

# Hormonal crises following receptor radionuclide therapy with the radiolabeled somatostatin analogue [ $^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$ ]octreotate

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## Abstract

**Introduction** Receptor radionuclide therapy is a promising treatment modality for patients with neuroendocrine tumors for whom alternative treatments are limited. The aim of this study was to investigate the incidence of hormonal crises after therapy with the radiolabeled somatostatin analogue [ $^{177}\text{Lu-DOTA}^0, \text{Tyr}^3$ ]octreotate ( $^{177}\text{Lu}$ -octreotate).

**Materials and methods** All  $^{177}\text{Lu}$ -octreotate treatments between January 2000 and January 2007 were investigated. Four hundred seventy-six patients with gastroenteropancreatic neuroendocrine tumors and three patients with metastatic pheochromocytoma were included for analysis.

**Results** Four hundred seventy-nine patients received a total of 1,693 administrations of  $^{177}\text{Lu}$ -octreotate. Six of 479 patients (1%) developed severe symptoms because of massive release of bioactive substances after the first cycle of  $^{177}\text{Lu}$ -octreotate. One patient had a metastatic hormone-producing small intestinal carcinoid; two patients had metastatic, hormone-producing bronchial carcinoids; two patients had vasoactive intestinal polypeptide-producing pancreatic endocrine tumors (VIPomas); and one patient had a metastatic pheochromocytoma. With adequate treatment, all patients eventually recovered.

**Conclusion** Hormonal crises after  $^{177}\text{Lu}$ -octreotate therapy occur in 1% of patients. Generally,  $^{177}\text{Lu}$ -octreotate therapy is well tolerated.

**Keywords** Lu-177-octreotate · Neuroendocrine tumors · Peptide receptor radionuclide therapy · Carcinoid crisis

## Introduction

Gastroenteropancreatic neuroendocrine tumors (GEPNETs) constitute a heterogeneous group of neoplasms. Two major GEPNET subcategories are intestinal endocrine tumors or carcinoids and pancreatic neuroendocrine tumors (PNETs). These tumors are often slow growing and may be associated with typical symptoms because of excessive and uncontrolled release of various metabolically active amines and peptides, such as serotonin, gastrin, glucagon, somatostatin, insulin, vasoactive intestinal polypeptide (VIP), and substance P. Pheochromocytomas are catecholamine-producing tumors, which generally arise in the adrenal medulla.

A so-called carcinoid crisis is a medical emergency caused by the excessive release of metabolically active amines or peptides that can occur spontaneously after manipulation of a carcinoid tumor, during induction of anesthesia, during surgery, endoscopy, or with chemotherapy [1–5]. The symptomatology involves profound flushing, hypotension, or extreme changes in blood pressure, diarrhea, bronchoconstriction, and arrhythmias [6]. So far, only one case of a carcinoid crisis after therapy with a radiolabeled somatostatin analogue has been described [7]. Another well-recognized endocrine emergency can occur in patients with pheochromocytomas. This is caused by the

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massive release of catecholamines, which can occur spontaneously, after manipulation of the tumor or during medical interventions [8].

Since the year 2000, patients with somatostatin receptor-positive metastatic, inoperable GEPNETs and malignant pheochromocytomas have been treated with the radiolabeled somatostatin analogue [ $^{177}\text{Lu}$ -DOTA<sup>0</sup>, Tyr<sup>3</sup>]octreotate ( $^{177}\text{Lu}$ -octreotate) in our institution. Results of  $^{177}\text{Lu}$ -octreotate treatment in these patients are promising, with tumor size reduction in 47% of the treated patients [9].

Although infrequent, hormonal release-induced crises can occur after  $^{177}\text{Lu}$ -octreotate treatment. In this study, we describe all patients who developed a hormonal crisis in association with peptide receptor radionuclide therapy with  $^{177}\text{Lu}$ -octreotate.

## Materials and methods

### Patients

All patients with neuroendocrine tumors treated in our institution treated with  $^{177}\text{Lu}$ -octreotate between January 2000 and January 2007 were included in this study. All patients fulfilled the inclusion criteria for  $^{177}\text{Lu}$ -octreotate therapy [9]. All patients gave written informed consent to undergo  $^{177}\text{Lu}$ -octreotate therapy. This therapy was approved by the medical ethical committee of our hospital.

### Methods

$^{177}\text{Lu}$ -octreotate was prepared as described previously [10].

Somatostatin analogue therapy was discontinued in 193 of 200 patients during  $^{177}\text{Lu}$ -octreotate therapy. Long-acting somatostatin analogues (Sandostatin LAR, Lanreotide Autogel) were discontinued 1 month before therapy. Thereafter, therapy was switched to an immediate release somatostatin analogue (Octreotide) that was discontinued 1 day before  $^{177}\text{Lu}$ -octreotate therapy. An infusion of amino acids (2.5% arginine, 2.5% lysine 1 l/4 h) was administered to reduce the radiation dose to the kidneys, starting 30 min before administration of 7,400 MBq  $^{177}\text{Lu}$ -octreotate. Generally, four cycles of  $^{177}\text{Lu}$ -octreotate were given.

Routine hematology and liver and kidney function tests, as well as serum chromogranin A measurements (CgA), were performed before each therapy cycle in all patients. Additionally, 5-hydroxy-indole-acid (5HIAA) measurements in 24-h urine in the carcinoid patients, serum vasoactive intestinal peptide in the VIPoma patients, serum gastrin in gastrinoma patients, and excretion of normetanephrines and metanephrines in the 24-h urine in the patients with a metastatic pheochromocytoma were measured (laboratory normal values: CgA < 100  $\mu\text{g/l}$ , 5HIAA < 50  $\mu\text{mol/}$

24 h, VIP 25–65 pg/ml, gastrin < 0.15  $\mu\text{g/l}$ , metanephrines < 2  $\mu\text{mol/24 h}$ , normetanephrines < 5.1  $\mu\text{mol/24 h}$ ).

## Results

### Patient characteristics

Four hundred seventy-nine patients with neuroendocrine tumors were studied: 262 men (55%), and 217 women (45%). Two hundred sixty-five patients (53%) had metastatic carcinoid tumors: 52 patients (11%) had metastatic neuroendocrine tumors of unknown origin, 124 patients (26%) had non-functioning PNETs, 35 patients (7%) had functioning PNETs, and 3 patients (1%) had metastatic pheochromocytoma. The mean age at the time of the first therapy was 56 years (range, 16–85), and the mean Karnofsky performance score was 90 (range, 50–100). The tumor burden in the majority of the patients was high with liver metastases in 88% and bone metastases in 26% of the patients. Before  $^{177}\text{Lu}$ -octreotate therapy, 42% of patients were using somatostatin analogues to reduce hormonal symptoms. Patient characteristics are shown in Table 1.

### Therapy and complications

The 479 patients received a total of 1,693 administrations of  $^{177}\text{Lu}$ -octreotate. Mild side effects within 24 h after  $^{177}\text{Lu}$ -octreotate therapy were nausea after 25%, vomiting after 10%, and increase of abdominal pain/discomfort after 9% of the treatment cycles.

After 10 of 1,691 (0.6%) administrations of  $^{177}\text{Lu}$ -octreotate in six patients (1%), readmission or prolonged hospitalization because of hormonal release-induced crisis was necessary. Two of 20 patients with bronchial carcinoids, 2 of 3 patients with a VIPoma, 1 of 241 patients with a digestive tract carcinoid, and 1 of 3 patients with a pheochromocytoma had a crisis. All patients developing a crisis had extensive metastatic disease, all patients had liver metastases, and three also had skeletal metastases. Post-therapeutic scintigrams showing  $^{177}\text{Lu}$ -octreotate uptake in the metastases are shown in Fig. 1. Also, all patients had clinically overt hormonal-release-related symptomatology, like flushing and severe diarrhea. In two of these patients, hormonal symptoms were so severe that discontinuation of somatostatin analogue therapy before peptide receptor radionuclide therapy was impossible. Characteristics of these patients are shown in Table 2. In all six patients, the hormonal crisis occurred during the first therapy cycle; three of the six patients developed the crisis during or directly after  $^{177}\text{Lu}$ -octreotate infusion, and the other three patients developed the crisis 48 h after  $^{177}\text{Lu}$ -octreotate infusion.

**Table 1** Patients' characteristics

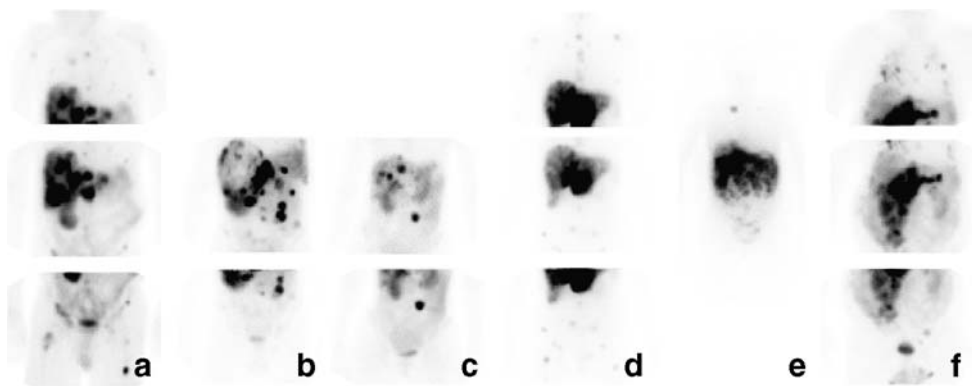
Tumor type	Number of patients	Somatostatin analogue pretreatment	Liver metastases	Bone metastases	CgA ( $\mu\text{g/l}$ ) median (range)	Relevant laboratory findings median (range)
<b>Carcinoids</b>						
-Digestive tract carcinoid	241	142	223	57	537 (22–787,742)	Urinary 5HIAA ( $\mu\text{mol}/24\text{ h}$ ) 222 (7–2,048)
-Bronchial carcinoid	20	7	16	13	1,252 (35–900,280)	Urinary 5HIAA ( $\mu\text{mol}/24\text{ h}$ ) 191 (15–1,440)
-Thymic carcinoid	4	0	1	1	294 (147–725)	–
<b>Functioning PNETs</b>						
-VIPoma	3	0	3	9	153 (22–318)	VIP (pg/ml) 470 (144–710)
-Insulinoma	11	3	8	4	1256 (69–21,509)	–
-Gastrinoma	21	8	19	5	2,282 (111–55,715)	Gastrin ( $\mu\text{g/l}$ ) 1.2 (0.03–22)
<b>Non functioning PNETs</b>	124	25	107	24	385 (26–162,710)	–
<b>Neuroendocrine tumour of unknown origin</b>	52	10	44	18	400 (23–29,110)	–
<b>metastatic pheochromocytoma</b>	3	1	1	2	5,666 (928–6,900)	–
<b>Total</b>	<b>479</b>	<b>200 (42%)</b>	<b>422 (88%)</b>	<b>124 (26%)</b>		

Digestive tract carcinoid (gastric, duodenum, short bowel, colon, and rectum carcinoids), PNETs (pancreas neuroendocrine tumors) laboratory normal values: CgA < 100  $\mu\text{g/l}$ , 5HIAA < 50  $\mu\text{mol}/24\text{ h}$ , VIP 25–65 pg/ml, gastrin < 0.15  $\mu\text{g/l}$ .

The treatment included high-dose octreotide, i.v. fluid replacement, and other supportive measures (as shown in Table 2); all patients fully recovered. In all six patients who developed a hormonal crisis after their first therapy cycle, additional precautions were taken before the administration of further therapy cycles, including continuation of somatostatin analogues, corticosteroids, prolonged observation in the hospital after therapy, and reduction of administered dosage of  $^{177}\text{Lu}$ -octreotate. Despite these precautions, three

patients developed a hormonal release-induced crisis again after a subsequent cycle of  $^{177}\text{Lu}$ -octreotate.

In two patients, hormonal release could be biochemically confirmed. We observed massive release of CgA in patient 1. CgA levels increased from 4,379 at baseline to 24,661  $\mu\text{g/l}$ , 24 h after  $^{177}\text{Lu}$ -octreotate. Multiple urinary normetanephrines measurements were performed in patient 6; severely increased excretion of normetanephrines was observed shortly after therapy with  $^{177}\text{Lu}$ -octreotate (Fig. 2)



**Fig. 1** Post-therapy scintigrams after  $^{177}\text{Lu}$ -octreotate of patient 1 (a), patient 2 (b), patient 3 (c), patient 4 (d), patient 5 (e), and patient 6 (f). Upper row Anterior images of the thorax, middle row anterior images of the abdomen, and lower row anterior images of the pelvic region.

Note that the focal increased  $^{177}\text{Lu}$ -octreotate accumulations in liver metastases in all patients and focal uptake in bone metastases in patients 1, 2, and 4. In patient 6, there was also uptake in multiple lung metastases

**Table 2** Characteristics of patients with a hormonal crisis after  $^{177}\text{Lu}$ -octreotate treatment

Case	Age/ Sex	Tumor	Years since diagnosis	Treatment before $^{177}\text{Lu}$ -octreotate	Clinical symp- toms before $^{177}\text{Lu}$ - octreotate	Relevant labora- tory findings before $^{177}\text{Lu}$ - octreotate	Continuation of somato- statin analogues prior to $^{177}\text{Lu}$ - octreotate	Onset of “crisis” in relation to administration of $^{177}\text{Lu}$ - octreotate	Predominant symptomatology	Treatment of “crisis”	Duration of hospitalization	Disease course
1	65/ M	Bronchial carcinoid with mediastinal lymph node, liver and bone metastases	4	External radiation therapy, octreo- tide LAR	Flushing and diarrhea, sev- eral carcinoid crises requir- ing hospitali- zation	CgA 4,379 $\mu\text{g/l}$ , uri- nary 5HIAA 399 $\mu\text{mol/24 h}$	No	Immediately	Nausea, worsen- ing of diar- rhea, severe flushing	Fluids i.v., octreotide, corticosteroids, metoclopramide, loperamide	5 days	2 more cycles of $^{177}\text{Lu}$ - octreotate treatment with- out discontinuation of octreotide treatment. Both again leading to hor- monal release requiring hospitalization. Died after 1 year because of progressive disease
2	62/F	Bronchial carcinoid with liver and bone metastases	11	Lobectomy left upper lobe, external radia- tion therapy, intra-bronchial laser coagulation of tumor, octreotide LAR, interferon-alpha	Flushing and diarrhea, car- cinoid crisis after intra- bronchial la- ser coagula- tion of tumor	CgA 110,000 $\mu\text{g}/\text{l}$ Urinary 5HIAA 978 $\mu\text{mol/24 h}$	No	After 2 days	Severe flushing, worsening of diarrhea, dehy- dration	Fluids i.v., corti- costeroids, octreotide	11 days	3 more cycles of $^{177}\text{Lu}$ - octreotate, with discontin- uation of octreotide treat- ment without serious side effects. Died after 1 year because of progressive disease
3	53/F	ViPoma with liver metastases	1	Distal pancreatec- tomy, radiofre- quency ablation of liver metasta- ses, cisplatin, etoposide, octreotide LAR	Severe diar- rhea, hypoka- lemia and dehydration	ViP 470 $\text{pg/ml}$ CgA 318 $\mu\text{g/l}$	No	After 2 days	Nausea, severe diarrhea, metabolic aci- dosis, hypokalemia dehydration	Fluids i.v., potas- sium, metoclo- pramide, octreo- tide	4 days	3 more cycles of $^{177}\text{Lu}$ - octreotate, with discontin- uation of octreotide treat- ment 1 year later improvement of general condition, less diarrhea and less flushing
4	44/F	ViPoma with liver and bone metastases	2	Streptozinone, 5-fluoracil and adriamycine, embolization of liver metasta- ses, lanreotide octreotide, loper- amid, potassium	Flushing and diarrhea hy- pokalemia and dehydra- tion	ViP 710 $\text{pg/ml}$ CgA 335 $\mu\text{g/l}$	Yes	Immediately	Severe diarrhea, metabolic aci- dosis, hypoka- lemia, dehy- dration	Fluids i.v., potas- sium, octreotide, loperamide, metoclopramide	13 days	2 more cycles of $^{177}\text{Lu}$ - octreotate, with continua- tion of octreotide and corticosteroids. After the second cycle again hormonal crisis requiring hospitali- zation. Died after 1 year because of progressive disease

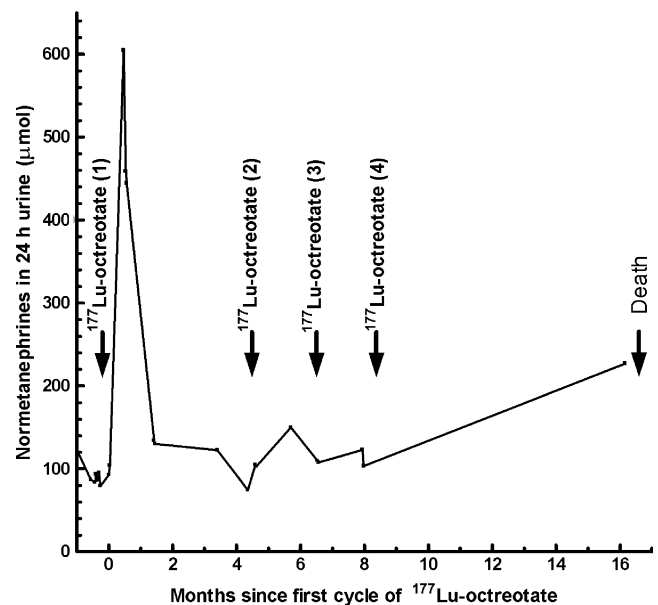
5	50/ M	Small intestinal carcinoid with liver metastases	15	Debulking surgery, interferon-alpha, 5-fluorouracil and leucovorin, octreotide LAR	Flushing and diarrhea	CgA 2950 µg/l, urinary 5HIAA 902 µmol/24 h	Yes	Immediately	Nausea, vomiting, flushing, hypotension	Fluids i.v., octreotide, metoclopramide	6 days	6 more cycles of <sup>177</sup> Lu-octreotate (half dose, 3,700 MBq) without discontinuation of octreotide. After second cycle, again hormonal crisis requiring hospitalization. Still alive after 2 years, still episodic diarrhea
6	63/ M	Malignant pheo- chromocytoma with lung bone abdominal lymphnode and liver metastases	2	Adrenalectomy, alpha- and beta-adrenergic blockade, octreotide	Nausea	Urinary normetanephrines 79 µmol/24 h, urinary metanephrines 10 µmol/24 h; CgA 6,900 µg/l	No	After 1 day	Hypotension, extensive sweating, cardiac ischemia	Fentolamine, octreotide, bisoprolol, morphine	2 months	3 more cycles <sup>177</sup> Lu-octreotate without side effects (with continuation of octreotide and corticosteroids). Died after 1 1/2 years because of progressive disease

**Discussion**

Hormonal crises after <sup>177</sup>Lu-octreotate therapy occur infrequently; only 6 of 479 patients with GEPNETs and malignant pheochromocytomas had a crisis. These patients all had preexisting clinically overt symptoms like flushing and diarrhea. All six patients had liver metastases, and three of six patients also had bone metastases. Patients who did not have a crisis after the first administration of <sup>177</sup>Lu-octreotate also did not develop a hormonal crisis after subsequent cycles.

In our series, two of three patients treated for metastatic VIPoma developed a hormonal crisis after <sup>177</sup>Lu-octreotate. VIPomas are associated with a well-defined clinical syndrome characterized by severe watery diarrhea, hypokalemia, and metabolic acidosis (Verner–Morrison syndrome) [11]. Also, 2 of 20 patients treated for metastatic bronchial carcinoid developed a carcinoid crisis. The carcinoid syndrome in patients with metastatic bronchial carcinoids is mediated by 5-hydroxytryptophan, its conversion to serotonin and/or by histamine[12]. The only other documented carcinoid crisis after radionuclide receptor therapy also involved a patient with a bronchial carcinoid [7]. Only one of the 241 patients with a carcinoid originating from the digestive tract had a hormonal crisis.

One of the three patients treated for a metastatic pheochromocytoma developed a pheochromocytoma crisis. Hormonal crises in pheochromocytoma patients because of massive release of catecholamines can lead to multiple clinical features including (episodic) hypertension or hypotension, myocardial



**Fig. 2** Normetanephrines in 24 h urine (µmol) of patient 6 after <sup>177</sup>Lu-octreotate treatment. Note the excessive release of normetanephrines after the first cycle of <sup>177</sup>Lu-octreotate. Normal value urinary normetanephrines: <5.1 µmol/24 h

ischemia, cardiomyopathia, pulmonary edema, and shock [13, 14]. After  $^{131}\text{I}$ -MIBG therapy, excessive catecholamine secretion with the above-mentioned severe symptomatology has been reported [15, 16].

No serious hormonal release-induced side effects were observed in patients with other tumors; there were no episodes of severe hypoglycemia in patients with metastatic insulinoma, and none of the patients with metastatic gastrinoma, non-functioning GEPNETs, or neuroendocrine tumors of unknown origin developed a hormonal crisis after  $^{177}\text{Lu}$ -octreotate.

The exact mechanism of increased hormonal release in the patients developing a hormonal crisis after  $^{177}\text{Lu}$ -octreotate is not fully elucidated. Several mechanisms may have accounted for the induction of such a crisis in our patients: (1) tumor lysis because of beta-irradiation from  $^{177}\text{Lu}$ , (2) discontinuation of short-acting somatostatin analogues before  $^{177}\text{Lu}$ -octreotate administration, (3) emotional stress response to hospitalization and/or therapy, or (4) administration of amino acids (2.5% arginine and 2.5% lysine). These amino acids might be used as substrates for increased hormone synthesis by the tumor cells.

Arguments for tumor lysis because of beta irradiation are the relatively late onset of complaints (>24 h after therapy) in patients 2, 3, and 6. Patients 1, 4, and 5 had direct onset of complaints during  $^{177}\text{Lu}$ -octreotate infusion; these crises cannot be explained by tumor lysis. In patients 4 and 5, the hormonal crisis might have been induced by emotional stress in combination with amino acid infusion. These patients continued their somatostatin analogue therapy. It is well known that emotional stress can provoke flushing [17]; therefore, it might also be possible that emotional distress, present in carcinoid patients [18], might have played a role in the development of the hormonal crises in these patients. In patient 1, the hormonal crisis might also be related to discontinuation of somatostatin analogue therapy. When possible, we stop somatostatin analogues before  $^{177}\text{Lu}$ -octreotate therapy to prevent competitive binding to the somatostatin receptors with  $^{177}\text{Lu}$ -octreotate. The basis for this approach is the finding of a decreased  $^{111}\text{In}$ -octreotide uptake by the tumor (although not significant) in patients continuing somatostatin analogue treatment compared to patients discontinuing somatostatin analogue treatment [19].

Direct receptor-mediated hormonal release by  $^{177}\text{Lu}$ -octreotate seems unlikely. Somatostatin receptor binding leads to decrease in hormonal secretion in the majority of patients. Therapy with somatostatin analogues in patients with metastatic carcinoid tumors results in symptomatic improvement in more than 70% of the patients and biochemical response in 50 to 60% of the patients [20, 21].

All patients received further cycles of  $^{177}\text{Lu}$ -octreotate after their first hormonal crisis. When re-treating these patients, continuation of somatostatin analogues in combi-

nation with corticosteroids is indicated [22, 23]. In one patient, we halved the administered activity to 3,700 MBq  $^{177}\text{Lu}$ -octreotate to decrease potential tumor lysis because of beta irradiation. Of course, important drawback of such a treatment protocol is that the tumor-absorbed radiation dose will also be decreased.

Recommended treatment of patients with hormonal crises are high-dose somatostatin analogues i.v., i.v. fluids, corticosteroids, and correction of electrolyte disturbances in patients with diarrhea and vomiting. Patients with metastatic pheochromocytoma should also be treated with alpha- and beta-adrenergic blockade. From the present experience, we also recommend continuation of somatostatin analogue therapy in patients with metastatic VIPomas and bronchial carcinoids who have symptomatology of (atypical) carcinoid syndrome.

## Conclusion

Hormonal crises after  $^{177}\text{Lu}$ -octreotate occur infrequently. In our series, only 6 of 479 patients had such a crisis. Patients treated for VIPoma or bronchial carcinoids are most at risk. All patients with a hormonal crisis eventually recovered. Other less serious side effects shortly after  $^{177}\text{Lu}$ -octreotate, such as nausea, vomiting, and abdominal pain, are more common and can be controlled by supportive measures. Generally,  $^{177}\text{Lu}$ -octreotate therapy is well tolerated.

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