

Amino acid-responsive Crohn's disease: a case study

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Purpose: This paper reviews the clinical course of a case of severe Crohn's disease and discusses the scientific ramifications of a novel treatment approach.

Patients and methods: A case study of a 72-year-old male with 22-year history of Crohn's disease whose clinical course had experienced no sustained remissions. The patient was treated with a protocol that utilized serotonin and dopamine amino acid precursors administered under the guidance of organic cation transporter assay interpretation.

Results: Within 5 days of achieving the necessary balance of serotonin and dopamine, the patient experienced remission of symptoms. This remission has been sustained without the use of any Crohn's disease medications.

Conclusion: In Crohn's disease, it is known that there is an increase of both synthesis and tissue levels of serotonin in specific locations. It is asserted that this is prima facie evidence of a significant imbalance in the serotonin-dopamine system, leading to serotonin toxicity. The hypothesis formulated is that improperly balanced serotonin and dopamine transport, synthesis, and metabolism is a primary defect contributing to the pathogenesis of Crohn's disease.

Keywords: serotonin, dopamine, organic cation transporters, OCT

Introduction

Symptoms of Crohn's disease in patients range on a spectrum from mild to very severe. Symptoms include diarrhea, abdominal pain, intermittent fever, rectal bleeding, loss of appetite, significant weight loss, arthralgias, fatigue, malaise, and headaches. Involvement of other organ systems beyond the intestinal tract, such as eyes, skin, and liver, may be present.¹

As there is currently no known cure, treatment is focused on symptom control. Complications secondary to medications prescribed for symptom control may occur. When the disease fails to respond to the milder medications, more aggressive medications are prescribed. Medication complications can be severe, including infections, serum sickness, drug-induced lupus, diabetes, cancers, and even death.²

This paper documents a case study of a patient with severe Crohn's disease. The patient had suffered with Crohn's disease of progressing severity for 22 years, during which time no sustained remission of symptoms was noted. The patient suffered profound complications from infliximab, 6-mercaptopurine, and prednisone. He experienced no sustained response from mesalamine, low-dose naltrexone, or dietary modification. The patient's clinical course was complicated by steroid-induced insulin-dependent diabetes. He also suffered from severe weight loss, depression, fatigue, mal-

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aise, headaches, purulent-mucinous diarrhea, rectal bleeding, bilious vomiting, and diffuse arthralgias. Complaints of back pain resulted in back surgery with negative operative findings and no relief of symptoms. Exploratory gallbladder surgery was done in response to abdominal pain. The pathologist's report of tissue submitted from the gallbladder surgery was negative for any pathology. In February 2004, the patient had progressed to the most severe state of his disease, losing 25% of his body weight. The patient was fully disabled and unable to work. He experienced constant symptoms of Crohn's disease despite attempts at medication alteration. At all times from his first confirmed attack of Crohn's disease in 1990 at age 19 years, he was on one or more prescription drugs to try to control the disease symptoms.

The patient achieved full remission of symptoms in a matter of days once the proper orally administered serotonin and dopamine amino acid precursor dosing values were established with the guidance of urinary organic cation transporter (OCT) functional status determination (herein referred to as OCT assay interpretation).

Material and methods

The patient was treated with a novel treatment protocol developed by NeuroResearch Clinics (Duluth, Minnesota, MN, USA). Peer-reviewed publications from 2009^{3,4} and 2010^{5,7} outlined a novel "three-phase model" of OCT response to simultaneous administration of serotonin and dopamine amino acid precursors in significant amounts, which is the basis for OCT assay interpretation. Obtained in this paper is a proposed novel OCT model that potentially describes the etiology of the "three-phase response" of serotonin and dopamine during simultaneous administration of their amino acid precursors in varied daily dosing values.

The protocol

Serotonin and dopamine exist in two states. The endogenous state is found when amino acid precursors are being administered. A competitive inhibition state is found when significant amounts of amino acid precursors of both serotonin and dopamine are administered simultaneously. This novel approach places serotonin and dopamine in the competitive inhibition state and then optimizes their transport in proper balance through the OCTs with OCT analysis interpretation. The approach was developed by medical research that started in 1997. Peer-reviewed research covering methodology, applications, and the scientific foundation of this novel approach was published in 2009^{3,4} and 2010.⁵⁻⁷ Optimization of the serotonin-dopamine system has applications in any condition

where an imbalance between serotonin and dopamine in transport, synthesis, or metabolism is present. The potential scope of applications is far-reaching.

The protocol utilized for treatment of Crohn's disease consisted of the amino acid dosing values listed in Table 1. This protocol has been covered in previous peer-reviewed research.^{3,7}

The initial step of the protocol is the simultaneous administration of serotonin and dopamine amino acid precursors with no OCT functional status determination in order to place the system into a competitive inhibition state. Three dosing levels were available, as noted in Table 1. At the first visit, the patient was started on level 1 amino acid dosing. The patient was then followed weekly for evaluation of response to the start or change in amino acid dosing levels. As described in the results section of this paper, dosing was implemented as per Table 1. The patients took the amino acid dosing values of each level at the times indicated in Table 1.

If the patient failed to achieve full relief of symptoms on level 3 dosing, a urine sample was collected and submitted for urinary serotonin and dopamine laboratory assay. This was followed by OCT assay interpretation. Based on OCT assay interpretation, the amino acid precursors of serotonin and dopamine were adjusted in an effort to achieve full relief of symptoms or a balance of urinary serotonin and dopamine in the Phase 3 therapeutic range, whichever came first.^{3,7}

OCT assay interpretation

The serotonin and dopamine filtered at the glomerulus are metabolized by the kidneys, and significant amounts do not make it to the final urine. Serotonin and dopamine found in the urine are monoamines synthesized in the proximal convoluted renal tubule cells and have never been found in the central nervous system or peripheral system. Serotonin and dopamine that are newly synthesized by the kidneys meet one of two fates. Urinary serotonin and dopamine levels are primarily dependent on the interaction of the basolateral monoamine transporters (OCT2s) and the apical monoamine transporters (OCTN2s) of the proximal convoluted

Table 1 Individual dosing value: milligrams of L-tyrosine/milligrams of 5-hydroxytryptophan*

Level	AM	Noon	4 PM	7 PM
Level 1	1500/150		1500/150	
Level 2	1500/150	1500/150	1000/300	
Level 3	1500/150	1500/150	1000/300	1000/300

Note: *The patient also received the following daily dosing values: 1000 mg of vitamin C, 220 mg of calcium citrate, 75 mg of vitamin B6, 400 µg of folate, 4500 mg L-cysteine, and 400 µg of selenium.

renal tubule cells of the kidneys.^{5,8} The OCTN2s⁸ of the proximal convoluted renal tubule cells transport serotonin and dopamine that is not transported by the OCT2.⁵ While in the competitive inhibition state, serotonin and dopamine not transported by the OCT2s are found in the final urine as waste.⁶ Although there are numerous other forces that interact with the newly synthesized renal monoamines, they are small compared with the effects of these transporters.⁵ Proper interpretation of urinary serotonin and dopamine levels in the competitive inhibition state determines the functional status of the OCT2s of the proximal convoluted renal tubule cells of the kidneys, known as OCT assay interpretation. The OCT2s exist in three different phases dependent on the status of the entrance gate and lumen saturation.³⁻⁷ Table 2 outlines the correlation between entrance gate status and lumen saturation.

The basis for OCT assay interpretation requires that the system be placed into the competitive inhibition state and then two or more urinary serotonin and dopamine assays performed while taking serotonin and dopamine amino acid precursors at significantly varied dosing values. The results are then compared in order to determine the change in urinary serotonin and dopamine levels in response to the change in amino acid precursor dosing values.³⁻⁷

Urinary serotonin and dopamine values found on assay were reported in micrograms of monoamine per gram of creatinine in order to compensate for fluctuations in urinary specific gravity. A urinary serotonin or dopamine value less than 80 or 475 µg of monoamine per 1 g of creatinine, respectively, is defined as a Phase 2 response. A urinary serotonin or dopamine value greater than 80 or 475 µg of monoamine per 1 g of creatinine, respectively, is interpreted as being in Phase 1 or Phase 3. Differentiation of Phase 1 from Phase 3 is as follows. If a direct relationship is found between amino acid dosing and urinary assay response, it is referred to as a Phase 1 response. An inverse relationship is referred

to as a Phase 3 response. The Phase 3 therapeutic range for urinary serotonin is defined as 80–240 µg of serotonin per 1 g of creatinine. The Phase 3 therapeutic range for urinary dopamine is defined as 475–1100 µg of dopamine per 1 g of creatinine.^{3,5-7}

Processing, management, and assay of the urine samples collected for this study were as follows. Urine samples were collected 6 hours prior to bedtime with 4:00 PM being the most frequent collection time point. The samples were stabilized in 6 N hydrochloric acid to preserve the dopamine and serotonin. The urine samples were collected after a minimum of 1 week, during which the patient was taking a specific daily dosing of amino acid precursor of serotonin and dopamine. No doses were missed. Samples were shipped to DBS Laboratories (Duluth, MN). Urinary dopamine and serotonin were assayed utilizing commercially available radioimmunoassay kits (3 CAT BSA IB885 and IB8527, both from Immuno Biological Laboratories, Inc., Minneapolis, MN). The DBS laboratory is accredited by Clinical Laboratory Improvement Amendments as a high-complexity laboratory. OCT assay interpretation was performed. Results were reported in micrograms of monoamine per gram of creatinine to compensate for specific gravity variances in the urine.

Results

An endoscopy examination, prior to treatment with amino acids while the disease was active, was performed in September 2005. Results revealed several aphthous ulcers in the terminal ileum. Tissue biopsy confirmed this diagnosis.

At the initiation of the amino acid protocol, the patient was still taking mesalamine, low-dose naltrexone, and escitalopram. The patient reported no relief of symptoms after any of these drugs were started. The escitalopram was discontinued at the start of amino acid treatment, and the mesalamine and low-dose naltrexone were continued.

At the first visit, the patient was started on level 1 amino acid dosing as per Table 1. One week later there was no change in symptoms, and the patient's amino acid dosing values were increased to level 2 (see Table 1). The patient achieved lessening of the symptoms when he was on level 2 amino acid dosing. At that point, the patient revealed that he felt that this approach was the best treatment he had experienced during the course of his 22-year illness. The amino acids were increased to level 3 dosing (see Table 1), with no further change in symptoms. After 1 week of level 3 dosing, a urine sample was obtained and analyzed. The reported values were then submitted for OCT assay interpretation.

Table 2 The following considerations exist with regard to the basolateral monoamine organic cation transporters of the proximal convoluted renal tubule cells*

	Phase 1	Phase 2	Phase 3
Serotonin or dopamine transporter entrance gates	Partially closed	Open	Open
Transporter lumen saturation	Unsaturated	Unsaturated	Saturated

Note: *In Phase 1, the serotonin and dopamine gates are partially closed, restricting access to the transporter. In Phases 2 and 3, the gates are open, allowing full access to the transporter by serotonin and dopamine. In Phases 1 and 2, the lumen of the transporter is not saturated with serotonin and dopamine. In Phase 3, the lumen of the transporter is saturated with serotonin or dopamine.⁵

When the first urine sample was collected for OCT assay interpretation, the patient was taking level 3 dosing: 900 mg 5-hydroxytryptophan (5-HTP), 5000 mg L-tyrosine, and 4500 mg L-cysteine with cofactors.

The first urinary assay revealed serotonin to be in Phase 3 (Table 2) with a reported value of 5150.7 μg of serotonin per 1 g of creatinine, and a dopamine in Phase 2 (Table 2) with a reported value of 206.4 μg of dopamine per 1 g of creatinine.

After the first OCT assay interpretation, the patient's daily amino acid dosing was increased by 1000 mg of L-tyrosine and 240 mg of L-dopa. At that point, the patient was taking the following in divided daily doses: 900 mg 5-HTP, 6000 mg L-tyrosine, 240 mg L-dopa, and 4500 mg L-cysteine with cofactors. After 1 week taking these new amino acid dosing values, there was no change in the patient's symptoms.

A second urine sample was submitted for analysis, followed by OCT assay interpretation. This revealed that the patient's urinary serotonin was in Phase 3 (Table 2) at 12,611.1 μg of serotonin per 1 g of creatinine, and his dopamine was in Phase 3 (Table 2) at 741.3 μg of dopamine per 1 g of creatinine.

The recommendation was to decrease the daily 5-HTP dosing by 300 mg per day, increase L-tyrosine by 1000 mg per day, and continue other amino acids as before. The patient was then taking the following in divided daily doses: 600 mg 5-HTP, 7000 mg L-tyrosine, 240 mg L-dopa, and 4500 mg L-cysteine with cofactors.⁵ Within 1 week of this dosing value change, the patient became asymptomatic, indicating that adequate OCT balance of the serotonin-dopamine system had occurred. The patient's response and remission with amino acid treatment was very impressive and relatively abrupt compared with the 22-year course of his disease. This profound resolution of symptoms was achieved within 6 weeks of the first clinic visit.

The patient noted the return of solid stools, no further vomiting, no more energy, increased motivation, and resolution of depressive symptoms. All prescription medications that the patient had been taking since the start of amino acid treatment were discontinued after 6 weeks of amino acid treatment, including mesalamine and naltrexone, with no return of symptoms. The amino acid dosing values that had induced relief of symptoms were continued.

Following remission of symptoms, the patient's sedimentation rate returned to the normal range. His weight stabilized at approximately 20 pounds above the lowest weight attained while disease symptoms were present. The patient reported that he was very comfortable at that weight. The

patient found that if he missed a dose of the amino acids, some of the Crohn's disease symptoms would return.

A third OCT assay interpretation was obtained 5 months later with amino acid dosing values that induced relief of symptoms. Urinary serotonin was reported as 9019.5 μg of serotonin per 1 g of creatinine and urinary dopamine was 604.3 μg of dopamine per 1 g of creatinine; both were in Phase 3 (Table 2). At this point, the patient was still asymptomatic. The recommendation was to decrease the daily 5-HTP dosage to 300 mg, decrease L-tyrosine dosing by 1000 mg per day, and continue other amino acids as before. After this dosing value change, the patient was then taking the following in divided daily doses: 300 mg 5-HTP, 6000 mg L-tyrosine, 240 mg L-dopa, and 4500 mg L-cysteine with cofactors. Following this change in amino acid dosing values, the patient continued to be asymptomatic, a state that exists to this day as long as he is compliant with the prescribed amino acid dosing values.

Endoscopy subsequent to remission of symptoms was performed in March 2011. This was 26 months after starting the amino acid protocol guided by OCT assay interpretation and 24 months after achieving relief of symptoms. This endoscopy was performed by the same gastroenterologist that performed endoscopy prior to remission of symptoms. At endoscopy, the patient was taking his amino acids daily with no prescription medications. He was taking no insulin or oral hypoglycemic agents, and his HbA_{1c} had returned to normal. There were no signs of diabetes or other illnesses. He had returned to full-time gainful employment, after a period of over 4 years during which he was fully disabled.

The gastroenterologist reported that for the first time in 10 years of caring for the patient, the Crohn's disease was in complete remission. This finding was verified by the pathologist after review of tissue samples submitted.

As of the time of writing this paper, the patient continues to do well with no infections or adverse reactions. He is gainfully employed and living a normal life. All follow-up testing, including sedimentation rates, have been normal.

Discussion

Scientific basis

The authors have documented a number of patients with Crohn's disease who experienced similar remission of symptoms with this approach. This case was selected for this paper due to the severity of disease in the patient.

Serotonin and dopamine levels inside and outside of the cell structures containing them are primarily a function of

transporter status.⁵ The question raised is how OCT assay interpretation of renal transporters relates to the OCTs of the gastrointestinal (GI) tract. The hypothesis is that performing OCT assay interpretation on one set of OCTs will give insight into transport of serotonin, dopamine, and their precursors at other OCTs throughout the body. Within 3–5 days of starting or changing amino acid precursor dosing values, serotonin, dopamine, and their precursors reach equilibrium throughout the body.^{3,5–7} At equilibrium, amino acid precursors, serotonin, and dopamine exert similar effects at cation transporters throughout the body.

In the competitive inhibition state, the serotonin and dopamine systems function as one system in transport, synthesis, and metabolism. Affecting change to one system will affect both systems in their functions. Serotonin, dopamine, and their amino acid precursors compete for transport at the OCTs. Significant increases in one monoamine will decrease monoamine and precursor transport of the other system through competitive inhibition. Transport of precursors into the cells is required in order to place them in an environment where synthesis takes place. The same enzyme, the L-aromatic amino acid decarboxylase enzyme (AADC), is responsible for synthesis of serotonin and dopamine. Creating an environment where precursors of one system are significantly increased without significantly increasing the precursors of the other system leads to decreased access to the AADC by precursors of the other system, with associated decreased synthesis and depletion due to competitive inhibition. Both serotonin and dopamine are metabolized by the monoamine oxidase (MAO) enzyme system. A significant increase in levels of one system will increase MAO activity, leading to increased metabolism and depletion of the other system.^{2,5,6}

In the intestinal tract of Crohn's patients there is excessive synthesis with associated increased tissue levels of serotonin.^{8,9} In Crohn's disease, high levels of serotonin dominate synthesis, metabolism, and transport, leading to dopamine and/or melatonin levels that are low relative to the balance needed to function properly with the serotonin levels present.⁵

OCT assay interpretation

As noted in previous peer-reviewed research by the authors, OCT phase determination defines the status of the serotonin and dopamine gates at the entrance to the basolateral monoamine OCT (open or partially closed) of the proximal convoluted renal tubule cells of the kidneys and the status of serotonin and dopamine saturation in these transporters (see Table 2).⁵

Proper interpretation of the findings requires the following explanation. Serotonin and dopamine both need to be in the competitive inhibition state when OCT assay interpretation is performed. This means that significant dosing values of both serotonin and dopamine need to be administered simultaneously. When in the competitive inhibition state, serotonin and dopamine are in full competition for transport, synthesis, and metabolism.^{3,5} Testing of the urine is only done after amino acid precursors of the monoamines are started in accordance with the protocol, placing the serotonin–dopamine system in the competitive inhibition state. Baseline testing in the endogenous state prior to administration of amino acid precursors is of no value, as these assay levels correlate with nothing. As noted in previous peer-reviewed literature, baseline testing of urinary serotonin and dopamine does not correlate with baseline assays performed on subsequent days in the same individual.⁵

Simplifying the patient to one or more amino acid precursors is not the key to optimal outcomes. The OCT needs to be challenged with serotonin and dopamine precursors in significant amounts to place transport in the competitive inhibition state so that proper OCT assay interpretation can be realized.⁵

The OCTN

There is a known genetic defect of OCTN1 and OCTN2 in the colon of patients suffering from Crohn's disease.⁹ All OCT and OCTN transporters are capable of transporting organic cations, including serotonin, dopamine, and their precursors.⁸ In Crohn's disease, the serotonin content of the mucosa and submucosa of the proximal and distal colon is increased.¹⁰ Increased synthesis of serotonin is known to be associated with Crohn's disease.¹¹ No reasonable explanation of the etiology of serotonin elevation in the colon tissue of Crohn's disease patients has been put forth previously.

It is postulated that the known OCTN1 and OCTN2 genetic deficit may be tied to the increased synthesis and tissue levels of serotonin seen with Crohn's disease. Based on OCT assay interpretation, it appears that a severe imbalance between serotonin and dopamine transport, synthesis, and metabolism is at the heart of Crohn's disease.

An imbalance of the serotonin–dopamine transport system has been linked to numerous diseases.^{3,5–7} It is proposed that much of the clinical constellation found with Crohn's disease may be induced by a serotonin toxicity of the colon exacerbated by relatively low levels of dopamine resulting from defective OCTN transport.

In the GI tract, serotonin is contained primarily in the enteroendocrine cells (ECs). The serotonin–dopamine transporter balance of the ECs controls paracrine–autocrine and/or endocrine mediators that modulate GI function.¹² It is asserted that proper treatment needs to include correct management of the serotonin and dopamine imbalance in transport, synthesis, and metabolism. The only definitive way to address these problems optimally is with OCT analysis interpretation in the competitive inhibition state that is established with proper amino acid precursor administration.

It is postulated that the patient's Crohn's disease was impacted in a positive manner as follows. It is known that there is increased synthesis of serotonin with increased serotonin levels in the proximal and distal colon.¹¹ Levels of the serotonin–dopamine system are impacted primarily by synthesis, uptake, and metabolism. For serotonin and dopamine to be synthesized, their amino acid precursors need to be transported into the structures where this occurs. There appears to be a defect in transport of serotonin precursors of the colon. Serotonin precursors are transported preferentially at the exclusion of dopamine precursors, leading to high levels of synthesis, high levels of serotonin in portions of the colon, and compromise of catecholamine synthesis. Properly balancing the serotonin and dopamine precursor transport leads to a decrease in serotonin synthesis, less serotonin in the tissue of the proximal and distal colon, and an increase in synthesis of dopamine, norepinephrine, and epinephrine. Increased serotonin levels of Crohn's disease lead to increased MAO activity, which without reciprocal increases of the catecholamines leads to increased metabolism of the catecholamines, further exacerbating the imbalance.

Other implications

With a case study such as this there is always the possibility that remission was coincidental to treatment. This patient had a 22-year history of progressively worsening Crohn's with no remissions and has been free of Crohn's disease symptoms clinically and on biopsy for 2.5 years since the appropriate dosing values of serotonin and dopamine amino acids were established. We leave it to the reader to speculate as to the odds of this being a spontaneous coincidental remission versus a response to properly balanced amino acids.

One other aspect of the patient's treatment needs to be discussed. The patient was suffering from depression. Previously published peer-reviewed literature by the authors indicates that this same approach with OCT assay interpretation for treatment of depression is effective.^{3,7} In this case study, the patient's depression resolved when the serotonin

and dopamine were balanced to the degree needed for relief of Crohn's disease symptoms. It is asserted that it was no coincidence that the patient's depression resolved simultaneously with the resolution of the symptoms of Crohn's disease.

Conclusion

In recent years, a genetic defect of the OCTN1 and OCTN2 of the colon has been identified in patients with Crohn's disease. The OCTN1 and OCTN2 are responsible for transport of cations, including the monoamines of the serotonin–dopamine system and their precursors. It is known in Crohn's disease patients that there is a marked increase in serotonin levels of the proximal and distal colon associated with a defect in serotonin synthesis. It remains to be proven whether a transport problem exists in the serotonin–dopamine system induced by the OCTN1 and OCTN2 genetic defect found in Crohn's disease. For now, these observations cannot be overlooked. Clearly, further studies relating to OCT analysis interpretation and the OCTN transporters of the colon as they relate to other abnormal findings associated with Crohn's disease are indicated.

This paper potentially opens the door to a new area of treatment and study in Crohn's disease patients. The goal of the paper is to stimulate further interest in these findings in order to duplicate, confirm, and invite scrutiny of these results.

Disclosure

Dr Marty Hinz is President of Clinical Research, Neuro-Research Clinics, Inc., Cape Coral, Florida, USA. Dr Thomas Uncini is Medical Director of DBS Labs, Duluth, Minnesota, USA. Dr Alvin Stein reports no disclosures.

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