Effect of peppermint oil and caraway oil on gastrointestinal motility in healthy volunteers: a pharmacodynamic study using simultaneous determination of gastric and gall-bladder emptying and orocaecal transit time

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SUMMARY

Background: Although peppermint oil and caraway oil are frequently used in herbal drugs for abdominal discomfort and pain, the pharmacological insights into their effects on the gastrointestinal tract are poor.

Methods: The pharmacodynamic effects of 90 mg peppermint oil (WS 1340) and 50 mg caraway oil (WS 1520) on the motility of the stomach and gall-bladder, and on the orocaecal transit time, in comparison with placebo, 10 mg cisapride and 10 mg n-butylscopolamine, were studied in 12 healthy volunteers. The study involved simultaneous ultrasonic determination of gastric and gall-bladder emptying, together with assessment of the orocaecal transit time using the lactulose H₂ breath test. The combination of these methods allows three gastrointestinal organs to be studied in one subject simultaneously.

Results: The antral filling time was comparable with placebo, peppermint oil, caraway oil and cisapride, whereas it was significantly shortened ($P = 0.04$, two-sided paired $t$-test) with n-butylscopolamine. The gastric emptying time did not differ significantly between placebo, peppermint oil, caraway oil and cisapride, but was significantly prolonged by n-butylscopolamine ($P = 0.04$, two-sided paired $t$-test). Complete inhibition of gall-bladder emptying was caused by both oils and n-butylscopolamine. Cisapride significantly shortened gall-bladder emptying compared with placebo ($P = 0.02$, two-sided signed rank test). The orocaecal transit time was significantly prolonged by peppermint oil ($P = 0.004$) and n-butylscopolamine ($P = 0.002$), but not significantly prolonged by caraway oil ($P = 0.06$); it was significantly shortened by cisapride ($P = 0.04$, all two-sided paired $t$-test).

Conclusions: Peppermint oil and caraway oil show a relaxing effect on the gall-bladder and the former slows small intestinal transit. Further studies should investigate the effects of both oils on a maximal contraction stimulus on the gall-bladder, and in patients suffering from motility disorders.

INTRODUCTION

Although peppermint oil and caraway oil are frequently used as herbal drugs for abdominal discomfort and pain, the pharmacological insights into their effects on the gastrointestinal tract are poor. Peppermint oil has demonstrated distinct inhibitory effects on gastrointestinal motility in in vitro and in vivo experiments, but pharmacodynamic studies on the effect of caraway oil are rare. In this study, the pharmacodynamic effects of peppermint oil and caraway oil on the motility of the stomach and gall-bladder and on the orocaecal transit time, in comparison with placebo, cisapride and n-butylscopolamine, were investigated in healthy volunteers.
volunteers. The study involved simultaneous ultrasonographic monitoring of gastric and gall-bladder emptying, together with the determination of the oroaeal transit time using the H₂ breath test.

The study was designed and performed in accordance with the principles of Good Clinical Practice, German Drug Law and the Declaration of Helsinki. The study protocol was approved by the local Independent Ethics Committee.

METHODS

Patients

The study was performed in six healthy female and six healthy male volunteers. The mean age ± S.E.M. was 33.3 ± 2.5 years (range, 24–51 years). Prior to inclusion in the study, each volunteer gave his/her written informed consent. In addition, the medical history was documented, a physical examination was carried out and an abdominal ultrasound was performed. Exclusion criteria for participation in the study were pregnancy, acute or chronic diseases of the gastrointestinal tract within the last 6 months, operations on the gastrointestinal tract (exception: appendectomy at least 1 year ago), intake of concomitant medication with influence on the gastrointestinal tract and known intolerance to the test substances.

Test drink and test substances

The test drink consisted of 400 mL apple juice (Ameka-Fruchtsaft GmbH & Co KG, Menden, Germany) with 10 mL of the non-absorbable disaccharide lactulose (Lactuflor, MEP Pharma GmbH, St. Ingbert, Germany).

To determine the individual emptying motility of the stomach and gall-bladder and the individual oroaeal transit time, a non-enteric-coated gelatine capsule containing 0.4 mL of a 0.9% NaCl solution was given as a placebo.

The test substances, one non-enteric-coated gelatine capsule with 90 mg peppermint oil (Menthae piperitae aetheroleum; WS 1340; registered trademark of Dr Willmar Schwabe GmbH & Co) in a volume of 0.10 mL or 50 mg caraway oil (Carvi aetheroleum; WS 1520; registered trademark of Dr Willmar Schwabe GmbH & Co.) in a volume of 0.055 mL, were administered orally. The substances correspond to the active ingredients of Enteroplant (Dr Willmar Schwabe Pharmaceuticals, Karlsruhe, Germany and Spitzner Pharmaceuticals, Ettlingen, Germany), an anti-spasmodic and anti-meteoristic drug. Both oils were obtained from Dr Willmar Schwabe GmbH & Co., 76227 Karlsruhe, Germany.

Cisapride and n-butylscopolamine, two substances with known pharmacodynamic effects on the gastrointestinal tract, were tested as references. Cisapride was given as one 10 mg tablet (Propulsin, Janssen-Cilag GmbH, Neuss, Germany) and n-butylscopolamine as one 10 mg drageé (Buscopen, Boehringer Ingelheim Pharma KG, Ingelheim, Germany).

Experimental design

In each volunteer, five investigations were performed on five different days, with a washout phase of at least 2 days after each investigation day. On the first day, placebo was given. On the following four investigation days, the four test substances were studied in a randomized sequence. Subjects were blind to placebo and the test substances.

The study started at 07.00 h, after a 12-h fast, with the sonographic measurements and the initial H₂ breath sample. Afterwards, the placebo capsule or one of the test substances was administered. The test drink, which had to be finished within 5 min, was given 15 min later. Subsequently, the sonographic measurements of the gall-bladder and the antrum were conducted at 5-min intervals over 1 h. Simultaneously, the H₂ breath test was performed (20, 40, 60, 80, 100, 120, 140 and 160 min after the test drink).

The statistical evaluation was performed by descriptive data analysis using the statistical evaluation system SAS (version 6.12).

Gastric emptying

Gastric emptying was determined by measuring the changes in the cross-sectional area of the gastric antrum according to the method published by Bolondi et al.¹³ The cross-section obtained by this method, corresponding to the sagittal plane passing through the superior mesenteric vein, presents an elliptical shape. The area (A) was calculated by measuring the longitudinal (L) and anteroposterior (B) diameters and using the formula:

\[ A = \pi/4(L \times B) \]
The stomach was considered to be empty when the cross-sectional area and the volume of the antrum returned to basal values and remained unchanged. The final gastric emptying time was calculated in relation to the start of the meal.

The measurement was performed ultrasonographically using an Aloka SSE-2200 ultrasound device with a 3.5-MHz probe.

**Gall-bladder emptying**

The sonographic determination of the gall-bladder volume was performed according to the method given by Dodds et al. The sagittal section through the central axis of the gall-bladder yields the measurement of the length \( L \). The axial section through the middle of the gall-bladder yields measurements of the width \( W \) and height \( H \). The gall-bladder volume was calculated using the formula:

\[
V = \frac{\pi}{6} (L \times W \times H)
\]

The measurement was performed ultrasonographically using an Aloka SSE-2200 ultrasound device with a 3.5-MHz probe.

**Orocaecal transit time**

The orocaecal transit time was determined by the non-invasive lactulose H\(_2\) breath test. As soon as lactulose reaches the colon, the metabolism of the non-absorbable disaccharide starts and the pulmonary H\(_2\) excretion in the expirate increases. The H\(_2\) content of the expirate was measured using a Micro-H\(_2\) apparatus (Micromedical Ltd, 60062 Northbrook, IL, USA).

Orocaecal transit was considered to be accomplished when an increase in H\(_2\) concentration of at least 15 p.p.m. over the basal concentration was measured.

**RESULTS**

**Gastric emptying**

As the antral cross-sectional area showed considerable inter-individual variation, relative changes of the antral area are presented (Figure 1a). The shape of the gastric emptying curves for placebo and for the test substances showed the well-known phases of ‘filling’, ‘lag’ and ‘emptying’. Antral filling was completed after 18.3 ± 1.7 min (mean ± S.E.M.) with placebo. n-Butylscopolamine significantly shortened the filling time to 11.3 ± 1.8 min \((P = 0.04, \text{ two-sided paired } t\text{-test})\). The other test substances did not influence the antral filling time. Stomach emptying was completed after 51.3 ± 2.3 min with placebo, whereas n-butylscopolamine significantly prolonged the emptying time to 57.1 ± 1.4 min \((P = 0.04, \text{ two-sided paired } t\text{-test})\). With peppermint oil, caraway oil and cisapride, no significant modification of stomach emptying was observed (Figure 1b).

**Gall-bladder emptying**

Gall-bladder emptying is represented as the percentage change in volume. With placebo, the time course shows...
a decrease in volume over 15 min (Figure 2a), followed by a 15-min lag phase, with maximum emptying of 28.6 ± 4.8% (mean ± S.E.M.) measured 30 min after taking the test drink (Figure 2b). The initial volume was restored after another 15 min. During the remaining observations, no significant modification of volume was measured.

Pre-treatment with n-butylscopolamine caused a complete inhibition of gall-bladder emptying and a continuous, marked increase in gall-bladder volume up to 83.9 ± 20.4% compared with the initial volume after 60 min (Figures 2a and 2b). Compared with placebo, the gall-bladder volume was significantly increased by n-butylscopolamine (P < 0.01, two-sided signed rank test).

Peppermint oil and caraway oil also caused a complete inhibition of gall-bladder emptying. Under the influence of both oils, an increase in volume was measured during the refilling phase of the placebo series, with a maximal increase of 44.4 ± 14.0% in the peppermint oil series and 49.7 ± 9.5% in the caraway oil series (Figures 2a and 2b). For both oils, the increase in gall-bladder volume was significant compared with placebo (peppermint oil, P = 0.04; caraway oil, P = 0.03; two-sided signed rank test).

The time course of gall-bladder emptying after pre-treatment with cisapride was significantly shortened compared with placebo (P = 0.02, two-sided signed rank test). The gall-bladder volume increased by 35.3 ± 9.1% with cisapride in the post-contraction phase (Figures 2a and 2b).

**Orocaecal transit time**

As shown in Figure 3, an orocaecal transit time of 65.0 ± 6.1 min (mean ± S.E.M.) was measured with placebo. Pre-treatment with peppermint oil and n-butylscopolamine caused a significant prolongation of the orocaecal transit time to 85.0 ± 7.8 min and 93.3 ± 9.0 min, respectively (P = 0.004 and P = 0.002, respectively; two-sided paired t-test). Caraway oil also tended to prolong the transit time, but this was not significant (73.3 ± 6.2 min; P = 0.06, two-sided paired t-test). With cisapride, a significant decrease to 53.3 ± 5.1 min was observed (P = 0.04, two-sided paired t-test).

Figure 2. Gall-bladder emptying shown as the mean relative change in gall-bladder volume. Negative values represent a decrease and positive values an increase in volume. (a) As a function of time; (b) volume changes induced by placebo and test substances, when the volume change was maximal under placebo (= 30 min after taking the test drink; mean values ± S.E.M., n = 12).

Figure 3. Orocaecal transit time measured by the lactulose H₂ breath test (mean values ± S.E.M., n = 12).
Tolerability

Two of the 12 volunteers observed mild side-effects during the study. Both subjects complained of eructation with peppermint taste with peppermint oil. In one case, eructation was associated with mild heartburn, which rapidly disappeared. The peppermint taste faded after 30 min and 2–3 h, respectively.

DISCUSSION

Simultaneous measurements of the motility of the gastrointestinal tract are advantageous as the pharmacodynamic effects caused by a test substance can be studied synchronously in different organs. This allows the different sensitivities of the various organs to a test substance to be observed in one experiment. The co-ordination of the different organs, controlled by neuronal and humoral mechanisms, can also be studied.16–18

Unlike earlier studies, our study combined an ultrasonicographic investigation of gastric and gall-bladder emptying with the H2 breath test by conducting these three measurements simultaneously. The use of these non-invasive and non-radiation-exposing procedures poses no ethical problems in clinical studies. Each procedure has been extensively studied and validated in earlier investigations, and is now commonly used in clinical practice.13–28

In agreement with other studies,17, 29, 30 we showed a dependence of gall-bladder contraction on gastric emptying of the test meal. With our non-fat test drink, gastric emptying was complete after 51 min. The gall-bladder showed only moderate contraction during measurement, a prerequisite for disclosing small inhibitory effects of the test substances.

Only n-butylscopolamine increased antral filling and delayed gastric emptying. No effect of peppermint oil and caraway oil was observed. Cisapride did not show the expected accelerating effect on gastric emptying, although the oroaeceleal transit time was significantly shortened. This was probably caused by the fast gastric emptying of our non-fat test drink and the small effect of cisapride on healthy subjects.32 In a study using a similar test solution and showing a similar short gastric emptying time, a small accelerating effect on gastric emptying was also observed with metoclopramide.19 According to pharmacokinetic studies, a sufficiently effective plasma concentration of cisapride should have been present under our experimental conditions.34 A significant accelerating effect on gastric emptying has been observed previously with 5 mg of cisapride.35

In our study, pharmacodynamic proof that peppermint oil and caraway oil inhibit gall-bladder contraction in humans was obtained for the first time. Peppermint oil also delayed oroaeceleal transit, whereas the delay was not significant with caraway oil. Spasmyotic action has been attributed to both oils,1, 2, 7–11, 36 but scientific knowledge about the mode of action is poor. The spasmyotic action of peppermint oil was demonstrated on isolated rabbit and rat intestine in 1921.17 Later, a calcium antagonistic effect of menthol, the main component of peppermint oil, was found.9, 38 Only slight effects have been assigned to caraway oil, as the pharmacodynamic effects have been poorly described previously.

Both gastric motility and secretion are affected by substance P,19 and many lines of evidence suggest that substance P plays an important role in nociception at the spinal level.40 With peppermint oil, recent studies have shown a non-competitive inhibition of the contraction response induced by 5-hydroxytryptamine and substance P on isolated smooth muscles.41 Therefore, a neuronal site of action of peppermint oil could also be possible. Moreover, a direct epithelial site of action was observed on small intestinal enterocytes.

Compared with n-butylscopolamine, peppermint oil and caraway oil caused a similarly effective inhibition of gall-bladder contraction, whereas the inhibition of oroaeceleal transit was more effective with n-butylscopolamine. The different effects on different organs, observed by simultaneous comparison, are in accordance with the different sensitivities of the various organs. Caraway oil, for example, caused a relaxation of the guinea pig tracheal musculature, but had no effect on the isolated longitudinal muscle of guinea pig ileum.42

The simultaneous investigation of gastric emptying, together with the oroaeceleal transit time, permits the non-invasive determination of the small intestinal transit time. n-Butylscopolamine delays gastric emptying as well as small intestinal transit. With peppermint oil and caraway oil, only small intestinal transit is delayed as gastric emptying is not influenced by either oil.

The relaxing effect on the gall-bladder and the delay in small intestinal transit found for peppermint oil and caraway oil in this study support the findings of several controlled clinical investigations with a combination of both essential oils in patients with functional
dyspepsia. In a pharmacodynamic study, an enteric-coated combination preparation of both oils was shown to act locally to cause smooth muscle relaxation. Considering the variety of symptoms in functional dyspeptic conditions, the combination of these two oils seems to be especially appealing, as their action principles can be expected to show a synergistic effect. In at least a proportion of patients with functional dyspepsia, lowered sensory thresholds are present, and the lack of an adaptive increase in thresholds for first perception after repeated mechanical stimulation may therefore play a role in the pathophysiology of functional dyspepsia. For a combination of peppermint oil and caraway oil, the following two action principles could be possible: (i) as a muscle relaxant, the combination may lead to a decreased stimulation of mechanoreceptors in gastrointestinal muscles and therefore to an inhibition of nociception; (ii) as a fundus relaxant, the combination may prevent the feeling of fullness, which is experienced by many patients suffering from functional dyspepsia.

In this study, the method of combined ultrasonographic measurement of gastric and gall-bladder emptying, together with the lactulose H2 breath test, is not only non-invasive, but also allows three gastrointestinal organs to be studied in one subject simultaneously.

Further investigations need to be conducted to study the effect of peppermint oil and caraway oil on a maximal contraction stimulus on the gall-bladder (e.g. after a fatty meal), to investigate the effect of a combination of both oils (as found in a number of herbal drugs) and to examine whether the pharmacodynamic effects can also be shown in patients suffering from motility disorders.

DEDICATION

This paper is dedicated to Professor Dr J. Köbberling on the occasion of his both birthday.

REFERENCES

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