Increase of urinary 5-hydroxyindoleacetic acid excretion but not serum chromogranin A following over-the-counter 5-hydroxytryptophan intake

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BACKGROUND: 5-hydroxyindoleacetic acid (5-HIAA) excretion is commonly measured for biochemical detection of carcinoid tumours. A 77-year-old woman was referred for elevated 24 h urine 5-HIAA excretion (510 μmol/day; normal is less than 45 μmol/day) and serum chromogranin A (CgA) (72.1 U/L; normal is less than 18 U/L), both subsequently normalized after discontinuation of 5-hydroxytryptophan (5-HTP). 5-HTP, a precursor of serotonin, is not commonly listed as a substance that increases 5-HIAA levels in urine. The effect of 5-HTP on CgA has not been previously described.

OBJECTIVES: To determine whether, and to what extent, oral 5-HTP increases urine 5-HIAA excretion and serum CgA levels in healthy volunteers.

PATIENTS AND METHODS: A randomized, prospective, double-blind, placebo-controlled crossover study, with a four-day washout period, was performed in a general community setting. Eight healthy subjects aged 22 to 58 years were recruited by advertising. Bedtime ingestion of 5-HTP 100 mg/day was compared with placebo ingestion for 10 days. Twenty-four hour urine excretion of 5-HIAA and serum CgA were the main outcome measures.

RESULTS: Median (range) urinary 5-HIAA excretion was 204 μmol/day (22 μmol/day to 459 μmol/day) during 5-HTP intake, compared with 18 μmol/day (12 μmol/day to 36 μmol/day) during placebo intake (P=0.017). 5-HTP did not affect clinical symptoms or serum CgA levels.

CONCLUSIONS: Oral 5-HTP increases urinary 5-HIAA excretion with considerable interindividual variation. In a small number of subjects, oral 5-HTP did not affect serum CgA levels. Therefore, increased 5-HIAA levels with normal CgA levels may suggest 5-HTP ingestion. The use of over-the-counter 5-HTP should be excluded as the cause of increased urinary 5-HIAA levels before initiating diagnostic tests to search for a carcinoid tumour. 5-HTP should be added to popular references as a substance that may cause increased 5-HIAA excretion.

Key Words: 5-hydroxytryptophan; 5-hydroxyindoleacetic acid; Carcinoid; Chromogranin A

5-hydroxyindoleacetic acid (5-HIAA) is a product of serotonin metabolism that is excreted in the urine. It is used as a first-line test for biochemical detection of suspected carcinoid syndrome, in which 5-HIAA excretion is usually elevated (1). In normal subjects, approximately 1% of dietary tryptophan is converted to serotonin (5-hydroxytryptamine), which is then metabolized to 5-HIAA (Figure 1). In patients with carcinoid syndrome, the conversion of tryptophan to serotonin can be
increased to approximately 70%, resulting in increased urinary 5-HIAA excretion. Urinary 5-HIAA levels can also be increased in malabsorption syndromes, such as celiac disease and Whipple’s disease, as well as by ingestion of drugs and food that contain serotonin. Therefore, during urine collection to screen for carcinoid syndrome, patients are advised to adhere to a strict diet, avoiding products that alter 5-HIAA excretion (Table 1) (2). These problems with the use of urinary 5-HIAA for detection of carcinoid tumours have led to a search for other helpful markers of carcinoid tumours. Chromogranin A (CgA) has recently been introduced as a marker to confirm a clinical suspicion of neuroendocrine tumours, including carcinoid tumours (2). CgA is produced by a number of different neuroendocrine tumours, including pheochromocytomas, medullary thyroid carcinomas and carcinoid tumours, as well as by other tumours such as small cell lung cancer (3). Thus, although the specificity of CgA has been reported to be as high as 98% in those known to have carcinoid syndrome, the specificity of CgA in those suspected of having a carcinoid tumour can be much lower (4).

Recently, we examined a 77-year-old woman with an elevated 24 h urine 5-HIAA level of 510 μmol/day (normal levels less than 45 μmol/day), obtained as part of a workup for fatigue. She denied any symptoms of wheezing, flushing or diarrhea. Her medical history included glaucoma (treated with eye drops) and untreated mild hypertension. Physical examination was unremarkable except for a mildly elevated blood pressure of 148/96 mmHg. Her creatinine level was not elevated (67 μmol/L). During the urine collection to measure 5-HIAA level, she had strictly avoided food or drugs listed to interfere with 5-HIAA excretion. However, upon specific questioning, she informed us that during the urine collection, she had continued daily intake of 100 mg 5-hydroxytryptophan (5-HTP), obtained from a health food store, for insomnia until two weeks before being seen. In addition, the serum concentration of CgA was elevated at 72.1 U/L (normal levels less than 18 U/L). After discontinuation of 5-HTP, her 24 h urine 5-HIAA excretion normalized to 18 μmol/day and then increased to 314 μmol/day during a rechallenge with 5-HTP.

The decision was made to determine whether, and to what extent, oral 5-HTP increases urine 5-HIAA excretion and serum CgA levels in healthy volunteers.

### PATIENTS AND METHODS

#### Subjects

Eight healthy volunteers who were 18 years of age or older were recruited via local advertising. During a screening visit, medical history, current medications, blood pressure, heart rate, height and weight were documented. Subjects were excluded if they were pregnant, taking antidepressants or other drugs that affect 5-HIAA excretion in urine, or participating in other studies. All volunteers provided written, informed consent before inclusion. The study was approved in writing by the local ethics committee, conducted in accordance with the Declaration of Helsinki and registered at <www.clinicaltrials.gov> under study identification number NCT00227136.

#### Protocol

The study was performed in a single centre and followed a prospective, double-blind, placebo-controlled, randomized, crossover design with two treatment periods of 10 days each, separated by a washout period of at least four days. Capsules containing 100 mg 5-HTP (Wiler PCCA Fine Chemicals, Canada) and identical-looking capsules containing lactose...
Patients taking medication, n

Systolic blood pressure, mmHg, median (range) 109 (92–128)

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E1=50 mV and E2=370 mV. The between-run coefficients of the guard set at –420 mV and detector cell potentials at

pressure liquid chromatography (ESA Biosciences, Inc) with

by the Coulochem III electrochemical detector for high-

an ambient temperature of 23°C. 5-HIAA levels were detected

was run at a flow rate of 1.2 mL/min, with the column kept at

Supelco, USA). The mobile phase purchased from Bio-Rad

matography column, 3 μm particle size, 15 cm by 4.6 mm,

extraction column, 3 μm particle size, 15 cm by 4.6 mm,

extracts prepared by this method were analyzed by reverse

kits (method 600-0087, Bio-Rad Laboratories, Germany). The

Beckman Coulter LS-20 analyzer (Beckman Coulter Inc, Canada). Urinary 5-HIAA concentrations were determined

Analytical methods

Urinary creatinine concentrations were analyzed on the

Urineal 5-HIAA excretion of 30 μmol/day.

study design allowed for a 95% power to detect an increase of

Based on the participation of eight subjects, the

Statistical analysis

Results are presented as the median (range) unless otherwise

RESULTS

Baseline characteristics

Eight volunteers completed the study. Their clinical characteristics are shown in Table 2. Compliance (assessed by pill count) was 100% for all volunteers; no significant side effects were noted. One female participant had high CgA levels (184 U/L and 26 U/L) during placebo and 5-HTP intake, respectively. She was using a proton pump inhibitor (PPI), which may have increased her CgA levels. Her CgA level returned to normal (8.9 U/L) 30 days after discontinuation of the PPI. Therefore, her CgA data were not included in the analysis.

Effects of 5-HTP on urine 5-HIAA and serum CgA levels

Treatment with 5-HTP resulted in a 10-fold increase of 24 h urinary 5-HIAA levels, from 18 μmol/day (12 μmol/day to 36 μmol/day) during placebo intake to 204 μmol/day during 5-HTP intake (22 μmol/day to 459 μmol/day; P<0.017). 5-HIAA excretion varied considerably between individuals and was above the upper limit of normal in seven of the eight participants after 5-HTP ingestion (Figure 2). To correct for potential variation of sample collection, the ratio of

Figure 2) Effect of 5-hydroxytryptophan (5-HTP) intake on urinary

5-hydroxyindoleacetic acid (5-HIAA) excretion in individual participants. Placebo and 5-HTP results were obtained from urine collected after 10 days of placebo or 5-HTP intake (100 mg at bedtime). Other products affecting urinary 5-HIAA excretion were avoided during both urine collections.
urine 5-HIAA to urine creatinine was calculated. This ratio increased from 1.4 μmol/day (0.9 μmol/day to 2.8 μmol/day) to 15.8 μmol/day (2.6 μmol/day to 40.0 μmol/day) during placebo and 5-HTP intake, respectively (P=0.012). 5-HTP administration did not affect serum CgA; levels were 6.2 U/L (4.2 U/L to 13.3 U/L) during placebo and 6.6 U/L (4.7 U/L to 12.6 U/L) during 5-HTP intake. 5-HTP intake did not result in significant beneficial effects on mood or sleep. No significant difference in adverse effects occurred between when participants were receiving 5-HTP and when they were receiving a placebo.

**DISCUSSION**

The present study demonstrates that oral intake of 5-HTP at a daily dose of 100 mg at bedtime results in a 10-fold increase in urinary 5-HIAA levels. It is critical to recognize nonprescription (over-the-counter) 5-HTP as a potential cause of increased 5-HIAA excretion, because oral ingestion of 5-HTP can easily enter into the pathway of 5-HIAA production (Figure 1). Falsely increased urinary 5-HIAA excretion may prompt costly further imaging studies in search of a carcinoid tumour and may be a source of unnecessary anxiety in patients. Further, although we did not measure the effect of 5-HTP in patients with documented carcinoid syndrome, we suggest that 5-HTP may also be a potential confounder when urinary 5-HIAA excretion is used to monitor these patients.

5-HTP can easily be obtained over-the-counter or via the Internet. 5-HTP is promoted as a harmless but essential amino acid that is necessary to sustain life, and that is beneficial for depression, anxiety, insomnia and obesity (5-10). The recommended dose varies from 50 mg to 1000 mg at bedtime; no data are available on the yearly sales volume (5-10). Patients often do not remember to inform their physicians of over-the-counter or herbal medications that they are taking. Further, physicians often fail to specifically ask about these preparations, especially because popular references such as <www.uptodate.com> or Harrison’s Principles of Internal Medicine (11) do not list over-the-counter 5-HTP as a substance that can interfere with 24 h urine 5-HIAA levels.

Several studies have shown increased serotonin metabolite excretion in response to 5-HTP ingestion (12-14). In 1976, increases in the levels of plasma 5-HTP and plasma 5-HIAA were first documented in two healthy controls after 5-HTP administration (12). In open-label trials for depression, oral 5-HTP administration resulted in significant four- to 14-fold and eight- to 22-fold increases in mean urinary 5-HIAA excretion in controls and depressed patients, respectively (13,14). These studies did not always control for confounders such as dietary serotonin intake or other medications such as acetaminophen and phenothiazines, and the adequacy of urine collection (24 h urine creatinine) was not documented.

In our randomized, double-blind, placebo-controlled, crossover study, we found a similar 10-fold increase in 24 h urinary 5-HIAA excretion, with large interindividual variation. Similar results were found when results were corrected for 24 h creatinine excretion. Normalization of urinary 5-HIAA levels occurred within 14 days of stopping 5-HTP and may well have occurred sooner. A kinetics study of 5-HTP administration in healthy volunteers demonstrated a biological half-life of 2 h to 7 h and a plasma clearance rate (of plasma 5-HIAA) of 0.1 L/kg/h to 0.23 L/kg/h, thereby indicating rapid elimination (15). To our knowledge, no study has specifically examined the time period to normalization of urinary 5-HIAA levels after discontinuation of oral 5-HTP, although a parallel kinetic profile is expected.

Unfortunately, even though urinary 5-HIAA has been used as the initial biochemical test for patients suspected of having a carcinoid tumour, biochemical detection utilizing urinary 5-HIAA elevation is often fraught with errors. Urinary 5-HIAA levels may be increased in malabsorption syndromes, as well as after ingestion of certain drugs or food containing serotonin (2,16). As well, the sensitivity of 5-HIAA urinary level varies depending on the type of carcinoid being detected (17). In particular, foregut carcinoids can easily be missed if using urinary 5-HIAA levels alone to detect them, because foregut carcinoids often lack the L-amino acid decarboxylase activity required for conversion of 5-HTP to 5-HIAA (4). Thus, due to this low sensitivity, urinary 5-HIAA levels should only be tested in patients in whom carcinoid syndrome is truly suspected (unlike in our patient) and in whom appropriate instructions (of food and drugs to be avoided) for collection of urinary 5-HIAA have been given.

CgA has recently been introduced as a confirmation test for clinical suspicion of neuroendocrine tumours, including carcinoid tumours (2). While the specificity of CgA can be as high as 98% in patients with known carcinoid syndrome (4), less information is available on the use of CgA as a screening test for carcinoid syndrome. Our study indicates that oral 5-HTP intake does not increase serum CgA levels. Therefore, in patients unwilling to stop 5-HTP intake, CgA determination may be a useful alternative test.

One volunteer had an elevated CgA level that normalized after discontinuation of her PPI. Use of a PPI, even over the short term, can result in an average 1.5- to 2.5-fold increase in CgA levels, although a 13-fold increase in the CgA level in response to PPI intake has been described (18,19). Thus, CgA levels may be helpful in assessing for carcinoid tumours in patients taking 5-HTP, as long as the causes for falsely elevated CgA levels (ie, essential hypertension, hepatic failure, renal failure, PPI use, chronic atrophic gastritis) are remembered (18-21).

There were several limitations to our study. First, we studied the impact of only one 5-HTP dose (100 mg per day) on 5-HIAA excretion and therefore cannot comment on a potential dose-response relationship. However, even in this small group of eight volunteers, urinary 5-HIAA excretion in response to 5-HTP varied widely, from 22 μmol/day to 459 μmol/day, suggesting that interindividual differences in serotonin metabolism may cause large variations in 5-HIAA excretion. To our knowledge, only one other study (13) documented variations in urinary 5-HIAA in response to oral 5-HTP administration, but this study demonstrated large variations between depressed and nondepressed patients. This finding is plausible, because other studies have documented interindividual variations in plasma metabolite formation after oral 5-HTP intake (15,22). Second, our study included only a small number of participants, and we did not include patients with documented carcinoid syndrome, in whom altered serotonin metabolism may change the magnitude of the effect of oral 5-HTP on 5-HIAA excretion and/or symptoms. Third, our study did not assess the impact of oral 5-HTP ingestion on 5-HTP and 5-HIAA levels in plasma. Recent studies have proposed the use of plasma platelet 5-HTP or plasma 5-HIAA levels as more convenient or better screening tests for the diagnosis of carcinoid syndrome (23,24). An open-label trial (13) of 150 mg 5-HTP daily for
seven days demonstrated variable changes (from a 25% decrease to a 75% increase) in plasma 5-HTP levels and a 33% to 60% increase in plasma 5-HIAA levels. Further studies may need to assess the impact of oral 5-HTP intake on plasma 5-HTP and plasma 5-HIAA levels.

Our index patient had an elevated CgA level that normalized one month after discontinuation of 5-HTP ingestion. This finding was not supported by the results of our crossover trial in healthy volunteers. Although she did have mild hypertension, her blood pressure had not improved enough in her follow-up visit to account for her improvement in CgA levels. Moreover, no other non-neoplastic causes of elevated CgA levels were found to contribute to her elevation in CgA level. Unfortunately, she declined to undergo further imaging studies. One year later, she is free of symptoms, but we cannot completely exclude the presence of a carcinoid tumour.

REFERENCES