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A Single-Centre Experience with Octreotide in the Treatment of Different Hypersecretory Syndromes in Patients with Functional Gastroenteropancreatic Neuroendocrine Tumors

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A B S T R A C T

The aim of this research was to assess the clinical and biochemical efficacy of the octreotide in the treatment of patients with various functional gastroenteropancreatic neuroendocrine tumors (GEP-NETs). The study included 14 patients treated with octreotide for 6 months. They were diagnosed with VIPoma, glucagonoma, gastrinoma, medullary thyroid carcinoma (solitary and as a part of MEN-II syndrome), pancreatic carcinoids (solitary and as a part of multiple endocrine neoplasia type-1 syndrome-MEN-1 syndrome) and midgut carcinoids. The patients presented with Verner-Morrison, glucagonoma, Zollinger Ellison and carcinoid syndrome respectively. All had a metastatic disease at the time of diagnosis and a positive octreoscan finding. Initially elevated chromogranin A (CgA) levels were detected in 11 (78.6%) and elevated 5-hydroxyindolacetic acid (5-HIAA) levels in 8 (57.1%) patients. Symptomatic efficacy assessments were made by diarrhea reductions during treatment course, and laboratory efficacy was assessed through changes in 5-HIAA and CgA levels. Assessments were made initially and following 6 months of therapy. Median urinary 5-HIAA and the number of stools decreased significantly ($p=0.016$ and $p=0.009$ respectively, $p<0.05$) while CgA levels had the decreasing tendency but not statistically significant ($p=0.14$). There was a positive correlation between the 5-HIAA reduction and the decrease in stool number at baseline and during treatment course ($p<0.05$). No correlation was observed between 5-HIAA and CgA levels and also there was no correlation between CgA reduction and symptomatic improvement. The results prove octreotide to be effective in reducing symptoms and biochemical markers associated with hypersecretory syndromes of GEP-NETs.

Key words: *gastroenteropancreatic neuroendocrine tumors, carcinoid syndrome, hypersecretory syndromes, octreotide, 5-hydroxyindolacetic acid, chromogranin A*

Introduction

Neuroendocrine tumors (NETs) are rare, heterogeneous and progressive tumors occurring in the pancreas, parafollicular thyroid cells (medullary thyroid carcinoma, MTC) and along the mucosa of the gastrointestinal system (GEP-NETs). Their incidence ranges from 1–3 patients/100,000 population/year for carcinoids and is even smaller for the pancreatic endocrine tumors (PET)[1,2]. The term carcinoid is used for midgut serotonin producing tumors, while their location elsewhere is unusual. Less than 10% of the carcinoids are associated with the carcinoid syndrome, and it almost always implies liver metastases. The syndrome comprises of diarrhea, flushing, bronchospasm and eventually right-sided heart failure due to excess serotonin release[3]. Other GEP-NETs, besides vasoactive substances and growth factors produce and release hormones responsible for the different hypersecretory syndromes, sometimes more endangering than the tumor mass itself. The typical GEP-NET hypersecretory syndromes include: Verner-Morrison syndrome resulting from the vasoactive intestinal polypep-

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tide (VIP) release, Zollinger-Ellison syndrome due to excess gastrin release, glucagonoma syndrome due to glucagon release[4,5]. The long and short acting somatostatin analogues have been shown to be effective in relieving flushing and diarrhea associated with hypersecretory GEP-NET syndromes, and indirect data suggest that somatostatin analogs may also have a beneficial effect on patient survival[6]. The aim of this analysis was to evaluate the acute octreotide effects on symptom control (after 6 months of treatment) and biochemical markers (5-hydroxyindolacetic acid-5-HIAA and chromogranin A-CgA) of neuroendocrine tumors.

Patients and Methods

Patients-the study included 14 GEP-NET patients with hypersecretory syndromes including Zollinger-Ellison (1 patient), glucagonoma (1 patient), Verner-Morrison (1 patient) and carcinoid syndrome (9 patients; 7 of them with midgut carcinoids and 2 with pancreatic carcinoids) together with 2 patients receiving octreotide due to medullary thyroid carcinoma (MTC). Two patients had a tumor as a part of multiple endocrine neoplasia syndromes type I and II. All patients were diagnosed and treated in the Department of Endocrinology, Diabetes and Metabolism University hospital »Sestre milosrdnice« in the period including 1990–2005. The diagnosis of the GEP-NET was confirmed patohistologically and/or by imaging procedures including somatostatin receptor scintigraphy (octreoscan). Nine of the patients were operated prior to the octreotide treatment for the tumor debulking; four patients were not operated as the exact location of the primary could not be confirmed and one patient with medullary thyroid carcinoma as a part of MEN II syndrome refused the proposed operation due to religious beliefs.

Treatment-after obtaining the GEP-NET diagnosis and assessing the hypersecretory status the octreotide treatment was initiated. All the patients diagnosed until 2000 received immediate-release octreotide subcutaneously titrated two to tree times daily till the relief of symptoms up to maximum 200 μg and 3 patients diagnosed afterwards started with prolonged-release intramuscular octreotide in the dose of 20 mg monthly. In all the patients the values of urinary 5-HIAA and CgA were assessed prior to the treatment start (baseline value) and then following 6 months of treatment. 5-HIAA was measured spectrophotometricaly with normal values below 72.8 nmol/L and for CgA a commercially available radioimmunoassay kit (CIS Biointernational, Gif-sur-Yvette, France) was used, the normal range being below 60 ng/ml.

Statistical Analysis-symptom frequency is presented as a mean number of stools per day prior to treatment and then after 6 months. For each patient mean symptom frequency was calculated according to the data obtained during patient/physician interview and included data from 3 worse days prior to the treatment (baseline) and on 6-month visit according to the between the visit data. Nonparametric statistics was used, Wilcoxon signed ranks test for the significance determination of changes in a single parameter and Spearman's test for the correlation between different parameters. The level of significance was set at $p<0.005$.

Results

All 14 patients (100%) had positive somatostatin receptor scintigraphy result (octreoscan) prior to the octreotide treatment. Nine patients (64.3%), with known primary were operated first for the tumor debulking, in four (28.6%) patients primary tumor could not be detected and metastases were not resectable so they were treated with octreotide alone and 1 (7.1%) patient with known

TABLE 1
BASELINE CHARACTERISTICS OF PATIENTS

Variable	n	Value
Age at diagnosis, yrs*	14	49.33
Age at treatment start, yrs*	14	53.8
Gender	14	
male		12 (85.7%)
female		2 (14.3%)
Race	14	
Caucasian		14 (100%)
Somatostatin receptor scintigraphy	14	
positive		14 (100%)
negative		
Type/site of GEP-NET	14	
pancreatic endocrine tumor (PET)	5	5 (35.7%)
VIPoma		1 (7.1%)
gastrinoma		1 (7.1%)
glucagonoma		1 (7.1%)
carcinoid		2 (14.3%)
gastrointestinal NET	7	7 (50%)
foregut carcinoid		0
midgut carcinoid		7 (50%)
hindgut carcinoid		0
medullary thyroid carcinoma (MTC)	2	2 (14.3%)
Presence of MEN syndromes	11	
MEN 1		1 (7.1%)
MEN 2		1 (7.1%)
Prior GI surgery		9 (64.3%)
Type of octreotide	14	
immediate-release		11(78.6 %)
prolonged-release		3 (21.4%)
Initial 5-HIAA elevation		8 (57.1%)
Initial CgA elevation		11 (78.6%)

*data presented as an average

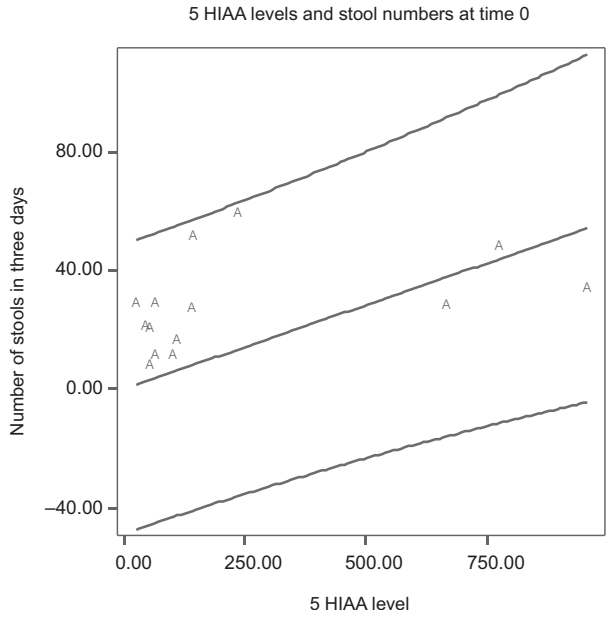

Fig. 1. Baseline correlation between the 5-HIAA and stool number.

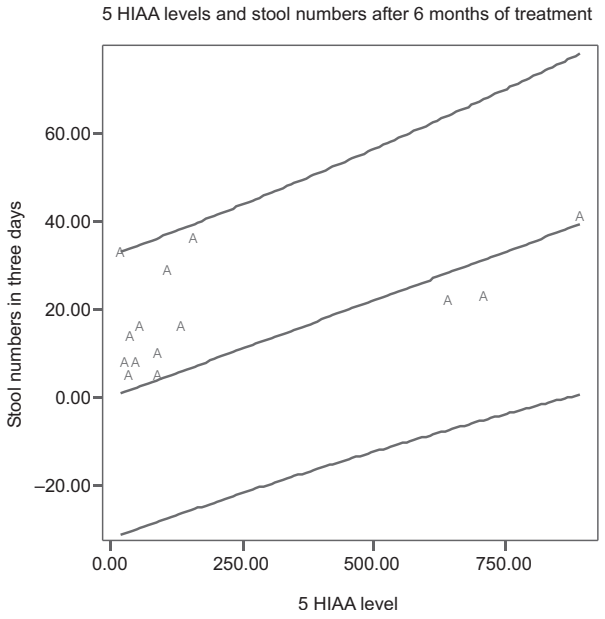

Fig. 2. Correlation between 5-HIAA and stool number after 6-months of treatment.

primary refused the proposed operation due to religious beliefs. The most common tumor site was midgut (64.3%), followed by pancreatic NET (28.6%) and MTC (14.3%). Average age at diagnosis was 49.33 years with youngest patient being diagnosed at the age of 12 and oldest at the age of 69. Octreotide treatment was initiated after average of 4.46 years following the diagnosis. The mean age of treatment start was 53.8 years. Above normal levels of 5-HIAA were recorded for 8 patients (57.1%) and above normal values of CgA for 11 (78.6%) patients initially (Table 1).

Statistically significant reduction in 5-HIAA ($p=0.016$) and diarrhea ($p=0.09$) was observed after 6-months of treatment. Although CgA levels had the decreasing tendency during treatment course, the reduction was not statistically significant ($p=0.140$). The correlation was noticed between the number of stools and levels of 5--HIAA initially (Figure 1) and there was also a positive correlation between the reduction of 5-HIAA and symptomatic improvement during the treatment course ($p< 0.05$, Figure 2). The same correlation was not statistically significant for the CgA ($p=0.024$). There was also no correlation noticed between the CgA and 5-HIAA levels.

Discussion

This single centre analysis has repeatedly proven the octreotide effectiveness in the treatment of symptoms associated with different hypersecretory neuroendocrine tumors. As NETs are rare, the data concerning biological treatment, especially its biochemical effects, resulting from tumor cell apoptosis, are still inconclusive[7,8]. After six months of treatment (the acute treatment phase) the symptomatic improvement (measured through diarrhea reduction) was significant both clinically and statistically. The diarrhea was chosen as a target symptom as it seemed most incapacitating and imposed the greatest burden on normal social life of patients. Among other hypersecretory symptoms present (flushing, wheezing) it was also the easiest symptom to quantify. There are several underlying mechanisms contributing to the diarrhea in NETs, among them tumor burden itself with biochemical substances such as serotonin, and postoperative malabsorption of bile acids and fat in surgically treated NET patients[8,9]. The good symptomatic response was also noticed in similar studies[13,14], although the reduction in stool number was somewhat greater in our patients. This is most probably because all our patients were, unlike patients in other studies, octreotide naïve, and also 64.3% of them (hence the number of surgically treated patients is somewhat greater in other studies) had a pre-octreotide treatment GI operation, which could adversely contribute to diarrhea. The maintenance of the positive response to octreotide remains to be seen during chronic treatment course, but according to our experience and results from other authors it is likely to diminish over the years of use, both clinically and biochemically. The exact reason for this tachyphylaxis is still unknown, but it seems to be more evident in patients receiving immediate-release octreotide than in patients on prolonged-release preparations. As in other similar studies, our patient sample was also small, so in order to determine the biochemical or molecular ground of the mentioned, more studies and meta analysis will be needed in future.

In addition to improvement in symptoms, levels of 5-HIAA reduced significantly while CgA levels, although showing the decreasing tendency, did not differ significantly. The similar biochemical improvement was also

observed in study by Ruszniewski[7] and like in our study it was more evident for the 5-HIAA than CgA. Baseline levels of 5-HIAA and CgA differed from the mentioned study and were slightly more positive for the 5-HIAA than CgA[7].

There was a positive correlation between baseline symptom severity and 5-HIAA level. Also, the significant reduction of number of stools per day during treatment course was noticed parallel to the reduction of the 5--HIAA levels. This symptomatic improvement is probably dependant on the direct effect the octreotide has on tumor metastases and their secretory activity measured through serotonin and its metabolite reduction[7–11]. Why the same correlation was not observed for the CgA and symptom severity still remains unanswered. According to all the data, octreotide is effective and safe in the treatment of hypersecretory symptoms of different neuroendocrine tumors[11–15]. It also has a beneficial effect on biochemical markers, somewhat greater on 5-HIAA than on CgA, a more ubiquitary NET marker.

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NAŠE ISKUSTVO S OKTREOTIDOM U LIJEČENJU PACIJENATA S RAZLIČITIM FUNKCIONALNIM NEUROENDOKRINIM TUMORIMA PROBAVNOG SUSTAVA I GUŠTERAČE

SAŽETAK

Cilj ovog istraživanja bila je procjena kliničke i biokemijske učinkovitosti oktreotida primijenjenog u liječenju bolesnika s različitim funkcionalnim neuroendokrinim tumorima probavnog sustava i gušterače (GEP-NET). U ispitivanje je bilo uključeno 14 bolesnika liječenih zbog VIPoma, glukagonoma, gastrinoma, medularnog karcinoma štitnjače, karcinoida gušterače te karcinoida embriogenetskog podrijetla srednjeg crijeva. Pacijenti su praćeni tijekom 6 mjeseci, a klinički su se prezentirali Verner-Morrisonovim, Zollinger-Ellisonovim, karcinoidnim te sindromom suviška glukagona. U trenutku postavljanja dijagnoze svi su bolesnici imali proširenu bolest te je kod svih bio pozitivan nalaz oktreoscana. Inicijalno povišene vrijednosti kromogranina A (CgA) nađene su u 11 (78.6%), a 5-HIAA u 8 (57.1%) bolesnika. Simptomatski učinak procjenjivan je redukcijom broja stolica, a biokemijski učinak kroz promijene u razini serumskih vrijednosti CgA i 5-HIAA u 24-satnom urinu na početku liječenja te šest mjeseci trajanja terapije oktreotidom. Na kraju ispitivanja došlo je do značajne redukcije vrijednosti 5-HIAA i broja stolica ($p=0.016$ i $p=0.009$), dok je kod CgA primijećena regresivna dinamika, no bez statističke značajnosti ($p=0.14$). Zamijećena je pozitivna korelacija između redukcije 5-HIAA i smanjenja broja stolica na početku ispitivanja te nakon 6 mjeseci liječenja ($p<0.05$). Nije zabilježena korelacija između vrijednosti 5-HIAA i CgA kao niti CgA i simptomatskog poboljšanja. Pripravci oktreotida pokazali su se učinkovitim u redukciji simptoma ali i biokemijskih biljega različitih funkcionalnih GEP-NETa.