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(54) Title: USE OF LIPASE INHIBITORS

(57) Abstract: The present invention refers to the use of lipase inhibitors, e.g. orlistat, for the manufacture of medicaments for treating, reducing or preventing functional dyspepsia, e.g. intensity of stomach fullness, nausea, bloating after ingestion of small or larger meals, especially of fat containing or fat rich meals, and the medicaments thus manufactured.

Use of Lipase Inhibitors

The present invention refers to the use of lipase inhibitors, e.g. orlistat, for the manufacture of medicaments for treating, reducing or preventing functional dyspepsia, e.g. intensity of stomach fullness, nausea, bloating after ingestion of small or larger meals, especially of fat containing or fat rich meals, and the medicaments thus manufactured.

Functional dyspepsia is a condition characterized by sensations of gastric fullness, nausea, bloating, gastric distress etc. after intake of small or larger meals, especially after intake of fat containing or fat rich meals. A large number of people are afflicted by this condition, continuously or more regularly in response to fat rich meals or fat rich meal items.

The arrival of lipid in the small intestinal lumen normally causes gastric relaxation, modulation of phasic motor activity, and pancreaticobiliary secretion. However, in patients with functional dyspepsia especially lipid provokes postprandial symptoms. Gastric and pancreatic lipases in the intestinal lumen hydrolyze triglycerides to free fatty acids, which may act on brain centers involved in dyspeptic symptoms.

Surprisingly, it has been found in a clinical model of functional dyspepsia that a lipase inhibitor, preferably orlistat, when administered orally, is useful in the treatment, reduction and prevention of functional dyspepsia. According to the present invention, inhibition of fat digestion reduces the intensity of postprandial dyspeptic symptoms

Orlistat, a gastrointestinal lipase inhibitor, also known as XENCIAL®, is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122, WO 00/09123, WO01/19340 and WO01/19378.

Addition of a lipase inhibitor like orlistat (THL, tetrahydrolipstatin) to a fat emulsion infused into the duodenum reduced the intensity of stomach fullness and sensitivity, nausea and bloating in a clinical model of dyspepsia, i.e. gastric distension with an inflatable balloon. This finding is very important since a large number of patients with digestive symptoms of unknown cause report that their symptoms frequently occur after ingestion of foods containing fat; by blocking the first step of intestinal lipid digestion these gastrointestinal symptoms can according to the present invention effectively reduced. Hence, the present invention has important clinical implications for the treatment of a subgroup of patients suffering from dyspepsia related to fat intolerance, in that partial inhibition of fat digestion may be an effective measure to relieve their symptoms. In summary, our data demonstrate the importance of inhibition of fat digestion for the suppression of postprandial symptoms.

The term "lipase inhibitor" refers to compounds which are capable of inhibiting the action of lipases, for example gastric and pancreatic lipases. For example orlistat and lipstatin as described in U.S. Patent No. 4,598,089 are potent inhibitor of lipases. Lipstatin is a natural product of microbial origin, and orlistat is the result of a hydrogenation of lipstatin. Other lipase inhibitors include a class of compounds commonly referred to as panclicins. Panclicins are analogues of orlistat (Mutoh et al, *J. Antibiot.*, 47(12):1369-1375 (1994)). The term "lipase inhibitor" refers also to synthetic lipase inhibitors for example described in International Patent Application WO99/34786 (Geltex Pharmaceuticals Inc.). These polymers are characterized in that they have been substituted with one or more groups that inhibit lipases. The term "lipase inhibitor" also comprises pharmaceutically acceptable salts of these compounds. In addition, the term "lipase inhibitor" also refers to 2-oxy-4H-3,1-benzoxazin-4-ones which have been described in International Patent Application WO00/40569 (Alizyme Therapeutics Ltd.), e.g. 2-decyloxy-6-methyl-4H-3,1-benzooxazin-4-one, 6-methyl-2-tetradecyloxy-4H-3,1-benzoxazin-4-one, and 2-hexadecyloxy-6-methyl-4H-3,1-benzoxazin-4-one.

Orlistat is a known compound useful for the control or prevention of obesity and hyperlipidemia. See, U.S. Patent No. 4,598,089, issued July 1, 1986, which also discloses processes for making orlistat and U.S. Patent No. 6,004,996, which discloses appropriate pharmaceutical compositions. Further suitable pharmaceutical compositions are described for example in International Patent Applications WO 00/09122, WO 00/09123, WO01/19340 and WO01/19378.

Additional processes for the preparation of orlistat are disclosed in European Patent Applications Publication Nos. 185,359, 189,577, 443,449, and 524,495.

In a preferred embodiment, the present invention refers to the use of a lipase inhibitor for the manufacture of medicaments for treating, reducing or preventing functional dyspepsia. Especially, the invention refers to the above use, wherein treating, reducing or preventing functional dyspepsia comprises reducing the intensity of gastric fullness, nausea, bloating during and after meal ingestion.

In an especially preferred embodiment of the present invention, the lipase inhibitor is orlistat.

Further, the invention refers to a method for treating, reducing or preventing functional dyspepsia comprising administering an effective amount of a gastrointestinal lipase inhibitor to a mammal. This method comprises reducing the intensity of fullness, nausea, bloating, gastric distress following ingestion of fat rich meals or fat rich meal items. The method especially claims the use of orlistat as lipase inhibitor.

Preferably, the lipase inhibitor is administered orally.

Accordingly, the present invention comprises an oral medicament for treating or preventing functional dyspepsia characterized in that it contains an effective amount of a lipase inhibitor, preferably orlistat.

The lipase inhibitor, e.g. orlistat is preferably orally administered from 30 to 720 mg per day in divided doses two to three times per day, especially during ingestion of fat rich food.

Preferred is wherein from 60 to 360 mg, most preferably 360 mg per day of a lipase inhibitor, preferably orlistat, is administered to a subject, preferably in divided doses two

or, particularly, three times per day. The subject may be a normal weight, an obese or an overweight human. Generally, it is preferred that the lipase inhibitor be administered with the meal containing fat. Furthermore, other illnesses like obesity and associated risk factors such as hypercholesterolemia, diabetes mellitus, etc. as described e.g. in U.S. Patent No. 4,598,089 and International Patent Application WO98/34630 can be treated in parallel.

Orlistat can be administered to humans in conventional oral compositions, such as, tablets, coated tablets, hard and soft gelatin capsules, emulsions or suspensions. Examples of carriers which can be used for tablets, coated tablets, dragées and hard gelatin capsules are lactose, maize starch or derivatives thereof, talc, stearic acid or its salts and the like. Suitable carriers for soft gelatin capsules are, for example, vegetable oils, waxes, fats, semi-solid and liquid polyols and the like. Moreover, the pharmaceutical preparations can contain preserving agents, solubilizers, stabilizing agents, wetting agents, emulsifying agents, sweetening agents, coloring agents, flavoring agents, salts for varying the osmotic pressure, buffers, coating agents or antioxidants. They can also contain still other therapeutically valuable substances. Alternatively, the lipase inhibitors may be administered in form of hard gelatine capsule or chewing tablets. The formulations may conveniently be presented in unit dosage form and may be prepared by any methods known in the pharmaceutical art (see above). Preferably, the lipase inhibitor, e.g. orlistat, may be administered according to the formulation shown in the Examples.

EXAMPLES

1. Materials and Methods

The reduction of dyspeptic symptoms by lipase inhibitors, particularly orlistat, has been shown in a clinical model of functional dyspepsia: Reduction of dyspeptic symptoms by orlistat in normal volunteers (healthy subjects without a history of gastrointestinal disease (8 female and 7 male), aged 24 - 38 years; normal body weight (BMI (kg/m^2): females: 21.9 ± 0.4, males: 23.4 ± 0.4) during infusion of a fat emulsion into the duodenum in a clinical model of idopathic dyspepsia (gastric distension).

Fat emulsions (Table 1) were infused intraduodenally via a single-lumen naso-duodenal polyvinyl tube as described previously (Feinle, AJP2000), while the stomach was distended. Gastrointestinal sensations were assessed by a visual analog questionnaire.

The gastric distension was performed by air through a gastric tube (OD: 3.5 mm, ID: 2.8 mm) which had an ultra-thin, flaccid polyethylene bag (capacity: 1100 ml) tied on to its distal end. The proximal end of the tube was connected via a three-way tap to the measurement and the balloon ports of a gastric barostat.

Studies were performed in a double-blind, placebo-controlled cross-over fashion in randomised order at least one week apart from each other. The subjects were comfortably seated in an upright position. At first, the minimal distending pressure (MDP) was determined by increasing intragastric pressure in steps of 1 mmHg/min. Pressure was then fixed at MDP and fasting tone recorded until variations in gastric volume were no longer observed. The MDP was 8 ± 1 mmHg and did not differ between study days. After 10 min ('baseline'), duodenal infusion of a fat emulsion commenced at a rate of 1 ml/min and was continued throughout the study. Two isobaric distensions were performed, 15 min apart from each other, by increasing intrabag pressure in steps of 1 mmHg/min, while corresponding volumes were monitored.

Gastrointestinal sensations of hunger, satiation, nausea, abdominal bloating and pressure were rated by the subjects on visual analogue scales (VAS). The VAS consisted of a 10 cm line, with 0 cm representing "sensation not present" and 10 cm "strongest sensation ever felt". Sensations were rated immediately before the start of and every 5 min

during the duodenal infusions. As soon as the subjects reported discomfort, the distension process was discontinued and the air immediately removed from the bag.

Table 1: Composition of the fat emulsions and median of fat droplet size distribution.

	LCT	LCT-orlistat
LCT	30.0 g	30.0 g
orlistat	-	240 mg
Soy lecithin	2.25 g	2.25 g
Ethanol	1.75 g	1.75 g
0.9 % saline	116.0 g	116.0 g
MPS	10.5 µm	8.5 µm

LCT, soybean oil, MPS, median of particle size distribution.

Fat emulsions with 20 % (w/w) oil were prepared from soybean oil with soy lecithin with and without orlistat (table 1). The soy lecithin was completely dissolved in ethanol before the oil was added and shaken to obtain a clear solution. Isotonic saline was then added, and the resulting dispersion was homogenized for 3 x 1 minute at 39 000 rpm using a homogenizer. Orlistat was completely dissolved in ethanol before the soy lecithin was added. The emulsions were used within one hour of preparation. The particle size distribution of the dispersed oil droplets in the emulsions was determined. The particle size of the emulsions remained unchanged and no signs of creaming were detected. Medians of the particle size distributions are listed in table 1.

2. Data analysis

Changes in gastric tone during duodenal infusions were quantified by calculating differences between mean volumes obtained at MDP during the baseline recording (10 minutes) and during the duodenal infusion.

During distensions, intragastric volumes during consecutive pressure steps were calculated by averaging the volume readings obtained during the last 20 s of each pressure step. These data were then used to construct pressure-volume profiles. Any differences between the profiles obtained during gastric distensions were evaluated by comparing areas under the curves (AUC).

Data were analyzed by ANOVA (analysis of variance), followed by post-hoc analysis, if statistically significant differences were obtained. Data are presented as means ± SEM. Probability values of $p < 0.05$ were regarded as statistically significant.

3. Responses during duodenal infusions

Infusion of an oil emulsion significantly increased gastric baseline volume ($p < 0.05$). Addition of orlistat completely abolished the volume change during infusions ($p < 0.05$).

4. Responses during gastric distensions

The orlistat-containing emulsion caused significantly less increase of intragastric volume during gastric distensions ($p < 0.05$), (as shown by AUCs, gastric volume at MDP + 4 mmHg and the slope of the p-V curve) than fat infusion alone (table 2).

Table 2: Pressure-volume relationships during gastric distensions and duodenal infusion of the fat

	LCT	LCT-orlistat
AUC (mmHg.ml)	1388 ± 75*	516 ± 54
Volume at MDP + 4 mmHg (ml)	533 ± 25*	245 ± 25
Slope (ml/mmHg)	94 ± 6*	52 ± 5

LCT, soybean oil. Data are means ± SEM. Significant differences: *, $p < 0.05$.

Increasing intragastric pressure resulted in an increase of scores for fullness, bloating, nausea and pressure, and a decrease of scores for hunger during all duodenal infusions. The changes were pronounced during fat infusion (indicated by the slope of the pressure-score curves, by the scores at MDP + 4 mmHg and also by the AUCs). The effects of LCTs were significantly diminished by orlistat, suggesting that triglyceride digestion products are required for the induction of postprandial sensations and symptoms.

Table 3: Parameters characterising symptoms during gastric distensions and duodenal infusion of the fat emulsions.

	LCT	LCT-orlistat
AUC (mmHg)		
Bloating	7.1 ± 1.1*	3.5 ± 0.6
Fullness	16.7 ± 1.1*	10.9 ± 1.0
Hunger	11.9 ± 1.3*	19.6 ± 1.4
Nausea	10.5 ± 1.3*	1.8 ± 0.6
Pressure/pain	9.2 ± 1.3*	5.8 ± 0.8
Score at MDP + 4 mmHg		
Bloating	2.8 ± 0.4*	1.3 ± 0.2
Fullness	5.8 ± 0.4*	3.8 ± 0.3
Hunger	1.7 ± 0.3*	4.3 ± 0.4
Nausea	4.5 ± 0.5*	0.9 ± 0.2
Pressure/pain	3.8 ± 0.4*	2.5 ± 0.3
Slope (1/mmHg)		
Bloating	0.5 ± 0.1*	0.2 ± 0.0
Fullness	0.8 ± 0.1*	0.5 ± 0.1
Hunger	-0.7 ± 0.1*	-0.3 ± 0.0
Nausea	0.9 ± 0.1*	0.2 ± 0.0
Pressure/pain	0.6 ± 0.1	0.5 ± 0.1

LCT, soy bean oil. Data are means ± SEM. Significant differences* from respective orlistat condition, $p < 0.05$.

The maximally tolerated pressure during gastric distension during duodenal fat infusion was significantly increased by orlistat ($p < 0.05$).

5. Pharmaceutical Compositions

A)

Ingredient	Quantity mg/Capsule
Orlistat	120.00
Microcrystalline Cellulose (AVICEL PH-101)	93.60
Sodium Starch Glycolate (PRIMOJEL)	7.20
Sodium Lauryl Sulfate	7.20
Polyvinylpyrrolidone (Povidone (K-30))	12.00
Purified Water*	———
Talc	0.24
Total	**240.24 mg**

*Removed during processing

Procedure:

1. Blend orlistat, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

B)

Ingredient	Quantity mg/Capsule
Orlistat	60
Microcrystalline Cellulose	46.8
Sodium Starch Glycolate	3.6
Sodium Lauryl Sulfate	3.6
Polyvinylpyrrolidone	6.0
Purified Water*	———
Talc	0.12
Total	120.12 mg

*Removed during processing.

Procedure:

1. Blend orlistat, microcrystalline cellulose, and sodium starch glycolate in a suitable mixer.
2. Granulate with solution of polyvinyl pyrrolidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

C)

Ingredient	Quantity mg/Capsule	
Orlistat	60	120
Lactose	40	80
Microcrystalline Cellulose	60	120
Sodium Lauryl Sulfate	5.7	11.4
Sodium Starch Glycolate	20	40
Polyvinylpyrrolidone	10	20
Purified Water*	—	—
Talc	0.2	0.4
Total	195.9 mg	391.8 mg

*Removed during processing.

Procedure:

1. Blend orlistat, lactose, microcrystalline cellulose and sodium starch glycolate in a suitable mixer.
2. Granulate with a solution of polyvinylpyrollidone and sodium lauryl sulfate in purified water.
3. Pass the granulation through an extruder, and pass the extrudate through a spheronizer to form pellets.
4. Dry the pellets at 30°C.
5. Add talc and mix.
6. Fill into hard gelatin capsules.

CLAIMS

1. Use of a lipase inhibitor for the manufacture of medicaments for treating, reducing or preventing functional dyspepsia.

2. The use according to claim 1 wherein treating, reducing or preventing functional dyspepsia comprises reducing the intensity of fullness, nausea, bloating, gastric distress after meal ingestion.

3. The use according to any preceding claim wherein lipase inhibitor is orlistat.

4. A method for treating, reducing or preventing functional dyspepsia comprising to a mammal administration of an effective amount of a gastrointestinal lipase inhibitor.

5. The method according to claim 4, wherein the method comprises reducing the intensity of fullness, nausea, bloating gastric distress following intake of rich and/or fat rich meals or fat rich meal items.

6. The method according to claim 4 or 5, wherein the lipase inhibitor is orlistat.

7. The method according to claim 4 or 6, wherein the administration is an oral administration.

8. An oral medicament for treating or preventing functional dyspepsia characterized in that it contains an effective amount of a lipase inhibitor.

9. An oral medicament as in claim 3, wherein the lipase inhibitor is orlistat.

10. The invention as defined herein.