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ORIGINAL ARTICLE

Role of a berberine-based nutritional supplement in reducing diarrhea in subjects with functional gastrointestinal disorders

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ABSTRACT

BACKGROUND: Berberine, an alkaloid obtained by extraction from *Berberis* spp., is a botanical that is widely used in the nutraceutical sector to control cholesterol and blood glucose levels. It is also a molecule that is effective in limiting diarrhea due to its multi-factorial properties, including its antimicrobial, gut eubiotic and antisecretive actions, and its ability to slow gut motility. In our routine clinical practice, we have suggested the use of a berberine-based nutraceutical, formulated with melatonin and depolymerized guar gum, to patients affected by functional diarrhea (FD) or by diarrhea-type irritable bowel syndrome (IBS-D).

METHODS: We have therefore retrospectively analyzed the clinical effect of such a nutritional supplement in these two sub-groups of patients.

RESULTS: Despite the highly pragmatic scheme of our study, our findings strongly confirm the antidiarrheal properties of berberine and recommend its use in some gut functional diseases characterized by frequent evacuation of mushy and/or watery stools. In fact, even after 30 days of treatment, the berberine-based nutritional supplement significantly reduces diarrheal events by 50–70%. After 90 days, this reduction improves to between 70 and 80%, with a reduction of more than 60% in the number of evacuations per week and with more than 50% of treated subjects demonstrating normalized, according to self-reported Bristol Stool Scale categorization, stool consistency. The product is well tolerated and adherence to the proposed therapy is good. Common side effects of the product are flatulence and meteorism, likely due to the "acarbose-like" berberine effects on gut α-glucosidase.

CONCLUSIONS: Patients, especially those preferring "natural" therapy, can be successfully treated, when affected by a gut functional disease characterized by diarrhea, by berberine-based products.

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KEY WORDS: Diarrhea; Melatonin; Berberis.

Traditionally, gut functional diseases (GFD) are defined by more or less specific symptoms and the absence of structural or biochemical abnormalities that can explain these symptoms. GFD are often characterized by chronic or recurrent abdominal symptoms of pain, also associated with either relief or exacerbation by defecation, or a change in bowel habits.[1, 2] Some GFD, including functional diarrhea (FD) and irritable bowel syndrome (IBS), can present diarrhea as a main symptom. Diarrhea, the pathophysiology of which is well covered elsewhere,[3] can be easily self-reported by patients and readily classified in terms of the presence of mushy or liquid stools according to the Bristol Stool Scale.[4] Diarrhea severely affects patient quality of life[5] and is frequently the reason

why a patient requires medical consultation with a general practitioner and/or a gastroenterologist.[6] Currently, a number of therapies exist to manage diarrhea, including loperamide, anticholinergic agents, rifaximin, bile acid binding agents, eluxadoline, and clonidine, and several other new compounds, some of which have already been evaluated in humans, are currently undergoing drug development.[7] It is becoming more common, in consultation with both the general practitioner and the specialist in gastroenterology, that the patient now tends to require a therapy that is perceived by the patient to be "natural." Although the concept of "natural" in medical terms certainly makes little sense, physicians should be aware, if so, of the existence of natural remedies, with antidiarrheal action, that are well documented as being effective and safe for human use.[8] Berberine, widely used in the nutraceutical sector, is certainly one of these substances, among those that acknowledge a plant origin, that has been better documented. PubMed citations related to berberine (in June 2019) number approximately 5,400 papers describing this compound in the context of such areas as intestinal infectious disease, lipidology, cardiology, diabetology, liver disease, and, in the most recent literature, in the fields of neurology and oncology.[9] Specifically, starting from 1949, berberine has been documented for its antidiarrheal properties with particular reference to diarrhea caused by *E. coli*, *V. cholerae*, *C. difficile*, and *H. histolytica*, probably linked to its antimicrobial properties.[10-15] Starting from around 2015, berberine also began to be described as a eubiotic, a molecule that is in some way able to improve the richness of the gut microbial consortium and which promotes the growth of probiotic or commensal bacteria endowed with protective functions. *Bifidobacterium* spp. and *Akkermansia muciniphila*, for instance, have been reported to be increased in the gut of the treated host.[16, 17] The antidiarrheal effects of berberine, observed with administration of 400 mg/day upwards, also appear to be linked to its important antisecretory effects, evident above all in diarrhea caused by *V. cholerae* and *E. coli*.[18-20] The antisecretory effects of berberine appear to be due to three main mechanisms, including an increase in the expression of NHE3 (Na^+/H^+ exchanger 3) and of the aquaporin system, along with strengthening of the intestinal tight junctions.[21, 22] The issue, however, is likely to be more complex and the antisecretory effects of berberine are also partly due to inhibition of the release of chloride anions and blockage of potassium channels in the intestine.[23, 24] The observation concerning K^+ blockage suggests also a possible mechanism mediated by the μ and δ opioid receptors actually located at the intestinal level.[25] It is well known that interaction with these receptors produces a slowdown of gut motility. Indeed, this slowdown was measured after treatment with berberine in the small intestine and corresponds, in humans, to an increase in transit times of approximately 38%.[26-28] It is therefore highly probable that the antidiarrheal effects of berberine are also mediated by its ability to induce a slowing of duodenal motility. The antidiarrheal effects of berberine appear to be evident even with different forms of diarrhea, including FD. Berberine, for instance, reduces iatrogenic diarrhea caused by oral metformin used to treat diabetic patients.[29] Moreover, it significantly reduces the signs and symptoms of IBS and diarrhea episodes both in mice, with experimentally induced IBD-D, and in patients with IBS-D.[30, 31] Berberine is commercially available at higher doses (500 mg/tablet) than that required (approximately 200 mg/tablet) to treat diarrhea, being a molecule that is widely used mainly for dyslipidemia and hyperglycemia.[32] Berberine has a very strong bitter taste and it is not possible to split tablets in two or administer it as a powder.[33] Therefore, in our routine practice we have suggested to subjects affected by FD (and those with IBS-D), who prefer not to use conventional pharmaceuticals, the use of a product developed to reduce diarrhea that also contains a lower quantity of berberine than usual (see the Materials and methods section). Our study is therefore a retrospective analysis of our recent clinical routine practice, with the aim of highlighting the role played by a nutritional supplement containing berberine in subjects with chronic FD.

Materials and methods

Study design and aim

Our study encompassed a retrospective analysis of the data obtained from routine procedures

conducted in the Digestive Endoscopy Dept. at Ceva Hospital (Italy) between June 2017 and May 2019. The aim of the study was to investigate the role played by a berberine-containing nutraceutical product in counteracting the condition of chronic FD. All patient data were completely anonymized and the study was performed in accordance with the ethical standards established by the local (CN) institutional committee. Despite the retrospective and anonymized features of the study, all patients submitted signed informed consent to publish the results.

Patient selection

Subjects considered eligible for our retrospective analysis were those diagnosed as being affected by FD or those with a diagnosis of IBS-D according to the Rome IV criteria for colorectal disorders.[34] We then excluded from our retrospective analysis celiac patients, subjects with wheat allergy or with lactose or oligosaccharide intolerance, or patients with a diagnosis of diverticular disease, or those affected by inflammatory bowel disease (IBD). We also excluded patients receiving treatment with antibiotics, rifaximin included, spasmolytics, and immunosuppressant drugs.

Analyzed parameters

Patients considered eligible were all those who agreed to complete a very basic questionnaire at the beginning of treatment. The questionnaires reported primary and secondary endpoints. The primary endpoints related to diarrhea (frequency, urgency, pain, burning, flatulence, meteorism, change in bowel habits) and stool consistency according to the Bristol Stool Scale. The symptoms relating to diarrhea listed above were each assessed on a 4-point scale (0: no symptoms, 1: mild, 2: moderate, 3: severe) at baseline and after 1, 2, and 3 months from the start of treatment while a total symptom score was calculated by summing the individual symptoms at each time point (maximum value: 21). By using the self-reported value obtained following categorization by the Bristol Stool Scale, we then analyzed stool consistency at baseline and after 3 months of treatment. The secondary endpoints were tolerability (0–10), declared adherence to the treatment (%), and the occurrence of side effects (the number of subjects and type of side effect observed during the period of treatment).

Treatment and product

Patients were recommended to use as a unique treatment a berberine-based nutraceutical, administered every day, every 12 hours, for 90 days. The product used was Dibiesse® coated tablets. Each tablet contains 250 mg of berberine (from *Berberis aristata* extract, standardized to not less than 97% of pure berberine); melatonin (0.5 mg); and depolymerized guar gum (DGG, 750 mg). The product is manufactured by Nutrilinea (Gallarate, VA, Italy) and traded by Pharmextracta (Pontenure, PC, Italy). The product was notified to the Italian Health Authorities in 2017 with notification number 92540.

Statistical analysis

The difference in terms of outcome was determined using the two-tailed Wilcoxon–Mann–Whitney test. The statistical software used was JMP 10 for Mac OsX and the threshold for statistical significance was 95%.

Results

Our study comprised a single-group, retrospective evaluation of the findings obtained by our routine clinical practice in managing subjects with FD or with diarrhea because of a diagnosis of IBS-D. As shown in Table I, along with demographic characteristics, eligible subjects had not been newly diagnosed and presented a high number of evacuations per week. All patients enrolled for our evaluation did ask for natural and possibly effective treatment, and were treated for 3 months with a berberine-based supplement. The trend regarding diarrhea symptoms is shown in Table II. The response to treatment was clearly apparent after the first month of treatment, where a reduction in symptom scores of approximately 50 and 70% is shown for IBS-D and FD, respectively. The trend continues with further treatment, reaching a reduction of more than 70 and 80% after 90 days of treatment for IBS-D and FD, respectively. Comparing the two sub-groups, berberine seems to be more effective in subjects with FD, where

TABLE I.—*Demographic and clinical characteristics of enrolled patients.*

Sex	N.	Age (year)	IBS-D/FD	Evacuations/week^	Time from diagnosis (months)
M	22	36.5±11.8	15/7	27.3±4.5	77.3±11.0
F	17	32.8±12.4	9/8	25.8±6.2	59.3±7.6

For IBS-D and FD the number of subjects per group is shown.
IBS-D: diarrhea-type irritable bowel syndrome; FD: functional diarrhea.
^Average value between F and M: 26.5±5.2.

TABLE II.—*Trend in total symptom score (average ± standard deviation) at baseline (T0) and after 1, 2, and 3 months of treatment.*

Group	T0	T1	T2	T3	Δ (T3 *vs.* TO)	E/W (T3)
IBS-D	15.4±2.8	8.6±1.9°	3.9±0.6^	4.2±0.4^	-72.7%	9.2±1.5*
FD	14.3±3.5	4.2±1.2^	2.9±0.3^	2.5±0.4^	-82.5%	8.9±1.4*

E/W (T3): number of evacuations per week after 3 months of treatment.
°P<0.01 *vs.* T0; ^P<0.001 *vs.* T0; *P<0.001 *versus* the same parameter registered at baseline and shown in Table I.

TABLE III.—*Self-reported Bristol Stool Scale (BSS) categorization evaluated at baseline (T0) and 3 months (T3) after the beginning of therapy. The number of subjects reporting each stool type is shown.*

BSS	IBS-D		FD		p (IBS-D)	p (FD)
	T0	T3	T0	T3	T3 *vs.* T0	T3 *vs.* T0
1	0	0	0	0	NS	NS
2	0	2	0	1	NS	NS
3	0	5	0	4	<0.01	<0.01
4	0	4	0	8	<0.01	<0.001
5	3	9	1	1	<0.01	NS
6	13	3	7	1	<0.01	<0.01
7	8	1	7	0	<0.01	<0.01

NS: not significant; IBS-D: diarrhea-type irritable bowel syndrome; FD: functional diarrhea.

the results compared to baseline become highly significant after only 30 days (*versus* 60 days for IBS-D). The number of evacuations per week is reported in Table I (baseline values) and in Table II (the values after 90 days). As shown, the berberine-based treatment reduced the number of evacuations by approximately 66% in both sub-groups. Table III reports the data relating to fecal consistency. The effect of the berberine-based product was very significant, and after 3 months, only 4 patients out of 21 at baseline still reported mushy or watery stool consistency in the IBS-D sub-group; similarly, in the FD sub-group, out of 14 subjects with stool types 6 and 7 as categorized by the BSS, only 1 subject still reported mushy stool consistency. As stool types 3 and 4 are considered "normal", 9 and 12 subjects in the IBS-D and FD sub-groups, respectively, reported normal stool consistency after 90 days of treatment. In both sub-groups, the results are highly significant. Finally, the secondary endpoints are presented in Table IV Tolerability to the treatment was acceptable in both sub-groups, while the declared adherence to therapy was very high for both sub-groups. Unexpectedly, side effects affected 17 (out of 24) and 10 (out of 15) patients within the IBS-D and FD sub-groups, respectively. Most patients reported flatulence and meteorism as the main side effect. Indeed, many researchers have reported the same side effects when berberine was used to control cholesterol and/or blood glucose. This unwanted effect could be due to the well-known action of berberine on gut glucosidase, and has also been reported as an acarbose-like effect.[35, 36]

Discussion

Our retrospective study represents our certainly pragmatic approach to treating diarrhea in patients with FD, and in those with IBS-D, requesting

TABLE IV.—*Tolerability (average±standard deviation), adherence (%), and side effects (number of subjects/total subjects) associated with therapy with a berberine-based supplement as evaluated at the end of treatment (90 days).*

Parameter	IBS-D	FD
Tolerability	7.5±1.5	8.2±1.0
Adherence	>95%	>95%
Side effects*	17/24	10/15

IBS-D: diarrhea-type irritable bowel syndrome; FD: functional diarrhea.
*In both the IBS-D and FD groups, most of the subjects reported flatulence and meteorism as the main side effect; only 2 subjects per group reported skin rashes (lasting 3–4 days) and 1 subject in the FD group reported gastric burning for the first week of treatment.

from general practitioners and specialists a "natural" but effective treatment. Our main option, according to our routine practice, is berberine. In our opinion, the results of our analysis demonstrate, as perhaps expected, the clinical efficacy of this alkaloid of botanical origin in significantly reducing the phenomenon of diarrhea, restoring in most cases a normal, or quasi-normal, stool consistency. This may be attributable not only to the ability of berberine to reduce small intestine transit time, but also, to the eubiotic properties of berberine, which have mainly been reported to favor *Bifidobacterium* spp. and *Akkermansia muciniphila*. The tested nutritional supplement does not contain berberine alone. It also contains low doses of melatonin and DGG. Both have been described, to different extents, as improving gut symptoms associated with IBS and to limit FD and/or iatrogenic diarrhea.[37-41] DGG has also been reported to play a role in improving the gut microbiota with regards to *Parabacteroides* taxa, normally affected in patients with IBS.[42, 43]

Limitations of the study

We are aware that our single-group, retrospective analysis has limitations. First of all, this has not been a prospective, randomized, double-blind, placebo-controlled clinical trial where the results would surely carry more weight. Second, our analysis does contain some important bias. For instance, we did not control any aspect of diet. Moreover, our observation lasted only three months and did not evaluate what happens during wash-out and when, or if, diarrhea occurs again. In addition, we have used only one dose of berberine (250 mg × 2/day). It could be that by using a different dosage, different results would be obtained. Finally, our observations were carried out on only 39 patients.

Conclusions

Despite all these, and perhaps even more limitations, we believe our study allows us to confirm the antidiarrhea role played by berberine and, at least in our experience, its effectiveness in cases of FD. In conclusion, berberine or a berberine-based product containing a single dose of approximately 250 mg of pure compound administered twice a day can be considered valid tools for a pragmatic approach to treating patients with non-organic diarrhea, especially when a non-conventional pharmaceutical treatment is preferred by the patient.

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Conflicts of interest.—Francesco Di Pierro is part of the scientific board of Pharmextracta. All other authors declare no conflicts of interest.

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