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Can an amino acid mixture alleviate gastrointestinal symptoms in neuroendocrine tumor patients?

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Abstract

Background: Neuroendocrine tumors, although relatively rare in incidence, are now the second most prevalent gastrointestinal neoplasm owing to indolent disease biology. A small but significant sub-group of neuroendocrine tumor patients suffer from diarrhea. This is usually secondary to carcinoid syndrome but can also be a result of short gut syndrome, bile acid excess or iatrogenic etiologies. Recently, an amino acid based oral rehydration solution (enterade® Advanced Oncology Formula) was found to have anti-diarrheal properties in preclinical models.

Methods: A retrospective chart review of all NET patients treated with enterade® AO was performed after IRB approval.

Results: Ninety-eight NET patients who had received enterade® AO at our clinic from May 2017 through June 2019 were included. Patients ($N = 49$ of 98) with follow up data on bowel movements (BMs) were included for final analysis. Eighty-four percent of patients (41/49) had fewer BMs after taking enterade® AO and 66% (27/41) reported more than 50% reduction in BM frequency. The mean number of daily BMs was 6.6 (range, 3–20) at baseline before initiation of therapy, while the mean number of BMs at 1 week time point post enterade® AO was 2.9 (range, 0–11).

Conclusions: Our retrospective observations are encouraging and support prospective validation with appropriate controls in NET patients. This is first published report of the potential anti-diarrheal activity of enterade® AO in NET patients.

Keywords: Neuroendocrine tumors, Amino acid oral rehydration solution, Diarrhea, Excess bowel movements

Background

Neuroendocrine tumors (NETs) are rare and unique slow growing tumors that can originate from varied organ sites [1]. The prevalence of NETs has increased in the United States over 6-fold from 1973 to 2012, primarily due to improved diagnostics for early-stage disease and potency of systemic treatments leading to improved survival in the metastatic setting [2, 3]. NETs are classified as non-functional or functional tumors; non-functional tumors do not secrete hormones, while functional, non-pancreatic, NETs primarily secrete serotonin, resulting in carcinoid syndrome [1]. Approximately 10–50% of patients with NETs will develop carcinoid syndrome [4–7] and its associated symptoms of flushing and frequent, often explosive, watery diarrhea (62–78%) [4, 5, 8]. Carcinoid syndrome diarrhea can be distressing with many patients reporting bowel movements (BM) ranging from two to 30 or more per day [9]. Patients with NETs may also have moderate to severe diarrhea due to other etiologies

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including toxicity from chemotherapy, radiation and sequelae of gastrointestinal surgery [10–17].

Diarrhea and BM frequency in functional NET patients is typically managed with somatostatin analogs and telotristat ethyl (tryptophan hydroxylase inhibitor). Over-the-counter anti-diarrheal medications are also often utilized for breakthrough diarrhea. However, it is not uncommon for NET patients to continue to have persistent debilitating diarrhea despite treatment with multimodal agents.

We examined the potential for enterade® Advanced Oncology (AO) Formula to reduce BM frequency in NET patients. Enterade® AO consists of a unique blend of five amino acids (Valine, Aspartic Acid, Serine, Threonine, Tyrosine) selected for their ability to restore bowel absorption and integrity [18]. Enterade® AO additionally contains electrolytes and flavors. Preclinical data suggest that enterade® AO can restore enteral integrity following radiation-induced gut damage in mice [15, 17, 19]. We previously reported our anecdotal experience with enterade® AO in a cancer patient who noted significant clinical improvement in gastrointestinal symptoms [20]. Non-toxic and inexpensive enteral nutritional therapies for decreasing diarrhea and BM frequency in NET patients, regardless of cause, can significantly improve patient quality of life and reduce patient and hospital costs [20]. Because of these observations, we elected to review our experience with enterade® AO in reducing BM frequency in NET patients undergoing cancer treatments.

Methods

Ethics statement

Retrospective chart review was conducted after appropriate University of Kentucky Institutional Review Board (IRB) approval.

Objective and hypothesis

A retrospective chart review of all NET patients treated with enterade® AO under supervision of a registered dietitian in an oncology clinic setting was performed. All NET patients managed at Markey Cancer Center are screened for chronic diarrhea that is co-managed by medical oncology and registered dietitians. Interventions include pharmacologic and counseling measures focused on diet and nutrition. Any patients experiencing 4 or more stools were instructed to consume one 8 oz. bottle of enterade® AO twice daily, 30 min before meals or 1 h after meals for at least 1 week. Patients were provided a one-week supply of samples (supported by Lockey Foundation Philanthropic Grant to Markey NET Clinic). If patients noted improvement in diarrhea, they were able to continue enterade® AO by buying the product over the counter. Most patients were followed up at 1 week over the phone to determine the number of BMs per day, and if the patient had any adverse side-effects from enterade® AO. Those who had no follow up at 1 week or were lost to follow up were not included in this analysis.

The clinical data were retrospectively reviewed with a primary objective of evaluating change in BM frequency from before the trial of enterade® AO suppression compared to after. The hypothesis was that enterade® AO, when combined with standard supportive care, would improve small bowel absorption, leading to a reduction in BM frequency.

Medical records were also reviewed to obtain demographic data, information on the tumor type and location, histopathology, frequency of diarrhea, and use of somatostatin analogs.

Statistical analysis

Data were analyzed using descriptive statistics to generate means and ranges. Robust linear regression was used to estimate the reduction in BM frequency afforded by use of enterade® AO as a function of initial severity of diarrhea. All statistical analyses were performed using Prism GraphPad, version 8.0.

Results

Patient characteristics

We identified 98 NET patients who had received enterade® AO at our clinic from May 2017 through June 2019. Patients ($N = 49$ of 98) with follow up data on BMs were included for final analysis. The average age was 61 years with a range of 33 to 84 years. Thirty-seven (75%) patients possessed gastroenteropancreatic NETs, 8 possessed bronchial NETs, 1 possessed a gynecological NET, and 3 possessed NETs of unknown primary origin. Twenty-eight patients (57%) had a history of prior bowel resection either for primary NET resection or debulking. Twenty-eight patients (57%) were on somatostatin analogs at the time of initiation of enterade® AO.

Antidiarrheal efficacy of enterade® AO

Eighty-four percent of patients (41/49) had fewer BMs after taking enterade® AO and 66% (27/41) reported more than 50% reduction in BM frequency. The mean number of daily BMs was 6.6 (range, 3–20) at baseline before initiation of therapy, while the mean number of BMs at day 7 after starting enterade® AO was 2.9 (range, 0–11).

The average time to improvement was 4.3 days. Five patients had a marked decrease in BMs during the study and their diarrhea completely resolved (zero diarrheal BMs) by the end of the study. One patient reported the side effect of constipation. There were no other adverse reactions reported. Figure 1 Illustrates the reduction in daily BM frequency for individual NET patients after using enterade for at least 1-week. Data are sorted and

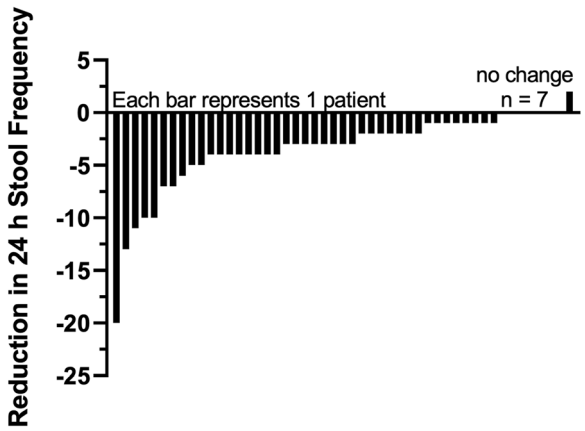

Fig. 1 Plot of reduction in daily bowel movement frequency after use of enterade for 1-week for $n = 49$ patients. Data are sorted and ordered from largest to smallest benefits to illustrate the effect magnitude and individual variability. Source: Author

ordered from largest to smallest benefits to illustrate the effect magnitude and individual variability for $n = 49$ patients.

Discussion

The principal finding from this retrospective chart review of NET patients experiencing life-limiting BM frequency was that consumption of enterade® AO resulted in a reduction in diarrhea, and that patients experiencing the most severe number of BMs appeared to derive the most benefit.

Traditionally, diarrhea in NET patients is managed with somatostatin analogs, anti-motility agents, and opioids. Nevertheless, some patients can continue to have persistent debilitating diarrhea despite the utilization of multi-modal agents. There are limited treatment options for controlling diarrhea in this population, especially for patients with severe, uncontrollable diarrhea. Somatostatin analogs are reported to be 65–84% effective in decreasing the frequency of BMs [21]. However, it is common for patients to become refractory to somatostatin analogs. Telotristat ethyl, the first and only drug approved by the United States Food and Drug Administration for carcinoid syndrome diarrhea refractory to somatostatin analogs, reduced diarrhea in 44% of NET patients [22]. While telotristat is a significant advance for carcinoid NET patients with diarrhea, there are still NET patients with both functional syndrome as well as non-syndromic diarrhea which can further benefit from optimization of anti-diarrheal strategies.

Enterade® is a proprietary blend of five amino acids (threonine, valine, serine, tyrosine, tryptophan) that acutely restores water and electrolyte losses by facilitating intestinal sodium and water transport with similar stoichiometry to glucose [23], but without stimulating chloride secretion like glucose [24] Used prophylactically and chronically as a treatment, enterade modulates intestinal transmembrane proteins to promote intestinotrophic villus regrowth, increase sodium and water absorption, decrease chloride and bicarbonate secretion, and reduce intestinal paracellular permeability [24] (Fig. 2). The benefits of enterade have been demonstrated by improvements in body weight maintenance and survival in mice with radiation enteritis and improved diarrhea outcomes in oncology patients suffering from toxic gut syndrome [24]. The potential benefits of a non-toxic and inexpensive enteral nutrition therapy like enterade® AO for effectively treating diarrhea in NET patients looks promising and should be explored further in a prospective study. Limitations of our current study include lack of control group and a heterogenous patient population, lack of designated follow up and lack of a uniform outcome measurement. As mentioned previously, diarrhea in NET patients can be due to carcinoid syndrome, short gut syndrome, bacterial overgrowth, bile acid colitis, steatorrhea etc. Our study was not controlled for potential confounders and did not consider the effect of supportive care medications in addition to enterade® AO. Furthermore, 50% of patients in the initial cohort did not have adequate follow up. It is possible that these patients derived less benefit from enterade® AO, and this loss to follow up introduced selection bias. Also, as the post-treatment BM frequency assessment was carried out approximately at 1 week, some potential heterogeneity could have been observed around time of outcome assessment. Despite these limitations, our early clinical observation suggests potential anti-diarrheal activity of enterade® AO and warrants validation of the product in a well-controlled prospective clinical trial.

Our findings support further investigations of enterade® AO for diarrhea mitigation in NET patients. This is not entirely surprising as the enterade® AO mechanisms of action include hyper-absorptive, anti-secretory, barrier tightening, and villi proliferation effects within intestinal epithelia [15, 17, 19] which directly combat many of the pathophysiological effects of disease and treatment (radiation and chemotherapy) [25, 26] (Fig. 2). Although the placebo effect and biased reporting of favorable outcomes cannot be ruled out as factors which influenced outcomes in our analysis, the clinical outcomes observed are promising and consistent with rigorous pre-clinical anti-diarrheal data; these findings warrant further affirming prospective research.

Conclusion

Eighty-four percent (41/49) of NET patients reported BM reduction with enterade® AO while 66% (27/41) reported more than 50% reduction in BM frequency. In conclusion, our retrospective observations are

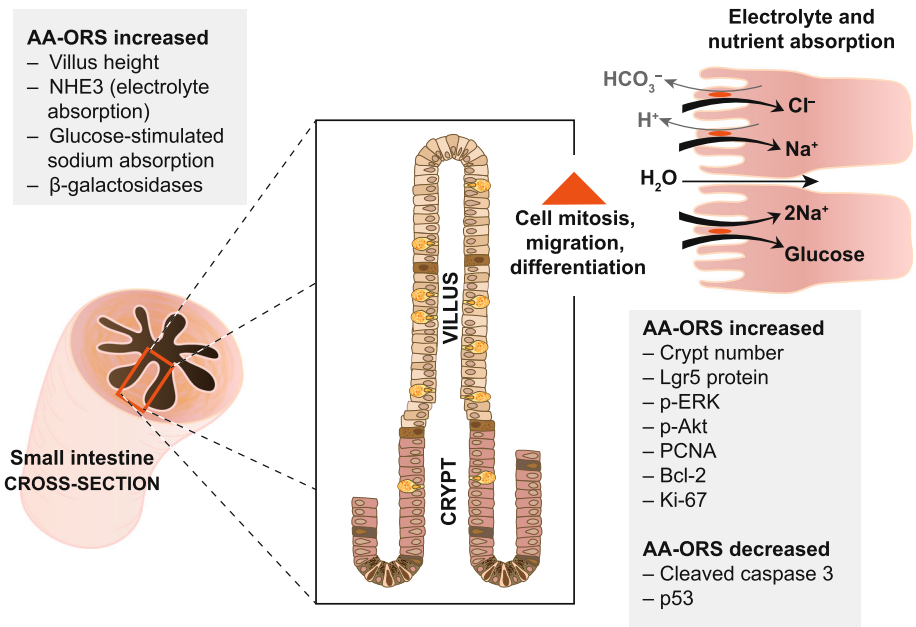

Fig. 2 Illustration highlighting mechanisms of action of enterade® Advanced Oncology Formula. Enterade modulates intestinal transmembrane proteins to promote intestinotrophic villus regrowth, increase sodium and water absorption, decrease chloride and bicarbonate secretion, and reduce intestinal paracellular permeability. See Yin et al., 2016 for further details. Source: Author

encouraging and support prospective validation in NET patients. This is first published report of potential anti-diarrheal activity of enterade® AO in NET patients. There are two ongoing prospective phase 2 studies (NCT02919670, NCT03722511) which are currently evaluating the ability of enterade® AO to reduce BM frequency and relieve gastrointestinal symptoms in this population.

Abbreviations
AO: Advanced Oncology; BM: Bowel movement; NET: Neuroendocrine tumor

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Authors' contributions
AC: conception, acquisition, interpretation of data; SD, RM, LL, SNC, JC, ZT, FS, RAR, and LA: acquisition and interpretation of data. All authors approved the manuscript and have agreed to be accountable for their contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the author was not personally involved, are appropriately investigated, resolved, and the resolution documented in the literature.

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Availability of data and materials
The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Patient consent is not applicable as this is a retrospective chart review. We however have the University of Kentucky IRB approval for chart review based retrospective study.

Consent for publication
Not applicable.

Competing interests
LL and SNC are employees of Entrinsic Bioscience, which manufactures enterade® AO. RR reports the following financial disclosures: Consulting: Curium, Advanced Accelerator Applications, Novartis, Astra Zeneca; Speaking: Merck, Advanced Accelerator Applications, Genentech, Ipsen, Guardant, Astra Zeneca; Research funding: Aadi Bioscience, Merck. The other authors have no conflicts of interest.

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References
1. Naraev BG, Halland M, Halperin DM, Purvis AJ, O'Dorisio TM, Halfdanarson TR. Management of Diarrhea in patients with carcinoid syndrome. Pancreas. 2019;48(8):961–72. https://doi.org/10.1097/MPA.0000000000001384.
2. ENETS/Cancer.Net. https://www.cancer.net/cancer-types/neuroendocrine-tumors/statistics.
3. Dasari A, Shen C, Halperin D, Zhao B, Zhou S, Xu Y, et al. Trends in the incidence, prevalence, and survival outcomes in patients with

neuroendocrine tumors in the United States. JAMA Oncol. 2017;3(10):1335–42. https://doi.org/10.1001/jamaoncol.2017.0589.
4. Aluri V, Dillon JS. Biochemical testing in neuroendocrine tumors. Endocrinol Metab Clin N Am. 2017;46(3):669–77. https://doi.org/10.1016/j.ecl.2017.04.004.
5. Rubin de Celis Ferrari AC, Glasberg J, Riechelmann RP. Carcinoid syndrome: update on the pathophysiology and treatment. Clinics (Sao Paulo). 2018;73(suppl 1):e490s.
6. Schnirer II, Yao JC, Ajani JA. Carcinoid--a comprehensive review. Acta Oncol. 2003;42(7):672–92. https://doi.org/10.1080/02841860310010547.
7. Shi DD, Yuppa DP, Dutton T, Brais LK, Minden SL, Braun IM, et al. Retrospective review of serotonergic medication tolerability in patients with neuroendocrine tumors with biochemically proven carcinoid syndrome. Cancer. 2017;123(14):2735–42. https://doi.org/10.1002/cncr.30633.
8. Herrera-Martinez AD, Hofland J, Hofland LJ, Brabander T, Eskens F, Galvez Moreno MA, et al. Targeted systemic treatment of neuroendocrine tumors: current options and future perspectives. Drugs. 2019;79(1):21–42. https://doi.org/10.1007/s40265-018-1033-0.
9. Pandit N, Khadka S, Sah R, Awale L, Dhakal S, Jaiswal LS, et al. Disappearing lump-an unusual presentation of large metastatic small bowel malignant melanoma. J Gastrointest Cancer. 2019;50(2):353–6. https://doi.org/10.1007/s12029-017-0031-x.
10. Maroun JA, Anthony LB, Blais N, Burkes R, Dowden SD, Dranitsaris G, et al. Prevention and management of chemotherapy-induced diarrhea in patients with colorectal cancer: a consensus statement by the Canadian working group on chemotherapy-induced diarrhea. Curr Oncol. 2007;14(1):13–20. https://doi.org/10.3747/co.2007.96.
11. Barillot I, Tavernier E, Peignaux K, Williaume D, Nickers P, Leblanc-Onfroy M, et al. Impact of post operative intensity modulated radiotherapy on acute gastro-intestinal toxicity for patients with endometrial cancer: results of the phase II RTCMIENDOMETRE French multicentre trial. Radiother Oncol. 2014;111(1):138–43. https://doi.org/10.1016/j.radonc.2014.01.018.
12. Li Q, Chen J, Zhu B, Jiang M, Liu W, Lu E, et al. Dose volume effect of acute diarrhea in post-operative radiation for gynecologic Cancer. Rev Investig Clin. 2017;69(6):329–35. https://doi.org/10.24875/RIC.17002373.
13. Battersby NJ, Juul T, Christensen P, Janjua AZ, Branagan G, Emmertsen KJ, et al. Predicting the risk of bowel-related quality-of-life impairment after restorative resection for rectal Cancer: a multicenter cross-sectional study. Dis Colon Rectum. 2016;59(4):270–80. https://doi.org/10.1097/DCR.0000000000000552.
14. Yde J, Larsen HM, Laurberg S, Krogh K, Moeller HB. Chronic diarrhoea following surgery for colon cancer-frequency, causes and treatment options. Int J Color Dis. 2018;33(6):683–94. https://doi.org/10.1007/s00384-018-2993-y.
15. Yin L, Gupta R, Vaught L, Grosche A, Okunieff P, Vidyasagar S. An amino acid-based oral rehydration solution (AA-ORS) enhanced intestinal epithelial proliferation in mice exposed to radiation. Sci Rep. 2016;6(1):37220. https://doi.org/10.1038/srep37220.
16. Yin L, Vaught L, Okunieff P, Casey-Sawicki K, Vidyasagar S. Amino acid hydration decreases radiation-induced nausea in mice: a Pica model. Adv Exp Med Biol. 2017;977:59–65. https://doi.org/10.1007/978-3-319-55231-6_9.
17. Yin L, Vijaygopal P, Menon R, Vaught LA, Zhang M, Zhang L, et al. An amino acid mixture mitigates radiation-induced gastrointestinal toxicity. Health Phys. 2014;106(6):734–44. https://doi.org/10.1097/HP.0000000000000117.
18. Luque L, Cheuvront SN, Mantz C, Findelstein SE. Alleviation of Cancer therapy-induced gastrointestinal toxicity using an amino acid medical food. Food Nutr J. 2020;5:216.
19. Gupta R. An amino acid-based oral rehydration solution regulates radiation-induced intestinal barrier disruption in mice. J Nutr. 2020;150:1100.
20. Hendrie JD, Chauhan A, Nelson NR, Anthony LB. Can an amino acid-based oral rehydration solution be effective in managing immune therapy-induced diarrhea? Med Hypotheses. 2019;127:66–70. https://doi.org/10.1016/j.mehy.2019.03.023.
21. Hofland J, Herrera-Martinez AD, Zandee WT, de Herder WW. Management of carcinoid syndrome: a systematic review and meta-analysis. Endocr Relat Cancer. 2019;26(3):R145–56. https://doi.org/10.1530/ERC-18-0495.
22. Kulke MH, Horsch D, Caplin ME, Anthony LB, Bergsland E, Oberg K, et al. Telotristat ethyl, a tryptophan hydroxylase inhibitor for the treatment of carcinoid syndrome. J Clin Oncol. 2017;35(1):14–23. https://doi.org/10.1200/JCO.2016.69.2780.
23. Bröer S, Fairweather SJ. Amino acid transport across the mammalian intestine. Compr Physiol. 2018;9(1):343–73. https://doi.org/10.1002/cphy.c170041.
24. Yin L, Vijaygopal P, MacGregor GG, Menon R, Ranganathan P, Prabhakaran S, et al. Glucose stimulates calcium-activated chloride secretion in small intestinal cells. Am J Phys Cell Phys. 2014 Apr 1;306(7):C687–96. https://doi.org/10.1152/ajpcell.00174.2013.
25. Harb AH, Abou Fadel C, Sharara AI. Radiation enteritis. Curr Gastroenterol Rep. 2014;16(5):383. https://doi.org/10.1007/s11894-014-0383-3.
26. Wardill HR, Bowen JM, Al-Dasooqi N, Sultani M, Bateman E, Stansborough R, et al. Irinotecan disrupts tight junction proteins within the gut : implications for chemotherapy-induced gut toxicity. Cancer Biol Ther. 2014;15(2):236–44. https://doi.org/10.4161/cbt.27222.

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