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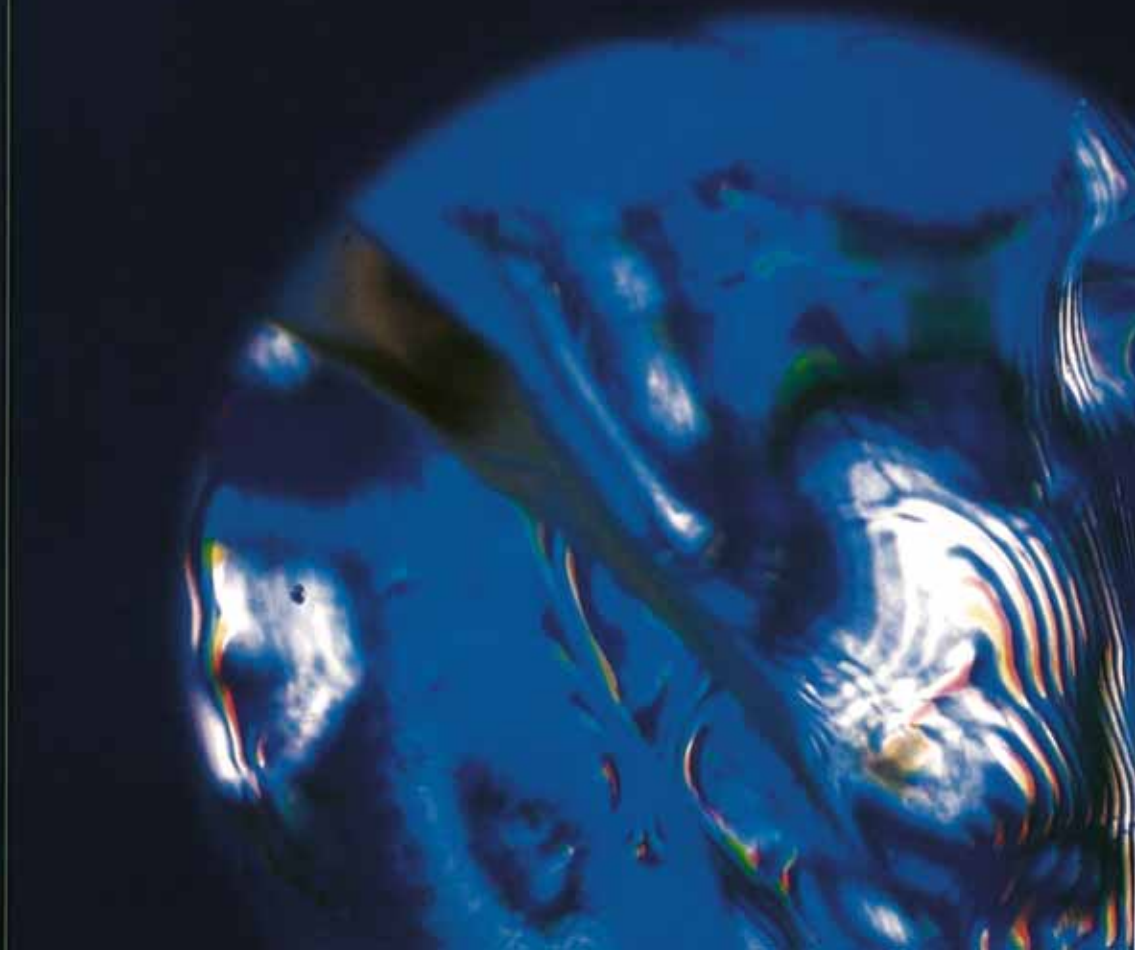

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EFFECTS OF A BICARBONATE-ALKALINE MINERAL WATER ON GASTRIC FUNCTIONS AND FUNCTIONAL DYSPEPSIA: A PRECLINICAL AND CLINICAL STUDY

MICHELE BERTONI[a], FILIPPO OLIVERI[a], MARTA MANGHETTI[a], ELENA BOCCOLINI[a], MARIA GRAZIA BELLOMINI[a], CORRADO BLANDIZZI[b], FERRUCCIO BONINO[a] and MARIO DEL TACCA[b,*]

[a]*Gastroenterology and Hepatology Units, University Hospital of Pisa, Pisa, Italy,* [b]*Division of Pharmacology and Chemotherapy, Department of Oncology, Transplants and Advanced Technologies in Medicine, University of Pisa, Pisa, Italy*

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The present study was performed in order to evaluate: (1) the influence of a bicarbonate-alkaline mineral water (Uliveto®) on digestive symptoms in patients with functional dyspepsia; (2) the effects of Uliveto® on preclinical models of gastric functions. Selected patients complained of dyspeptic symptoms in the absence of digestive lesions or *Helicobacter pylori* infection within the previous 3 months. They were treated with Uliveto® water ($1.5\,l\,day^{-1}$) for 30 days. Frequency and severity of symptoms were assessed at baseline and day 30 by a score system. Preclinical experiments were carried out on rats, allowed to drink Uliveto® or oligomineral water for 30 days. Animals then underwent pylorus ligation to evaluate gastric secretion of acid, pepsinogen, and mucus. In separate experiments, gastric emptying was assessed. Crenotherapy was associated with a relief of epigastric pain, retrosternal pyrosis, postprandial fullness and gastric distention. At preclinical level, Uliveto® water increased acid and pepsinogen secretions as well as gastric emptying, without changes in bound mucus. The enhancing actions of Uliveto® on gastric secretions and emptying were prevented by L-365,260, an antagonist of gastrin/CCK-2 receptors. These findings indicate that a regular intake of Uliveto® favors an improvement of dyspeptic symptoms. The preclinical study suggests that the clinical actions of Uliveto® water depend mainly on its ability to enhance gastric motor and secretory functions.

KEY WORDS: functional dyspepsia, mineral water, crenotherapy, gastric functions, gastrin.

INTRODUCTION

Dyspepsia is a heterogeneous pathological condition characterized mainly by epigastric pain or discomfort in patients with normal endoscopic findings [1, 2]. The occurrence of dyspeptic symptoms represents a frequent reason for medical consultation in primary and secondary care, and it is now well recognized that structural (or organic) lesions of digestive tissues are found only in a minority of patients with dyspepsia [3, 4].

Dyspepsia, in the absence of a clinically identifiable structural lesion causing symptoms, is usually referred to as functional dyspepsia [4, 5]. At present, the pathophysiology of this syndrome is poorly understood. However, since a structural explanation is lacking, a disturbance of some gastrointestinal functions is believed to play a role in the development of symptoms [5]. In particular, it is currently accepted that digestive alterations associated with functional dyspepsia may include: (a) abnormal upper gastrointestinal motility and visceral perception, that has been postulated to account for postprandial distress, nausea, bloating and early satiety; (b) increased sensitivity to gastric acid, with or without inflammation of the mucosa, that may, in some cases, account for upper abdominal pain [6]. Motility disturbances that have been detected in some, but not all, patients with functional dyspepsia consist of delayed gastric emptying and postprandial antral hypomotility [7, 8].

The current rationale for drug treatment of functional dyspepsia is based on altering the pathophysiological

*Corresponding author. Divisione di Farmacologia e Chemioterapia, Dipartimento di Oncologia, dei Trapianti e delle Nuove Tecnologie in Medicina, Università di Pisa, Via Roma, 55, 56126 Pisa, Italy.
E-mail: m.deltacca@do.med.unipi.it

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Table I
Chemico-physical properties of Uliveto® water and control oligomineral water used in the present study

	Uliveto® water	*Control water*
Li^+	0.2 mg l^{-1}	0.1 mg l^{-1}
Na^+	113.7 mg l^{-1}	4.6 mg l^{-1}
K^+	11.6 mg l^{-1}	0.46 mg l^{-1}
Mg^{2+}	29.8 mg l^{-1}	3.7 mg l^{-1}
Ca^{2+}	202.2 mg l^{-1}	57 mg l^{-1}
Sr^{2+}	0.7 mg l^{-1}	0.19 mg l^{-1}
F^-	1.4 mg l^{-1}	0.14 mg l^{-1}
Cl^-	121.4 mg l^{-1}	7.7 mg l^{-1}
HCO_3^-	683.2 mg l^{-1}	180 mg l^{-1}
NO_3^-	5.9 mg l^{-1}	1.2 mg l^{-1}
SO_4^{2-}	151 mg l^{-1}	8.5 mg l^{-1}
SiO_2	7 mg l^{-1}	3.7 mg l^{-1}
CO_2	820 mg l^{-1}	130 mg l^{-1}
pH (20 °C)	6.0	7.79
Dry residue (180 °C)	986 mg ml^{-1}	176 mg ml^{-1}

mechanisms which are believed to be associated with the development of symptoms. For this purpose, the use of various drugs, including prokinetics, antacids, inhibitors of gastric acid secretion, gastroprotective agents and antispasmodic drugs, has been proposed for the management of the dyspeptic syndrome [4, 6]. However, in spite of many efforts, the pharmacological treatment for patients with functional dyspepsia remains unsatisfactory, as clinical studies indicate that drug therapy usually achieves only a partial relief of symptoms in the majority of cases [6, 9].

Clinical observations suggest that changes in the lifestyle and eating behavior as well as the use of natural products, including mineral waters, may play an adjuvant role in the management of functional dyspepsia [10, 11]. In particular, mineral waters, depending on their peculiar chemical and physical properties, may modulate various functions at different levels of the digestive tract, and therefore it has been proposed that regular and prolonged courses of crenotherapy with specific mineral waters may be of benefit in patients complaining for functional dyspeptic symptoms [11].

Uliveto® is a bicarbonate-alkaline mineral water, characterized by a relatively high content of bicarbonate, calcium, and magnesium ions (Table I), that has been reported to enhance the effects of high-fiber diet on stool frequency and laxative consumption in patients with functional motor alterations of the distal intestine [12]. Previous clinical studies have also shown that bicarbonate-alkaline mineral waters can enhance the rate of gastric emptying, an action that may contribute to the relief of some dyspeptic symptoms [11, 13]. Accordingly, in the present study an attempt was made to assess whether Uliveto® water may positively affect the occurrence and/or the severity of dyspeptic symptoms. For this purpose, Uliveto® water was continuously administered for 30 days to patients affected by functional dyspepsia to evaluate the pattern of their digestive symptoms both before and at the end of crenotherapy. Additional *in vivo* experiments were also performed on preclinical models in order to gain insight into the influence exerted by Uliveto® water on gastric secretory and motor functions.

MATERIALS AND METHODS

Clinical investigation

Patients and study design. The patients examined in this study were selected among those with uninvestigated dyspepsia who were referred by general practitioners to the endoscopy service of the Gastroenterology Units of Pisa University Hospital between January and June 2000. Among out-patients with normal upper endoscopy, only those with proven functional dyspepsia were admitted to the study. The inclusion criteria were: (a) history of dyspeptic symptoms lasting at least 3 months before entering the study; (b) presence of at least one of the symptoms listed below; (c) frequency and severity of the dominant dyspeptic symptom with a score of at least 3 (as described later). Exclusion criteria were: presence of *Helicobacter pylori* infection on the basis of concomitant positive urease production test (CLO test) and histology (within the previous 3 months); presence of erosive/ulcerative esophagitis or gastroduodenal erosion/ulcer/scar documented by upper endoscopy (within the previous 3 months); irregular bowel evacuation (within the previous 30 days); irritable bowel syndrome; other organic gastrointestinal or systemic diseases; diabetes; abnormal biochemical changes; pregnancy or lactation; previous abdominal surgery (except appendectomy); use of drugs able to interfere with digestive mucosal integrity, gastric secretion or gastrointestinal motility, including corticosteroids, non-steroidal antiinflammatory drugs, histamine H_2 receptor antagonists, proton pump blockers, prokinetics, and antispasmodics (within the previous 30 days). The occurrence of these conditions was ruled out by clinical interview, careful physical examination, electrocardiogram, blood chemistry, hematology, urine analysis, abdominal ultrasonography and upper endoscopy. Fully informed consent was obtained from each patient entering the study and the investigation was approved by the local University Hospital Ethics Committee.

After evaluation of the dyspeptic symptoms in terms of incidence, frequency and severity at the time of enrollment (day 0), the intake of Uliveto® water (1.5 l day^{-1}) was prescribed to all patients for 30 consecutive days. A further assessment of both frequency and severity of dyspeptic symptoms was carried out at the end of crenotherapy (day 30).

Scoring of dyspeptic symptoms. The presence of the following symptoms was evaluated prior to enrollment as well as at the end of crenotherapy: (i) epigastric pain; (ii) epigastric burning; (iii) feeling of postprandial fullness; (iv) feeling of early satiety; (v) feeling of gastric distention; (vi) nausea; (vii) vomiting; (viii) retrosternal pyrosis; (ix) regurgitation; (x) dysphagy.

The prevalence of the above symptoms was estimated immediately before the beginning of crenotherapy (day 0) and expressed as percent values. Both before (day 0) and at the end (day 30) of crenotherapy, the frequency and severity of dyspeptic symptoms were also evaluated, on the basis of specific questionnaires, and graded semiquantitatively by means of score values. The frequency was scored as: 0 (never); 1 (rare; 1 day per week); 2 (occasional; 2–3 days per week); 3 (frequent; 4–6 days per week); 4 (extremely frequent; 7 days per week). The severity was scored as: 0 (none); 1 (mild; does not interfere with usual daily activities); 2 (moderate; usual daily activities are disturbed but not modified); 3 (severe; usual daily activities are markedly disturbed and affected); 4 (extremely severe; rest at bed is required).

Preclinical investigation

Animals and experimental design. A series of experiments was carried out on male Wistar rats, weighing 200 g. They were fed standard laboratory chow and tap water *ad libitum*, and were not used for at least 1 week after their delivery to the laboratory. The animals were housed, six in a cage, in temperature-controlled rooms on a 12-h light cycle at 22–24 °C and 50–60% humidity. Their care and handling were in accordance with the provisions of the European Community Council Directive 86-609, recognized and adopted by the Italian Government.

At the beginning of the experimental period, the animals were housed in single cages and allowed to drink either Uliveto® water or a commercial oligomineral water (control water) *ad libitum* for 30 days. The respective chemico-physical properties of Uliveto® and control oligomineral water are displayed in Table I. During the 30-day period of exposure to the mineral waters, both the changes in body weight and the intake of water were carefully monitored. On day 30, animals of both groups were subjected to different experimental procedures, in order to perform quantitative evaluations of gastric acid and pepsinogen secretions, levels of mucus bound to the gastric epithelial surface, and gastric emptying rate. In all cases, 24 h before the experiments, the animals were maintained in single cages, provided with wire net bottoms in order to prevent coprophagy, and deprived of food. Free access to water *ad libitum* was allowed until 1 h before starting the experimental procedures. In experiments aiming to assess the putative role played by gastrin in the digestive effects exerted by Uliveto® or control water, animals were treated with L-365,260 (5 μmol kg^{-1} i.p.), an antagonist of gastrin/CCK-2 receptors, 10 min before starting experimental procedures. The dose of L-365,260 was selected on the basis of a previous study where this drug was able to antagonize the effects of gastrin on gastric secretory functions in rats [14].

Evaluation of gastric acid, pepsinogen and mucus secretions. Assessment of gastric acid, pepsinogen and mucus secretions was carried out on pylorus-ligated rats as previously reported [15]. At the time of the experiment, during a short anesthesia with diethyl ether, the abdomen was opened through a midline laparotomy, the duodenum was exteriorized, the pylorus was ligated, and the abdominal incision was closed with clips. The animals were then allowed to recover from anesthesia for 10 min. Two hours later the rats were sacrificed, the esophageal–gastric junction was ligated, and the whole stomach was excised. The gastric content was emptied, carefully collected in graduated centrifuge tubes, and centrifuged at 1000 ***g*** for 10 min in order to assess the net volume of luminal fluid (milliliters per 2 h). Samples with more than 0.5 ml of sediment were discarded. The luminal fluid collected from each stomach was then used for the quantitative evaluation of both acid and pepsinogen secretion. The stomach was used for the quantitative evaluation of mucus levels adherent to the gastric epithelial surface.

The level of acidity in the gastric content was measured by automatic potentiometric titration to pH 7.0 with 0.01N NaOH, using an Autotitrator pH Meter PHM82 (Radiometer, Copenhagen, Denmark) and evaluated as H^+ output (μEqH^+ per 2 h). The levels of pepsinogen in the gastric content were determined according to the method previously reported [14]. Briefly, 2 ml of 2.5% bovine hemoglobin were added to tubes containing 0.5 ml of 0.3N HCl and 0.5 ml of the gastric content. Samples were then incubated for 10 min at 37 °C and the reaction was stopped by the addition of 5 ml 0.3N trichloroacetic acid. After agitation and filtration, the optical density was measured at 280 nm by an Uvikon 930 spectrophotometer (Kontron Instruments, Milan, Italy). The results were compared to a standard curve generated in an identical manner, using known amounts of porcine pepsin (1 μg = 3 peptic units). Data were expressed as micrograms of pepsin per 2 h.

The quantitative estimation of mucus levels bound to the gastric epithelial surface was performed as previously reported [15]. After pylorus ligation for 2 h and collection of the gastric contents, as reported above, the stomachs were opened along the lesser curvature, washed with saline, and weighed. The glandular portion of the stomachs was excised and immersed for 2 h in 0.1% Alcian blue in a 0.16 M sucrose solution buffered with 0.05 M sodium acetate (pH adjusted to 5.8 with 1N HCl). The unbound dye was then removed by two subsequent washings of 15 and 45 min in 0.25 M sucrose solution, and the mucus-bound dye was eluted by immersing the stomach in a 0.5 M $MgCl_2$ solution for 2 h. The solution obtained was shaken with diethyl ether, and the optical density of the aqueous phase was read at 605 nm with a Uvikon 930 spectrophotometer (Kontron Instruments). The amount of Alcian blue extracted per gram of wet glandular tissue was then calculated from standard curves and expressed as micrograms of dye per gram.

Evaluation of gastric emptying. The quantitative evaluation of gastric emptying was carried out according to the method previously reported by Varga and Scarpignato [16]. For this purpose, a solution containing phenol red (0.6 g l^{-1}) was used as a liquid meal. Three milliliters of

Table II
Score values obtained for frequency and severity of dyspeptic symptoms both before (day 0) and after crenotherapy with Uliveto® water (day 30) in patients with functional dyspepsia

Symptom	*Frequency*		*Severity*	
	Day 0	*Day 30*	*Day 0*	*Day 30*
Epigastric pain	2.11 ± 0.31	1.67 ± 0.47*	2.67 ± 0.29	1.78 ± 0.49**
Retrosternal pyrosis	2.60 ± 0.34	1.70 ± 0.42**	2.60 ± 0.31	1.60 ± 0.40**
Epigastric burning	2.33 ± 0.24	1.78 ± 0.40	2.67 ± 0.17	1.44 ± 0.34**
Postprandial fullness	2.50 ± 0.31	0.83 ± 0.32***	2.58 ± 0.26	0.83 ± 0.34***
Gastric distension	2.88 ± 0.30	1.25 ± 0.41***	2.38 ± 0.26	1.25 ± 0.41*

Values reported for both frequency and severity are the mean ± SEM obtained from 8 to 12 patients. Significance of differences between values obtained at day 30 and the respective control values obtained at day 0 (Student's *t*-test for paired data). * $P < 0.05$. ** $P < 0.01$. *** $P < 0.001$.

pre-warmed (37 °C) test meal were instilled directly into the gastric lumen by a polyethylene orogastric catheter. Fifteen minutes later, the rats were sacrificed, their stomachs were rapidly removed and the luminal content was collected by gravity into graduated tubes. The stomach was then rinsed with 3 ml of saline solution (154 mM NaCl) and the resulting washing solution was added to the recovered gastric content. The phenol red concentration in the mixture was then measured by a spectrophotometer at 560 nm, following the addition of 0.1N NaOH, and the total amount of the dye marker recovered from the gastric lumen was calculated. Gastric emptying was expressed as the volume of dye marker solution emptied over a period of 15 min, and expressed as milliliters per 15 min.

Statistical analysis

The results obtained from both clinical and preclinical investigation are given as mean ± SEM. The significance of differences was evaluated by Student's *t*-test for paired data (clinical investigation) or one way ANOVA followed by Student–Newman–Keuls test (preclinical investigation). In all cases, *P* values lower than 0.05 were considered significant; '*n*' indicates the number of patients (clinical investigation) or the number of animals (preclinical investigation).

RESULTS

Clinical investigation

The group of patients, who met the inclusion criteria and were admitted to the study, consisted of 8 males and 10 females, aged between 25 and 75 years (median age: 52 years). At the time of enrollment (day 0) the prevalence of dyspeptic symptoms in the study group was as follows: epigastric pain, 9/18 (50%); epigastric burning, 9/18 (50%); postprandial fullness, 12/18 (67%); early satiety, 2/18 (11%); feeling of gastric distension, 8/18 (44%); nausea, 4/18 (22%); vomiting, 2/18 (11%); retrosternal pyrosis, 10/18 (55%); regurgitation, 3/18 (16%); dysphagy, 4/18 (22%). Dyspeptic symptoms with prevalence equal or higher than 40% were taken into account for further efficacy analysis of crenotherapy. The mean values obtained for frequency and severity of such symptoms both at baseline and after a 30-day course of crenotherapy with Uliveto® water, are displayed in Table II. Evidence was thus obtained that the regular intake of Uliveto® water for 1 month was associated with a consistent relief of epigastric pain, retrosternal pyrosis, postprandial fullness and feeling of gastric distension (in terms of both frequency and severity), as well as epigastric burning (only with regard for severity).

Preclinical investigation

In animals exposed to control mineral water ($n = 30$), the body weight at the beginning of the experimental period (day 0) accounted for 188.4 ± 13.7 g and increased regularly up to 239.6 ± 18.5 g at day 30. In animals treated with Uliveto® water ($n = 30$), the body weight changed from 192.6 ± 14.7 g (day 0) to 247.5 ± 20.3 g (day 30), these values being not significantly different from those obtained in animals exposed to control mineral water. The daily intake of water, in control animals, accounted for 120.3 ± 13.7 ml at the starting of the experimental period (day 1), and this value remained at a steady level up to day 30 (123.5 ± 15.7 ml). Analogously, in animals receiving Uliveto® water, the daily water intake was similar to that recorded in control animals, and did not vary significantly from day 1 (126.9 ± 14.6 ml) to day 30 (122.4 ± 11.8 ml).

In control rats subjected to pylorus ligation for 2 h ($n = 20$), a gastric secretory volume of 1.48 ± 0.9 ml 2 h^{-1} was detected; the acid and pepsinogen outputs accounted for 131.3±11.6 μEqH^+ 2 h^{-1} and 59.1±9.6 μg pepsin 2 h^{-1}, respectively. In these animals, the pretreatment with the gastrin/CCK-2 receptor antagonist L-365,260 did not significantly modify both acid and peptic secretory activities [Fig. 1(A, B)]. Under the same experimental conditions, in animals exposed continuously for 30 days to Uliveto® water ($n = 20$), pylorus ligation was associated with a significant increase in both acid (41.38%) and peptic gastric secretions (43.24%). The increments of these gastric secretory activities no longer occurred when animals were treated with L-365,260 10 min prior to pylorus ligation [Fig. 1(A, B)]. The Alcian blue recovery from the gastric mucus layer of control rats accounted for 96.5 ± 5.2 μg dye g^{-1}. This value did not change significantly when animals were treated with L-365,260 10 min before pylorus ligation. Analogously, in rats subjected to

Uliveto® water intake for 30 days followed by pylorus ligation, the Alcian blue recovery from gastric adherent mucus was similar to that obtained in control animals and was not significantly modified by pretreatment with L-365,260 [Fig. 1(C)].

Under control conditions ($n = 10$), a gastric emptying rate of 2.26 ± 0.15 ml $15\,min^{-1}$ was estimated, this digestive motor function being insensitive to the blockade

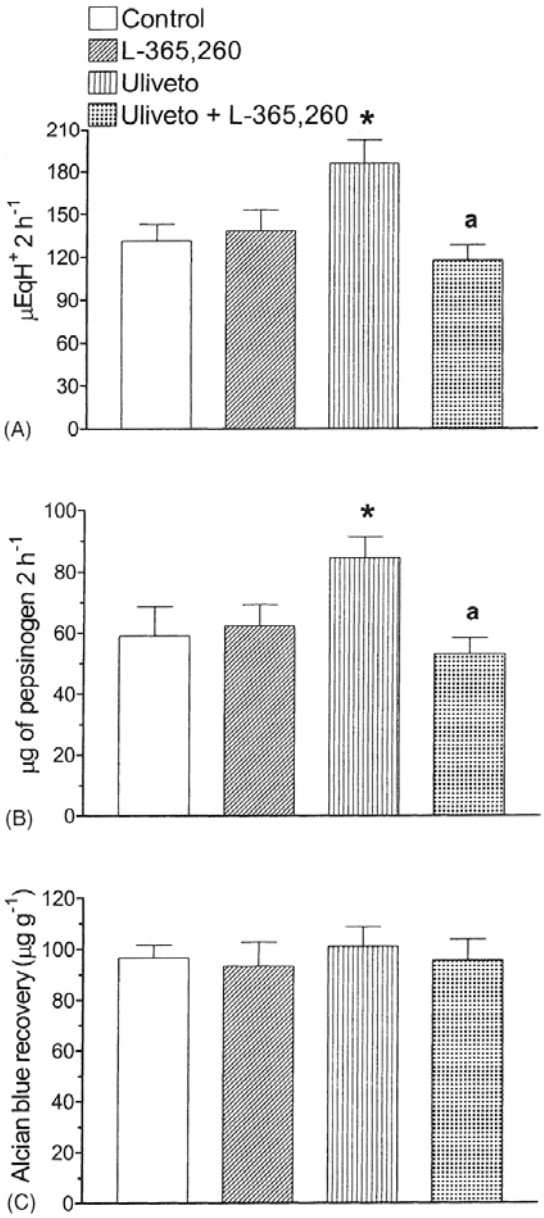

Fig. 1. Effects of a 30-day exposure to Uliveto® water, either alone or in the presence of L-365,260 (5 μmol kg^{-1} i.p.), on gastric acid secretion (A), gastric pepsinogen secretion (B), or Alcian blue recovery from gastric mucus layer (C) in conscious rats subjected to pylorus ligation. Control animals were allowed to drink a commercially available oligomineral water for 30 days and were then subjected to the experimental procedure either in the absence or in the presence of L-365,260. In all cases, L-365,260 was administered 10 min prior to perform pylorus ligation. Columns indicate the mean values obtained from 20 animals ± SEM (vertical lines). $^{*}P < 0.05$, significant difference from control values; $^{a}P < 0.05$, significant difference from values obtained in animals allowed to drink Uliveto® water alone.

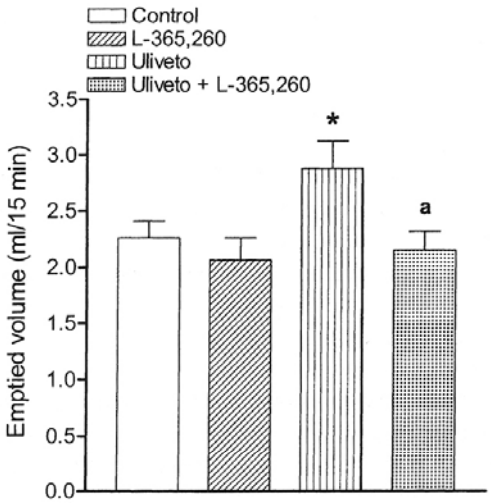

Fig. 2. Effects of a 30-day exposure to Uliveto® water, either alone or in the presence of L-365,260 (5 μmol kg^{-1} i.p.), on gastric emptying in conscious rats. Control animals were allowed to drink a commercially available oligomineral water for 30 days and were then subjected to the experimental procedure either in the absence or in the presence of L-365,260. In all cases, L-365,260 was administered 10 min prior to start the procedure for the evaluation of gastric emptying. Columns indicate the mean values obtained from 10 animals ± SEM (vertical lines). $^{*}P < 0.05$, significant difference from control values; $^{a}P < 0.05$, significant difference from values obtained in animals allowed to drink Uliveto® water alone.

of gastrin/CCK-2 receptors with L-365,260. Under the same experimental conditions, animals allowed to drink Uliveto® water ($n = 10$) showed a significant enhancement of gastric emptying (27.43%), that was fully inhibited in the presence of L-365,260 (Fig. 2).

DISCUSSION

Functional dyspepsia is characterized by a variety of symptoms usually referred to the upper digestive tract, the pathophysiology of which is still poorly understood [5]. At present, pharmacological treatments allow only a partial relief of symptoms in the majority of dyspeptic patients [6], and it has been suggested that some mineral waters might exert an adjuvant role in the medical management of dyspepsia, depending on their peculiar chemico-physical properties [11]. On this basis, the present study was performed to examine the effects of Uliveto® water on a group of patients with functional dyspepsia. Evidence was thus obtained that one month of crenotherapy with this mineral water exerts a positive influence on dyspeptic symptoms, particularly those which are usually referred to underlying functional disturbances of antro-duodenal motor activity.

The observation that the intake of Uliveto® water promoted the relief of postprandial fullness and gastric distension, both in terms of frequency and severity, suggests that this mineral water might favor a positive modulation of coordinated gastric motility, thus leading to an improved pattern of gastric emptying, with a subsequent attenuation

of dyspeptic symptoms occurring in the postprandial period. This hypothesis is in line with the findings of previous clinical investigations on patients with functional dyspepsia, where bicarbonate-alkaline mineral waters were shown to enhance the gastric emptying rate, as measured by means of scintigraphic techniques after ingestion of test meals labeled with radionuclides [10, 13]. Additional support to this view comes from the present preclinical experiments, where a significant increment of gastric emptying rate was detected in animals subjected to the phenol red assay after 1 month of continuous exposure to Uliveto® water.

Of interest, the present preclinical study provided evidence that, in addition to the increase in gastric emptying, the animals, which were allowed to drink Uliveto® water and were then subjected to pylorus ligation for 2 h, displayed a significant enhancement of gastric acid and pepsinogen secretions, without concomitant changes in the pre-epithelial mucus layer. These findings support the view that Uliveto® water might promote a combined positive modulation on both motor and secretory gastric functions, with a subsequent overall improvement of upper digestive processes in the clinical settings.

The paucity of knowledge currently available on the digestive effects of mineral waters makes it difficult to figure out the mechanisms through which Uliveto® water is able to induce an enhancement of gastric functions. However, the peculiar electrolyte composition of this mineral water allows to hypothesize that its positive influence on dyspeptic symptoms may depend on the relatively high concentrations of calcium or bicarbonate ions. For instance, studies performed on both humans and animal models have previously shown that the intragastric application of calcium causes a significant increment of acid secretion through a local stimulation of gastric mucosa [17, 18], and that, conversely, calcium channel blockers exert inhibitory actions on gastric secretions evoked by different stimulants, including pentagastrin, bombesin and insulin [19, 20]. Moreover, calcium ions can also act directly on antral mucosa to elicit the release of gastrin [18, 21]. Overall, it is conceivable that calcium ions, provided with Uliveto® water to the gastric mucosa, may contribute to the mechanisms accounting for the antidyspeptic action exerted by this mineral water.

Due to the high concentration of bicarbonate ions, Uliveto® water is expected to increase the pH level in the gastric lumen. This change may be relevant to the antidyspectic actions exerted by Uliveto® water in different ways: firstly, it has been observed that the exposure of proximal duodenal mucosa to gastric acid contents results in a slowing of gastric emptying [22, 23], and therefore the lowering of gastric acidity may counteract the occurrence of this inhibitory reflex; secondly, variations of gastric pH may affect the release pattern of digestive hormones known to have pivotal roles in the regulation of gastric functions. For instance, it has been well established that the acidification of gastric luminal contents inhibits the release of gastrin, and that maintaining intragastric pH above 3 increases the magnitude and duration of the gastrin response after a meal [21]. Since gastrin acts as a stimulant of different gastric functions, including the enhancement of antral motor activity and gastric emptying [24, 25], and in our preclinical study a prolonged intake of Uliveto® water was associated with significant increments of both acid/peptic secretions and emptying, we were prompted to perform additional experiments in animals pretreated with L-365,260, a selective antagonist of gastrin/CCK-B receptors [26]. Under those conditions, Uliveto® water was no longer able to promote the activation of gastric functions, thus suggesting that gastrin might play a role in the digestive effects of this mineral water.

In conclusion, the present study indicate that a regular course of crenotherapy with Uliveto® water may favor the relief of digestive symptoms in patients with functional dyspepsia. The results obtained with the preclinical investigation support the view that Uliveto® water may exert a positive influence on gastric functions, and suggest that the release of endogenous gastrin might account for these actions.

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