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Intestinal spasmolytic effects of STW 5 (Iberogast®) and its components

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Abstract

Functional gastro-intestinal diseases as the irritable bowel syndrome are very common in the population and are characterized by a broad spectrum of symptoms which mostly are related to spastic or paralytic intestinal function without defined histopathological changes of the tissue. Due to the multifactorial pathogenesis a multifactorial therapy with multi-target action seems to be reasonable. STW 5 (Iberogast®), its constituent herbal extracts and some isolated compounds were used in an *in vitro* model provided by intestinal samples from guinea pig in order to test their activity on histamine-induced contractions and spontaneaous motility, respectively. For comparison the known spasmolyticum papaverine was used. The results show that the lytic effect of the phytotherapeuticum on histamine-induced contraction represents additively the actions of the different components and corresponds to approx. 10 μM of papaverine. Spontaneous peristaltic motion was differently modulated by the various constituent extracts. The experiments with silibinin, glycyrrhicine, chelidonine, and protopine showed that the effects of the extracts were not comparable to those of the respective chemical constituents.

Keywords: Spasmolysis; Functional intestinal syndromes; Irritable bowel syndrome (IBS); Functional dyspepsia (FD); Histamine-induced contractions; Iberis amara; Chelidonium majus; Glycyrrhiza glabra; Silybum marianum; Angelica archangelica; Matricaria recutita; Carum carvi; Mentha piperita; Melissa officinalis

Introduction

Irritable bowel disease and dyspepsia have a very high morbidity of about 25% of the population and involve functional impairment of the gut without visible histopathological changes (Talley et al., 1992; Talley, 1998; Tack and Lee, 2005; Kleibeuker and Thijs, 2004; Cremonini and Talley, 2004; Allescher, 2006). It is assumed that different causal mechanisms contribute to these diseases which can be related to nutritional factors, factors from the gastrointestinal wall itself, and from the autonomic and central nervous system, respectively. The symptoms reveal to be manifold, however, in many cases a spastic, sometimes a paralytic behaviour of the intestine is found. There are many different approaches for drug therapy, however, due to the chronic nature of these diseases, phytotherapy and complementary medicine are of special relevance in practical medicine (Gundermann et al., 2003; Vozeh, 2003; Allescher, 2006). STW 5 (Iberogast®), an established gastrointestinal phytotherapeutic medication consistent of 9 extracts from different plants was successfully tested in randomized, double blind clinical studies (Holtmann et al., 2004; Melzer et al., 2004; Rösch et al., 2006) and showed modulating effects on contractility of intestinal peparations *in vitro* (Okpanyi et al., 1993; Germann et al., 2006; Ammon et al., 2006). In order to characterize further the effects of the complete fixed combination, of its constituents, extracts and, in some cases, of isolated phytochemical compounds present in the extracts, on

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small intestine peristaltic function, the organ chamber model was used.

Materials and methods

Plant materials

100 ml STW 5 (Iberogast®) contains 15.0 ml of an ethanolic (extraction medium 50% ethanol by volume) fresh plant extract of *Iberis amara totalis* (bitter candytuft, 1:1.5–2.5) as well as ethanolic (with 30% ethanol by volume) plant drug extracts from: Angelica root (1:2.5–3.5) 10.0 ml, Chamomile flower (1:2.5–3.5) 20.0 ml, caraway fruit (1:2.5–3.5) 10.0 ml, milk thistle fruit (1:2.5–3.5) 10.0 ml, lemon balm leaf (1:2.5–3.5) 10.0 ml, peppermint leaf (1:2.5–3.5) 5.0 ml, greater celandine herb (1:2.5–3.5) 10.0 ml and liquorice root (1:2.5–3.5) 10.0 ml. The medicine contains 31% ethanol by volume.

Guinea pig ileum preparation

The guinea pigs (male, Hartley, 250–350 g body weight, Charles River, Kisslegg, Germany) were caged according to legal rules in groups of 4–6 animals and had standard chow and water ad libitum. The preparation of the gut was performed principially as described by Arul et al. (2002). After cervical dislocation a distal part of the ileum (8–10 cm) was excised, cleaned and dissected to rings of a length of 6 mm.

Measuring device for ileal contractions

The tissues were mounted in a thermostated measuring chamber (37 °C) which was constructed according to that described in more detail elswhere (Lang et al., 1995). The rings were perforated at both ends in a distance of 4 mm, and with the aid of two needles of stainless steel the rings were fixed into the measuring chamber so that one end was connected to a nano screw, the other to a force transducer (SG3-0.25, SWEMA, Stockholm). Contractions could be recorded after tuning (MGCplus, Hottinger Baldwin Messtechnik, Darmstadt). The chamber (volume approx. 10 ml) was continuously perfused (10 ml/min) by Tyrode solution (composition in mM: NaCl 118, KCl 5.3, $NaH_2PO_4 \times H_2O$ 1.5, $MgSO_4 \times 7H_2O$ 1.2, $CaCl_2 \times 2H_2O$ 2.5, Hepes 10, glucose 5, pH 7.4).

Histamine and papaverine were dissolved in the Tyrode solution and administered to the tissue. The plant extracts were directly applied in a dilution of 1:100. Control measurements with the solvents only were performed.

Some extracts were compared with the effects of known main compounds applied in the same concentration as present in the corresponding extract. These were: Silibinin (2.20 mg/ml, corresponding to 2.06 mg/ml silimarin) from milk thistle fruit, glycyrrhicic acid (ammonium salt) from liquorice root (6.63 mg/ml), and chelidonine and protopine (0.47 and 0.05 mg/ml, respectively) from greater celandine herb.

Experimental protocol

In order to investigate the effects of STW 5 and the different plant extracts on histamine-induced contractions, the tissue specimen were prestretched by 2 mN and equilibrated for 20 min. Thereafter, histamine (10^{-5} M) in Tyrode solution was applied and the contraction was recorded. Reproducibilty of the stimulation was tested with 6 independent tissue samples by repeated application up to 3 times which revealed no significant changes in the mechanical responses. Thereafter the respective extract or agent was added to the Tyrode solution to preincubate the tissue for 10 min, then to the stimulating solution (containing 10^{-5} M histamine) and the contraction response was again measured. The contrations under the influence of the herbal drugs were related to the preceding control contractions set 100%. For testing the different extracts, fresh intestinal specimen were used. For controls papaverine (10 or 50 μM/l) was used.

In some preparations in which spontaneous peristaltic motility occurred, the drug effect on frequency and amplitude of the contractions was recorded.

Statistics

Statistical calculations conducted with by the Wilcoxon test. Significant differences were defined at p-values <0.05.

Results

The effects of STW 5 and its constituent different plant extracts on histamine induced contractions are shown in Table 1. The whole drug and most of the single extracts act inhibitory on this type of stimulation. The most pronounced effects were found for the extracts from angelica root and chamomile flower. Also STW 5 showed a significant inhibition, whereas no effect was seen for the extract from greater celandine herb. Papaverine at a concentration of 10 μM/l was significantly less active than STW 5 itself, at 50 μM/l it was stronger than all herbal extracts studied.

Comparing the effects on histamine-induced contraction of main compounds of 3 herbal extracts which were

Table 1. Effects of STW 5 and its components on histamine-induced contraction in guinea pig ileum

Extract	Force of histamine-induced contraction (control = 100% in each case)			
	N	Mean value	S.D.	*p*
Angelicae radix	8	53.7	17.6	*
Silybi mariani fructus	10	72.0	31.0	n.s.
Carvi fructus	7	84.5	12.6	*
Chelidonii herba	10	102.9	27.8	n.s.
Iberis amara totalis	8	88.0	21.6	n.s.
STW 5	6	76.5	9.6	*
Liquiritiae radix	8	79.9	24.8	*
Matricariae flos	7	64.1	18.0	*
Melissae folium	7	79.6	13.5	*
Menthae piperitae folium	9	75.0	18.9	*
Papaverine (10 μM)	4	81.5	5.7	*
(50 μM)	4	31.4	11.2	**

Mean values ± S.D. are expressed in relation to the control contraction in the presence of the solute = 100%, (*N*) specimen of different animals, n.s. not significant, * $p<0.05$, ** $p<0.01$.

Table 2. Effect of main components of the extracts of milk thistle fruit, greater celandine herb and liquorice root, respectively, on histamine-induced contraction in guinea pig ileum

Extract	Force of histamine-induced contraction (control = 100% in each case)			
	N	Mean value	S.D.	*p*
Silybi mariani	10	72.0	31.0	n.s.
Silibinin	8	89.6	21.8	n.s.
Chelidonii herba	10	102.9	27.8	n.s.
Chelidonine	3	67.2	4.3	*
Chelidonine + Protopine	7	77.5	15.6	*
Protopine	7	88.9	14.6	n.s.
Liquiritiae radix	8	79.9	24.8	*
Glycyrrhicic acid	3	98.5	3.5	n.s.
Papaverine (10 μM)	4	81.5	5.7	*
(50 μM)	4	31.4	11.2	**

Mean values ± S.D. are expressed in relation to the force of the control contraction in the presence of the solute = 100%, (*N*) specimen of different animals, n.s. not significant, * $p<0.05$, ** $p<0.01$, the isolated components were applied in the same concentration as present in the respective extract.

available in pure form it is obvious that in all 3 cases there are clear differences (Table 2). Whereas the extract from greater celandine herb was without effect, at least

Table 3a. Effect of the components of STW 5 on frequency of spontaneous peristaltic motion of guinea pig ileum

Extract	Alteration of frequency (control = 100% in each case)			
	N	Mean value	S.D.	*p*
Angelicae radix	12	97.4	9.7	n.s.
Silybi mariani fructus	16	94.6	33.4	n.s.
Carvi fructus	12	100.4	16.4	n.s.
Chelidonii herba	12	120.1	25.4	n.s.
Iberis amara totalis	18	103.1	16.2	n.s.
Liquiritiae radix	20	98.6	14.6	n.s.
Matricariae flos	12	78.0	29.6	*
Melissae folium	12	92.1	11.7	*
Menthae piperitae folium	14	88.4	14.7	**

Mean values ± S.D. are expressed in relation to the control contraction in the presence of the solute = 100%, (*N*) specimen of different animals, n.s. not significant, * $p<0.05$, ** $p<0.01$.

Table 3b. Effect of the components of STW 5 on maximal force of spontaneous peristaltic motion of guinea pig ileum

Extract	Alteration of contraction force (control = 100% in each case)			
	N	Mean value	S.D.	*p*
Angelicae radix	8	95.1	12.3	n.s.
Silybi mariani fructus	16	115.4	44.0	n.s.
Carvi fructus	12	105.2	36.4	n.s.
Chelidonii herba	12	171.0	56.7	**
Iberis amara totalis	18	91.8	12.2	*
Liquiritiae radix	20	104.8	65.1	n.s.
Matricariae flos	12	107.2	48.0	n.s.
Melissae folium	12	82.1	16.7	*
Menthae piperitae folium	12	68.3	42.8	**

Mean values ± S.D. are expressed in relation to the control contraction in the presence of the solute = 100%, (*N*) specimen of different animals, n.s. not significant, * $p<0.05$, ** $p<0.01$.

the alkaloid chelidonine showed a strong inhibitory effect. Just opposite effects were found in liquorice root and milk thistle, both extracts acted spasmolytic, yet, the main compounds as glycrrhic acid and silibinin, respectively, were without significant effect.

The effects of the herbal extract on spontaneous peristaltic activity of ileum of guinea pig is shown in Table 3a and Table 3b. The results reveal different actions: with respect to effects on contraction amplitude,

the extracts from celandine herb, *Iberis amara*, Melissae folium and Menthae piperitae folium have significant effects on contraction amplitude, the first enhancing, the other three decreasing. With respect to the frequency of the peristaltic motion celandine showed again enhancing effect whereas chamomile, melissa and peppermint showed decreasing effects.

Discussion

The results show that with respect to peristaltic motion of ileum the main action of STW 5 (Iberogast®) and its constituent extracts from different plants is inhibition of contraction. When histamine is used as a putative mediator of irritable bowel disease, most of the extracts, especially those of angelica root and chamomile flower, and STW 5 itself reduce significantly contraction force and spastic behavior. Even when the spontaneous peristaltics where studied, reflecting the physiologic situation *in vivo*, some extracts showed relaxing or inhibiting effects. Only greater celandine herb revealed activating effects in this model. Former investigations have shown that STW 5 and its components are also effectively inhibiting contractions in guinea pig ileum induced by acetylcholine. In this reaction the extract from peppermint leafs was the most effective one (Okpanyi et al., 1993; Ammon et al., 2006). One can conclude, that all the different components contribute to the overall effect of STW 5.

However, the question whether there are modulating interactions between the components either enhancing or reducing the overall activity of STW 5 cannot be answered from the results presented here. Since the variances of the results are rather high, only a very rough calculation can be made showing more or less additive activities of the components. In cases of more precise determinations as i.e. in the measurements of the antioxidative properties, supraadditive effects can be shown for STW 5 and its components (Germann et al., 2006, Heinle et al., 2006). Yet, when applied in multifactorial diseases of the digestive system, a multicomponent system like the extracts used here could be effective by influencing different pathophysiological mechanisms.

Another general question of phytotherapy is whether the effect(s) of a whole extract can be explained by the effect of a single main substance. In order to study this aspect, the extracts of milk thistle fruit, liquorice root, and greater celandine herb, respectively, were studied and compared with some compounds present within the respective extract. The results of these orientating experiments show that in all three examples there are significant differences with respect to the effects on histamine-induced contractions, although spasmolytic effects were already described also for silymarin (silibinin) from milk thistle (Seeger, 1971), for the flavonoides from liquorice root (Chandler, 1985; Hahn and Nahrstedt, 1993) and for chelidonine from greater celandine herb (Wrocinski, 1963; Vahlensiek et al., 1995). Similar differences were also found when these substances and extracts were tested for their antioxidative properties (Germann et al., 2006) and receptor binding (Simmen et al., 2006). Therefore one can conclude that in many, probably most cases the pharmacological effect of a plant extract cannot be ascribed to only one constituent substance.

Also for the other extracts spasmolytic effects were described using different models and might be important for therapeutic efficacy of STW 5 (Di Carlo et al., 1993; Forster et al., 1980; Izzo et al., 1996; Reiter and Brandt, 1985). Further studies can clarify the exact mechanisms of action, i.e. to answer whether the spasmolytic effects of the herbal extracts are due to a direct influence on smooth muscle function (Härmälä and Vuorela, 1991, Schemann et al., 2006), or on the regulatory network of the enteric nervous system (Sibaev et al., 2006; Müller et al., 2006).

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