Neuroendocrinology Letters Volume 40 No. 7-8 2020
ISSN: 0172-780X; ISSN-L: 0172-780X; Electronic/Online ISSN: 2354-4716
Web of Knowledge / Web of Science: Neuroendocrinol Lett
Pub Med / Medline: Neuro Endocrinol Lett

ORIGINAL ARTICLE

Evaluation of 5-hydroxyindoloacetic acid excretion in urine in patients with small intestine neuroendocrine neoplasm and carcinoid syndrome treated with somatostatin analogues

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Submitted: 2019-11-30 Accepted: 2019-12-12 Published online: 2019-12-20

Key words: **5-hydroxyindoloacetic acid; carcinoid syndrome; somatostatin analogues**

Neuroendocrinol Lett 2019; **40**(7-8):315–318 **PMID:** 32304367 NEL407819A03

Abstract

BACKGROUND: The assessment of hormonal function of neuroendocrine neoplasm (NEN) is an important stage in the diagnosis and monitoring of these diseases treatment. Objective of this study was to analyze the results of urinary excretion of 5-hydroxyindoloacetic acid (5-HIAA) in patients with carcinoid syndrome treated with somatostatin analogues, depending on the histologic maturity, degree of liver involvement and stage of the disease.

METHODS: The final group comprised of 41 patients. All patients were subject to surgical removal of the primary site. Presence of hepatic metastases was determined in all patients. All patients were treated with somatostatin analogues. The 5-HIAA urine excretion was determined using the ELISA immunoenzymatic method.

RESULTS: The mean excretion of 5-HIAA in patients with histological maturity grade G1 was 45.64 mg/24h, while in the group G2 the mean excretion was 108.41 mg/24h and was higher than in the group G1 (p=0.003). In the analysis of 5-HIAA value depending on the degree of liver involvement, the mean value of 5-HIAA excretion in patients with 10% liver involvement was 38.99 mg/24h, whereas in patients with 25% liver involvement this value was considerably higher and amounted 131.00 mg/24h (p< 0.001). In patients with disease progression the mean excretion was 117.37 mg/24h compared to the group of patients with stabilization of the disease, where the mean value was lower and amounted to 39.39 mg/24h (p<0.001).

CONCLUSION: Assessment of 5-HIAA excretion in patients with carcinoid syndrome is of considerable significance in the diagnostics and monitoring of the treatment.

INTRODUCTION

The assessment of hormonal function of neuroendocrine neoplasm (NEN) of the gastrointestinal tract is an important stage in the diagnosis and monitoring of these diseases treatment. In biochemical diagnostics, specific (5-HIAA - 5-hydroxyindoloacetic acid, serotonin, insulin, gastrin) and non-specific (CgA - chromogranin A, neuron specific enolase) markers of neuroendocrine tumors are used (Glinicki & Jeske 2011; Gut *et al.* 2016). 5-HIAA acid is a metabolite of serotonin excreted in urine. This is the most useful test in the initial diagnosis of carcinoid syndrome. Two 24-hours urine collections are recommended in order to determine 5-HIAA for diagnostic purposes. One 24-hours urine collection for 5-HIAA analyzes is sufficient to monitor the treatment. It is also recommended that the 5-HIAA concentration in the 24-hours urine collection should be determined by high-pressure liquid chromatography. Three days before the 24-hours urine collection, the patient should avoid certain foods (nuts, chocolate, avocado, pineapple) and medications (phenobarbital, methyldopa, chlorpromazine, heparin, paracetamol) to eliminate false positive and negative results. The test may give false negative results in patients with bronchial and stomach NEN. In a study conducted in patients with midgut carcinoid, elevated concentrations of 5-HIAA were observed in 60-73% (specificity almost 100%). The 5-HIAA concentration depends on the tumor mass. Daily excretion of 5-HIAA in urine may be normal in patients with carcinoid without metastases, as well as in patients with carcinoid syndrome without concomitant diarrhea, although these situations are extremely rare (Tirosh *et al.* 2018). The reference values range from 2 to 6 mg/24h. Elevated values up to 30 mg/24h are sometimes observed in patients with malabsorption syndrome. The aim of this study was to analyze the results of urinary excretion of 5-HIAA in patients with carcinoid syndrome treated with SSA analogues, depending on the histological maturity of the tumor, the degree of liver involvement and the stage of disease progression.

MATERIAL AND METHODS

The studied group of patients with diagnosed small intestine NEN consisted of 41 patients, including 29 women (70.7%) and 12 men (29.3%). The mean age of men was 60.41 ± 4.90 years, whereas in women it was 64.20 ± 10.39 years. All patients underwent surgery to remove the primary focus with histopathological evaluation according to WHO classification in 2017. The degree of maturity of G1 was found in 19 (46.3%) tissue specimens and G2 (53.7%) in the remaining 22 specimens. All patients were subjected to thorough diagnostic imaging (abdominal ultrasonography, computed tomography of the chest, abdominal cavity and pelvis) and complementary biochemical tests (chromogranin A, serotonin, 5-HIAA) in order to evaluate clinical advancement. Metastases to liver were found in all examined patients (10% liver involvement in 23 cases, 25% liver involvement in 18 cases). All patients presented symptoms of carcinoid syndrome in the form of diarrhea, facial redness (flush), telangiectasia and myopathy symptoms. In each case, in order to qualify for treatment with somatostatin analogues, receptor scintigraphy was performed with ^{99m}Tc-EDDA/HYNIC-TOC. The intensity of radiolabel accumulation in liver metastases was assessed on the basis of the qualitative scale developed by E. Krenning (grade 0-4). In the group of studied patients the degree of accumulation of radiolabel in the liver was 3 and 4 according to Krenning scale. The study group was treated with somatostatin analogues in the period from 2014 to 2018, receiving LAR octreotide at a dose of 30mg (i.m.) or lanreotide autogel at a dose of 120mg (s.c.) every 4 weeks. The control of biochemical parameters in the form of urinary excretion of 5-HIAA acid was performed every 3 months. In turn, imaging in the form of abdominal computed tomography was performed every 6 months in order to obtain an objective assessment of the response to treatment using RECIST 1.1 criteria. The excretion of 5-HIAA acid in urine was determined by immunoenzymatic ELISA with the use of Immuno-Biological Laboratories antibodies. Daily excretion of 5-HIAA in urine was calculated according to the formula; mg/24h = mg/l x V, where V is the volume of urine excreted per day. An important element in the 24-hour urine collection is acidification of urine with 6M hydrochloric acid in the amount of 10ml/1000ml of urine. The reference value range is 2-6 mg/24hour.

Statistical evaluation

Quantitative variables were analyzed by calculating the mean, standard deviation, median, minimum quartiles and maximum values. The values of quantitative variables in two groups were compared using the Mann-Whitney test. Correlation between two quantitative variables was analyzed using Pearson's or Spearman's coefficient. The significance level of 0.05 was assumed in the analysis. Therefore, all p values below 0.05 were interpreted as indicating significant relationships. The analysis was performed in the R program, version 3.3.1.

RESULTS

Evaluation of 5-HIAA excretion results depending on grading

The mean excretion of 5-HIAA in the group of patients with cancer histological maturity grade G1 was 45.64 ± 27.48 mg/24h, while in the group with histological maturity grade G2 the mean excretion of 5-HIAA was 108.43 ± 49.19 mg/24h and was significantly higher than in the group G1 (p=0.003). Similar relationship was observed in the analysis of the last values

of 5-HIAA, i.e., in group G1 the mean of the last values of 5-HIAA was 63.92 ± 34.17 mg/24h, and in group G2 it was 191.96 ± 64.35 mg/24h (p=0.001).

Evaluation of 5-HIAA excretion results depending on the degree of liver involvement

In the analysis of 5-HIAA value depending on the degree of liver involvement, the mean value of 5-HIAA excretion in patients with 10% liver involvement was 38.99 ±16.99 mg/24h, whereas in patients with 25% liver involvement this value was considerably higher and amounted 131.00 ± 55.36 mg/24h (p< 0.001). In the analysis of the last values of 5-HIAA excretion in the first group, the mean of the last values was 49.17 ± 27.68 mg/24h and was significantly lower compared to the second group, where the excretion of 5-HIAA was 238.44 ± 113.12 mg/24h (p<0.001).

Evaluation of the results of 5-HIAA excretion in relation to the stage of disease progression

In the analysis of 5-HIAA excretion in urine in the group of patients with disease progression the mean excretion was 117.37 ± 55.91 mg/24h compared to the group of patients with stabilization of the disease, where the mean excretion of 5-HIAA was significantly lower and amounted to 39.39 ± 19.68 mg/24h (p<0.001). However, in the analysis of the last values, the mean excretion in the last measurements in the group with disease progression was 214.48 ± 114.12 mg/24h and was significantly higher than in the group with disease stabilization, where the value of 5-HIAA acid excretion was 45.77 ± 29.66 mg/24h (p<0.001).

DISCUSSION

In our study we observed that the values of 5-HIAA were significantly higher in patients with neuroendocrine neoplasm histological maturity grade G2 and in patients with 25% liver involvement and progression of disease process. Similar results are presented by Laskaratos *et al.* in their meta-analysis of 147 patients with midgut tumors, where the excretion of 5-HIAA was higher with a higher degree of disease progression (Laskaratos *et al.* 2018). Allen *et al.* state that the determination of serotonin and 5-HIAA levels is important in monitoring the treatment of carcinoid syndrome, especially in patients with concomitant carcinoid heart disease (Allen *et al.* 2007). The etiology of fibrosis caused by excess serotonin is described by Druce *et al.* on the basis of the analysis of 45 patients treated for cardiological complications in the course of carcinoid syndrome (Druce *et al.* 2009). Hutcheson *et al.* in their paper report that tricuspid valve damage is induced by 5-HT2B receptor stimulation (Hutcheson *et al.* 2011). Spectacular effects were achieved by using telotristat, an inhibitor of serotonin synthesis, in the treatment. Two large clinical trials with this drug, TELESTAR and TELECAST, prove the regression of many clinical symptoms such as diarrhea, facial redness or excessive fibrosis in patients with carcinoid syndrome (Kulke *et al.* 2014; Lamarca *et al.* 2016). These studies also demonstrated that a single determination of 5-HIAA excretion in morning urine is comparable to a 24-hour urine collection (Tellez *et al.* 2013). In turn, Zandee believes that the evaluation of serotonin and 5-HIAA excretion in urine is of limited use in the treatment monitoring due to the influence of many factors not related to the disease, such as diet, drugs or other co-morbidities (Zandee *et al.* 2016). Oberg and Modlin present completely new biomarkers of neuroendocrine neoplasms in the form of circulating gene transcripts, micro-RNAs or cancer cells themselves derived from the tumor. The sensitivity and specificity of the above determinations is much higher compared to CgA, serotonin and 5-HIAA (Oberg *et al.* 2015; Modlin *et al.* 2014). Treatment with SSA analogues significantly reduces serotonin secretion and 5-HIAA excretion, especially in patients with carcinoid syndrome. SSAs have antiproliferative and antisecretory properties. The results of the CLARINET study on the use of lanreotide autogel in NEN confirmed the antiproliferative effect of this analogue. Two-year treatment with lanreotide autogel 120 mg every 4 weeks showed no progression of the disease or death in 62% of patients treated, compared to 22% of patients receiving placebo (Caplin *et al.* 2016). Similar results were obtained in the PROMID study, where Lar octreotide was used in patients with midgut cancer G1 (Arnold *et al.* 2009). Treatment with long-acting SSA is the treatment of choice in case of carcinoid syndrome symptoms. To sum up, it should be mentioned that although 5-HIAA is not an ideal biomarker in clinical practice, it is still an important element in the diagnosis and monitoring of treatment of patients with NEN.

CONFLICT OF INTEREST

The authors have no conflict of interest.

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