STW 5 (Iberogast) Therapy in Gastrointestinal Functional Disorders

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Keywords

Clinical study · Multi-target · Evidence-base

Abstract

Background: Functional gastrointestinal disorders (FGIDs) are very common and affect populations worldwide. A majority of patients are affected by a variety of heterogeneous gastrointestinal symptoms (GIS) related to the upper and lower digestive system with frequent overlap and mostly of mild to moderate degree. The herbal medicinal preparation STW 5 is documented as an effective therapeutic option for treating FGID. **Studies Conducted in Summary:** STW 5 has been in use for more than 50 years in clinical practice and proven to be effective and safe in the management of FGID. The high efficacy of STW 5 on symptoms clustered in functional dyspepsia (FD) and irritable bowel syndrome (IBS) as well as on individual abdominal symptoms is demonstrated in 5 controlled, randomized double-blind studies in FD and in one trial conducted in patients with IBS. In addition the beneficial therapeutic effect of STW 5 on FGD as well as safety issues have been reported in a series of non intervention-al studies conducted in several thousands of adult patients and including 980 children. An additional study has been performed addressing the question as to how quickly the therapeutic effect is obtained after STW 5 administration. **Key Messages from These Studies:** STW 5 is an effective phyto-medication for treating patients with FD and IBS. STW 5 acts beneficially on abdominal symptom clusters as well as

on individual GIS in adults and children. The time to onset of action is rapid, well tolerated and safe. The repetitive use of STW 5 is an appropriate option in clinical practice for patients with FGID.

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Published by S. Karger AG, Basel

Introduction

Functional gastrointestinal disorders (FGIDs) are very common and affect populations worldwide. FGID are more prevalent in communities adhering to the western lifestyle [1], since these disorders are significantly influenced by dietary habits [2]. The burden of disease is significant for the individual patient as well as for the society with respect to health economics. There is ongoing research in developing new and effective therapies for FGID. This development faces several challenges:

- Symptoms of FGID are reported according to different anatomical and functional classifications such as the upper and the lower gastrointestinal tract. Symptoms are by convenience attributed to either functional dyspepsia (FD) and irritable bowel syndrome (IBS), but even then the symptoms are heterogeneous and overlapping between the various classifications.
- There are multiple etiologies and pathomechanisms as possible origins of the clinically noted symptoms. These etiologies and pathomechanisms in clinical

Table 1. Clinical studies with STW 5 in the treatment of FD

Reference	Targeted complaints	Design	Number of patients: total/STW 5	Study aim
[4]	Non-ulcer dyspepsia	Double-blind, placebo-controlled	243/82	Efficacy superior to placebo
[5]	Functional dyspepsia	Double-blind, placebo-controlled	60/20	Efficacy superior to placebo
[6]	Functional dyspepsia	Double-blind, reference-controlled, double-dummy	186/61	Efficacy equivalent to cisapride
[7]	Functional dyspepsia	Double-blind, placebo-controlled	308/157	Efficacy superior to placebo
[8]	Functional dyspepsia with emphasis on gastric emptying	Double-blind, placebo-controlled	103/44	Efficacy superior to placebo

practice are usually difficult to attribute to the individual patient.

- Based on these considerations, it is very difficult to identify a specific targeted therapy for an individual patient. Best responses in targeted therapy are currently obtained in patient groups diagnosed with well-defined symptoms such as acidic reflux or epigastric pain in FD, or of diarrhea or constipation in IBS.

A recent symposium report with focus on the therapeutic management of IBS by adopting stringent criteria of an evidence-based approach illustrates an important but selective progress in patients with well-defined symptom patterns. However, the report also gives evidence for the significant limitations of the currently available treatment approaches [3]. The conclusion of the report recognizes the role of the clinician in the integration of the best available evidence from clinical trials into the own clinical experience, which enables the individual patient to get the best of treatment with the least risk.

A majority of patients are affected by a combination of various and heterogeneous gastrointestinal symptoms (GIS) of mild or moderate degree. For this group of patients, the herbal medicinal preparation STW 5 has been shown to provide significant therapeutic benefits.

In basic and translational research, this herbal combination product consisting of 9 extracts from medicinal plants has shown to have distinct activities exerted on gastrointestinal motor functions and pain perception including visceral hypersensitivity [Allescher and Abdel-Aziz, in this issue]. The therapeutic experience with STW 5 was founded based on its clinical use for more than 50 years in Germany. A notable number of clinical trials has been conducted over the years, confirming a significant benefit and providing reassuring experience with respect to safety.

In this study, we report on the clinical experience we have had with STW 5 as a multi-target approach in FD and IBS, and on its effect on individual symptoms related to these functional gastrointestinal syndromes.

STW 5 in FD and the Treatment of Symptoms of the Upper Gastrointestinal Tract

Five controlled, randomized double blind studies were conducted with STW 5 in patients with FD (Table 1). Comparators were placebo in 4 of these studies, and the prokinetic drug cisapride (today no longer in use for safety reasons) in one trial. In all studies, STW 5 was shown to have a significant beneficial effect, superior to that of the placebo. In the case of the reference-controlled trial, the efficacy of STW 5 was found to be equivalent to that of the prokinetic drug. In none of these studies, there were relevant safety concerns with STW 5.

STW 5 has a long and positive reputation from empirical evidence in the treatment of patients with GFD. The first prospective trial was reported in 1994 and included 243 patients with a defined GFD. The authors reported a significant improvement versus placebo with 2 different preparations: STW 5 (commercial preparation Iberogast) and an experimental preparation with only 6 herbal extract constituents (STW-II) [4]. No difference was noted in the therapeutic efficacy between STW 5 and STW-II. Significance over placebo was also confirmed for STW 5 in a double-blind, placebo-controlled trial involving 60 patients affected by FD [5].

A larger, multicentre and placebo-controlled trial with 308 patients with FD was then performed to provide a better database with respect to patient numbers and diagnosis. In this study, the diagnostic criteria for

Fig. 1. Changes of gastrointestinal summary (GIS) score in 8 weeks of treatment [7].

FD were strictly adhering to Rome II-criteria. Therapy was accordingly targeted to specific symptom characteristics [7]: postprandial fullness, early satiety, epigastric pain and epigastric burning. Following a wash-out phase of 7 days, patients were randomized to 8 weeks of treatment with either STW 5 (3×20 drops/day) or placebo. The primary endpoint was a change in the GIS score after 4 and 8 weeks. An improvement of the GIS was observed in both groups (Fig. 1) but was found significantly higher in the STW 5 group than it was with placebo. This difference was deemed clinically important. Assessments of global efficacy by investigators and patients confirmed the observed superiority of STW 5. It is important to emphasize that during the 6-month follow-up, patients treated for 8 weeks with STW 5 remained free of recurrent episodes for a longer period than patients who had received placebo. There were no clinically relevant changes of laboratory parameters and no serious adverse events during the study period. The proportion of patients reporting non-serious adverse events was not different in both treatment groups [7].

In another trial, the effect of STW 5 was compared with the effect of the prokinetic agent cisapride, assuming a specific effect on dysmotility-related symptoms [6]. The primary endpoint of this non-inferior trial was the improvement of the GIS after 4 weeks. Forty-three patients receiving STW 5 and 45 patients treated with cisapride were included in the confirmatory analysis. Both substances did not differ in their efficacy, with the expected advantage of STW 5 of having a better safety profile [6].

The finding of Rösch et al. [6] is supported by a clinical-experimental study conducted among healthy subjects. It was found that STW 5 has a dual effect on the stomach – it brought about a relaxation of the gastric fundus and enhanced the motility of the antrum [9].

Overall, a beneficial effect of STW 5 can be anticipated in the individual patient with symptoms related to gastric dysmotility. However, this effect is not based on the regulation of gastric emptying. Braden et al. [8] included 103 patients with FD in a randomized clinical trial. The patients were treated for 28 days either with STW 5 or with placebo. The primary end point of the study was symptom improvement based on a validated GIS score. The measurement of the effect of STW 5 on gastric emptying was a secondary study parameter. Patients underwent a ¹³C octanoic acid breath test for the assessment of the gastric half-emptying time. Treatment with STW 5 resulted in an improvement of the GIS ($p = 0.08$) and in a higher proportion of patients with symptom response compared to placebo ($p = 0.03$). STW 5 had, however, no effect on gastric emptying when compared with placebo [8]. The beneficial effects of STW 5 observed in this study were, therefore, most likely related to changes of visceral perception or hypersensitivity.

STW 5 in IBS and the Treatment of Symptoms of the Lower Gastrointestinal Tract

The beneficial application of STW 5 in the treatment of IBS is shown in more than 3,000 patients in non-interventional studies. Klein-Galzcinsky and Sassin [10] reported a

Fig. 2. Percentage of patients with time of onset of symptom relief following STW 5 intake on the first day of therapy (study reported in [13] and additional data obtained from authors).

4-week observational study on therapy with STW 5 in 2,548 patients with IBS. At the end of the study, a significant improvement of all individual symptoms by more than 65% was reported. The global effect was rated as “very good” or “good” in 81% of cases by physicians and in 78% of cases by patients themselves. Tolerability was rated in 98% of patients participating in the study as “very good” or “good” [10].

Vinson and Radke [11] conducted a non-interventional study with STW 5 in 980 children with FGID for one week. They received STW 5 at a dose of 10–20 drops 3 times daily. Symptoms were assessed on a GIS composed of 14 items included in FD and IBS symptoms. The sum of the score of upper and lower GIS was reduced from 16.1 ± 18.9 score points to 3.8 ± 4.2 score points, with 38.6% of children reporting complete relief and absence of symptoms. Tolerability was judged to be excellent or good in 94.8% of cases, with only 4 mild adverse events with potential relation to STW 5 reported [11].

The therapeutic effect of STW 5 on symptoms related to IBS observed in the non-interventional studies has been confirmed in a randomized, double-blind multicenter placebo-controlled clinical trial that was performed to investigate the efficacy and safety of STW 5 in patients with IBS [12]. A total of 208 patients were randomized to receive STW 5 in 2 different formulations or placebo, the study duration was 4 weeks. The primary study endpoint was the effect of STW 5 on an abdominal symptom score composed of 8 IBS-specific symptoms evaluated on the 4-point Likert scale. STW 5 reduced the

IBS symptom score and was significantly superior to placebo. Among individual symptoms, abdominal pain over all 4 abdominal quadrants showed a significant and clinically important response superior to placebo. The tolerability assessed by investigators and patients was “very good” or “good” (STW 5: 98% of cases; placebo: 89%; rating by physicians). No serious adverse events were reported [12].

Time to Onset of Clinically Measurable Effects of STW 5

An important clinical question concerns the time to the onset of symptom relief by STW 5 in FGID. This has been addressed in a recently published non-interventional multicentre study by Raedsch et al. [13] in 272 patients with FGID diagnosed according to Rome III criteria. The patients took STW 5 at a dose of 3×20 drops daily. Complaints were measured on a visual analogue scale (VAS), with reduction of symptom severity as early as 15 min after intake by 1.4 ± 1.7 cm VAS from 5.2 ± 3.2 cm at baseline. After 1 h, more than 90% of the maximum effect of an improvement by 3.2 ± 2.6 cm VAS was reached. Improvements were also found on the GIS score, with a mean reduction from 12.5 ± 6.1 to 3.5 ± 3.8 points at the end of the study ($p < 0.0001$). The substantial improvement of symptoms rapidly obtained after the intake of STW 5 is shown in Figure 2. Tolerability was excellent, with none of the 4 adverse events considered related to STW 5 intake [13].

Safety of STW 5

The safety profile of STW 5 has been carefully evaluated in all prospective randomized trials, with additional data obtained from non-interventional studies. The incidence of adverse events documented with STW 5 in controlled clinical trials is very low and not different from placebo. The observations included usual minor and transient, mostly gastrointestinal adverse events, with few patients reporting hypersensitivity. No abnormal values in clinical blood chemistry were reported from the studies where they were included. STW 5 was well tolerated in all examined populations (including children), independent of concomitant diseases. There was no hint of STW 5 having any kind of interactions with other drugs [11, 14].

Conclusion

STW 5 is an evidence-based herbal medicinal preparation approved for use in the therapy of FD and IBS. The evidence is based on 5 controlled, randomized double

blind studies in FD and one in IBS. A fast onset of effects was also demonstrated; these effects contribute to the therapeutic benefit. The observations from controlled trials are corroborated by large observational and post-marketing studies. STW 5 is effective in relieving several individual abdominal symptoms in the context of IBS, although it is not a specific drug for diarrhoea or constipation in general.

STW 5 is included in German therapy guidelines for both upper and lower FGID [15, 16]. STW 5 shows a favorable safety and tolerability profile important for a preparation used for FGID, which usually require repetitive, intermittent or long-term therapy. The positive safety profile is further underlined by the experience gathered from children with functional abdominal symptoms [11].

Disclosure Statement

Advisory board: Steigerwald.
Speakers fee: Bayer-Steigerwald.

References

- 1 Lovell RM, Ford AC: Global prevalence of and risk factors for irritable bowel syndrome: a meta-analysis. *Clin Gastroenterol Hepatol* 2012;10:712–721.e714.
- 2 Zito FP, Polese B, Vozzella L, Gala A, Genovese D, Verlezza V, Medugno F, Santini A, Barrea L, Cargiolli M, Andreozzi P, Sarnelli G, Cuomo R: Good adherence to mediterranean diet can prevent gastrointestinal symptoms: a survey from southern Italy. *World J Gastrointest Pharmacol Ther* 2016;7:564–571.
- 3 Chey WD: Symposium report: an evidence-based approach to IBS and CIC: applying new advances to daily practice: a review of an adjunct clinical symposium of the American college of gastroenterology meeting October 16, 2016, Las Vegas, Nevada. *Gastroenterol Hepatol (N Y)* 2017;13(2 suppl 1):1–16.
- 4 Buchert D: Wirksamkeit und verträglichkeit von iberogast bei patienten mit gesicherter non-ulcus dyspepsie. *Z Phytother* 1994;15:45–46.
- 5 Madisch A, Melderis H, Mayr G, Sassini I, Hotz J: Ein phytotherapeutikum und seine modifizierte rezeptur bei funktioneller dyspepsie. Ergebnisse einer doppelblinden plazebo-kontrollierten vergleichsstudie. *Z Gastroenterol* 2001;39:511–517.
- 6 Rösch W, Vinson B, Sassini I: A randomised clinical trial comparing the efficacy of a herbal preparation STW 5 with the prokinetic drug cisapride in patients with dysmotility type of functional dyspepsia. *Z Gastroenterol* 2002;40:401–408.
- 7 von Arnim U, Peitz U, Vinson B, Gundermann KJ, Malfertheiner P: STW 5, a phytopharmakon for patients with functional dyspepsia: Results of a multicenter, placebo-controlled double-blind study. *Am J Gastroenterol* 2007;102:1268–1275.
- 8 Braden B, Caspary W, Börner N, Vinson B, Schneider AR: Clinical effects of STW 5 (Iberogast) are not based on acceleration of gastric emptying in patients with functional dyspepsia and gastroparesis. *Neurogastroenterol Motil* 2009;21:632–638.e625.
- 9 Pilchiewicz AN, Horowitz M, Russo A, Maddox AF, Jones KL, Schemann M, Holtmann G, Feinle-Bisset C: Effects of iberogast on proximal gastric volume, antropyloroduodenal motility and gastric emptying in healthy men. *Am J Gastroenterol* 2007;102:1276–1283.
- 10 Klein-Galzcinsky C, Sassini I: P25: Post-Marketing Surveillance of the Efficacy and Tolerability of Iberogast for the Therapy of Colon Irritable: 10th Annual Meeting of the German Society for Phytotherapy, 11–13 November. Münster, 1999, p 125.
- 11 Vinson B, Radke M: The herbal preparation STW 5 for the treatment of functional diseases in children aged 3–14 years: a prospective non-interventional study. *Gastroenterology* 2011;140:S102.
- 12 Madisch A, Holtmann G, Plein K, Hotz J: Treatment of irritable bowel syndrome with herbal preparations: results of a double-blind, randomized, placebo-controlled, multi-centre trial. *Aliment Pharmacol Ther* 2004;19:271–279.
- 13 Raedsch R, Vinson B, Ottillinger B, Holtmann G: Early onset of efficacy in patients with functional and motility-related gastrointestinal disorders: a noninterventional study with Iberogast®. *Wien Med Wochenschr* 2017, Epub ahead of print.
- 14 Ottillinger B, Storr M, Malfertheiner P, Allescher HD: STW 5 (Iberogast®) – a safe and effective standard in the treatment of functional gastrointestinal disorders. *Wien Med Wochenschr* 2013;163:65–72.
- 15 Malfertheiner P, Holtmann G, Peitz U, Birkner B, Arnold R, Hotz J, Leodolter A, Mossner J, Robra BP: Teilnehmer der Leitlinien-Konferenz der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten: [Guidelines of the German society of digestive and metabolic diseases for treatment of dyspepsia]. *Z Gastroenterol* 2001;39:937–956.
- 16 Layer P, Andresen V, Pehl C, Allescher H, Bischoff SC, Classen M, Enck P, Frieling T, Haag S, Holtmann G, Karaus M, Kathemann S, Keller J, Kuhlbusch-Zicklam R, Kruijs W, Schemann M, van der Voort I, Dathe K, Preiss JC: S3-Leitlinie Reizdarmsyndrom: Definition, Pathophysiologie, Diagnostik und Therapie. Gemeinsame Leitlinie der Deutschen Gesellschaft für Verdauungs- und Stoffwechselkrankheiten (DGVS) und der Deutschen Gesellschaft für Neurogastroenterologie und Motilität (DGNM). *Z Gastroenterol* 2011;49:237–293.