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Relation of diagnostic serum amylase levels to aetiology and severity of acute pancreatitis

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Abstract

The sensitivity of diagnostic serum amylase (>1000 iu/l) was assessed in 417 patients with acute pancreatitis as a result of gall stones (258), alcohol (104), or miscellaneous causes (55), of whom 111 (27%) had a clinically severe attack (including 34 deaths). On hospital admission, an amylase value diagnostic of pancreatitis was found in 96·1% of all mild cases and in 87·4% of severe cases ($p<0·001$); at 48 hours these values were 33·3% and 48·2% respectively ($p=0·026$). Diagnostic amylase levels for alcoholic patients were found in 86% of mild cases on admission and in 76% of severe cases ($p<0·001$, compared with other groups). The diagnostic levels were also significantly lower at 24 hours for both the alcoholic and miscellaneous groups compared with the gall stone group ($p<0·001$). Eight of 27 (30%) patients with a serum amylase activity <1000 iu/l had pancreatic necrosis compared with 12 of the remaining 390 (3·1%) patients ($p<0·001$); the mortality was also significantly different (44% *v* 5·6% respectively, $p<0·001$). These data support the view that more sensitive tests for acute pancreatitis are needed for routine use especially in those whose disease has an alcoholic aetiology.

The serum amylase activity rises sharply within the first 24 hours of an attack of acute pancreatitis and then declines steadily to normal levels over the following 5–7 days.[1 2] Although a number of abdominal and extra-abdominal conditions can result in a high amylase activity,[3] in patients with an appropriate clinical picture, the specificity and the sensitivity are well over 90%.[4 5] With the generally available Phadebas method (normal range 70–300 iu/l), the level diagnostic of acute pancreatitis is considered to be >1000–1200,[1 5 6] although an MRC study used a level >2000 iu/l.[7] However, any value above the upper limit of normal is sometimes used by authors from Europe[8] and North America.[9] While it is generally stated that the amylase activity has no prognostic importance,[10 11] precise details relating this to both aetiology and the severity of the attack are surprisingly lacking.

A number of studies have challenged the primary diagnostic role of serum amylase, and a case has been made for the use of serum lipase instead,[3 12 13] as it remains raised for a slightly longer period.[14] In a study in which computed tomography was used[8] to assess the pancreas, a normal amylase activity (<160 iu/l) was seen in 19% of 352 attacks of acute pancreatitis;[8] implicitly, a diagnostic level in this study was taken as any value above the upper limit of normal. No difference was found between patients with a normal serum amylase value and the subsequent clinical course. Most patients presented at least two days after the onset of the attack, 34% had a gall stone aetiology, and 29% had a clinically severe course.[8] If the results in this study were applicable to Britain, these would strengthen the case for the routine use of lipase. The value of amylase determination as a diagnostic tool may be influenced by the prevalence of different aetiological factors, the proportion of severe attacks, and the time that patients are usually admitted to hospital after the onset of an attack, and the present study was undertaken to assess these relations in two hospitals from the Midlands region of England.

Patients and methods

In the 10 year period up to January 1990, 417 consecutive patients presenting to Leicester Royal Infirmary and Dudley Road Hospital, Birmingham with a clinical diagnosis of acute pancreatitis were personally reviewed by at least one of the authors (Table I). The senior author (JPN) was involved in the management of patients at both hospitals, which was in principal very similar. Patients with pancreatitis as a result of trauma, metastases, carcinoma, cytotoxic therapy, and iatrogenic causes were excluded. The diagnosis was based on a serum amylase activity on admission to hospital of >1000 iu/l (normal range 70–300 iu/l; Phadebas method)[15] in the presence of compatible clinical findings in 385 patients. Lipaemic serum was diluted before determination of serum amylase.[16] A diagnostic level of >900 iu/l was also accepted in five patients with associated hyperlipidaemia.[3] Only 11 of these 390 (2·8%) patients had presented >36 hours after the onset of the attack.

The remaining 27 patients presented with an amylase level <1000 iu/l. In 23 patients, the diagnosis was based on a subsequent increase in the serum amylase to >1000 iu/l, a urinary amylase >3000 iu/l, or acute pancreatitis confirmed by computed tomography, laparotomy, or necropsy (see Results). The other four patients had an amylase level of 435–904 iu/l without confirmatory tests but with an otherwise typical clinical picture (see Results). Confirmation of the diagnosis in these four cases was not possible because the pancreas could not be visualised by ultrasonography and the patients would not comply with subsequent investigation.

Diagnostic information additional to the amylase determination and clinical findings was provided by computed tomographic examination, which was abnormal in 188 patients. Between 1984 and 1987 computed tomography was used to assess its role in prognostication and

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TABLE I *Details of the 417 patients with acute pancreatitis*

Aetiology	*No (%)*	*Median age (range) (years)*	*Women (no (%))*	*Predicted severe (no (%))*	*Clinically severe (no (%))*
Gall stones	258 (61·9)	63 (22–96)	159 (61·6)	85 (34·0)	71 (27·5)
Alcohol	104 (24·9)	41 (14–74)	17 (16·3)	10 (9·6)	25 (24·0)
Miscellaneous	55 (13·2)	58 (28–87)	26 (47·3)	17 (30·9)	15 (26·3)
Total	417 (100)	58 (14–96)	202 (48·4)	112 (26·9)	111 (26·6)

TABLE II *Number and type of complications according to aetiology*

Complication	*Gall stones*	*Alcohol*	*Miscellaneous*	*Total*
Pseudocyst	22	9	2	33
Pancreatic abscess	3	4	2	9
Pancreatic necrosis	11	4	5	20
Duodenal obstruction	1	0	0	1
Gross ascites	3	2	4	9
Pleural effusion	7	6	1	14
Respiratory failure	18	15	6	39
Cardiac failure	5	0	2	7
Renal failure	3	1	2	6
Multisystem failure	7	3	3	13
Acute cholangitis	25	0	1	26
Disseminated intravascular coagulation	1	0	0	1
Cerebrovascular accident	1	0	1	2
Portal vein thrombosis	1	1	0	2
Pulmonary embolus	1	1	0	2
Deaths (no (%))	21 (8·1)	5 (4·8)	8 (14·5)	34 (8·1)

to follow the course of pancreatitis.[17 18] Subsequently, it was used only in assessing severe cases of pancreatitis. Other confirmatory investigations were ^{111}Indium leukocyte scanning (abnormal in a further 50 patients) and ultrasound (abnormal in a further 43). In 17 cases, the diagnosis was confirmed only at laparotomy or necropsy.

A modified Glasgow system of staging patients as 'predicted mild' or 'predicted severe' was used.[19] In addition, patients were classified as 'clinically mild' or 'clinically severe' according to whether local pancreatic or systemic complications developed. The aetiology of the attack was based on pancreaticobiliary imaging – ultrasound, oral cholecystography, endoscopic retrograde cholangiopancreatography (ERCP), and computed tomography – as well as an alcohol and drug history and more specific investigations where appropriate, including determination of fasting lipids.[20] The serum amylase was also recorded at 24 hours, 48 hours, 72 hours, and 5–7 days after admission.

The pattern of serum amylase changes during the first week of the attack was analysed according to aetiology and predicted severity and actual outcome.

Statistical analysis was undertaken using the χ^2 test with Yates's correction as appropriate for categorical variables and the Kruskall-Wallis and two tailed Mann-Whitney U test for continuous variables (Minitab computer Package, University of Pennsylvania). Significance was taken at the level of $p<0·05$.

Results

The aetiology and severity of the attacks of acute pancreatitis are shown in Table I. The miscellaneous group (n=55) comprised 45 patients with idiopathic pancreatitis; the remainder had attacks caused by hyperlipidaemia (n=5), hyperparathyroidism (n=3), and collagen disorders (n=2). Only five patients predicted to have a mild attack died (1·6%) compared with 29 patients with a predicted severe attack (25·7%; $\chi^2=643$, df=1, $p<0·001$). The differences in mortality in relation to aetiology were not statistically significant ($\chi^2=4·53$, df=2, $0·5<p>0·1$) (Table II).

Details of patients presenting with an amylase activity <1000 iu/l and with confirmatory evidence of acute pancreatitis are shown in Table III; similarly, those without such evidence are presented in Table IV. Sixteen of these 27

TABLE III *Details of patients presenting with a serum amylase of <1000 iu/l and with confirmatory evidence of acute pancreatitis*

Patient no	*Age (years)*	*Sex*	*Aetiology*	*Predicted severity*	*Admission amylase (iu/l)*	*Presentation >36 hours*	*Maximum amylase (iu/l)*	*Urinary amylase (iu/l)*	*Pancreatic complications*	*CT*	*Laparotomy*	*PM*
1	67	M	GS	S	202	—	1458 (72 hours)	—	Ascites	—	—	—
2	69	M	ID	S	566	—	5584 (24 hours)	—	Necrosis	—	—	+
3	61	M	GS	S	860	3 days	860 (OA)	—	Necrosis	—	+	+
4	49	M	GS	S	520	—	520 (OA)	—	Necrosis	—	+	—
5	70	F	ALC	S	200	3 weeks	200 (OA)	—	Necrosis	—	+	—
6	49	F	GS	M	390	—	390 (OA)	—	Pseudocyst	—	+	—
7	54	M	ALC	S	412	8 days	412 (OA)	—	Pseudocyst	+	—	—
8	66	F	ALC	S	620	7 days	620 (OA)	—	Necrosis	+	+	—
9	64	M	ALC	M	576	6 days	710 (24 hours)	5376	—	—	—	—
10	48	M	ALC	M	300	7 days	970 (72 hours)	7900	—	—	—	—
11	26	M	ALC	M	405	—	405 (OA)	26 884	—	—	—	—
12	25	M	HLIP	M	588	3 days	588 (OA)	—	—	—	+	—
13	21	M	ALC	M	790	4 days	790 (OA)	8922	—	—	—	—
14	29	M	ALC	S	284	3 weeks	284 (OA)	—	Abscess	+	+	—
15	26	M	HLIP	M	708	2 weeks	708 (OA)	—	—	—	+	—
16	60	F	ALC	M	530	9 days	530 (OA)	2820	Pseudocyst	—	+	—
17	50	F	ID	S	638	4 days	3250 (12 days)	—	Necrosis	—	—	—
18	22	M	ALC	M	560	—	3800 (48 hours)	—	—	—	—	—
19	28	M	ALC	M	998	—	1246 (24 hours)	—	—	—	—	—
20*	22	M	ALC	M	468	—	2310 (7 days)	—	—	—	—	—
21†	22	M	ALC	M	940	—	5970 (24 hours)	—	—	—	—	—
22	64	M	ALC	S	475	7 days	475 (OA)	—	Necrosis	—	+	+
23	62	F	ALC	S	244	—	492 (29 days)	—	Necrosis	—	+	+

OA=On admission; GS=gall stones; ID=idiopathic; ALC=alcohol; HLIP=hyperlipidaemia; CT=computed tomography; US=ultrasound; PM=post mortem.
* US serial examinations confirmed an enlarged oedematous pancreas.
† Indium – leukocyte scan confirmed acute pancreatitis.

TABLE IV *Details of patients presenting with a serum amylase value of <1000 iu/l on admission in whom diagnosis was based hyperamylasemia and clinical picture alone*

Patient no	Age (years)	Sex	Aetiology	Predicted severity	Admission amylase (iu/l)	Presentation >36 hours	Maximum amylase (iu/l)
24	32	M	ALC	M	904	4 days	904 (OA)
25*	21	M	ALC	M	435	5 days	435 (OA)
26	72	M	ALC	M	900	3 days	900 (OA)
27*	30	M	ALC	M	526	—	526 (OA)

OA=On admission; ALC=alcohol; M=mild.
* Confirmed previous attacks.

TABLE V *Serial serum amylase levels according to aetiology and severity*

Aetiology	Severity*	Serum amylase (mean (95% CI) (iu/l))				
		On admission	24 hours	48 hours	72 hours	5–7 days
Gall stones	CM	5271 (666)	2186 (455)	951 (257)	346 (67)	308 (82)
	PM	5617 (600)	2599 (586)	1399 (310)	398 (122)	525 (198)
	CS	6129 (1874)	3478 (894)	1564 (703)	925 (486)	1541 (941)
	PS	5960 (831)	3915 (1131)	1505 (598)	675 (731)	643 (1154)
Alcohol	CM	3358 (794)	1092 (319)	645 (231)	422 (137)	379 (196)
	PM	3294 (594)	1040 (290)	1459 (196)	415 (143)	440 (147)
	CS	2679 (1198)	3042 (1850)	1738 (1045)	559 (292)	270 (192)
	PS	3296 (1899)	3497 (1878)	470 (2058)	440 (188)	346 (316)
Miscellaneous	CM	5017 (2562)	2711 (3889)	1804 (3987)	594 (2550)	197 (161)
	PM	5358 (3595)	2620 (6376)	1716 (5341)	642 (2321)	812 (3071)
	CS	4499 (4210)	4321 (5319)	1742 (2946)	341 (563)	421 (862)
	PS	5950 (3993)	4831 (5343)	1720 (3281)	391 (380)	431 (686)
All cases	CM	3894 (1000)	2641 (631)	1992 (672)	889 (837)	731 (670)
	PM	4571 (1394)	2178 (543)	1625 (447)	525 (761)	629 (471)
	CS	3942 (1574)	2977 (1648)	1741 (1023)	1203 (794)	831 (1454)
	PS	5609 (2013)	3911 (1074)	1332 (877)	733 (531)	509 (983)

* Clinically mild (CM), severe (CS); predicted mild (PM), severe (PS).

TABLE VI *Time course of diagnostic serum amylase levels according to aetiology and clinical severity*

Aetiology	Clinical severity	% with serum amylase >1000 iu/l (%>300 iu/l)				
		On admission	24 hours	48 hours	72 hours	5–7 days
Gall stones	Mild	100 (100)	77·5 (93·8)	33·7 (82·6)	7·1 (46·4)	5·0 (25·0)
	Severe	91·5 (98·8)	81·6 (91·5)	43·9 (70·7)	17·0 (53·2)	10·4 (41·7)
Alcohol	Mild	86·0 (100)	37·0 (88·9)	26·2 (73·8)	7·7 (38·5)	12·9 (38·7)
	Severe	76·0 (96·0)	80·0 (100)	50·0 (70·0)	7·7 (46·2)	6·3 (25·0)
Miscellaneous	Mild	94·7 (100)	33·3 (66·7)	36·4 (72·3)	9·1 (45·5)	9·5 (33·3)
	Severe	86·7 (100)	100 (100)	50·0 (100)	0 (50)	42·9 (71·4)
All cases	Mild	96·1 (100)	56·7 (78·0)	33·3 (80·4)	7·3 (44·5)	6·6 (27·9)
	Severe	87·4 (98·2)	82·4 (94·7)	48·2 (72·2)	15·0 (56·7)	11·9 (40·3)
All cases	χ^2	10·52	12·60	4·97	3·85	2·84
Mild *v* severe	p	<0·001	<0·001	0·026	0·05	0·066

patients (59%) presented more than 36 hours after the start of the attack. Eight (30%) of the patients with an amylase activity <1000 iu/l had pancreatic necrosis compared with 12 (3·1%) of the remaining 390 patients (χ^2=39·0, df=1, p<0·001). All four of the patients with pancreatic necrosis caused by alcohol presented with a low amylase value. There were also 12 deaths (44%) in patients with a low amylase value compared with 22 deaths (5·6%) in patients presenting with a diagnostic level (χ^2=50·8, df=1, p<0·001).

The actual values of serum amylase in the different groups and in relation to disease severity are shown in Table V. There was no difference overall between mild and severe cases, using prognostic or clinical criteria. Patients in the alcoholic group had lower admission serum amylase values for both mild and severe disease compared with the gall stone group or the miscellaneous group (all p<0·05 at least). Patients with clinically severe disease showed an increase in mean amylase activities for the first 24 hours compared with mild cases (p<0·05). For other aetiologies, irrespective of severity, there was a fall in the level during the first 24 hours (all p<0·05 at least). Patients with clinically severe pancreatitis associated with gall stones, however, had higher values than clinically mild cases at 24 hours to 5–7 days (all p<0·05). Similarly, patients with clinically severe gall stone associated pancreatitis had higher amylase values than patients with clinically severe alcohol induced pancreatitis (all p<0·05) and those in the miscellaneous group at 72 hours and 5–7 days (all p<0·05).

Diagnostic levels of serum amylase are shown in Table VI. There was a lower incidence of diagnostic serum amylase (>1000 iu/l) in alcoholic patients on hospital admission (χ^2=323, df=2, p<0·001). At 24 hours after admission, both the alcoholic and miscellaneous groups also had a lower incidence of diagnostic serum amylase level compared with the gall stone group (χ^2=15·8, df=2, p<0·001). Patients with clinically mild disease had a significantly higher

incidence of diagnostic amylase levels on admission to hospital but this was reversed at 24, 48, and 72 hours later and this trend was apparent at one week (Table VI).

Discussion

In assessing the accuracy of a diagnostic test it is important to compare this with the 'gold standard' diagnostic tool for the disease. In the case of acute pancreatitis, this is histology, but it is impractical for a large study. Since we wished to examine the sensitivity of a diagnostic amylase level (>1000 iu/l), a compatible clinical picture with any raised amylase value was used and/or in conjunction with other confirmatory information if this was less than the diagnostic level. While computed tomography was not used in all our patients, we do not feel that this negates the study. Confirmatory investigations were available in 298 (71%) of the patients; of the remainder only four had an amylase level of <1000 iu/l and all had a value that was above the upper limit of normal (Table IV). We showed previously that computed tomography was abnormal in 94% of patients with a typical clinical picture of acute pancreatitis and an amylase value of >1000 iu/l,[18] while Clavien *et al*[21] reported a sensitivity for computed tomography of 91% in patients with a compatible clinical and amylase value above the normal level. (Precise specificity figures for computed tomography are not known but it is likely to be close to 100%).

On admission to hospital, a diagnostic amylase level was found in 96·1% of patients with clinically mild disease and in 87·4% of those with severe disease. These percentages would be 100% and 98·2% if an amylase level >300 iu/l were used. On balance such a high sensitivity, given previously reported specificity rates of over 90%,[4 5] suggests that the serum amylase value is an excellent diagnostic test but there were also a number of important diagnostic limitations.

While the rapid fall in the serum amylase activity is well recognised after the start of the attack,[1 2] the loss of diagnostic sensitivity over the first 48 hours was dramatic. Although the mean serum values were well over 1000 iu/l at 48 hours in all aetiological groups, only 33·3% of patients with mild disease and 48·2% of those with severe disease actually achieved this level. If a level >300 iu/l were to be used over this period for diagnosis (see Table VI), it would be associated with a lower specificity of 86%.[4] For comparison, the sensitivity of lipase above the upper limit is 99% but the specificity is only 87% so the gain of using lipase in this way would only be marginal.[4] Either serum elastase-1 or trypsin assay would seem to offer the greatest diagnostic advantage after the initial 48 hours,[12 14] but there are technical difficulties and with only limited studies the case for their routine use is far from clear cut.[3]

The diagnostic sensitivity of amylase in the group with pancreatitis caused by alcohol was significantly worse than in the other groups on hospital admission and both the alcohol and miscellaneous groups had a lower diagnostic 'pick up' rate at 24 hours (Table VI). It is in these groups, therefore, that the routine application of lipase seems justified. Patients with clinically severe disease also had lower diagnostic levels on hospital admission but this was subsequently reversed. This is so despite the lack of prognostic significance of absolute values of amylase.[10 11]

Our study is consistent with that of Gullick,[22] which suggested that the serum amylase value would be determined by two factors – the direct relation between the amylase level and the degree of pancreatic duct obstruction and the inverse relation with the severity of the disease. Patients with gall stone pancreatitis had significantly higher admission serum amylase levels than alcoholics, as previously reported.[23–25] Although there was a much steeper decline in amylase levels for gall stone patients compared with the alcohol group as shown by Hiatt *et al*,[26] gall stone patients with clinically severe attacks tended to maintain higher mean amylase levels compared with other groups, probably due to 'persisting' pancreatic duct obstruction.[27]

Patients with an amylase value <1000 iu/l were more liable to have pancreatic necrosis; moreover this was more frequently associated with death. Reference to Tables III and IV indicates that this was not simply due to a delay in presentation. In other studies, this distinction may have been obscured because of reference to mean rather than diagnostic amylase levels or increased delay in presentation, or both.[2 8]

Patients with lipaemic serum may have artificially low levels of serum amylase,[16 20] but this is not always the case.[28] This can largely be overcome by diluting the serum[16] and by accepting a lower diagnostic threshold, as is our policy. The urinary amylase value may be helpful if this is raised but there is no advantage over serum amylase when used routinely.[29] Repeating the serum amylase determination at 4–6 hours would be helpful but only three of 27 patients with initially low levels in this study achieved diagnostic levels at 24 hours. Maintaining a high index of suspicion is essential since a high proportion of patients are diagnosed only at necropsy. In a series of 126 patients dying of pancreatitis, this occurred in 53 (42%) cases; moreover, only 5 (9%) had had amylase estimations and these were all normal or subdiagnostic.[30]

In conclusion, there is a strong case for the continued use of amylase determinations in patients with suspected gall stone pancreatitis. Given the comparatively lower diagnostic rate for alcoholic patients and those with an obscure aetiology, however, there is a strong case for the routine introduction of more specific assays such as lipase.[30 31] This is contrary to the view we have previously held. In places where there is a high prevalence of alcoholic pancreatitis, this should probably become the diagnostic test of choice. Patients with unexplained severe upper abdominal symptoms and a normal or only marginally raised serum amylase value require computed tomography in order to determine the presence of severe pancreatitis.[32]

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