

Niacin (Nicotinic Acid) a Putative Treatment for Hypochlorhydria: Re-analysis of Two Case Reports

Jonathan E. Prousky, N.D., FRSH;¹ Claire Kerwin, N.D.²

Abstract

Fifty to sixty percent of patients with symptoms of chronic or recurrent discomfort concentrated at the upper abdomen can be diagnosed with what is termed functional dyspepsia or nonulcer dyspepsia (NUD). Other symptoms include belching, bloating, heartburn, nausea or vomiting. Insufficient stomach acid, a condition known as hypochlorhydria, might be responsible for the symptoms of NUD. Two case reports suggest that niacin (nicotinic acid) might be an effective treatment for hypochlorhydria. Several mechanisms of action are proposed to outline niacin's potential role in the maintenance of hydrochloric acid (HCl) secretion. For example, niacin directly stimulates histamine release from gastric mast cells. Increased histamine levels lead to hydrogen ion (H⁺) production and eventually more HCl. Another mechanism purports that subsequent increase in nicotinamide adenine dinucleotide (NADH) levels following niacin supplementation stimulates the mitochondrial production of adenosine triphosphate (ATP). ATP provides the necessary fuel to drive the process of generating HCl from parietal cells. Finally, niacin supplementation might help normalize gastric pH. Optimal gastric pH helps regulate gastrin levels, as well as supports other important physiological functions. Considering the billions of dollars spent annually on both over-the-counter and prescription drugs for this disorder, the use of niacin should be a therapeutic consideration when gastric pH analy-

sis has demonstrated hypochlorhydria. Future studies that include more patient case reports and more rigorous controls are needed before recommending this treatment to all patients who have been diagnosed with NUD.

Introduction

Dyspepsia is defined as chronic or recurrent discomfort concentrated at the upper abdomen and is associated with belching, bloating, heartburn, nausea or vomiting.¹ It affects approximately twenty-five percent of the population each year, even though most affected persons do not seek medical care for it.^{2,3} Fifty to sixty percent of patients with dyspepsia are considered to have functional or nonulcer dyspepsia (NUD); no specific etiology can be identified.⁴⁻⁶ Up to forty percent of dyspepsia is caused by peptic ulcer disease and reflux esophagitis, with less than two percent of cases being the result of gastric or esophageal cancer.⁴ It is possible that the cause of NUD might be due to insufficient gastric acid secretion, a condition known as hypochlorhydria. The symptoms associated with hypochlorhydria include bloating or distention after eating, heartburn/epigastric distress, malaise, prolonged sense of fullness and/or flatulence after eating, nausea after taking supplements and diarrhea or constipation.^{7,8} It is evident that there is a significant overlap between symptoms associated with hypochlorhydria and those symptoms associated with NUD.

A potential therapeutic approach for the treatment of NUD is to augment the production of gastric hydrochloric acid (HCl) when hypochlorhydria is suspected. The mechanisms underlying the secretion of gastric HCl are complicated and not well

1. Assistant Professor of Clinical Nutrition & Clinical Faculty, The Canadian College of Naturopathic Medicine, Toronto, Ontario. Correspondence: 1255 Sheppard Avenue East, Toronto, Ontario M2K 1E2. E-mail: jprousky@ccnm.edu.

2. Apt #2 31-Meadowbrook Road, Toronto, ON M6B 2S5. email: ckerwin@hotmail.com.

understood. It is known that histamine is the most important mediator of HCl secretion.⁹ It is also known that gastric parietal cells require a sufficient supply of mitochondrial adenosine triphosphate (ATP) to facilitate the generation of hydrogen ions (H⁺) for HCl production.¹⁰ An appropriately acidic gastric pH helps to maintain normal gastrin levels and also facilitates other important physiological functions. This report of two cases demonstrates the successful treatment of suspected hypochlorhydria with non-sustained release preparations of niacin (nicotinic acid). The vitamin might have decreased the symptoms of NUD in these two patients by increasing HCl secretion through the release of gastric histamine, facilitating optimal parietal cell dynamics and maintaining an acidic gastric pH.

Case Reports

In 2001, a 28 year-old Caucasian male of Jewish descent presented to my private office at the Canadian College of Naturopathic Medicine (CCNM) with complaints of fatigue and constant abdominal bloating after meals. These symptoms had persisted for three months. He began to take niacin at incremental dosages of 100 mg, eventually working up to 1200 mg/day. Within three days of supplementation there was a noticeable increase in energy and a significant decrease in abdominal bloating. Occasionally no abdominal bloating occurred. The patient remained on 1200 mg/day of niacin for two months. When the patient went off the vitamin (due to the holiday of Passover) he experienced diarrhea, blood in the stools and abdominal pain. After Passover, he resumed niacin at a dosage of 750 mg/day and these symptoms quickly abated. He continued on 750 mg/day of niacin for two more months with a significant relief of his symptoms. Occasional episodes of abdominal bloating and belching still occurred.

In 2001, a 28 year-old Caucasian male of European ethnicity presented to my pri-

vate office at CCNM with similar, but more severe, complaints. He reported a history of frequent abdominal bloating of at least 15 years duration, occasional abdominal pain, regurgitation of stomach contents and repeated belching. He was previously diagnosed with gastroesophageal reflux disease (GERD). Despite trying various standard medical treatments for the past seven years his symptoms had not significantly abated. When he came to see me, he was experiencing about four flare-ups of GERD-related symptoms every month. Only Zantac[®] and Gaviscon[®] supplementation gave him symptomatic relief. A trial course of oral niacin was recommended. Soon after taking 2000-3000 mg/day of niacin his stomach regurgitation ceased and no more flare-ups occurred. The patient also reported a fifty percent reduction in his symptoms of belching and abdominal bloating. This patient was followed for almost one year after initiating niacin treatment, and he continues to do well. He has not had another flare-up of his previous gastroesophageal reflux symptoms.

Discussion

Both of these patients had a therapeutic response to niacin, as demonstrated by an improvement in their symptoms of hypochlorhydria. In these case reports, gastric acid analysis was not performed prior to and during treatment. Therefore, it cannot be determined if these patients had true hypochlorhydria. It is likely that niacin supplementation was at least partially responsible for the amelioration of their gastrointestinal symptoms. However, other factors, such as placebo effect or dietary/environmental changes, cannot be ruled out as positive therapeutic influences.

Niacin might be an important nutrient for the health of the gastric mucosa and for the secretion of HCl. Achlorhydria, a condition denoting an absence of stomach acid, is an additional clinical feature of the classical niacin-deficiency disease (pella-

gra).¹¹ Two of the potential side effects of niacin supplementation are heartburn¹² and excessive acid secretion.¹³ Therefore, niacin must impact various parameters of the gastrointestinal system. We propose several mechanisms of action that might explain how niacin could influence HCl secretion and help maintain the optimal health of the gastric system (Figure 1, p4).

The gastric mucosa contains an abundance of histamine-containing mast cells as well as acid-secreting parietal cells.¹⁴ Niacin is a potent releaser of histamine from mast cells¹⁵ and also has been shown to stimulate the secretion of the dermally-derived vasodilator, prostaglandin D2 (PGD2).^{16,17} Niacin might stimulate the gastric mast cells to release histamine (1). The histamine released from gastric mast cells would then be available to bind to the histamine type II (H2) receptors on the parietal cells, leading to the generation of H+ and the eventual production of HCl.

Specifically, an exchanger (4) might be stimulated by either one or the other neurotransmitter-hormonal substances, with histamine being the most important. Parietal cell carbonic anhydrase stimulates H2O to combine with CO₂, resulting in carbonic acid (H₂CO₃). This maintains the neutrality of the interior of the parietal cell by the generation of a new hydrogen ion (H⁺) from H₂CO₃ to replace the secreted H+. The bicarbonate ion (HCO₃⁻) passes into the blood in order to maintain electrical neutrality by replacing the chloride ion (Cl-) that has been actively secreted into the gastric lumen.

Niacin is efficiently absorbed across the intestinal lumen by passive diffusion at high concentrations (2).¹² All metabolically active tissues require niacin derived coenzymes to function properly.¹⁸ For example the coenzyme, NADH (nicotinamide adenine dinucleotide), plays a critical role in complex I of the mitochondrial respiratory chain.¹⁰ Parietal cells contain the largest concentration of mitochondria among

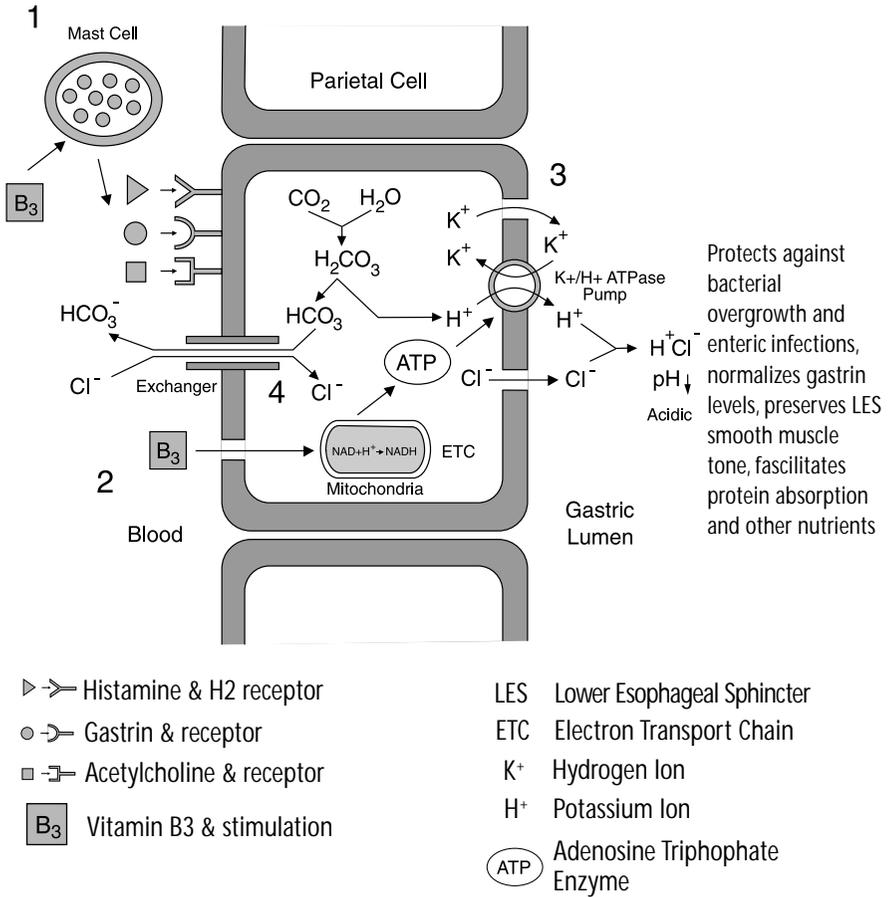
all eukaryotic cells,¹⁹ with half of their volume occupied by mitochondria.¹⁰ Free energy released in the process of oxidative phosphorylation within the mitochondria is used to produce ATP. One of the main initiators of mitochondrial oxidative phosphorylation is NADH. The ATP synthesized from mitochondrial energy drives the exchange of the potassium ion (K+) for H+. This process occurs within the canalicular membrane of the parietal cell.¹⁰ Chloride ions are also actively transported into the parietal cell lumen where they combine with hydrogen ions to form HCl.^{9,10} Therefore, niacin derived NADH is essential for optimal mitochondrial functioning, leading to the production of ATP that drives the generation of HCl from the parietal cells.

Maintenance of optimal gastric pH through niacin administration might have a positive effect upon gastrin levels (3). Hypergastrinemia is common in a gastric environment deficient in stomach acid.²⁰⁻²³ High gastrin levels could disrupt the smooth muscle tone of the lower esophageal sphincter (LES); enabling stomach contents to reflux into the esophagus.⁷ Ensuring adequate HCl secretion through niacin supplementation might maintain an appropriately acidic gastric pH. Optimal pH might normalize gastrin levels and preserve the smooth muscle tone of the LES so that the stomach contents do not reflux. Adequate gastric pH would help render the stomach sterile against pathogens, prevent fungal and bacterial overgrowth of the small intestine, facilitate the flow of bile and pancreatic enzymes, and enable the proper absorption of protein and other nutrients.^{7,24}

Conclusion

In his review of dyspepsia, Greenbaum has delineated some pertinent facts about the financial aspects of this condition:²⁵ An estimated forty percent of adults in the Western world have repeated episodes of dyspepsia and, in the United States, two to

Figure 1. Niacin's theoretical effect upon acid secretion



five percent of all primary care visits are for this condition. More than \$1.3 billion are spent annually on prescription drugs for dyspepsia in the United States. This does not include the costs of over-the-counter (OTC) medications, which are presumed to be at least equal to the annual prescription costs for this condition. It is evident that there is a significant financial burden to the health care system with the conventional treatment of NUD.

OTC medications for dyspepsia include antacids and H₂-receptor antagonists. These medications are associated with

nutrient depletion. Antacids can induce copper deficiency,²⁶ malabsorption of folic acid,²⁷ and depletion of phosphorus.²⁸ H₂-receptor antagonists, such as cimetidine, can reduce the absorption of folic acid²⁹ and vitamin B₁₂,³⁰ as well as hepatic vitamin D 25-hydroxylase activity.³¹

Assuming that hypochlorhydria is a factor in symptoms of NUD, and if one considers the tremendous health care costs and substantial time lost from work associated with NUD,³² clearly the use of an inexpensive, yet therapeutically valuable alternative such as niacin is warranted. Ni-

acin does not cause nutrient depletion, but adverse effects associated with its use, can occur at doses similar to the ones prescribed to the patients in the case reports. Adverse effects reported from the use of niacin include hyperuricemia, hyperglycemia, pruritis, nausea, diarrhea and aggravation of peptic ulcers.³³⁻³⁵ The use of niacin is contraindicated in gout, conditions with documented hypersecretion of gastric acid, peptic ulcer disease, and in gastric or esophageal cancers. These two patients tolerated niacin well and had no adverse effects that prevented them from continuing treatment. Most of the evidence regarding niacin toxicity involves the use of sustained release preparations. A theoretical potential for hepatic toxicity is the major concern.³⁶ Long-term use of the non-sustained release preparation of niacin has a remarkable therapeutic index with an extremely low incidence of adverse effects.^{37,38} However, even when using the non-sustained release preparation of niacin, careful monitoring of liver function every six months is prudent.

In a previous report, it was hypothesized that a niacin dependency (i.e. an increased need for the vitamin that is not being met through dietary intake alone) might be responsible for the development of hypochlorhydria and achlorhydria and even *Helicobacter pylori* (*H. pylori*) infection.³⁹ It appears that niacin does favorably impact several important parameters of gastric acid secretion and, proper gastric acid secretion is further associated with optimal non-immunological defenses.⁴⁰ There is a strong association between *H. pylori* infection and hypochlorhydria.^{41,42} Therefore, an uncorrected niacin dependency might also increase susceptibility to *H. pylori* infection. Niacin might be a potential and novel therapeutic agent for its eradication.

Based on these two reports, a non-sustained release preparation of niacin appears to be safe and potentially curative for the treatment of NUD if, in fact, it is associ-

ated with hypochlorhydria. Niacin could also be a treatment option for the eradication of diagnosed *H. pylori* infection with concomitant hypochlorhydria. Before considering the use of niacin as a treatment option, the clinician might want to utilize one of two fairly non-invasive methods for analyzing gastric acid. These are the Gastro-Test[®] and the Heidelberg pH capsule gastric analysis.⁴⁴ Another useful indirect measure of hypochlorhydria is the presence of increased urinary indican.^{45,46} However, this test is not specific for hypochlorhydria. Future studies and more patient case reports are necessary before recommending niacin to all patients with NUD, and possibly after a diagnosis of *H. pylori* infection has been established.

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