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Original article

Effect of enteric coated sodium bicarbonate, enzymes and bile combination on the absorption of fat in chronic pancreatitis

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SUMMARY

The effects of (A) H_2-receptor antagonist (ranitidine) and enzyme preparation with bile constituents (Digestal forte), (B) Digestal forte and $NaHCO_3$, (C) $NaHCO_3$ alone, or (D) Digestal forte alone, on the increase of lipolysis, were studied in a double-blind, randomized, prospective, controlled cross-over study in 10 patients with chronic pancreatitis (CP) and steatorrhea. All preparations were enteric-coated tablets except ranitidine.

The ^{14}C triolein breath test was used to monitor the lipolytic effect of the regimens, the parameter for the efficacy assessment being cumulative recover (CR) of $^{14}CO_2$ after 6 hours. Before the treatment patients underwent the same test procedure.

The regimen B produced significantly higher increase in CR, as compared to other regimens ($p<0.01$). A, B and D regimens induced a significant increase in CR compared to baseline CR ($p<0.01$), while regimen C had no effect ($p>0.05$). No differences were observed between the regimes A and D ($p>0.05$).

The results showed that exogenous lipolytic action of Digestal forte remained unaffected by ranitidine ($p>0.05$). This study suggests that the adding of bicarbonate with Digestal forte may play an important role in the regulation of lypolysis in these patients.

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INTRODUCTION

Inactivation of enzymes contained in pancreatic supplements by gastric acid has been known for many years.[1]

Pancreatic lipase is irreversibly inactivated by gastric acid at pH 4.0 and below. On the other hand, the pH over 7.5 appears to be the optimum for the lipase activity in vitro, depending on the bufer aplied.[2] Low pH present in the duodenum can stimulate release of duodenal secretin. This causes the secretion of large volumes of biliary and pancreatic fluids in duodenum. However, the secretion of bicarbonate from the pancreas fails to take place because of pancreatic insuficiency, and the duodenum may be much more acidic than normal.[3,4]

In patients with pancreatic insufficiency low gastric and duodenal pH values were found to correlate negatively with fat absorption.[5]

Several studies have shown high incidence of gastric hypersecretion in patients with chronic pancreatitis/CP/.[6,7]

Concurrent administration of antacids or H_2-receptor antagonists with enzymes aims at prevention of excessive enzyme inactivation by gastric acid, resulting in an increased availability of lipase in duodenum and jejunum.[3,8]

The administration of these agents, however, fails to eliminate steatorrhea, and their use remains restricted to individual patients, only.

The efficacy of sodium bicarbonate in the prevention of pancreatic enzyme inactivation remains disputable because of adverse effects such as belching, gastric dis-

tention, heartburn, and development of gastric erosions due to the potential rebound effect associated with the administration of the agent. This should be kept in mind since the therapy of such patients is the lifelong one.

New formulation of sodium bicarbonate enteric-coated (EC) tablet was developed at ICN Yugoslavia. Tablet is provided with an enteric film coating that delays dissolution of the tablet before it reaches the duodenum. Complete disintegration of the tablet occurs at pH 5.5 and higher.

EC sodium bicarbonate increases pH of enteric contents and, therefore, provides for substitution of insufficient pancreatic bicarbonate secretion. Bicarbonate ions decrease the pH optimum for human lipase in vitro.[9]

In this study, the ^{14}C triolein breath test was used to compare the effects of four treatments on the lipolytic catalytic action. The regimens administered included H2-receptor antagonist ranitidine and an enzyme with bile constituents (Digestal forte); Digestal forte and sodium bicarbonate; sodium bicarbonate alone, and Digestal forte preparation alone.

MATERIALS AND METHODS

The study medication included H_2-antagonist ranitidine, 150mg tablets (Ranitidin, zorka Farma, Yogoslavia); enzyme preparation with bile constituents (Digestal forte, ICN Yugoslavia), each enteric-coated tablet containing protease 600 IU, amylase 9,000 IU and lipase 12,000 IU, desiccated ox bile -25mg and hemicellulase - 50mg; sodium bicarbonate, 670mg enteric-coated tablets; placebo I tablets, identical in appearance to Digestal forte and to EC sodium bicarbonate tablets; and placebo II tablets, identical in appearance to Ranitidin. Both Digestal forte and sodium bicarbonate EC tablets dissolved at pH 5,5 or higher in vitro.

The objective of this double-blind, randomized, prospective, controlled cross-over clinical study was to compare the efficacy of four different treatment regimens in increasing the lipolytic effect in patients with chronic pancreatitis and steatorrhea. The treatment regimens included: (A) Ranitidine plus Digestal forte plus placebo I, (B) placebo II plus Digestal forte plus sodium bicarbonate, (C) placebo I nd II plus sodium-bicarbonate, and (D) placebo I and II plus Digestal forte. The study was conducted according to the principles of the Declaration of Helsinki, with the study protocol approved by the Ethics Committee of the Clinical Hospital Center "Zvezdara" in Belgrade.

Ten patients of both sexes (6 males and 4 females), age range 39-66 years, with verified chronic pancreatitis (DiMagno's criteria 1997),[10] who gave written informed consent to their participation in the study, were studied. All patients had severe steatorrhea with fat excretion of more than 30g per 24 hours and high fecal fat concentration (>.8,4%). Fecal fat was determined by the van de Kamer method.[11]

Fecal chymotrypsin concentration, determined in a specimen of fresh stool, was <3U/g.[12]

Women of childbearing potential who were not using an effective form of contraception, subjects with a history of hepatic or pulmonary disease, those with severe renal insufficiency, severe psychic disorders, malignancies, or any other disorders that may result in the malabsorption syndrome were excluded. Also excluded were those treated with H_2-receptor antagonists within 4 weeks before the study.

Ranitidin or placebo II (one tablet) was given 30 minutes before the test meal. The other two study drugs or placebo I tablets were given with the test meal. Digestal forte was given in two EC tablets, as well as sodium bicarbonate or placebo I.

Any previous enzyme and antacid treatments were discontinued 3 days before the initiation of the study treatment. During these 3 days the stool was collected daily for determining steatorrhea.

The patients were randomly assigned one of four treatment regimens. After a three-day washout period, patients were switched to other treatment regimen.

Fasting-state ^{14}C-triolein test was performed after a 12-hour fast, the first one being a baseline, and the subsequent four tests being performed with each of the 4 regimens described.

Glyceryl ^{14}C-Triolein Breath Test

The oil phase of the test meal contained glyceryl-tri ^{14}C-oleate (148 MBq), Amersham, dissolved in 20g of edible oil. For emulsification of the substrate, 5g Arabic gum and 5g lecithin were dissolved in 300ml of water. The oil was then added gradually to the aqueous phase and emulsified by manual stirring for 30 minutes.

A sample of expired CO_2 was trapped in hyamine hydroxide (Packard) CO_2 trapping solution with thymolphthalein as an indicator, in a glass scintillation.[13,14]

The samples of expired CO_2 were taken over the entire 360-minute period of breath collection, starting im-

mediately after a test meal (at 0 min), every 30 minutes after ingestion of the test meal. The sample radioactivity was measured by a liquid scintillation beta counter LKB WALAC. Pulse per minute count (cpm) was converted to disintegrations per minute (dpm) by external standardization.

Efficacy Assessment and Statistical Analysis

Assessment of capabilities of the study regimens to achieve the lipolytic catalytic effect was performed by measurement of cumulative $^{14}CO_2$ recovery within 6 hours (CR) that was, expressed as percent dose, determined by summation of $^{14}CO_2$ expired at each 30-min interval. The assumption was that expired CO_2 amounted to 9 mmol/kg/h, and that expiration was linear during each 30-min interval.

Statistical analysis of the CR results obtained by a Fisher test for analysis of variance.

RESULTS

The study included four women and six men, aged 50.3±2.9 years ($\bar{x}$±SD), with chronic pancreatitis for 6.6±1.8 years and fecal fat of 60.0±28.2 g per day ($\bar{x}$±SD). The values for cumulative $^{14}CO_2$ recovery for each patient are presented in Table 1.

Each of the treatment regimens studied led to highly significant increase in CR values, as compared to the baseline CR values ($p<0.01$), except for enteric-coated Na-bicarbonate alone, which failed to produce any significant increase of CR $^{14}CO_2$ ($p>0.05$).

The CR values obtained with the combination of Digestal forte plus EC Na-bicarbonate were highly statistically significantly raised compared to the CR values obtained with other treatment regimens ($p<0.01$).

The mean CR after Digestal forte was higher than that obtained with Digestal forte and ranitidine combined, but failed to reveal any significance ($p>0.05$).

DISCUSSION

Despite the fact that pathophysiology of pancreatic steatorrhea has been extensively studied and that pharmacological studies of the availability of pancreatic enzyme preparations have led to beneficial therapeutic regimens, the most efficacious therapy for pancreatic steatorrhea still remains elusive.[15,16]

It is generally accepted that the most suitable treatment both in terms of pharmaceutical formulation and lipolytic enzymes dosage should be individually designed for each patient.[15] On the other hand, monitoring of the pharmacotherapeutic effects of exocrine pancreatic substitution appears to be hindered by certain objective obstacles. Follow-up of pharmacotherapeutic effects of pancreatic enzyme requires somewhat extended period of time (at least 4-6 weeks). Objective parameters to be

Table 1. Cumulative output of $^{14}CO_2$ (percent dose administered) by treatment regimens in each individual patient (N=10) % dose of $^{14}CO_2$ after 6 hours

Patient No	O	A	B	C	D
1	2.8	1.3	13.3	9.2	7.8
2	7.9	10.9	16.1	17.6	15.6
3	0.3	13.7	14.3	0.8	5.2
4	0.2	10.6	11.2	3.9	10.0
5	2.4	8.1	12.8	1.3	4.3
6	3.3	17.2	18.7	4.7	15.4
7	1.3	4.3	12.9	1.4	12.2
8	0.3	2.4	8.4	0.8	5.7
9	6.7	14.8	15.9	8.8	9.7
10	3.8	10.7	16.3	4.0	14.9
$\bar{X}_i$±SE	2.9±0.8	9.4±1.6	14.0±0.9	5.2±1.6	10.1±1.3

O: No treatment
A: One tablet Ranitidine + 2 tabs Digestal Forte + 2 tabs Placebo II
B: One tablet Placebo I + 2 tabs Digestal Forte + 2 tabs $NaHCO_3$
C: One tablet Placebo I + 2 tabs Placebo II + 2 tabs $NaHCO_3$
D: One tablet Placebo I + 2 tabs Placebo II + 2 tabs Digestal Forte

used in the assessment of therapeutic effects of pancreatic enzymes include collecting of stools over a 72-hour period, determining the amount of steatorrhea (g/24 h) and body weight measurement.[15] However, in cross-over studies the assessment could hardly be based on the measurement of body weight.

Due to the structure of the patient population studied (alcoholics, diabetics, individuals inclined to indulgence in food and alcohol), the results obtained are hardly interpretable if an investigator cannot ascertain that a comparable amounts of fatty food were ingested by the patient while on different treatments.

Due to the methodological problems described, the clinical studies conducted so far failed to address the issues of pharmacodynamics and pharmacotherapeutic effects of such agents, but were mainly focused on the issue of the availability of pancreatic enzymes formulations. Mundlos et al 1990, compared the availability of a pellet formulation of pancreatic enzymes and an equivalent pancreatin formulation (total lipase 100,000 IU) combined with cimetidine taken 30 min before meal and pancreatin.[17] The availability assessment of the two treatments was based on the comparison between the CR values obtained 2 hours and 4 hours after a cholesteryl-^{14}C-octanoate test meal. Cholesteryl octanoate breath test has shown that adding of cimeditine increases lipolytic effect of pancreatin as compared to pellets with an equivalent lipolytic activity to that of pancreatin. Administration of pancreatin pellets alone had no effect.

In this study, the glyceryl-triolein breath test was used for the indirect assessment of the lipolytic effect, by comparison between the CR values obtained within 6 hours after the test meal. The choice of the glyceryl-triolein breath test for the study can be explained by several reasons. Firstly, with regard to the catalytic sensitivity of pancreatic lipase, the glyceryl-triolein substrate has been thoroughly studied. Secondly, the orocecal transit in patients with chronic alcoholic pancreatitis appears to be delayed by 50% compared to the controls; it usually takes 2.5 hours for completion.[18,19]

We assumed that the CR value of $^{14}CO_2$ requires at least 5 hours and that the assessment of lipolytic effect can be performed only after that. The 6-hour time chosen was twice longer than the time required for the test meal to reach the colon.

As our results have demonstrated, the lipolysis in patients with chronic pancreatitis could be increased significantly by the administration of a formulation containing a combination of pancreatic enzymes and bile extract ($p<0.01$). Two tablets of Digestal forte (total lipase of 24,000 IU) proved sufficient for the lipolytic activity that was superior to that achieved with no treatment.

Being prevented by the reasons of ethics to establish experimental conditions which would allow evaluation of the effect of enteric-coated tablets containing pure pancreatin, we can assume that our results do correlate with the results obtained by Mundlos et al. The administration of cimetidine prevents precipitation of bile[20] in acid duodenal content on one hand, while providing for the environmental pH more optimal for lipolysis, on the other. Digestal forte enteric-coated tablets enable lipolysis at optimum pH ($pH>5.5$), in the presence of exogenous bile (25 mg).

Our results have shown that addition of ranitidine to Digestal forte does not increase lipolytic activity ($p>0.05$). The increase in lipolytic activity may be achieved by combined administration of H_2-receptor antagonists with pancreatic enzyme preparations, aimed at preventing precipitation of endogenous bile or by adding exogenous bile with pancreatic enzyme preparations in enteric-coated forms, with the aim of providing for both fat emulsification and lipolysis at optimum pH conditions.

If administered concurrently with enteric-coated Digestal forte combination, enteric-coated sodium bicarbonate may, on the other hand, provide for an additionally increased lipolysis ($p<0.01$). Enteric coated sodium bicarbonate alone does not increase lipolysis produced by endogenous lipases ($p>0.05$) (Table 1).

Significant bicarbonate-induced activation of human lipase in the presence of cholates and colipase has been confirmed by an in vitro study,[9] as bicarbonate ions may additionally activate lipase, as well as reduce optimum pH for its maximum activity.

It is, also, well known that pancreatin preparations contain sufficient colipase.[21] Substitution therapy combining enteric-coated Digestal forte and sodium bicarbonate contributes to an adequate emulsifying effect (bile and bicarbonate), leading to the optimal environment for lipolysis (intraluminal pH >5.5, presence of lipase and colipase).

The results obtained suggest that adding of bicarbonate and bile extract may increase lipolytic activity of pancreatic enzyme preparations ($p<0.01$). The future studies should investigate the pharmacotherapeutic efficacy of a combined substitution therapy (sodium bicarbonate, bile extract, pancreatic enzymes) in an enteric-

coated form, as compared to enzyme therapy in a larger patient population, including the measurement of steatorrhea and of body weight, together with monitoring the adverse effects of such a treatment.

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