

Can the Antisecretory Factor Be Considered a New Therapy for the Short Bowel Syndrome?

Maria Teresa Viggiani, Alfredo Di Leo and Michele Barone 

Gastroenterology Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), University of Bari, Azienda Universitaria Ospedaliera Consorziata – Policlinico Bari, Bari, Italy.

Nutrition and Metabolic Insights
Volume 12: 1–4
© The Author(s) 2019
Article reuse guidelines:
sagepub.com/journals-permissions
DOI: 10.1177/1178638819852061



ABSTRACT

BACKGROUND AND OBJECTIVE: The antisecretory factor (AF) exerts antisecretory and anti-inflammatory properties in the bowel. The aim of this study was to evaluate the effect of exogenous AF (Salovum) or cereals stimulating the endogenous AF (SPC-Flakes), given alone or in combination, in patients with short bowel syndrome (SBS).

METHODS: Patients received Salovum alone at T₀-T₁, Salovum plus SPC-Flakes at T₁-T₂, and SPC-Flakes alone at T₂-T₃. At T₀ and T₃, water balance, weight, lean mass (FFM), total body water (TBW), extracellular water (ECW), and nutritional and inflammatory biochemical parameters were evaluated. The water balance was also measured at T₁, T₂, and 30 days (T_S) from the end of treatment.

RESULTS: Among the 7 patients enrolled, 2 discontinued treatment due to side effects and 1 was excluded after a cancer was diagnosed. Salovum alone or with SPC-Flakes did not improve the intestinal absorption in patients with SBS, while the administration of SPC-Flakes alone lead towards a trend of increased faecal volume. Weight, FFM, TBW, and ECW, as well as nutritional and inflammatory status, did not statistically change at the end of treatment (T₃) as compared with T₀. At T_S water balance was restored.

CONCLUSION: The administration of exogenous AF or the stimulation of endogenous AF seems to be unable to offer an effective therapy in patients with SBS. On the contrary, their administration appears to aggravate fluid loss and induce side effects.

KEYWORDS: Salovum, SPC-Flakes, intestinal failure, intestinal absorption

RECEIVED: March 13, 2019. **ACCEPTED:** March 18, 2019.

TYPE: Case Report

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

DECLARATION OF CONFLICTING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

CORRESPONDING AUTHOR: Michele Barone, Gastroenterology Unit, Department of Emergency and Organ Transplantation (D.E.T.O.), University of Bari, Azienda Universitaria Ospedaliera Consorziata – Policlinico Bari, Piazza Giulio Cesare 11, 70124 Bari, Italy. Email: michele.barone@uniba.it

Introduction

The short bowel syndrome (SBS) is a pathological condition caused by extensive intestinal surgical resections or congenital diseases leading to a severe reduction of the absorptive intestinal surface.¹ SBS is the main cause of chronic intestinal failure (IF) that occurs when gut function declines below the minimum necessary for the absorption of macronutrients and/or water and electrolytes, requiring intravenous supplementation for the maintenance of health and/or growth.¹

The traditional management of SBS involves the use of specialized diets, anti-diarrhoea/antisecretory drugs and parenteral nutrition (PN) or intravenous fluids (IVF) to meet nutritional requirements, while intestinal transplantation is applied only in patients that cannot be managed with traditional approaches.² New pharmacological therapies for SBS have been aimed at improving intestinal adaptation to increase the bowel absorption capacity and reduce the patient's dependence on PN. However, somatotropin demonstrated only temporary beneficial effects in all randomized clinical trials, because the increased body weight and intestinal absorption disappeared after the therapy was discontinued.²⁻⁴ Teduglutide, a recombinant glucagon-like peptide 2, was able to increase both the height of intestinal villi and the depth of crypts,²⁻⁴ inducing a reduction of PN volume (in 79% of the cases) or PN

discontinuation (in 21% of the cases).⁵ However, the elevated cost of this drug and its unavailability in many European countries are limits to its use.

A different therapeutic approach to the treatment of SBS was attempted by Lange et al⁶ through the use of modified cereals (SPC-Flakes, Medifood, Switzerland) that stimulate the endogenous production of the antisecretory factor (AF). This hormone controls water and electrolyte transport through cellular membranes by inhibiting GABAergic effects on intestinal epithelium.^{7,8} Davidson and Hickey⁹ have also suggested a possible role of AF as an anti-inflammatory agent. Most of the AF in plasma is present in inactive form and is activated after exposure to intestinal bacteria or after the intake of foods that create a hypertonic environment in the intestine.¹⁰ Clinical studies in patients suffering from inflammatory bowel diseases and neuroendocrine tumours treated with SPC-Flakes have yielded encouraging results.¹¹⁻¹⁴ On the contrary, in patients with SBS, the number of bowel movements remained unmodified during and after treatment with SPC-Flakes (54 g/day) for 2 weeks.⁶ However, the latter study suffered from some limitations: (1) only the number of bowel movements was evaluated and not faecal volume; (2) the SPC-Flakes dosage was not adjusted for body weight as recommended by the producer; (3) the period of administration of SPC-Flakes was too short (the



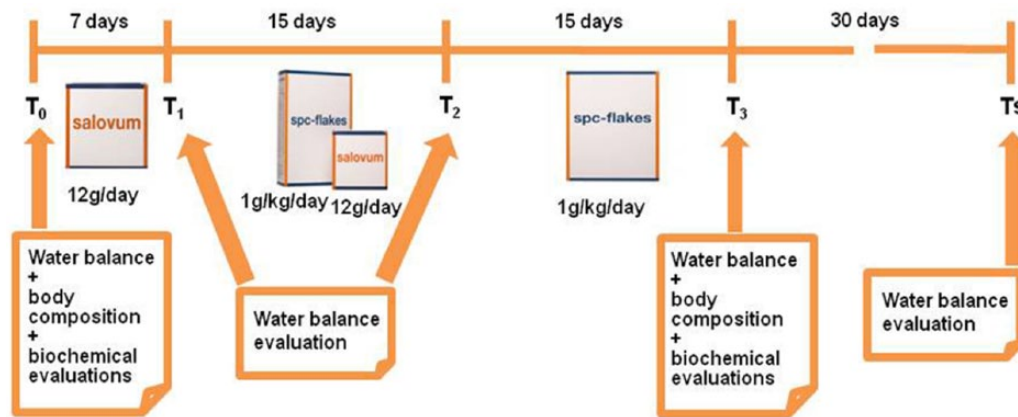


Figure 1. Study design. It describes length and type of treatment, Salovum and SPC-Flakes dosages, and parameters evaluated at specific intervals.

endogenous AF is activated between 14 and 28 days after administration of SPC-Flakes); (4) the administration of the exogenous AF (Salovum, PIAM Farmaceutici SPA, Genova, Italy) was not tested.

In our study, we evaluated, for the first time, the effect of Salovum alone followed by a combination of Salovum with SPC-Flakes and then SPC-Flakes alone, administered for a total duration of 37 days in patients with SBS and chronic IF undergoing PN. To this purpose, intestinal absorption, hydration, nutrition, and inflammation were assessed to evaluate the possibility of reducing the PN/IVF support.

Methods

We enrolled 7 patients affected by SBS with chronic IF requiring PN support. These patients were followed as outpatients by the nutritional team of the Gastroenterology Unit. We excluded patients with acute IF or chronic IF due to causes other than SBS, and patients with faecal volume/stoma effluent <300 mL/day. Informed consent was obtained from each patient, and the study was conducted in agreement with the ethical guidelines of the Declaration of Helsinki and received the approval by the local Ethics Committee.

Before enrolment, all patients were invited to discontinue their chronic anti-diarrhoea therapies. At baseline (T_0), in addition to demographic and clinical data, the following parameters were recorded: faecal volume/stoma effluent, urinary volume, PN volumes, amount of liquid taken orally, weight, height, lean mass (FFM), total body water (TBW), extracellular water (ECW), dietary intake, and blood tests.

According to the clinical classification of chronic IF proposed by Pironi et al,¹ taking into account the calories and liquids infused, our patients were categorized into subtypes.

The daily faecal volume/stoma effluent, urinary volume, and oral liquids intake were obtained by calculating the average of 3 consecutive days. Weight and height were measured using a digital scale with altimeter (Soehnle 7831, Soehnle srl Italy, Como, CO, Italy), and the body mass index (BMI) was expressed as kg/m².

FFM, TBW, and ECW were measured by bioelectrical impedance analysis (BIA 101, Akern srl, Pontassieve, FI, Italy) and expressed as percentage of body weight.¹⁵ TBW values were considered normal at 50% to 60% in men and 55% to 65% in women, and ECW values at 43%.¹⁶

To evaluate the daily dietary intake, an experienced dietitian collected a dietary history and, with the help of software (Winfood3, Medimatica Srl, Colonnella, TE, Italy), calculated the average calorie intake. C-reactive protein (CRP) was measured to assess the patients' inflammation status, while albumin, transferrin, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides were measured to assess nutritional status.

Patients were invited to take SPC-Flakes without food or beverages, dividing the total daily amount in 3 administrations. Salovum was taken with bread in 3 doses per day. Study design was reported in Figure 1.

Statistical analysis was performed using Wilcoxon exact test for paired data. Statistical significance was set at $P < 0.05$ and was performed using SPSS version 21.0 software.

Results

Among the 7 patients enrolled in the study, 2 patients discontinued treatment within the first week due to side effects (abdominal pain, increased stoma effluent and decreased diuresis). In addition, 1 patient was excluded from the analysis because, after the end of the study, he was affected by pancreatic cancer.

Among the remaining 4 patients, 1 discontinued the treatment before T_3 because he developed an acute infectious gastroenteritis. None of these 4 patients suffered treatment-related side effects. Demographic and clinical characteristics of these patients are shown in Table 1.

All patients were adults with a good nutritional status (stable body weight and normal BMI). According to the clinical classification of chronic IF proposed by Pironi et al,¹ 2 patients were classified as B2 subtype, 1 patient as C2 subtype, and 1 patient as C3 subtype.

Table 2 shows the water balance comparing the faecal volume/stoma effluent, the urinary volume, and the oral liquid intake volume at T₁, T₂, T₃, and T_s with baseline (T₀). Input fluids (PN and oral liquid intake) remained constant throughout the treatment. Statistical analysis showed no statistically significant differences in faecal volume/stoma effluent at T₁ (after therapy with Salovum), at T₂ (after combination therapy with Salovum plus SPC-Flakes), at T₃ (after therapy with only SPC-Flakes), and at T_s (30 days after the end of treatment) compared with T₀. However, a trend towards increased of faecal volume/stoma effluent was observed at T₃. No statistically significant change in diuresis was noted.

At the end of treatment, there were no changes of either weight or dietary intake, or FFM (Table 3).

At the beginning of the treatment, 2 of the 3 patients showed a TBW under the normal values that did not change significantly at the end of treatment. However, a trend towards increased of ECW was observed at T₃.

Table 1. Demographic and clinical characteristics of patients.

No. of patients	4
M/F	3/1
Age (mean ± SD)	66.5 ± 9.9
BMI (mean ± SD)	24.2 ± 2.3
No. of patients with/without enterostomy	2/2
Diagnosis	
• Crohn disease	1
• Complicated diverticulitis	1
• Intestinal infarction	2
PN volume (mL) (mean ± SD)	1683.2 ± 558.8
Calorie intake by PN (kcal) (mean ± SD)	731.2 ± 197.2

Abbreviations: BMI, body mass index; PN, parenteral nutrition.

Table 2. Water balance during and after treatment.

	T ₀ VS T ₁	P ^a	T ₀ VS T ₂	P ^a	T ₀ VS T ₃	P ^a	T ₀ VS T _s	P ^a
N. of pts.	4 vs 4		4 vs 4		3 vs 3		3 vs 3	
Faecal or stoma effluent volume	928.0 ± 509.6 vs 1021.5 ± 606.0	0.62	928.0 ± 509.6 vs 977.7 ± 557.9	0.62	726.3 ± 381.6 vs 907.3 ± 382.9	0.25	726.3 ± 381.6 vs 1020.0 ± 651.0	0.50
Urinary volume	1735.0 ± 621.8 vs 1832.0 ± 647.6	0.25	1735.0 ± 621.8 vs 1711.0 ± 670.6	0.87	1952.3 ± 544.7 vs 1772.3 ± 909.9	0.75	1952.3 ± 544.7 vs 1879.0 ± 740.6	0.75
Oral liquids taken	833.2 ± 514.6 vs 879.2 ± 668.7	0.87	833.2 ± 514.6 vs 966.7 ± 803.0	1	1016.6 ± 442.0 vs 1141.6 ± 764.7	1	1016.6 ± 442.0 vs 1091.6 ± 787.5	1

All volumes reported are expressed as ml. Values are expressed as mean ± SD.

^aBy Wilcoxon exact test.

Biochemistry parameters of nutritional status and inflammation state also remained constant (Supplementary Table I).

Discussion

The management of the SBS is challenging, because even the new therapies are not completely effective, are expensive, are associated to significant side effects, and are not always able to allow a complete discontinuation of PN. Therefore, it is important to find new strategies that can overcome these limitations. Our study was conducted in an attempt to improve the intestinal absorption in patients with SBS, using foods for special medical purposes already available on the market in America and Europe, which are inexpensive and safe.

In the past, Lange et al⁶ did not achieve good results with SPC-Flakes when administered in patients with SBS. However, this failure could be explained by the fact that the endogenous AF production is reduced in relation to the intestinal length.⁶ Moreover, the dosage and duration of therapy were not adequate. Our study endeavoured to overcome these limitations by proposing treatment with Salovum, which does not require intestinal integrity for its activation, followed by an adequate dosage and duration of SPC-Flakes.

Our study showed that Salovum does not improve the intestinal absorption in patients with SBS either when used alone or in combination with SPC-Flakes. Indeed, monotherapy with SPC-Flakes leads a trend towards increased intestinal secretions, probably as a result of the hypertonic environment, determining a further passage of liquids in the impaired intestine that is unable to activate sufficient amounts of endogenous AF. This increase did not reach statistical significance for the low number of patients. However, the increase of the intestinal secretions did not induce dehydration because the TBW remained stable. The nutritional status and inflammation state were not affected by the treatment.

The high proportion of patients suffering side effects and the poor efficacy of the therapy caused us to suspend the study and any further enrolment of patients.

Table 3. Anthropometric evaluations and body composition before (T_0) and after treatment (T_3).

	T_0	T_3	P^a
Weight (kg)	63.1 ± 6.0	62.8 ± 6.3	1
Dietary intake (kcal)	1165.6 ± 257.2	1302.6 ± 572.0	0.75
FFM (%)	63.6 ± 8.6	65.3 ± 9.0	0.50
TBW (%)	49.6 ± 7.2	50.6 ± 7.3	0.50
ECW (%)	49.3 ± 8.0	52.3 ± 6.1	0.25

Data obtained in 3 patients are expressed as mean ± SD.

Abbreviations: ECW, extracellular water; FFM, lean mass; TBW, total body water.

^aBy Wilcoxon exact test.

In conclusion, the exogenous administration of AF or stimulation of endogenous AF does not seem to offer an effective antisecretory and anti-inflammatory therapy in patients with SBS.

Author Contributions

MTV and MB equally contributed to the conception and design of the research; MTV contributed to the acquisition and analysis of the data; MTV and MB contributed to the interpretation of the data; MTV, ADL, and MB drafted the manuscript. All authors critically revised the manuscript, agree to be fully accountable for ensuring the integrity and accuracy of the work, and read and approved the final manuscript.

Supplemental material

Supplemental material for this article is available online.

ORCID iD

Michele Barone  <https://orcid.org/0000-0001-8284-5127>

REFERENCES

1. Pironi L, Arends J, Baxter J, et al. ESPEN endorsed recommendations. Definition and classification of intestinal failure in adults. *Clin Nutr*. 2015;34:171–180.
2. Kelly DG, Tappenden KA, Winkler MF. Short bowel syndrome: highlights of patient management, quality of life, and survival. *JPEN*. 2014;38:427–437.
3. Jeppesen PB, Pertkiewicz M, Messing B, et al. Teduglutide reduces need for parenteral support among patients with short bowel syndrome with intestinal failure. *Gastroenterology*. 2012;143:1473.e3–1481.e3.
4. O'Keefe SJ, Jeppesen PB, Gilroy R, Pertkiewicz M, Allard JP, Messing B. Safety and efficacy of teduglutide after 52 weeks of treatment in patients with short bowel intestinal failure. *Clin Gastroenterol Hepatol*. 2013;11:815.e1–e3–823.e1–e3.
5. Pevny S, Maasberg S, Rieger A, et al. Experience with teduglutide treatment for short bowel syndrome in clinical practice [published online ahead of print August 2, 2018]. *Clin Nutr*. doi:10.1016/j.clnu.2018.07.030.
6. Lange S, Bosaeus I, Jennische E, Johansson E, Lundgren BK, Lonnroth I. Food-induced antisecretory factor activity is correlated with small bowel length in patients with intestinal resections. *APMIS*. 2003;111:985–988.
7. Lange S, Lonnroth I, Palm A, Hyden H. The effect of antisecretory factor on the permeability of nerve cell membrane to chloride ion. *Pflugers Arch*. 1987;410:648–651.
8. Rapallino MV, Cupello A, Lange S, Lonnroth I. Antisecretory factor peptide derivatives specifically inhibit [3H]-gamma-amino-butyric acid/36Cl⁻ out→in permeation across the isolated rabbit Deiters' neuronal membrane. *Acta Physiol Scand*. 2003;179:367–371.
9. Davidson TS, Hickey WF. Distribution and immunoregulatory properties of antisecretory factor. *Lab Invest*. 2004;84:307–319.
10. Johansson E, Lonnroth I, Jonson I, Lange S, Jennische E. Development of monoclonal antibodies for detection of antisecretory factor activity in human plasma. *J Immunol Methods*. 2009;342:64–70.
11. Bjorck S, Bosaeus I, Ek E, et al. Food induced stimulation of the antisecretory factor can improve symptoms in human inflammatory bowel disease: a study of a concept. *Gut*. 2000;46:824–829.
12. Eriksson A, Shafazand M, Jennische E, Lange S. Effect of antisecretory factor in ulcerative colitis on histological and laborative outcome: a short period clinical trial. *Scand J Gastroenterol*. 2003;38:1045–1049.
13. Finkel Y, Bjarnason I, Lindblad A, Lange S. Specially processed cereals: a clinical innovation for children suffering from inflammatory bowel disease. *Scand J Gastroenterol*. 2004;39:87–88.
14. Laurenus A, Wangberg B, Lange S, Jennische E, Lundgren BK, Bosaeus I. Antisecretory factor counteracts secretory diarrhoea of endocrine origin. *Clin Nutr*. 2003;22:549–552.
15. Viggiani MT, Lorusso O, Natalizio F, Principi M, Di Leo A, Barone M. Influence of chemotherapy on total energy expenditure in patients with gastrointestinal cancer: a pilot study. *Nutrition*. 2017;42:7–11.
16. Sengun S, Uslu A, Aydin S. Application of multifrequency bioelectrical impedance analysis method for the detection of dehydration status in professional divers. *Medicina (Kaunas)*. 2012;48:203–210.