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Octreotide suppression test in diagnosing and predicting the outcome of therapy in patients with neuroendocrine tumors. Preliminary report

Test hamowania oktreotydem w diagnostyce i prognozowaniu skuteczności terapii u chorych z guzami neuroendokrynnymi. Doniesienie wstępne

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Abstract

Introduction: Chromogranin A (CgA) is a non-specific marker of neuroendocrine tumors (NET) and is important in monitoring the disease course and NET treatment.

Aim of the study: Usefulness of suppression test of CgA secretion with octreotide in diagnosis and predicting the therapy outcome in NET patients.

Material and methods: The study included 32 patients with NET of gastrointestinal tract, lung and of unknown origin. CgA level in blood plasma on fasting, before and 30, 60, 90 and 120 minutes after subcutaneous administration of 100 μg octreotide, was determined in all patients. The subjects were divided into two subgroups with relation to CgA level and to the results of somatostatin receptor scintigraphy (SRS).

Results: Statistically significant CgA decrease after octreotide administration in all study time points and positive results of SRS were found in the patients with the elevated CgA level. No statistically significant decrease of CgA level after octreotide was found in the group with normal CgA levels. In this group, 13 patients had a negative result of SRS, and somatostatin receptors expression was found in one patient. Tolerance of somatostatin analogs (SSA) therapy was very good.

Conclusions: Octreotide suppression test with CgA level assessment in NET patients is a simple, straightforward examination, providing information on the predicted response to the applied SSA and the data on initial clinical tolerance of those agents. This examination can also be a screening test useful in planning the treatment with SSA in patients with NET.

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***Key words**: neuroendocrine tumors, chromogranin A, octreotide test*

Streszczenie

Wstęp: Chromogranina A (CgA) jest niespecyficznym markerem guzów neuroendokrynnych (NET). Jest ona przydatna w monitorowaniu przebiegu choroby i leczenia chorych z NET.

Cel pracy: Użyteczność testu hamowania wydzielania CgA z użyciem oktreotydu w diagnostyce i prognozowaniu skuteczności terapii chorych z guzami neuroendokrynnymi.

Materiał i metody: Do badania włączono 32 chorych z guzami neuroendokrynnymi układu pokarmowego, płuc i o nieznanym miejscu pochodzenia. U wszystkich badanych oznaczano stężenie CgA w osoczu krwi na czczo, przed oraz 30, 60, 90 i 120 minut po podaniu podskórnym 100 μg oktreotydu. Badane osoby podzielono na dwie podgrupy w zależności od stężenia CgA oraz wyniku scyntygrafii receptorów somatostatynowych.

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Wyniki: U chorych z podwyższonymi stężeniami CgA wykazano znamienne statystycznie obniżenie stężenia CgA po podskórnym podaniu oktreotydu w badanych punktach czasowych oraz dodatni wynik scyntygrafii receptorów somatostatynowych (SRS). W grupie chorych z prawidłowymi stężeniami CgA nie wykazano statystycznie znamiennego obniżenia stężenia CgA po podaniu oktreotydu. W tej grupie 13 chorych miało ujemny wynik SRS, u jednego chorego stwierdzono ekspresję receptorów somatostatynowych. Tolerancja leczenia analogami somatostatyny (SSA) była bardzo dobra.
Wnioski: Wykonywanie testu z oktreotydem z oznaczaniem stężeń CgA u chorych z guzami neuroendokrynnymi jest prostym, łatwym do wykonania badaniem dającym informacje o przewidywanej odpowiedzi na zastosowanie analogów somatostatyny, jak również dostarczającym danych na temat wstępnej tolerancji klinicznej tych preparatów. Badanie to może być przesiewowym, przydatnym testem w planowaniu leczenia analogami somatostatyny u chorych z NET.

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***Słowa kluczowe**: guzy neuroendokrynne, chromogranina A, test z oktreotydem*

Introduction

Chromogranin A (CgA) is a non-specific marker of neuroendocrine tumors (NET). It is stored and secreted into blood circulation together with other peptide hormones and biogenic amines from the neuroendocrine cells through exocytosis and therefore it can be detected in blood [1]. CgA is a stable molecule, its levels can be elevated in most NETs, especially in classical carcinoid tumors where CgA levels can be increased from 100 to 1000 times [2]. The elevated CgA levels, both in functioning and non-functioning tumors, are connected with the presence of metastases, mainly in the liver [1]. The increased CgA levels occur in 94% pancreatic tumors, 99% malignant carcinoid tumor and gastroenteropancreatic neuroendocrine tumors (the highest levels are found in metastasing midgut NETs) [3].

Treatment with somatostatin analogs (SSA) reduces CgA, mainly in the patients with carcinoid tumors, through suppression of CgA synthesis and secretion from tumor cells. However, in the case of the disease progressing at the time of SSA analog treatment, the increased CgA level can reflect a lack of control of tumor secretion function and/or its growth [2].

Octreotide was the first discovered synthetic somatostatin analog. Its half-time is longer than the native somatostatin's one and it is (following the subcutaneous administration) 1.5–2.5 hours [4]. The biological influence of somatostatin and its analogs happens directly on somatostatin receptors (sstr) localized on the surface of endocrine cells. There are 5 subtypes of the known somatostatin receptors (sstr1-5). Octreotide has the greatest affinity to somatostatin receptors type 2 and smaller to types 5 and 3 [5, 6]. Many NETs have a great number of receptors for somatostatin (80% of them show the expression of type 2 receptor) and therefore it can be imaged by radiolabelled SSA [7]. Long-term somatostatin analogs can control the symptoms of hormonally active NETs which shows the expression of somatostatin receptors [6, 8, 9].

There is still shortage of studies on the application of somatostatin analogs suppression of CgA secretion in diagnosis of patients with NET [2].

Aim of the study

The objective of the study was to carry out an octreotide suppression test of CgA levels in patients with neuroendocrine tumors and to show the usefulness of the test in connection with the result of somatostatin receptor scintigraphy and the clinical evaluation of medication tolerance in including patients for somatostatin analog treatment.

Material and methods

The study included 32 patients with neuroendocrine tumors of gastrointestinal tract, lung and of unknown origin hospitalized in the Division of Endocrinology in Zabrze. The average age of the patients was 62 years (± 38 years). The study group consisted of 14 women (mean age 63 years) and 18 men (mean age 60 years). During the course of the disease 24 patients underwent surgery due to neuroendocrine tumors of gastrointestinal tract, 9 of them had substitutive chemotherapy, and 8 have not been treated since they were recently admitted to the hospital.

Chromogranin A levels were determined before and 30, 60, 90 and 120 minutes after subcutaneous administration of 100 μg octreotide (Sandostatin, Novartis). The study group was divided into two groups with relation to chromogranin A level in point 0 (group I included 18 patients with elevated CgA levels, group II consisted of 14 patients with normal CgA levels) and the result of SRS. The patients with other coexisting diseases and conditions which could influence the chromogranin A levels, i.e. neoplastic diseases (of kidneys, prostate, breast, ovary, small cell lung carcinoma, thyroid medullary carcinoma), pheochromocytoma, neuroblastoma, ACTH-dependent Cushing's syndrome, liver,

renal and cardiac insufficiency were excluded from the study. The patients who had administered proton pump inhibitors or H2-blockers had repeated examination after a ten-day break in the drug administration.

CgA was evaluated by the immunoenzymatic test for chromogranin A quantitative marking in blood plasma by EDTA (DakoCytomation, Denmark). Sensitivity and specificity of the set comes to 85% [10], reference values range 2–18 U/l. ELISA set for CgA marking is a simplified immunoenzymatic sandwich test with two antibodies, where samples and antichromogranin A conjugated by peroxidase are incubated in microwells coated with antichromogranin A.

All patients had somatostatin receptor scintigraphy with use of ^{99m}Tc HYNIC-Tyr^3-octreotate (Tektrotyd, OBRI Polatom, Poland) done in the Department of Nuclear Medicine and Endocrine Oncology of the Oncology Institute in Gliwice.

The evaluation of clinical symptoms related to the medication tolerance was performed in all the patients 24 hours after the octreotide test (questionnaire no 1).

Statistical analysis was carried out with the use of Friedman test ($p < 0.05$) and Wilcoxon test.

Results

Table I and II present CgA levels in individual patients with relation to type of GEP NET according to WHO classification, a presence of metastases and somatostatin receptor expression.

In the patients with the elevated CgA levels (group I) a statistically significant decrease of CgA level after subcutaneous octreotide administration in the time points of the 30, 60, 90 and 120 minutes (Fig. 1, Table III) and a positive result of somatostatin receptor scintigraphy were shown. Over 40% decrease of CgA level in 61% of the patients in the 90 minute test (Table IV) and in 70% patients in the 120 minute test (Table V) was found. In the group of patients with normal CgA levels, no statistically significant decrease of CgA levels after octreotide administration was shown. In this group, 13 patients had a negative result of somatostatin receptor scintigraphy, in one patient a sstr expression was found (Table II).

Table VI shows the evaluation of the presence of clinical symptoms according to questionnaire no 1 in all NET patients before and after octreotide administration. Dermal lesions at injection site, allergic reactions, headaches, dizziness were not observed.

Discussion

Chromogranin A is a non-specific marker of neuroendocrine tumors which levels are considerably elevated in groups of patients, especially with metastases, what was confirmed in our study. The increased CgA levels were shown in group I, in which most of the neuroendocrine tumors were hormonally active, and metastases were found in majority of the patients. One-third of the group did not show hormonal activity, which is consistent with data of other authors who claim that non-functioning neuroendocrine tumors can often cause elevated CgA levels in blood [11]. Group II included patients with normal CgA levels, with non-functioning tumors, after radical surgical treatment and with pulmonary neuroendocrine tumors. Metastases were found in this group only in 4 cases. Normal CgA levels in this group (for example, patients with metastases) could be a result, on the one hand, of sensitivity and specificity of chromo-granin A marking and on the other hand, of the lack of hormonal activity of those tumors and the localization of primary focus in lungs. Our observations confirm other authors' opinions, i.e. Peracchi et al. [11], in tests where sensitivity and specificity of CgA marking was 27–81% and it was related to primary focus localization and degree of disease advancement [11].

In our study the statistically significant decrease of CgA was found in the group with elevated CgA levels after octreotide subcutaneous administration at the study time points, i.e. 30, 60, 90, and 120 minutes of the test. 40% decrease of CgA level was shown in 61% of patients at 90 minutes of the test and in 70% of patients at 120 minutes of the test.

There are few reports in literature on the application of octreotide suppression of CgA secretion in diagnosis of patients with NET. In the study carried out by Oberg et al. [2], who qualified patients with hormonally active gastroenteropancreatic tumors (GEP) for somatostatin analog treatment, 50% decrease of CgA level at the time from 90 to 120 minutes since subcutaneous 100 μg octreotide administration was shown. The differences in our results could be a result of a different sensitivity and specificity of the sets used for CgA assessment and of a heterogeneous group of patients taking part in the study (gastroenteropancreatic, lung and of unknown primary focus neuroendocrine tumors).

On the basis of those observations, a short-term octreotide test with CgA level measurement before the drug administration and at 90 and/or 120 minutes after its administration can be suggested because here in most of the patients the CgA level decreases by over 40%. This simple test can be useful in the case of a decision about somatostatin analog therapy while waiting for somatostatin receptor scintigraphy since this examination is not commonly available.

Table I
NET patients with the elevated CgA levels (group I)

Tabela I
Chorzy z NET z podwyższonymi stężeniami CgA (grupa I)

Patient's initials	WHO type	Tumor origin	Hormonal activity	Metastases presence	CgA before octreotide [U/l]	CgA 30′ after octreotide [U/l]	CgA 60′ after octreotide [U/l]	CgA 90′ after octreotide [U/l]	CgA 120′ after octreotide [U/l]	SRS
J.T.	II	Unknown	NF	L,T	1042.30	905.30	810.69	688.37	416.92	(+)
M.N.	II	Meckel's diverticulum	F	L	360.00	316.00	173.85	155.10	131.09	(+)
S.C.	II	Small intestine	F	L	384.06	238.42	199.53	150.41	120.01	(+)
Z.K.	II	Pancreas	NF	L	379.29	291.65	237.99	225.40	214.88	(+)
S.K.	II	Pancreas	F	LN	358.46	385.37	272.77	252.02	249.35	(+)
Z.H.	II	Unknown	NF	L	456.80	342.60	296.92	274.80	205.56	(+)
T.J.	II	Unknown	F	L	119.91	184.51	103.27	108.52	108.18	(+)
J.M.	II	Pancreas	F	L,B	810.40	664.76	625.92	576.80	545.60	(+)
L.D.	II	Small intestine	F	LN	700.00	689.99	466.42	382.72	347.24	(+)
K.P.	II	Small intestine	F	L	402.80	315.16	261.50	248.91	238.39	(+)
L.M.	II	Pancreas	NF	L	256.50	229.59	170.81	150.06	147.33	(+)
C.W.	II	Unknown	F	L, LN	534.60	446.96	393.30	380.71	370.18	(+)
K.M.	II	Small intestine	F	L	768.50	622.86	480.71	461.96	437.95	(+)
W.S.	II	Small intestine	F	L	302.74	215.10	161.44	148.85	138.33	(+)
L.F.	II	Stomach	NF	L	199.00	139.30	119.40	100.00	84.50	(+)
S.K.	II	Pancreas	F	LN	700.00	689.99	466.42	382.72	447.24	(+)
E.S.	III	Unknown	NF	P	269.23	205.44	78.56	98,78	114.36	(+)
H.Ch.	I	Stomach	F	No	51.63	46.87	38.41	37.58	31.18	(+)

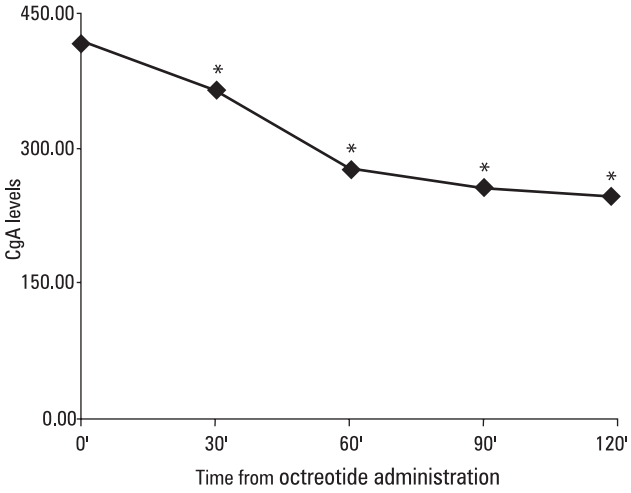
NF — non-functioning tumor, F — functioning tumor, L — metastases in liver, T — metastases in thyroid, LN — metastases in lymph nodes, B — metastases in bones, P — pulmonary metastases, SRS — somatostatin receptors scintigraphy, No — no metastases

Table II
NET patients with normal CgA levels (group II)

Tabela II
Chorzy z NET z prawidłowymi stężeniami CgA (grupa II)

Patient's initials	WHO type	Tumor origin	Hormonal activity	Metastases presence	CgA before octreotide [U/l]	CgA 30′ after octreotide [U/l]	CgA 60′ after octreotide [U/l]	CgA 90′ after octreotide [U/l]	CgA 120′ after octreotide [U/l]	SRS
E.W.	I	Lung	NF		12.04	9.55	12.04	11.08	8.87	(–)
J.W.	II	Rectum	NF	L	10.54	13.41	10.96	10.13	9.72	(+)
Z.S.	II	Pancreas	NF		13.08	13.08	11.74	7.50	7.36	(–)
H.B.	I	Stomach	NF		11.42	12.33	14.64	16.35	20.86	(–)
J.K.	II	Unknown	NF	LN	18.63	18.44	12.39	10.96	25.93	(–)
G.T.	II	Unknown	NF	L	22.18	24.76	23.12	22.55	16.99	(–)
A.J.	II	Lung	NF	C,O	15.57	13.08	11.74	11.52	7.36	(–)
A.C.	I	Rectum	NF		14.67	13.20	11.50	10.00	9.75	(–)
U.R.	I	Colon	NF		10.60	9,80	8,30	7,50	7,00	(–)
M.B.	I	Stomach	NF		16.70	15,50	14,30	13.60	12.40	(–)
S.B.	I	Small intestine	NF		8.02	7.93	7.61	7.77	7.01	(–)
H.K.	I	Lung	NF		7.77	7.50	7.00	7.00	7.07	(–)
G.W.	I	Pancreas	NF		20.03	18.50	9.46	9.26	8.18	(–)
D.Sz.	I	Small intestine	NF		16.34	16.03	15.96	6.01	12.81	(–)

NF — non-functioning tumor, L — metastases in liver, LN — metastases in lymph nodes, C — metastases in cerebellum, O — metastases in ovary, SRS — somatostatin receptors scintigraphy



*p < 0.05 vs. CgA before octreotide administration

Figure 1. *CgA levels before (0) and 30, 60, 90 and 120 minutes after subcutaneous administration of 100 μg octreotide in patients with NET in group I*

Rycina 1. *Stężenia CgA przed (0) oraz 30, 60, 90 i 120 minut po podskórnym podaniu 100 μg oktreotydu w grupie I chorych z NET*

Table IV

Decrease of CgA level [%] in group I with NET at 90 minutes after octreotide administration

Tabela IV

Obniżenie stężenia CgA [%] w grupie I chorych z NET w 90 minucie testu po podaniu oktreotydu

Decrease of CgA level	< 40%	40–60%	> 60%
Number of patients	39%	50%	11%

61% patients with decreased CgA level > 40%

Table V

Decrease of CgA level [%] in group I with NET at 120 minutes after octreotide administration

Tabela V

Obniżenie stężenia CgA [%] w grupie I chorych z NET w 120. minucie testu po podaniu oktreotydu

Decrease of CgA level	< 40%	40–60%	> 60%
Number of patients	30%	45%	25%

70% patients with decreased CgA level > 40%

Table III

Mean decrease of CgA level after octreotide (100 μg) administration at individual time points [%] in group I with NET

Tabela III

Średnie obniżenie stężenia CgA po podaniu oktreotydu (100 μg) w poszczególnych punktach czasowych [%] w grupie I chorych z NET

Time since octreotide administration	30′	60′	90′	120′
Decrease of CgA level [%]	16%	32%	43%	45%

The study performed by Shi et al. [12] showed that both a result of octreotide suppression test and somatostatin receptor scintigraphy can be useful in qualifying patients for treatment with long-term somatostatin analogs.

The diagnosing and evaluation of neuroendocrine tumors advancement includes CgA level assessment in blood (NET biochemical tumor marker) and SRS. In our study, we showed the expression of somatostatin receptors in all patients with elevated CgA levels, which is consistent with the observations of Kalkner et al. [13]

Table VI

Evaluation of clinical symptoms in all NET patients of the study groups before and after octreotide 100 μg s.c. administration

Tabela VI

Ocena objawów klinicznych w grupie badanych chorych przed i po podaniu oktreotydu 100 μg s.c.

Clinical symptoms	Number (N) and (%) of patients presenting clinical symptoms before octreotide administration	Number (N) of patients who after octreotide administration:			
		decreased symptoms	the symptoms not changed	increased symptoms	developed new symptoms
Abdominal pain	7 (22%)	3	3	1	0
Diarrhea	6 (19%)	3	2	1	1
Flushing	6 (19%)	4	2	0	0
Nausea	1 (3%)	1	0	0	0
Vomiting	1 (3%)	1	0	0	0
Dyspepsia	4 (12.5%)	1	3	0	0
Dyspnea	5 (15.5%)	1	4	0	0

Questionnaire 1
Presence of clinical symptoms related to the medicine tolerance in patients with NET before and after octreotide administration

Kwestionariusz 1
Obecność objawów klinicznych w powiązaniu z tolerancją leczenia u pacjentów z NET przed i po podaniu oktreotydu

Symptom	I	II				
		a	b	c	d	e
Abdominal pain						
Diarrhea						
Flushing						
Nausea						
Vomiting						
Dyspepsia						
Dyspnea						
Allergic reactions						
Dermal lesions at injection site						
Headache						
Dizziness						
Other symptoms						

I — clinical symptoms before octreotide administration; II — clinical symptoms after octreotide administration; a — no symptoms; b — developed new symptoms; c — symptom elevation; d — no changes in relation to the symptom so far; e — symptom decrease

who showed that there is a correlation between a positive result of somatostatin receptor scintigraphy and the elevated CgA level in blood, although SRS seems to be more sensitive than CgA, it is as specific as CgA [13, 14].

In the group with normal CgA levels, 13 patients had a negative result of somatostatin receptor scintigraphy. Somatostatin receptor expression was found in one patient with the NET of the hindgut type with metastases in the liver. Our results are consistent with the observations of Cimitan et al. [14] who proved that specificity of somatostatin receptor scintigraphy and CgA assessment for neuroendocrine tumors comes to 94%. They [14] also observed false positive results of scintigraphy in the case of a patient with a limited disease, while false positive CgA marking was found in a patient with well differentiated neuroendocrine carcinoma with accompanying arterial hypertension and arrhythmia. In our study, somatostatin receptor scintigraphy was done with the use of ^{99m}Tc HYNIC-Tyr^3-octreotate (tectrotide), where as most studies described in literature applied ^{111}In-pentetreotide, which is where the diversity in results can come from.

Our study proved a good tolerance to short-term somatostatin analogs. In the study groups, 24 hours after subcutaneous short-term octreotide administration, an alleviation of paroxysmal flushing was noted in 4 patients, decreased number of stools per day in 3 patients, and an increase of abdominal pain and diarrhea only in one patient. According to the published data, somatostatin analogs are safe drugs, easy to use and well tolerated by patients [9]. Meteorism, diarrhea or abdominal pain occur in less than 10% of patients under the treatment [15, 16].

Summarizing the results of our observation, it can be stated that octreotide test with CgA level assessment in patients harboring — neuroendocrine tumors is a simple, straightforward examination providing information on a possible response to somatostatin analogs and also supplying details on initial clinical tolerance of those agents. This examination can also be an useful screening test in planning the somatostatin analog therapy in patients with NET.

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