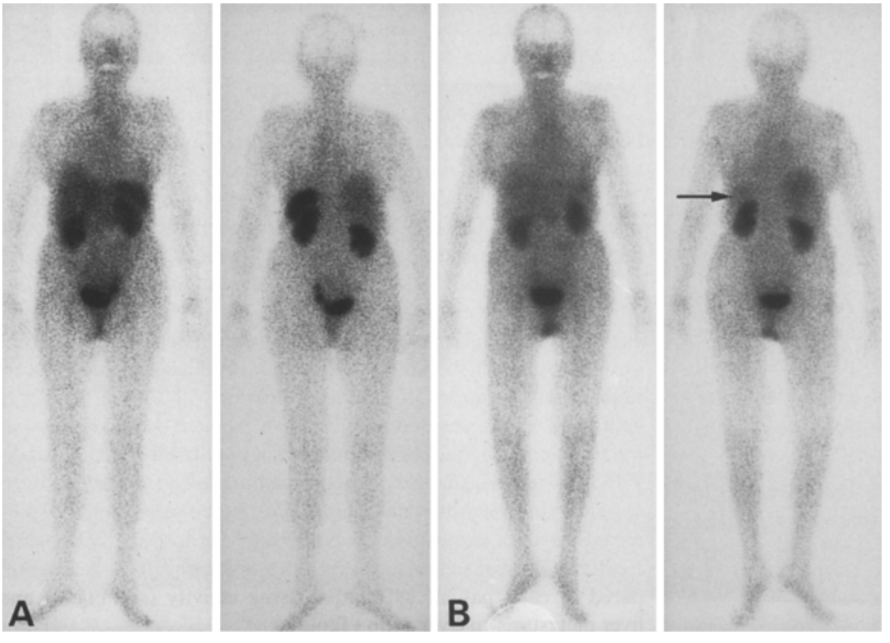

Fig. 1a, b. Whole-body image (4 h p.i.). **a** Initial SRS study. **b** SRS study during octreotide treatment (600 μg/day), showing markedly reduced accumulation of ^{111}In-pentetreotide in the spleen (*arrow*)

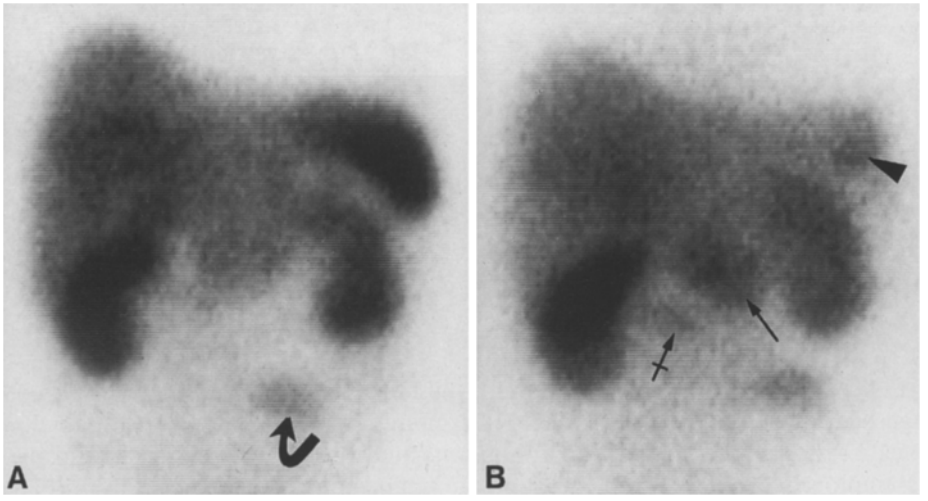

Fig. 3a, b. Planar images of the abdomen of a patient with liver metastases of a midgut carcinoid (4 h p.i.; supine position). **a** Initial SRS study. **b** Repeat study during octreotide treatment (600 μg/day). Both hepatic tumour manifestations are detectable only in **b**, not in **a**. The large metastasis (*arrow*) shows increased tracer enhancement, whereas the visibility of the smaller one (*arrowhead*) is the result of reduced radioactivity of the spleen. *Curved arrow:* metastatic lymphoma at the mesenteric root; *crossed arrow:* metastatic lymphoma at the hepatic hilus

Although Bakker et al.'s data suggest that octreotide pretreatment may compromise tumour targeting by SRS – at least in his experimental setting –, it remains unclear whether a common therapeutic octreotide regimen would have the same effect in humans. In general, a period of octreotide withdrawal for at least 12 h is recommended by the manufacturer.

In contrast to the animal tumour model, we found the decrease in ^{111}In-pentetreotide accumulation to be most pronounced in the spleen, but it was also present in the liver and kidney. Furthermore, visualization of hepatic metastases was enhanced in all patients. These unexpected results may be explained by the different ratio of cold to labelled SMS analogue in the experimental model and the human system. While the therapeutic dose of octreotide was 600 μg/day, the diagnostic dose of pentetreotide for SRS was only 10 μg, resulting in an octreotide-to-pentetreotide ratio of 60:1. A complete saturation of tumoural somatostatin receptors is unlikely to be achieved with this therapeutic regimen.

Conclusion. Negative receptor scintigraphy in patients with known carcinoid metastases of the liver does not rule out the presence of high-affinity somatostatin binding sites. The tumour might express these receptors only to a lesser extent, which results in a non-diagnostic target-to-non-target ratio. In this situation, i.e. clinically manifest carcinoid syndrome and known liver involvement, it might be useful to repeat the receptor scintigraphy at the time of octreotide treatment to elucidate the receptor positivity of the liver metastases as the rationale for the treatment with somatostatin analogues.

From a practical point of view, our data suggest that a period of octreotide withdrawal is not mandatory whenever SRS is intended to be performed and this will be of benefit in patients with severe carcinoid syndrome. Furthermore, if radiotherapy with labelled somatostatin analogue becomes available, the altered distribution of the radiopharmaceutical by pretreatment might play an important role in reducing the radiation burden of physiological tissue as well as in enhancing the tumour dose.

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