A TRIAL OF 'TRASYLOL' IN THE TREATMENT OF ACUTE PANCREATITIS

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'Trasylol', an inhibitor of trypsin and kallikrein prepared from bovine parotid gland, has recently been made available for the treatment of acute pancreatitis. Some have claimed good results in the experimental animal[1-2] and in man,[3-5] but this has not been confirmed by others.[6] The enthusiasm of McHardy *et al.*[3] for trasylol was tempered by their not having carried out a controlled clinical evaluation of the drug, a shortcoming noted in most of the other reports as well.

The subjective and objective differences in patients with acute pancreatitis present numerous difficulties in assessing the therapeutic value of a drug such as trasylol. The severity of the pain, the duration of the acute attack, and the serum-enzyme levels vary from patient to patient and, indeed, in the same patient subject to repeated attacks. In addition, the relative severity of the attack in gallstone pancreatitis compared with alcoholic pancreatitis necessitates consideration of the aetiological factors in evaluating therapy.

The results of a controlled trial of the use of trasylol in the treatment of acute pancreatitis will be presented in this paper. The conditions of the trial will be defined,

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TABLE I. ATTACK RATE AND DIAGNOSTIC CRITERIA IN 32 PATIENTS WITH ACUTE PANCREATITIS

Type of pancreatitis	Cases	Sex	Attack rate		Diagnostic criteria				
			First attack	Had previous attacks	Laparotomy abnormal	Pancreatic-function test		Serum enzymes	
						Diagnostic	Supporting	Diagnostic	Supporting
Alcoholic	21	M	5	16	15	5	(10)	1	(20)
Non-alcoholic:									
Cholelithiasis	8	6 F, 2 M	3	5	6*	0	(4)	2	(6)
Pregnancy	1	F	1	0	0	0	(0)	1	(0)
Hyperlipaemia	1	F	0	1	1	0	(1)	0	(1)
Unknown	1	F	0	1	1	0	(0)	0	(1)
Total	32		9	23	23*	5	(15)	4	(28)

In 5 patients the diagnosis was made from a typical history, grossly elevated serum enzymes and an abnormal pancreatic-function test, and in 4 the diagnosis was made from a typical history and grossly elevated serum enzymes only.

*The pancreas was normal in 1 additional patient operated on 3 weeks after an acute attack.
The numbers in brackets refer to positive evidence supporting the diagnosis previously made on other criteria.

and the results in the alcoholic and non-alcoholic groups will be considered separately.

MATERIAL

The series comprised 32 consecutive patients with acute pancreatitis referred to the Gastro-intestinal Service. A clear relationship of alcohol to the onset of the attack was elicited in 21 patients. Of the remaining 11, 8 had associated cholelithiasis, 1 was pregnant and another had hyperlipaemia. The cause of the pancreatitis could not be ascertained in 1.

Table I shows the sex distribution, the attack rate and the diagnostic criteria for pancreatitis in the 32 patients. The alcoholic and non-alcoholic groups are discussed separately.** All 21 patients in the alcoholic group were males, whereas 9 of the 11 patients in the non-alcoholic group were females. Nine patients were seen during their first attack of pancreatitis, and 23 had a history of one or more previous episodes of abdominal pain; recurrent attacks had occurred in 16 of the alcoholic group (76%) and 7 of the non-alcoholic group (64%).

Laparotomy confirmed the diagnosis of pancreatitis in 23 of 24 patients submitted to operation. In this series surgery was carried out as an emergency diagnostic measure in 7 patients, while pancreatitis had been confirmed in the past by operation in 16. Laparotomy did not confirm the presence of pancreatic disease in 1 patient subjected to elective biliary surgery 1 month after her last attack of gallstone pancreatitis; the gross elevation in serum enzymes during the acute attack was, however, considered diagnostic of acute pancreatitis.

The diagnosis in 5 of the patients who were not operated on was established by a clinical history of pancreatitis and the finding of an elevated serum-enzyme level and abnormal pancreatic function as measured by the pancreatic-function test. In the other 3 patients diagnosis was established on the history and the finding of grossly elevated serum-enzymes. Abnormal pancreatic function was found in 20 of 23 patients so tested; 2 of the remaining 3 had surgical confirmation of pancreatitis, and the third showed gross elevation in serum enzymes associated with a clinical history of gallstone pancreatitis.

**See article by Marks *et al.* on p. 1039 of this issue of the *Journal*.

Three patients incorrectly diagnosed as having acute pancreatitis on the basis of clinical features and mild hyperamylaseaemia, were started on treatment, but were taken out of the trial 6 - 12 hours later when the diagnostic error became apparent. Two showed radiological evidence of air under the diaphragm and were operated on for perforated duodenal ulcer, while laparotomy in the third revealed peritonitis from salpingitis.

METHOD OF STUDY

A. In-vitro Studies with Trasylol

The inhibition of trypsin activity by trasylol was studied by adding graded doses of trasylol to varying dilutions of crystalline trypsin. Standards of crystalline trypsin ('tryptar'*) were prepared in 0·5 ml. of phosphate buffer (pH 7·8) to contain 125, 150, 200, 250, 300, 350, 500 and 1,000 units of tryptic activity per 0·5 ml. The actual trypsin values of the standards were then determined by the method of Nardi.[7,8]

Varying dilutions of trasylol were added to each of these specimens. The recommended dose of trasylol (30,000 units given over 24 hours) was calculated to yield, at most, a level of 5 units of trasylol per ml. of blood volume, allowing for the hypothetical proviso that it remained in the circulation for the full 24 hours. Five units of trasylol were therefore made up in 0·2 ml. of phosphate buffer, added to the standard trypsin solutions, and tryptic activity was again determined. The tests were repeated using 5\, 12·5 and 25 times the above dose, containing 25, 62·5 and 125 units of trasylol per 0·2 ml. respectively.

Results of In-vitro *Studies*

Table II shows the measured values of tryptic activity determined in the trypsin standards and the corresponding levels obtained when the test was repeated after adding 5, 25, 62·5 and 125 units of trasylol to the standard trypsin solutions. The difference between the trypsin values in the standards and that found after the addition of trasylol was expressed as a percentage and termed the 'percentage inhibition' of tryptic activity.

The percentage inhibition was slight (mean=17·5%) when 5 units of trasylol were used; this dosage corresponded to the recommended dosage scheme. Further increase in the concentration of trasylol resulted in a progressive reduction of tryptic activity. However, with 25 units (5 times the recommended dose) the mean percentage inhibition was still only 28%. It was only after adding 62·5 and 125 units (12·5 and 25 times the recommended dose of trasylol) that marked inhibition could be demonstrated. The mean percentage inhibition in these was 63% and 72% respectively.

* Manufactured by Armour Inc.

TABLE II. *In-vitro* TESTS WITH TRASYLOL

Trypsin alone (standard trypsin solutions—units/0·5 ml.)	*Trypsin plus trasylol*							
	*5 units trasylol**		*25 units trasylol***		*62·5 units trasylol†*		*125 units trasylol§*	
	Trypsin (units/ 0·5 ml.)	*% inhibition*	*Trypsin (units/ 0·5 ml.)*	*% inhibition*	*Trypsin (units/ 0·5 ml.)*	*% inhibition*	*Trypsin (units/ 0·5 ml.)*	*% inhibition*
130	110	**15**	100	**23**	55	**58**	58	**55**
150	90	40	—	—	35	80	35	80
200	—	—	130	35	40	80	0	100
240	—	—	180	25	80	67	65	73
300	185	40	—	—	60	80	40	87
350	350	0	250	29	117	67	102	70
540	480	10	—	—	175	68	125	77
1,082	1,072	**0**	—	—	1,060	**0**	686	**36**
Mean % inhibition		17·5		28		63		72

*Calculated recommended dose (CRD).
**5×CRD.
†12·5×CRD.
§25×CRD.

Table II also shows that trasylol appeared to inhibit crystalline trypsin most effectively at levels usually found in the serum in acute pancreatitis, i.e. 150 - 500 tryptic units. Inhibition of trypsin by trasylol was relatively less pronounced at the very high levels (1,082 units) or at levels slightly higher than the upper limit of normal (100 units).

B. **In-vivo Studies with Trasylol**

The patients were divided into 4 groups according to the severity of the attack and the treatment given (Table III):

Controls

Group I—analgesics, anticholinergics and antacids only: There were 5 patients in this group, all with mild attacks of pancreatitis. Four of the patients had alcoholic and 1 non-alcoholic pancreatitis. Patients unable to gain admittance to hospital were treated on an outpatient basis.

Group II—gastric suction plus analgesics and anticholinergics: This group included 12 patients, 8 with alcoholic and 4 with non-alcoholic pancreatitis. The abdominal pain was more pronounced than in group I, and 3 of the 4 patients in the non-alcoholic group were shocked.

TABLE III. PATIENT GROUPS

	Total (32)	*Alcoholic (21)*	*Non-alcoholic (11)*
Controls:			
Group I—analgesics, anticholinergics and antacids only; all mild cases	5	4	1
Group II—gastric suction plus analgesics and anticholinergics	12	8	4
Total	17	12	5
Trasylol-treated:			
Group III—Trasylol in 'conventional' doses (30,000 u/day) plus gastric suction, analgesics and anticholinergics	6	3	3
Group IV—Trasylol in greatly increased doses (5–10 fold—150,000 to 300,000 units/day) plus gastric suction, analgesics and anticholinergics	9	6	3
Total	15	9	6

Trasylol-treated

Group III—trasylol in recommended doses plus gastric suction, analgesics and anticholinergics: Six patients, 3 with alcoholic and 3 with non-alcoholic pancreatitis were given the recommended amount of trasylol. This consisted of an intravenous injection of 10,000 units on admission, 30,000 units per day intravenously in electrolyte solutions for 3 days and 10,000 units per day by intravenous injection for a further 3 days. Pain was pronounced in all patients, and 1 of the patients with alcoholic pancreatitis was shocked.

Group IV—trasylol in greatly increased doses (5 - 10 fold) plus gastric suction, analgesics and anticholinergics: Nine patients, 6 with alcoholic and 3 with non-alcoholic pancreatitis received large doses of intravenous trasylol. These consisted of 20,000 units administered intravenously on admission and a daily dose of 150,000 - 300,000 units intravenously for a further 3 days. Severe pain was a feature in all cases. Three patients with alcoholic and 2 with non-alcoholic pancreatitis were shocked.

Assessment of Response

The response to therapy was assessed as follows:

1. *Clinical assessment:* Each patient was interrogated and examined daily with special reference to the following parameters: (*a*) abdominal pain; (*b*) pulse, temperature and blood pressure; and (*c*) abdominal tenderness or rigidity. Patients in whom previous attacks had occurred were of particular interest, in that the duration and severity of pain in past attacks could be compared with that found in the present attack.

2. *Biochemical determinations:* The following serum determinations were carried out daily on blood samples taken between 8 and 10 a.m.: (*a*) amylase, by Pimstone's method[9,10] (upper limit of normal 140 units); (*b*) lipase, by Pimstone's method[10]* (upper limit of normal 0·25 units); and (*c*) trypsin, by Nardi's method[7,8] (upper limit of normal 100 units).

*See article by Bank *et al.* on page 1061 of this issue of the *Journal*.

TABLE IV. ALCOHOLIC PANCREATITIS—DURATION OF PAIN

Type of treatment	No. of cases	Number shocked	Duration of pain from onset of treatment (mean days)				P
			Attack in trial		Previous attacks		
Controls: (12)							
Group I	4		8·0	5·3**	7·2	6·6†	n.s.
Group II	8		3·3*		6·0		
Trasylol: (9)							
Group III	3	1	2·7	1·7**	6·0	7·3†	<0·01
Group IV	6	3	1·2*		7·8		

*P <0·05 **P <0·01 †P=n.s.

n.s.=not significant.

RESULTS

A. Clinical

Alcoholic Pancreatitis

Pain: The duration of abdominal pain in the 4 groups after the onset of treatment is shown in Table IV. In the trasylol-treated groups, the mean duration of pain was 2·7 days in the patients given the recommended dosage. The pain was more persistent in the control patients. It should be noted that the attacks were more severe in the trasylol-treated groups, which included 4 shocked patients. On the other hand, the control groups, and particularly group I, had relatively mild abdominal pain. The mean duration was 8 days in the group treated on anticholinergics alone, and 3·3 days in the patients treated with gastric suction and intravenous fluids. The mean duration in the trasylol-treated cases (groups III and IV) was 1·7 days, and significantly less (P<0·01) than the mean duration in the control groups (groups I and II). This difference, however, did not allow for the fact that group I control subjects were denied the possible benefit of continuous gastric aspiration and intravenous replacement therapy. The results in group II were therefore compared with those obtained in group IV—the patients given the calculated effective dosage schedule of trasylol. The duration of pain in the latter was again significantly less than the duration of pain in the control group (P<0·05). It is of interest that the mean duration of pain in control patients treated without 'drip and suction' was more than twice that in the controls receiving this form of treatment, but the difference was not significant at the 5% level. Table IV (column 5) shows the duration of pain in the previous attacks in patients with relapsing pancreatitis who took part in the present trial. The mean duration of pain in the previous attacks in those treated with trasylol in the trial was 7·3 days, whereas the mean duration while on trasylol therapy was 1·7 days. This difference was also significant (P<0·01). Three patients had 2 or more attacks during the period of the trial. Two of these patients had trasylol therapy during one of the attacks; in one it was associated with a reduction in pain from 3 days to 1 day, and in the other from 8 days to 1 day.

Other features: Fever, tachycardia and abdominal tenderness tended to persist for longer than the duration of pain in the majority of patients, but in some these objective parameters returned to normal when the pain subsided. There appeared to be little difference between the control and the trasylol groups with regard to the duration of fever and tachycardia. The effect of trasylol on the blood pressure could not be critically examined, since there were no shocked patients in the control group. All 4 shocked patients in the trasylol-treated group recovered, however. Two patients in the trasylol group developed a pseudocyst of the pancreas, despite the rapid disappearance of pain following the commencement of trasylol therapy.

Non-alcoholic Pancreatitis

Trasylol therapy did not appear to influence the duration of pain in patients with non-alcoholic pancreatitis (Table V). These patients were frequently desperately ill, particularly if stones were present in the common bile duct. Three of the 11 patients died during the attack; these comprised 2 of 5 patients in the control group and 1 of 6 in the trasylol-treated group. The 1 patient who died despite trasylol therapy was a 75-year-old female who had been acutely ill for 3 days before admission to hospital; she had been given the recommended dose of trasylol.

TABLE V. NON-ALCOHOLIC PANCREATITIS—DURATION OF PAIN IN PATIENTS WHO RECOVERED

	No. of cases	Duration of pain from onset of treatment (mean days)			
		Attack in trial		Previous attacks	
Controls (5)		3*		2	
Group I	1	3·0	3·0	7·0	3·0
Group II	2*	3·0		2·0	
Trasylol (6)		5**		3	
Group III	2**	1·7	2·0	2·0	1·75
Group IV	3	2·5		1·6	

The differences in duration of pain between the various groups are not statistically significant.
*Excludes 2 patients who died during the attack.
**Excludes 1 patient who died during the attack.

B. Biochemical Results

1. *Elevated Serum-enzyme Levels 72 Hours after Onset of Treatment*

Seventy-two hours (Table VI) was arbitrarily selected

as the time at which to assess the effect of treatment on the serum-enzyme levels. Table VI shows that serum amylase and lipase varied from group to group, and that this variation applied to both the alcoholic and non-alcoholic forms of the disease. However, serum trypsin was normal

TABLE VI. ABNORMAL SERUM ENZYMES AT 72 HOURS AFTER ONSET OF TREATMENT

	No. of cases	Number of patients and percentage with abnormal enzymes at 72 hours compared with onset of attack					
		Amylase		Lipase		Trypsin	
		No.	%	No.	%	No.	%
A. Alcoholic:	21						
Controls							
Group I ..	4	0/2	0	0/1	0	2/4	50
Group II ..	8	2/7	30	2/4	50	4/8	50
Trasylol							
Group III ..	3	1/3	33	2/2	100	2/2	100
Group IV ..	6	2/6	33	2/6	33	0/4	0
B. Non-alcoholic	11						
Controls							
Group I ..	1	0/0	0	0/0	0	0/1	0
Group II ..	4	2/4	50	0/1	0	3/3	100
Trasylol							
Group III ..	3	1/3	33	0/1	0	2/3	66
Group IV ..	3	1/3	33	1/3	33	0/3	0

at 72 hours in every case in group IV (increased doses of trasylol) in both the alcoholic and non-alcoholic groups.

2. *Relationship between Pain and Serum-enzyme Levels on Leaving Hospital*

In both alcoholic and non-alcoholic pancreatitis the pain disappeared before the serum-enzyme levels became normal in a greater proportion of the trasylol-treated cases than of the controls. Thus the pain disappeared before the serum-enzyme levels had returned to normal in 42% of the control and 78% of the trasylol-treated patients in the alcoholic group, and in 20% of the control and 60% of the trasylol-treated patients in the non-alcoholic group.

3. *Increase in Serum-enzyme levels during Treatment*

Rises in the serum-enzyme levels of 30% or more, compared with the previous day's levels, occurred in 47% of the controls and in 53% of the trasylol cases. The increase over the previous day's level in all trasylol-treated patients could be related either to discontinuation or reduction of the trasylol therapy.

ILLUSTRATIVE CASE REPORTS

Alcoholic Pancreatitis

Case 1. G.D., aged 30 years, presented with a 9-year history of excessive alcoholic intake associated, during the past 5 years, with recurrent attacks of acute pancreatitis. Fig. 1 shows the clinical and biochemical results obtained during 2 attacks, the first while treated as a control (group II) and the second while treated with large doses of trasylol (group IV). Rapid symptomatic improvement occurred when treated with trasylol, but an intrapancreatic cyst became manifest on the tenth day.

Case 2. M.A., aged 29 years, presented with a 5-year history of excessive alcohol intake, and a 2-year history of recurrent attacks of acute pancreatitis. Fig. 2 shows results obtained during 3 attacks, 1 of which was treated with trasylol (group IV) and 2 without trasylol (group I, group II). Large doses of trasylol appeared to produce rapid symptomatic improvement without affecting the serum enzymes to the same

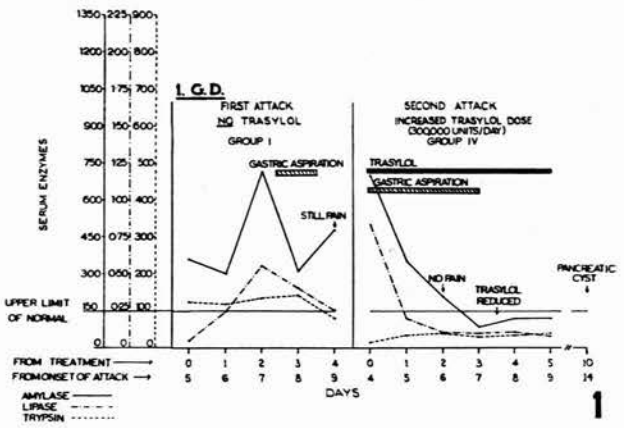

Fig. 1. Treatment and response in case 1.

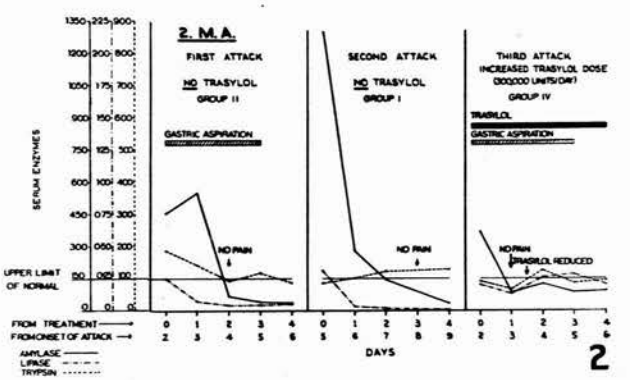

Fig. 2. Treatment and response in case 2.

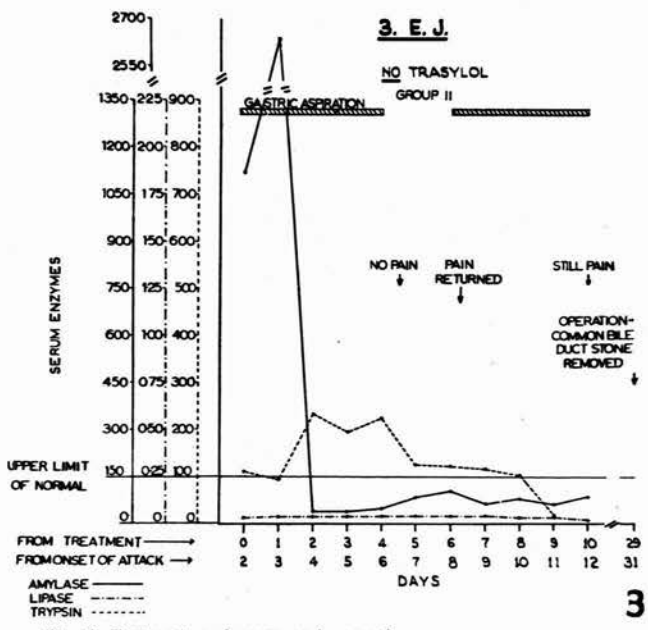

Fig. 3. Treatment and response in case 3.

extent. An increase in the level of serum enzymes occurred after the dose of trasylol was reduced.

Non-alcoholic Pancreatitis

Case 3. E.J., aged 69 years, presented with a severe attack of acute pancreatitis. She was treated as a control (group II). The pain continued for 12 days and was associated with persistent elevation of serum trypsin, despite normal amylase and lipase values (Fig. 3). Symptomatic improvement was delayed until cholecystectomy and the removal of stones from the common bile duct on the 29th day.

Case 4. E.L., aged 55 years, presented with a 2-year history of recurrent attacks of acute pancreatitis. The diagnosis of acute pancreatitis was confirmed at laparotomy during the initial attack, but no gallstones were noted. The recent attack was particularly severe and associated with shock. He was treated with trasylol (group IV). The pain and serum enzymes settled within a few days (Fig. 4), but fever, jaundice and gastroduodenal obstruction persisted for about 10 days. An exacerbation of symptoms and increase in serum enzymes occurred on discontinuing trasylol. Operation revealed gross enlargement of the pancreas with peripancreatic necrosis. This precluded adequate visualization and palpation of the

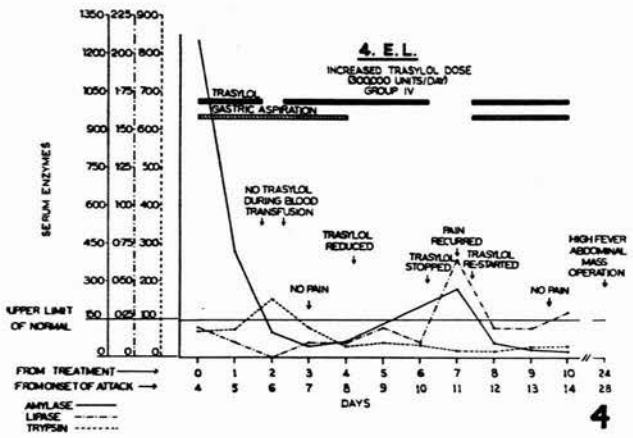

Fig. 4. Treatment and response in case 4.

common bile duct, but an operative cholangiogram showed no obvious abnormality. However, numerous gallstones of various sizes were discharged through the cholecystotomy drain on the third postoperative day.

DISCUSSION

The treatment of acute pancreatitis has hitherto consisted of analgesics, antibiotics, anticholinergics, continuous gastric aspiration, and fluid and electrolyte replacement. These measures, while clearly of benefit, are directed largely at the prevention of further pancreatic damage rather than the combating of the pathological processes occurring in the disease. Our findings support the claims made by previous workers[1-5] regarding the inhibitory effect of trasylol on trypsin, the proteolytic enzyme considered to be the major factor in initiating and maintaining pancreatic necrosis.

The administration of 150,000 - 300,000 units of trasylol per day, instead of the recommended dose of 30,000 units per day, was prompted by the results of *in-vitro* studies, and the most satisfactory *in-vivo* results were in fact obtained using this increased dosage level. Since the commencement of this trial, other workers[3-5] have also suggested an augmented dosage scheme.

Despite the inherent difficulties in conducting a clinical trial in acute pancreatitis, our results suggested that trasylol was of value in reducing the duration of the pain, at least in patients with alcoholic pancreatitis. In addition, satisfactory reduction of serum trypsin to within normal limits was achieved in all patients given large doses of trasylol. The tendency for the pain to disappear before objective clinical and biochemical improvement becomes evident poses a difficult question which, although unexplained, should not detract from the therapeutic usefulness of the drug.

The relatively poor results obtained in patients with non-alcoholic pancreatitis and, in particular, those with gallstone pancreatitis, may be construed as evidence against the usefulness of trasylol in patients with the more fulminating variety of the disease. However, the number of these patients was small, and treatment usually commenced a few days after the onset of illness. It is possible that early intensive treatment, before the onset of irreversible damage, may have produced better results in these patients.[11] The development of pseudocysts or sloughing of the pancreas following a seemingly good response to trasylol therapy in a few of our patients is in keeping with the experience of others,[12] who assumed that the complication antedated the commencement of therapy.

SUMMARY

The value of trasylol in the treatment of acute pancreatitis has been studied by comparing clinical and biochemical parameters of the disease in control and trasylol-treated patients.

In-vitro studies suggested that the recommended dosage scheme of trasylol might not be adequate in patients with acute pancreatitis. An increased dosage scheme (150,000 - 300,000 units per day) was employed in some patients on the basis of these *in-vitro* studies.

Trasylol therapy resulted in a significant reduction in the duration of pain in patients with alcoholic pancreatitis. High doses of trasylol restored elevated serum-trypsin levels to normal within 72 hours.

Less satisfactory results were obtained in patients with gallstone pancreatitis, and the possible causes for this are considered.

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