Prevention of Pancreatogenic Disorders by Infusion of Monomer-Electrolyte Solutions in Combination with Dalargin

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Chronic experiments on dogs have shown that in acute pancreatitis cardiac and liver disorders arise before pronounced changes in blood amylase level. Liver and hemodynamics disorders develop earlier than profound functional changes in the pancreas. Dalargin (50 μg/ml), a synthetic enkephalin analogue, stimulated the absorbing function of the small intestine. Intravenous administration of dalargin together with intraintestinal infusion of a monomer-electrolyte solution effectively prevented the development of profound functional disorders of the pancreas as well as hemodynamic and volemic disturbances.

Key Words: *dalargin; monomer-electrolyte solution*

Enzyme toxemia together with hemodynamic and volemic disturbances plays a significant role in the pathogenesis of systemic disorders developing in acute pancreatitis [1,5,11]. Pathogenic therapy of this disease includes timely control over the local pathological process with protease inhibitors which regulate protein synthesis or secretory function [8, 10,12]. Circulating Leu-enkephalins modulate the production of pancreatic enzymes [8,12], peristaltic and secretory activity of the gastrointestinal tract [8], and central hemodynamics [1]. The broad spectrum of enkephalin activity is due to the modeling effect of this neuropeptide on premotor neurons responsible for the consumatory behavior. Various blood-replacing solutions have been used for the correction of water-electrolyte disorders [10,13]. Intraduodenal infusion of monomer-electrolyte solutions (MES) effectively corrects experimental disorders of systemic hemodynamic and intestinal-hepatic circulation [4]. Experimental findings were confirmed by clinical practice [7].

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Volemic, central hemodynamic, and intestinal-hepatic circulatory disturbances play the key role the in the pathogenesis of systemic disorders occurring in acute pancreatitis. In the present study we explored the possibility of timely correction and prevention of pancreatogenic complications by means of intraintestinal infusion of MES in combination with intravenous injection of the synthetic enkephalin analog dalargin.

MATERIALS AND METHODS

In the first series of experiments we examined the effect of 50 μg/kg dalargin on absorbing activity of the intestine in conscious dogs (35 experiments). Surgical procedure allowing for the assessment of the rate of MES absorption in the intestine was were described elsewhere [3].

In the second series of chronic experiments (n=14) we modeled acute pancreatitis. For this purpose, we catheterized Wirsung's duct and inserted a fistula into the duodenum. The experiment was started 2-3 days after the surgery. Acute pancreatitis was induced by injecting bile (0.3 mg/kg body weight) into the catheter.

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TABLE 1. Blood Contents of Some Enzymes In Acute Pancreatitis and after Its Correction *(M±m)*

Observation period	ALT, nmol/sec×liter	AST, nmol/sec×liter	LDH, μmol/sec×liter	Amylase, g/h×liter
Initial level	235±19.1	355.1±24.7	5.69±0.41	76.8±6.8
Pancreatitis (*n*=14):				
1.5 h	442±33.5*	522±46.6*	8.59±0.69*	88.13±7.4
2.5 h	705±64.2*	710.0±68.3*	9.10±0.83*	145.92±12.1*
Pancreatitis 4 h (*n*=7):				
MES infusion	317.5±26.3	497.2±37.9	6.19±0.54	657.4±49.8*
Dalargin+MES	509±43.6*	643±58.4*	31.24±0.23*	83.71±7.5

Note. *$p<0.05$ compared with the initial level.

The second series experiments were subdivided into two groups. In the first group we studied the effect of intraduodenal infusion of MES on acute pancreatitis. In the second group MES infusion was combined with intravenous injection of 50 μg/kg dalargin.

The volume of circulating blood, cardiac output, and liver blood flow were determined by impedancometry [6]. Hematocrit, osmolarity, and blood gases were estimated. Serum concentrations of alanine and aspartate aminotransferases (ALT and AST), lactate dehydrogenase (LDH), and amylase were determined by biochemical methods. The volume of circulating plasma, protein content, and oxygen transport parameters (oxygen consumption, delivery, and extraction) were calculated. The pancreas of died animals was excised for morphological studies.

RESULTS

Immediately after intravenous injection of dalargin the rate of resorption in the intestine increased by 26% (by 80% in some dogs). This was accompanied by pronounced and prolonged decrease (by 73%) in the secretion of duodenal contents through the fistula.

A slight increase was observed in blood amylase concentration within the first 1.5 h of acute pancreatitis (Table 1). Blood concentrations of LDH, AST, and, to a greater extent, ALT increased significantly. The concentrations of all studied enzymes increased considerably after 2.5 h (Table 1), the volume of circulating plasma, protein content, particularly that of albumin, cardiac output, and liver blood flow decreased (Tables 2 and 3). Irrespective of decreased cardiac output, oxygen consumption increased due to increased tissue extraction of oxygen (Table 3).

Intraintestinal infusion of MES 4 h after bile injection in Wirsung's duct increased the volume of circulating blood and particularly the plasma volume (Table 2). However, cardiac output and tissue extraction of oxygen decreased, which led to reduction in oxygen consumption (Table 3). After MES infusion, blood concentrations of ALT, AST and LDH decreased, while that of amylase continued to grow (Table 1).

TABLE 2. Volume of Circulating Blood and Serum Proteins at Different Stages of Acute Pancreatitis and after Its Correction *(M±m)*

Observation period	Cardiac output, ml/kg	Volume of circulating blood, ml/kg	Volume of circulating plasma, ml/kg	Total protein		Albumin		Globulin	
				g/liter	g/kg	g/liter	g/kg	g/liter	g/kg
Initial level	300±6.5	73.00±2.0	39.8±1.6	56.5±2.01	2.245±0.09	24.50±0.8	0.976±0.06	32.0±1.10	1.269±0.08
Pancreatitis (*n*=14):									
1.5 h	309±7.4	69.56±1.8	36.54±1.9	50.68±1.92	1.841±0.04*	20.433±0.7	0.751±0.04	30.118±1.14	1.104±0.07
2.5 h	300±8.6	52.12±2.2*	27.56±1.8*	47.742±1.88*	1.472±0.06*	20.418±0.5*	0.567±0.04*	27.296±1.08*	0.911±0.04*
Pancreatitis 4 h (*n*=7):									
MES infusion	300±6.4	60.00±2.4	37.2±2.1	51.4±1.93	1.912±0.08	20.58±0.4*	0.765±0.06	30.93±1.33	1.150±0.06
Dalargin+MES	287±6.1	79.88±2.1	45.77±2.2	47.742±0.84*	2.200±0.07	20.418±0.6*	0.947±0.09	27.296±1.12	1.251±0.08

Note. Here and in Table 3: *$p=0.05$ compared with the initial level.

TABLE 3. Liver Blood Flow, Cardiac Output, and Oxygen Transport in Acute Pancreatitis and after Its Correction *(M±m)*

Observation period	Blood flow, ml/kg	Cardiac output, ml/kg	Po_2, mm Hg	Arteriovenous difference, vol.%	Oxygen delivery, ml/min×kg	Oxygen consumption, ml/min×kg	Oxygen extraction, %
Initial level	43.5±2.1	198.8±9.5	80.8±2.5	7.25±0.49	32.23±2.4	13.93±1.1	43.26±3.2
Pancreatitis (*n*=14):							
1.5 h	33.40±1.3	170.9±7.6	90.69±5.3	9.28±0.84	28.69±2.1	16.55±1.2	53.64±4.6
2.5 h	23.92±1.4*	147.11±4.9*	97.28±6.7	13.62±1.21*	27.40±2.2	19.36±1.4*	75.57±6.1*
Pancreatitis 4 h (*n*=7):							
MES infusion	32.05±1.8*	109.34±3.7*	90.9±6.1	8.79±0.73	18.69±1.04*	9.33±0.81*	49.75±3.7
Dalargin+MES	47.76±2.3	191.84±1.03	83.09±6.4	5.94±0.41	29.65±2.1	11.14±0.95	37.97±2.8

In combination with injection of dalargin MES infusion markedly decreased blood amylase concentration (Table 1). There was no increase in this parameter 4 h after bile injection into Wirsung's duct. However, in many dogs blood ALT, AST, and LDH concentrations remained at a high level (Table 1). The circulating blood volume, cardiac output, and liver blood flow continued to increase. The oxygen-transport function of the blood improved (Tables 2 and 3).

Previously, we showed that excessive secretion of proteolytic enzymes and products of their interaction with various substances occurring in acute pancreatitis [2,9,13] has a negative effect on cardiac activity and liver function, which is consistent with the literature data [2,5,9]. Disturbances in central and liver hemodynamics arise at the earliest stages of pathological process in the pancreas, under conditions of a very low blood amylolytic activity.

We have demonstrated low effectiveness of enteral correcting therapy without any control over the enzymatic activity of the pancreas. Although the absorbing function was preserved after 2.5 h of developing pathological process in the pancreas, administration of MES had no therapeutic effect: the process was not arrested, leading to tissue hypoxia, aggravation of cardiac and hepatic disorders, and death of the animals against the background of acute hemorrhagic pancreatic necrosis.

In dogs treated by MES and dalargin the process was principally different: a decrease in the production and secretion of pancreatic enzymes was accompanied by restoration of circulating blood volume, cardiac output, oxygen-transporting function of the blood, and liver hemodynamics to the initial level.

Thus, our study has shown that in acute pancreatitis cardiac disorders and liver dysfunctions occur at the early stages of the pathological process, prior to its biochemical manifestations. The development of liver and hemodynamic disorders is faster than that of profound functional changes in the pancreas, which in combination with suppressed antitoxic function of the liver [1,8] and aggravated tissue hypoxia renders the process irreversible.

Our result show that dalargin not only reduces excessive secretory activity of the pancreas, but also stimulates absorbing function of the small intestine. Intravenous injection of dalargin in a dose of 50 μg/kg in combination with intraintestinal infusion of MES (20 ml/kg) at the early stages of acute pancreatitis effectively prevents pancreatic and liver dysfunction as well as volemic and hemodynamic disorders.

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