Inhibitory effect of various cytostatics and cycloheximide on acute experimental pancreatitis in rats

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SUMMARY Cycloheximide, 5-azacytidine, and 4-methoxybenzoyl- β -bromoacrylate (Cytembena) block the development of experimental acute pancreatitis in rats when mediated by the administration of 5% bile solution into the pancreas *in vivo*. Six hours after drug treatment the pathological changes, evaluated macroscopically or using histological sections of the pancreas, were significantly decreased. The drugs affected the amount of abdominal fluid and lowered its lipase and amylase activity. The known inhibitory mechanism of the active drugs and the possible advantage of cycloheximide for clinical use are briefly mentioned.

Acute pancreatitis is accompanied by haemorrhagic and necrotic changes (Carey, 1973; Palmer, 1975). The main lesion is necrosis of acinar cells and the clinical course of the illness depends on how much of the exocrine part of the pancreas is destroyed (Edlund, 1970). The relation between the pancreas and the products of its secretion, the phenomenon of autodigestion, and all the features of acute pancreatitis are continually being studied (Beck *et al.*, 1965; Creutzfeldt and Schmidt, 1970; Becker, 1973; White and Allan, 1974). In the course of development of acute pancreatitis different acinar enzymes are activated. At the forefront of today's chemotherapy of the disease are drugs which block the activity of pancreatic enzymes and their autodigestive action on the organism. At present the curative action of trypsin inhibitors—for example, Trasylol, Antilysin—is well established (Beck *et al.*, 1965; Nugent and Atendido, 1965; Baden *et al.*, 1969; Mališ *et al.*, 1972).

Pancreatic tissue is characterised by a high rate of synthesis of proteins and nucleic acids (Walther *et al.*, 1974; Cohen and Kulka, 1974). It is suggested that drugs interfering with the synthesis of these macromolecules affect the formation of pancreatic enzymes. Similar drugs are often used as cytostatics.

Recently, Johnson *et al.* (1973) observed that 5-fluorouracil favourably affects the course of experimental pancreatitis in dogs. In our earlier study (Korbová *et al.*, 1974) we found that 5-azacytidine affects gastric secretion in rats as well as the incidence of experimental gastric ulcers and depresses the secretion of enzymes from the pancreas. Similarly, 5-bromo-2'-deoxyuridine was found to exert a selective inhibitory effect on embryonic rat pancreas (Walther *et al.*, 1974). Consequently, we decided to investigate the effect of certain drugs that interfere with the synthesis of nucleic acids and proteins in the course of acute experimental pancreatitis in rats.

Methods

Several methods of producing acute experimental pancreatitis are known—for instance, perfusing the bile ducts (Elliott *et al.*, 1958; Beck *et al.*, 1964), interstitially administering different compounds (Keith *et al.*, 1958; Waterman *et al.*, 1969), or by the action of various stimuli or inducers (Bawnik *et al.*, 1974; Schiller *et al.*, 1974; Backwinkel *et al.*, 1975; Lombardi *et al.*, 1975). In the present study 90 male rats (Wistar, 250-300 g) were kept on a standard diet and separated into several groups. Laparotomy was carried out under mild ether narcosis and 0.6 ml 5% bile solution was administered interstitially into the

pancreas (Keith *et al.*, 1958). After six hours of treatment the animals were killed by cervical dislocation and the volume of abdominal fluid was measured. The macroscopic changes (necrosis) in the pancreas and in the abdominal cavity were evaluated as shown in Table 1. In this classification the highest number of points was allocated to haemorrhagic and necrotic changes, followed by necrosis of the pancreas, and oedema and necrosis in the abdominal cavity.

After killing the animals the pancreas was removed and kept on solid carbon dioxide at -30°C . Another group of animals was used for the histological examination. The pancreas was fixed in neutral formaldehyde and sections of the tissue were stained with haematoxylin and eosin. Collected blood was immediately centrifuged and serum as well as abdominal fluid was kept at -18°C .

Trypsin and chymotrypsin were measured after homogenisation of the pancreas in aqueous 0.5% NaCl containing 0.05% CaCl_2 (pH 5.2) in the ratio of 1:4 (w:v) under cooling in a glass homogeniser. Proteinase activity was measured photometrically after activation by enterokinase (Organon) or by trypsin (Spofa). For trypsin estimation synthetically prepared N- α -tosyl-L-arginine-p-nitroanilide was used as the substrate (Mališ *et al.*, 1974), for chymotrypsin N- α -succinyl-L-phenylalanine-p-nitroanilide (Suphena). Lipolytic activity was assayed photometrically according to Raderecht (1959), amylase was measured according to Teller (1950), and protein content according to Lowry *et al.* (1951). Enzyme activities are expressed as milligrams of crystalline trypsin and chymotrypsin per gram of protein or in milligrams of reaction products (amylase—reducing sugars, lipase—phenol) per 100 ml of serum. Enzyme activity in the abdominal fluid was expressed as mg per ml, or per total volume of the fluid. The statistical significance of the data was evaluated by Student's *t* test.

5-Azacytidine (Čihák, 1975) (4-amino-1- β -D-ribofuranosyl-1,3,5-triazin-2-one) was prepared in the Institute of Organic Chemistry and Biochemistry in Prague. Cytembena (Slavíková *et al.*, 1971) (sodium *cis*- β -4-methoxybenzoyl- β -bromoacrylate), and Antilysin (natural polypeptid isolated from lung) (Mansfield *et al.*, 1960) were supplied by Spofa, Prague, and cycloheximide (Actidione) was from Calbiochem, Lucerne. The drugs were administered subcutaneously, except for Antilysin, which was injected intraperitoneally, immediately after infiltration of the pancreas by the bile solution.

Results

All the drugs tested, except Antilysin, caused macro-

Table 1 *Classification of necrotic changes in pancreas and abdominal cavity according to macroscopic evaluation*

Changes	Classification points
Pancreas	
Oedema	0-10
Necrosis	0-20
Haemorrhage	0-30
Abdominal cavity	
Necrosis of mesenterium and intestinal serosa	0-5
Necrosis of retroperitoneal fatty tissue	0-4

Table 2 *Effect of various drugs on extent of necrosis in pancreas and abdominal cavity caused by 5% bile solution*

Drug	Rats (no.)	Dose (mg/kg)	Classification	
			Points $\pm$ SE	%
Control	25		45.1 $\pm$ 5.4*	100
Antilysin	13	100 000 KIU	43.4 $\pm$ 3.1	96.0
Cytembena	13	2.0	16.3 $\pm$ 2.0*	36.1
5-Azacytidine	13	4.85	17.0 $\pm$ 2.9*	37.6
Cycloheximide	13	0.25	11.4 $\pm$ 1.3*	25.2

* $P < 0.01$.

scopic changes in the pancreas which were not observed in control animals receiving bile solution only. The most effective drug in the treatment of acute experimental pancreatitis was cycloheximide (Table 2). However, 5-azacytidine and Cytembena also significantly reduced the pathological changes observed in the pancreas. Haemorrhagic and necrotic pancreatitis was observed only exceptionally after the administration of the three drugs. Most of the changes included focal necrosis and oedema. After the administration of cycloheximide very little haemorrhagic necrosis was observed, areas of oedema were smaller, and the appearance of the lower third of the pancreatic tissue was practically normal.

The macroscopic differences are in agreement with the histological observations. After the interstitial administration of a 5% bile solution the majority of acini in the pancreas of animals not treated with the drugs were necrotic with extensive haemorrhage both in necrotic areas and in the surrounding interstitial tissue; here also there was a mixed inflammatory cell population and considerable oedema (Fig. 1). Administration of Cytembena, 5-azacytidine, and cycloheximide caused necrosis which was not characterised by haemorrhage, and was localised in a narrow strip of the periphery of lobulus with a mixed inflammatory cell population and environmental oedema (Fig. 2). Small haemorrhagic changes

Fig. 1 *In untreated animals interstitial administration of 5% bile solution causes necrosis and extensive haemorrhage in most of the pancreatic acini and in the surrounding tissue. Oedema and inflammatory cells can be seen in the interstitium. $\times 400$.*

Fig. 2 *In animals treated with Cytembena interstitial administration of 5% bile solution causes oedema, infiltration, and necrosis on the periphery of lobulus only. $\times 400$.*

Table 3 Reduction of haemorrhagic fluid in abdominal cavity and its amylase and lipase activity in rats treated simultaneously with 5% bile solution and various drugs

Drug	Rats (no.)	Dose (mg/kg)	Abdominal fluid		Amylase		Lipase	
			(ml $\pm$ SE)	(%)	(Somogyi U $\pm$ SE)	(%)	(mg $\pm$ SE)	(%)
Control	28		3.99 $\pm$ 0.29*†	100	1863.1 $\pm$ 175.8*	100	16.0 $\pm$ 1.6	100
Antilysin	13	100 000 KIU	5.00 $\pm$ 0.51	125	1769.0 $\pm$ 127.1	94	18.5 $\pm$ 2.2	115
Cytembena	13	2.0	2.95 $\pm$ 0.51	71	1349.7 $\pm$ 193.7	70	14.8 $\pm$ 2.1	92
5-Azacytidine	13	4.85	2.68 $\pm$ 0.57†	67	726.8 $\pm$ 183.9*	39	11.2 $\pm$ 2.9	70
Cycloheximide	13	0.25	2.26 $\pm$ 0.33*	57	1205.0 $\pm$ 237.1*	64	11.2 $\pm$ 2.8	70

* P < 0.01. † P < 0.05.

were observed only in 8% of cases. After Antilysin had been administered histological patterns did not differ from the control sections of the pancreas.

The administration of the tested drugs (with the exception of Antilysin) also lessened the haemorrhagic fluid in the abdominal cavity. The decline in its volume after treatment with 5-azacytidine and cycloheximide was statistically significant. At the same time the level of lipase and amylase activity in the abdominal fluid was decreased (Table 3). The level of trypsinogen and chymotrypsinogen in the pancreas was unchanged, as was the glucose level in serum and abdominal fluid and the serum lipase activity. However, after the administration of 5-azacytidine and cycloheximide the activity of serum amylase was significantly depressed (Table 4). The administration of Antilysin resulted in the lowering of trypsinogen and chymotrypsinogen in the homogenised pancreas only (Table 5). The decline of both enzymes was statistically significant.

Discussion

Cycloheximide, 5-azacytidine, and Cytembena, compounds that favourably affect the course of experimental acute pancreatitis in rats (Table 2), have one feature in common. They act on the synthesis of nucleic acids and interfere with the synthesis of proteins in different tissues, mainly in rapidly proliferating ones (Veselá *et al.*, 1970; Novi *et al.*, 1973; Reichman and Penman, 1973). The pancreas and

Table 4 Effect of various drugs on serum amylase activity

Drug	Rats (no.)	Dose (mg/kg)	Amylase	
			(Somogyi U $\pm$ SE)	(%)
Control	28		7217.8 $\pm$ 291.2*	100
Cytembena	13	2.0	6329.1 $\pm$ 367.0	87.6
5-Azacytidine	13	4.85	5072.7 $\pm$ 733.4*	70.2
Cycloheximide	13	0.25	4738.0 $\pm$ 877.0*	65.6
Control untreated	10		2228.0 $\pm$ 111.0	

* P < 0.01.

Table 5 Depression of trypsinogen and chymotrypsinogen in homogenised pancreas of rats treated simultaneously with 5% bile solution and Antilysin

Drug	Rats (no.)	Dose	Trypsinogen		Chymotrypsinogen	
			(mg/g protein)	(%)	(mg/g protein)	(%)
Control	28		17.2 $\pm$ 2.5*	100	324.0 $\pm$ 21.8†	100
Antilysin	13	100 000 KIU	6.0 $\pm$ 1.2*	34	240.0 $\pm$ 19.4†	74

* P < 0.005. † P < 0.01.

some parts of the gastrointestinal tract (stomach, small intestine) (Cairnie *et al.*, 1965) are organs with a high rate of turnover of proteins.

Cycloheximide is widely used as an inhibitor of protein synthesis in eukaryotes. It interferes with the synthesis of proteins on cytoplasmatic ribosomes (Baliga *et al.*, 1969); however, care must be taken in interpreting its inhibitory effects (Timberlake and Griffin, 1974). After the administration of this antibiotic the activity of several enzymes was found to be enhanced (Čihák, 1975; Levine *et al.*, 1975). 5-Azacytidine, successfully used in the treatment of acute leukaemia in childhood (Hrodek and Veselý, 1971), has a polyvalent inhibitory mechanism (Čihák, 1974). The drug is incorporated into different types of RNA, causes degradation of polyribosomes, and inhibits maturation of 45 S precursor ribosomal RNA (Čihák, 1975). As a result, inhibition of protein synthesis occurs (Reichman and Penman, 1973; Čihák, 1975), although the activity of several enzymes was also found to be increased after the use of this drug (Čihák *et al.*, 1973; Čihák and Veselý, 1973). Cytembena, active in the treatment of gynaecological tumours (cf. Jandová *et al.*, 1971), inhibits *de novo* purine biosynthesis (Slavíková *et al.*, 1966). The drug causes a rapid and intensive inhibition of DNA biosynthesis (Jackson *et al.*, 1975), and, at higher doses, inhibition of protein synthesis was observed (Veselá *et al.*, 1970; Jackson *et al.*, 1975).

Like 5-azacytidine, 5-fluorouracil interferes with the development of pancreatitis. Johnson *et al.* (1973) observed a favourable effect of 5-fluorouracil on the

survival of dogs with experimental acute pancreatitis. The action of the analogue can also be explained, assuming that it interferes with the synthesis of nucleic acids (Wilkinson and Pitot, 1973) and proteins. In our earlier study, we observed (Korbová *et al.*, 1974) that 5-azacytidine affects gastric secretion and depresses the secretion of hydrochloric acid. The administration of cycloheximide (Young *et al.*, 1963) blocks the synthesis of proteins and results in a syndrome characterised by vomiting, diarrhoea, and progressive acidosis.

In the present study we used cytostatics, which do not inhibit protein synthesis immediately after their administration. However, their effect on experimental acute pancreatitis was observed in a short-term experiment lasting six hours. Apart from the direct or indirect action of these compounds on the synthesis of proteins one has to take into consideration other possible mechanisms as well as the lessened gastric secretion resulting in the lower release of secretin and pancreozymin in the duodenum. It is possible that there is an alteration in the response of the exocrine pancreas to the changed diet (Lavau *et al.*, 1974) caused by a blocked dietary absorption in cycloheximide or 5-azacytidine-treated animals (Korbová *et al.*, 1974). Also the secretion of digestive enzymes from the pancreas (Rothman and Isenman, 1974) can be impaired by the action of these drugs.

At present it is difficult to explain how cycloheximide, 5-azacytidine, or Cytembena actually affect experimental acute pancreatitis induced by interstitial administration of bile solution and prevent the autodigestion of the pancreas. Cycloheximide, which is relatively non-toxic (Young and Dowling, 1975), was active in our experiments at low doses thus permitting its possible clinical use.

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