http://dx.doi.org/10.22537/jksct.14.2.83
pISSN: 1738-1320 / eISSN: 2508-6332

Journal of The Korean Society of Clinical Toxicology

원 저

중독 환자에서 고아밀라아제혈증의 발생률, 관련 요인 및 임상적 영향

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The Incidence, Associated Factors and Clinical Impact of Hyperamylasemia in Self-poisoning Patients

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Purpose: This study was conducted to investigate the incidence, associated factors and clinical impact of hyperamylasemia in self-poisoning patients.

Methods: This study was based on a toxicology case registry of patients treated from 2009 to 2013 at a tertiary care university hospital. We retrospectively investigated the demographics, clinical variables, laboratory variables and intoxicants. Hyperamylasemia was defined as an elevation in serum amylase level to above the upper normal limit within 24 hours after admission. We analyzed the predisposing factors and clinical outcomes of patients in the hyperamylasemia group.

Results: Hyperamylasemia was identified in 49 (13.3%) of the 369 patients. Using multivariate logistic regression, the odds ratios for HA were 3.384 (95% confidence interval, 1.142-8.013, *p*=0.014), 3.261 (95% confidence interval, 1.163-9.143, *p*=0.025) and 0.351 (95% confidence interval, 0.154-0.802, *p*=0.013) for pesticides, multi-drug use and sedatives, respectively. In the hyperamylasemia group, the peak amylase levels during 72 hours were correlated with the peak lipase levels (r=0.469, *p*=0.002) and peak aspartate aminotransferase levels (r=0.352, *p*=0.013). Finally, none of these patients had confirmed acute pancreatitis.

Conclusion: Hyperamylasemia occurred rarely in these self-poisoning patients, and pesticide and multi-drug use were independent predictors of hyperamylasemia. Peak amylase levels were correlated with the peak lipase and aspartate aminotransferase levels.

Key Words: Hyperamylasemia, Pancreas, Poisoning

Introduction

An elevation of serum levels of amylase is commonly an expression of various pancreatic disorders such as inflammatory or neoplastic pancreatic disease[1]. Amylase is synthesized in the pancreatic acinar cells or other tissues, but the pancreas and the salivary glands are main source of the elevation of serum amylase concentration.

Hyperamylasemia (HA) may be secondary to an

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투고일: 2016년 9월 5일 1차 심사일: 2016년 9월 29일
게재 승인일: 2016년 10월 25일

imbalance between pancreatic release and renal clearance[2], but liver damage is also suspected to play a role in inducing pancreatic HA[3]. The pathogenesis of HA in metabolic disorders such as diabetic ketoacidosis and acidemia remains unclear[4]. HA may be associated with lung and ovarian cancer[5,6]. It has been suggested that the cause may be an ectopic production of pancreatic enzymes by the tumors, but some Authors have also postulated that the tumor cells may cause an inflammatory response resulting in marked release of the pancreatic enzymes normally produced in these tissues into the blood stream. However, an elevation of pancreatic enzymes, generally mild, may be a non-specific phenomenon without any clinical implication[7].

HA is rarely encountered in patients with self-poisoning[8-15]. Although HA in association with pancreatic disease is commonly encountered in clinical practice, many patients are erroneously labeled as having acute pancreatitis (AP), despite the absence of clinical features to support this diagnosis[16]. In previous studies, some intoxicants have been associated with HA without clinical evidence of AP[8,9]. However, because these studies were limited due to the inclusion of a specific drug, the incidence of HA in self-poisoning patients was not known. Many drugs have been suspected to cause AP[8-15], and drug-induced AP accounts for above 1% of total AP[17,18]. This incidence was underestimated because of difficulties in determining the causative agent[19]. In addition, AP accounted for 0.1% in a study using the adverse drug reaction reporting system[20]. However, no study to investigate the incidence of AP in self-poisoning patients has been conducted. We examined consecutive self-poisoning patients in one teaching hospital over a 5-year period and evaluated the occurrence of HA in these patients.

This study aimed to determine the HA frequency in self-poisoning patients and to investigate the associative factors and their clinical impacts, such as the occurrence of AP.

Methods

We conducted a retrospective observational study using a prospective collected toxicology registry at a tertiary university hospital. The subjects were patients who had visited the ED for treatment following self-poisoning between January 2009 and December 2013. Patients who were ⟨18 years of age or who had a pancreatic disorder were excluded. We also excluded patients who were discharged from the ED without a blood work analysis. Based on the toxicology registry, the data included demographics (age, gender, underlying disease, time from episode to admission and alcohol co-ingestion), clinical variables (whether gastric lavage was performed or charcoal was administered), self-inflicted intoxicants, laboratory variables and clinical outcomes (whether hospitalization was required, whether the patient died prior to hospital discharge and whether there was oral mucosa/salivary gland injury or abdominal pain). Substances were classified according to the 2011 Annual Report of the American Association of Poison Control Centers' National Poison Data System: 29th Annual Report[21]. Two emergency physicians independently reviewed the registry of toxicology and medical charts during the study period, and a third investigator resolved any discrepancies. The institutional review board approved the study protocol prior to data analysis (KC15RISI0222). Informed consent was waived because of the retrospective nature of the study.

In keeping with our toxicology registry for self-poisoning patients, serum levels of amylase, serum blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST), serum alanine aminotransferase (ALT), total bilirubin, creatine phosphokinase (CPK), and lactate dehydrogenase (LDH) were serially investigated from these patients at admission, 12 h, 24 h, and daily. Additional or serial serum lipase and direct bilirubin were evaluated at the discretion of the attending physicians. Drug-induced HA was defined as an elevated serum amylase level of above the upper normal limit during 24 hours after admission. The patients were classified into one of two

groups according to their serum amylase levels: the HA group or the non-HA group. To evaluate the associative factors for HA, we examined the characteristics of each group and analyzed the predisposing factors of the HA group.

To differentiate possible causes influencing the serum amylase level, we evaluated the association between amylase and other laboratory values. Finally, we assessed the development of AP in these patients. AP was defined by the presence of 2 of the 3 following criteria: (i) characteristic abdominal pain, (ii) a serum amylase and/or lipase level at least three-fold greater than the upper limit of normal and/or (iii) characteristic findings of AP on contrast-enhanced computed tomography (CT)[22].

The categorical variables are expressed as numbers and percentages, and continuous data are expressed as the mean±standard deviation or the median and interquartile range (IQR) according to a normal distribution. To compare the distributions of the characteristics between the two groups, Student's t-test was performed for continuous variables, and the chi-squared test was conducted for categorical variables. Variables related to HA were evaluated by multivariate logistic regression analysis, with estimations of odds ratios (ORs) and 95% confidence intervals (CIs). Bivariate associations between amylase and other laboratory values were evaluated using the Pearson

Table 1. Comparison of demographic and clinical characteristics between the hyper-amylasemia and non- hyper-amylasemia groups

	Total cohort (N=369)	Hyperamylasemia (N=49)	Non-hyperamylasemia (N=320)	*p*-value
Male, n (%)	77 (20.9)	8 (16.3)	69 (21.6)	0.401
Age, mean±SD, years	39.5±17.5	44.6±21.6	38.8±16.6	0.076
Underlying disease				
Hypertension, n (%)	41 (11.1)	8 (16.3)	33 (10.3)	0.212
DM, n (%)	19 (5.1)	4 (8.2)	15 (4.7)	0.305
Hepatitis, n (%)	7 (1.9)	0 (0.0)	7 (2.2)	0.296
Malignancy, n (%)	12 (3.3)	3 (6.1)	9 (2.8)	0.224
Time from episode to admission, median (IQR), min	119.0 (54.0, 349.0)	201.0 (69.5, 601.5)	112.0 (53.3, 299.3)	0.029
Drug				
Analgesics, n (%)	64 (17.3)	10 (20.4)	54 (16.9)	0.543
Anticonvulsant, n (%)	3 (0.8)	0 (0.0)	3 (0.9)	0.496
Antidepressant, n (%)	41 (11.1)	5 (10.2)	36 (11.3)	0.828
Antihistamine, n (%)	38 (10.3)	5 (10.2)	33 (10.3)	0.981
Cardiovascular drug, n (%)	6 (1.6)	1 (2.0)	5 (1.6)	0.805
GI preparation, n (%)	1 (0.3)	0 (0.0)	1 (0.3)	0.695
Hormone, n (%)	7 (1.9)	2 (4.1)	5 (1.6)	0.229
Sedative, n (%)	145 (39.3)	8 (16.3)	137 (42.8)	<0.001
Chemical, n (%)	11 (3.0)	1 (2.0)	10 (3.1)	0.678
Cleaning agent, n (%)	2 (0.5)	1 (2.0)	1 (0.3)	0.125
Fumes, n (%)	4 (1.1)	0 (0.0)	4 (1.3)	0.431
Pesticide, n (%)	22 (6.0)	8 (16.3)	14 (4.4)	0.001
Multi-drug, n (%)	19 (5.1)	7 (14.3)	12 (3.8)	0.002
Unknown, n (%)	6 (1.6)	1 (2.0)	5 (1.6)	0.805
Alcohol co-ingestion, n (%)	94 (25.5)	11 (22.4)	83 (25.9)	0.602
Gastric lavage, n (%)	134 (36.3)	17 (34.7)	117 (36.6)	0.800
Charcoal administration, n (%)	224 (60.7)	28 (57.1)	196 (61.3)	0.584
Oral mucosal injury, n (%)	6 (1.6)	3 (6.1)	3 (0.9)	0.008
Abdominal pain, n (%)	15 (4.1)	3 (6.1)	12 (3.8)	0.434
Need for hospitalization, n (%)	115 (31.2)	37 (75.5)	78 (24.4)	<0.001
Mechanical ventilator care, n(%)	16 (4.3)	7 (14.3)	9 (2.8)	<0.001
Death before discharge, n (%)	4 (1.1)	1 (2.0)	3 (0.9)	0.487

SD: standard deviation, DM: diabetes mellitus, IQR: interquartile range

correlation coefficient. All analyses were performed using SPSS 16 (SPSS, Chicago, IL), and differences with a p-value〈0.05 were considered statistically significant.

Results

1. Total participants

In total, 369 self-poisoning patients visited the ED during the study period. The mean patient age was 39.5±17.5 years and ranged from 18 to 87 years. Of the patients, 77 (20.9%) were male, and 292 (79.1%) were female. The median time from the episode to admission was 119.0 min (IQR 54.0, 349.0). The most common drug type was sedatives (n=145, 39.3%), followed by analgesics (n=64, 17.3%), antidepressants (n=41, 11.1%), and antihistamines (n=38, 10.3%). Gastric lavage was performed in 134 patients (36.3%), and charcoal administration was performed in 224 patients (60.7%). One hundred fifteen patients (31.2%) required hospitalization, and 4 (1.1%) died prior to discharge. Of the patients who died before discharge, three visited the ED with pesticide poisoning, and one visited the ED with glacial acetic acid poisoning (Table 1).

2. Clinical outcomes and associating factors of hyperamylasemia

HA was identified in 49 (13.3%) of the 369 patients. No significant differences were observed between the HA and non-HA group regarding age, gender, underlying disease, whether gastric lavage was performed, and whether charcoal was administered (Table 1). The median time from the episode to admission was significantly longer in the HA group than in the non-HA group (201.0 min, IQR [69.5, 601.5]; 112.0 min, IQR [53.3, 299.3], respectively, p=0.029). The HA group was more likely to use pesticides (16.3% vs. 4.4%, p=0.001) but less likely to use sedatives than the non-HA group (16.3% vs. 42.8%, p〈0.001). The incidence of cases involving multiple drugs was higher in the HA group than in the non-HA group (14.3% vs. 3.8%, p=0.002).

Regarding the clinical outcome, clinical severity that required hospitalization was significantly more common in the HA group (75.5% vs. 24.4%, p〈0.001), but death prior to hospital discharge was not significantly different between groups. Mechanical ventilator care was also significantly different between the groups (14.3% vs. 2.8%, p〈0.001). The incidence of oral mucosal injury was significantly different between the two groups (6.1% vs. 0.9%, p=0.08). Six patients (3 patients who ingested chemical agents, 1 who ingested cleaning agents, and 2 who ingested pesticides) complained of oral pain, but they showed no clinical evidence of salivary-gland injury. The presence of abdominal pain did not significantly differ between the groups (p=0.434).

Of the fourteen patients who had an amylase level meeting the definition of AP (serum amylase ≥3 times the upper limit of normal), none presented abdominal pain consistent with the disease. In 4 HA patients, abdominal CT scans were evaluated, but there was no characteristic finding of AP. Finally, none of the HA patients was diagnosed with AP.

Multivariate logistic regression analysis indicated that pesticide and multi-drug use were independent predictors of HA (respectively, OR: 3.384, [95% CI, 1.142-8.013], p=0.014 and OR: 3.261, [95% CI, 1.163-9.143], p=0.025). In contrast, sedative use was associ-

Table 2. Multivariate logistic regression analysis of independent risk factors for hyper-amylasemia

Variables	Odds ratio for hyperamylasemia	95% confidence interval	p-value
Time from episode to admission*	1.000	1.000-1.001	0.131
Sedative	0.351	0.154-0.80	0.013
Pesticide	3.384	1.142-8.013	0.014
Multi-drug	3.261	1.163-9.143	0.025

*: per min

ated with the non-HA group (OR: 0.351 [95% CI, 0.154-0.802], p=0.013) (Table 2).

3. Hyperamylasemia and other laboratory variables

Serial serum levels of amylase (n=49) and lipase (n=41) in the HA patients are displayed in Fig. 1. Most patients (n=34, 69.4%) had initial amylase levels that were above the upper limit of normal (176 U/L). In 12 patients (24.5%), the amylase levels rose above the upper limit of normal at 12 hours, and 3 patients (6.1%) had amylase levels at 24 hours that were above the upper normal limit. The peak amylase level mainly occurred on admission or 12 hours after admission. In contrast, the time course of the changes in the serum lipase levels trended toward the peak lipase levels being more delayed than the peak amylase levels.

The peak levels of other laboratory values in the HA group were compared with those of the non-HA group (Table 3). The lipase level was significantly higher in the HA group than in the non-HA group (27.1 U/L, IQR [14.5, 55.2]; 16.8 U/L, IQR [10.4, 26.4], respectively, p=0.002). The AST level was also significantly higher in the HA group than in the non-HA group (26.0 U/L, IQR [19.5, 41.5]; 22.0 U/L, IQR [18.0, 28.0], respectively, p=0.015). In contrast, the levels of BUN, creatinine, ALT, total bilirubin, and direct bilirubin were not significantly different. We evaluated bivariate associations between amylase and other laboratory values using Pearson correlation coefficients. Fig. 2 displays scatter plots illustrating the associations between peak levels of amylase and peak lipase in all of the HA patients. The peak amylase levels were moderately correlated with peak lipase levels (r=0.469, p=0.002, n=41). The peak levels of amylase were also correlated with peak AST levels (r=0.352, p=0.013, n=35) (Table 4).

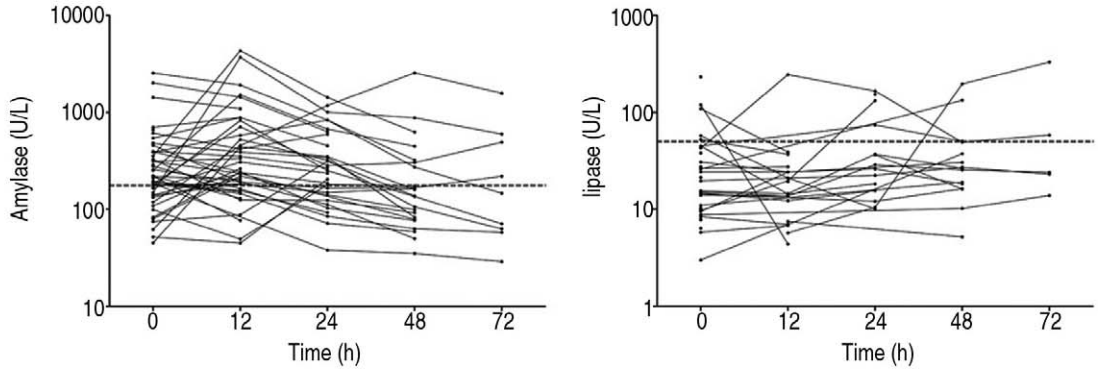

Fig. 1. Time course of changes in serum levels of amylase in hyperamylasemia patients (n=49). Dash line indicates the upper limit of normal level of serum amylase and lipase (respectively, 176 U/L and 50 U/L).

Table 3. Comparison of peak serum level of other laboratory values between the hyperamylasemia group and the non-hyperamylasemia group

	Hyperamylasemia (N=49)	Non-hyperamylasemia (N=320)	p-value
Lipase, median (IQR), U/L	27.1 (14.5, 55.2)[a]	16.8 (10.4, 26.4)[b]	0.002
Blood urea nitrogen, median (IQR), mg/dL	11.4 (8.9, 20.3)	11.5 (8.9, 14.1)	0.307
Creatinine, median (IQR), mg/dL	0.7 (0.6, 0.9)	0.7 (0.6, 0.8)	0.573
Aspartate aminotransferase, median (IQR), U/L	26.0 (19.5, 41.5)	22.0 (18.0, 28.0)	0.015
Alanine aminotransferase, median (IQR), U/L	18.0 (12.6, 25.5)	17.0 (12.0, 27.0)	0.618
Bilirubin, total, median (IQR), mg/dL	0.6 (0.5, 0.9)	0.6 (0.4, 0.8)	0.105
Bilirubin, direct, median (IQR), mg/dL	0.2 (0.1, 0.3)[c]	0.2 (0.1, 0.2)[d]	0.398

IQR: interquartile range

[a] n= 41, [b] n=209, [c] n=35, [d] n=178

Discussion

In the present study, HA was a rare finding in the self-poisoning patients (49/369; 13.3%); however, no patient was diagnosed with clinical AP. Pesticide and multi-drug use were independent predictors of HA development in these patients in this study, and sedative use was more frequent in the non-HA patients.

Our findings of the associations of intoxicants with HA occurrence are consistent with those previously published in the literature. HA with or without clinical evidence of AP has been described with organophosphate (OP), paracetamol, and opioid intoxication[8-15]. Sahin et al. reported HA in 4/47 (9%) adults with OP

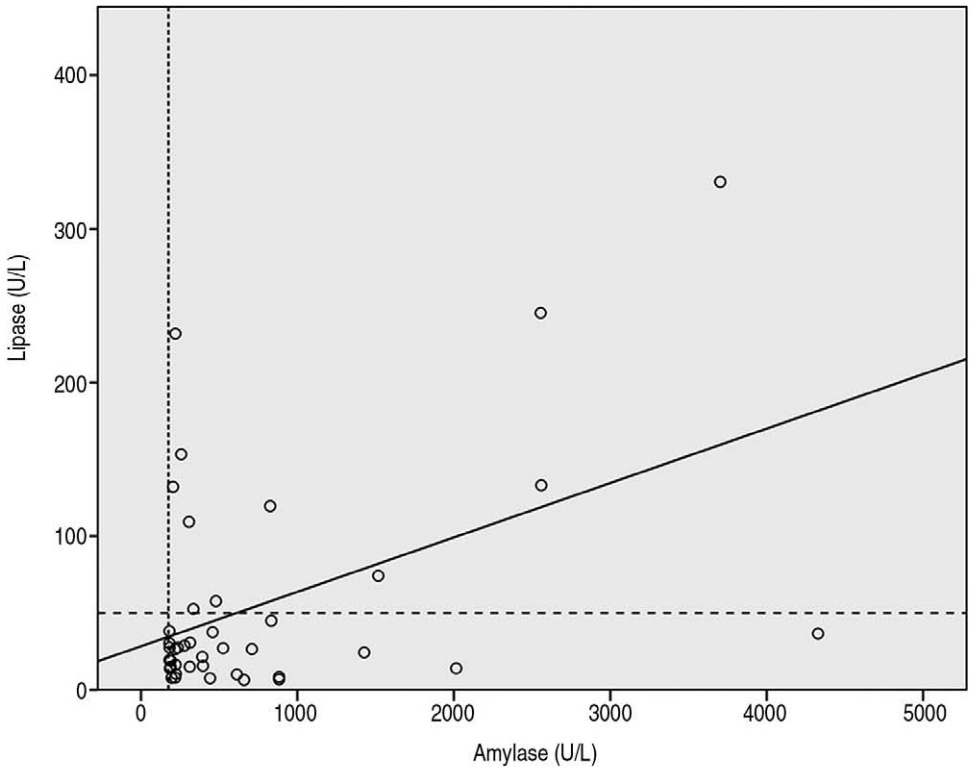

Fig. 2. Scatter plot illustrating the association between the peak amylase level and peak lipase level during 72 hours after admission in all hyperamylasemia patients. The amylase level and lipase level are mild correlated (Pearson correlation coefficient=0.469, p= 0.002, n=41). Dash line indicates the upper limit of normal level of serum amylase and lipase (respectively, 176 U/L and 50 U/L).

Table 4. Bivariate comparison analysis between the peak level of amylase and other laboratory tests in hyperamylasemia patients (N=49)

	Amylase	
	Correlation coefficient*	p-value
Blood urea nitrogen	0.017	0.909
Creatinine	0.277	0.054
Aspartate aminotransferase	0.352	0.013
Alanine aminotransferase	0.117	0.424
Bilirubin, total	-0.131	0.371
Bilirubin, direct**	0.026	0.882
Creatine phosphokinase	0.263	0.068
Lactate dehydrogenase	0.193	0.184

* Pearson's rho test.

** Serum levels of direct bilirubin were check in 35 patients.

poisoning[8]. In another study, HA was observed in 44/121 (36%) patients with OP poisoning[9]. Of our patients, HA occurred in 8/22 (36.3%) with pesticide poisoning, and pesticide use was an independent predictor of HA. Notably, this condition occurred in 6/9 (66.7%) patients with OP poisoning.

Dressel et al. have presented clinical and experimental evidence in dogs for acute anticholinesterase-induced pancreatitis. These results suggest that occurrence of HA after of anticholinesterase insecticide intoxication is the result of hypersecretion and pharmacologic ductal obstruction[23]. According to Ikizceli et al., the amylase is likely produced in the pancreas because animal studies have demonstrated OP-induced pancreatic damage[24]. In clinical studies, HA in OP poisoning patients has been associated with pancreatic edema and, rarely, with necrotizing pancreatitis[10,11].

In the present study, analgesics were not significantly correlated with HA occurrence, but many patients with paracetamol poisoning specifically exhibited HA (11/53, 20.7%). The pathophysiology of HA in paracetamol poisoning is uncertain, but in mice, paracetamol-arylated proteins are detectable in pancreatic tissue as soon as 4 hours after the administration of a toxic dose, indicating that the pancreas may be directly susceptible to paracetamol toxicity[25]. Opioids are classified as analgesics, and one of the four patients with opioid poisoning in this study exhibited HA. A few cases of opiate-induced AP have been reported in the literature[14,15], and codeine is a class Ia drug associated with AP[26].

Sedatives were the most common drug type in our patients. However, sedative use was statistically associated with the non-HA group, which is a novel finding. Contrary to previous evidence of AP and HA from case reports, our study examined consecutive self-poisoning patients and evaluated the occurrence of HA in these patients. Therefore, we could present toxic materials negatively associated with the occurrence of HA.

According to Lancashire et al., over 525 drugs from different classes are suspected to cause AP as a side effect[27]. The use of new drugs that are suspected to cause this condition continues to increase. However, most evidence of AP or HA caused by self-poisoning is from case reports[10-15], and the true incidence of AP in these patients is not known.

According our results using a toxicology registry, HA was identified in 13.3% of total self-poisoning patients, and based on the USA guidelines for AP, no patient was ultimately diagnosed with AP. Our incidence of AP is correlated with one previous study, which reported only three patients with pancreatitis in a total number of 506 cases of OP intoxications[28]. Based on the diagnosis of amylase/lipase levels more than three times above the upper limit of normal, we excluded patients with smaller enzyme level increases. Although once believed to be rare, some patients with AP have normal or mildly elevated amylase levels[29,30]. As an etiology, AP with normal amylase levels at admission is more likely to involve alcohol[31], which has the same mechanism as drug-induced AP. Moreover, in some HA patients who present with decreased mentality or severe respiratory failure, mechanical ventilator care may mask characteristic abdominal pain and disrupt abdominal imaging studies. Furthermore, negative CT findings have been reported in 24% to 67% of AP patients[32]. Lee et al. reported the clinical significance of HA in 121 OP poisoning patients. Of these, 5 cases with presumptive diagnosis of AP were evaluated with abdominal CT, and 2 cases presented with negative CT finding of AP[9]. Therefore, our AP incidence might be underestimated due to these causes.

In addition to pancreatic enzyme release into the blood stream by acinar cell damage, other possible causes of amylase elevation are amylase production from different tissues, such as the salivary gland, biliary etiologies and a decreased rate of clearance[7,33]. Suzuki et al. reported a salivary-type HA in one patient with theophylline poisoning[34]. However, our study did not include the measurement of amylase iso-enzymes, and there was no case of gross salivary gland injury. In a regression analysis of the peak laboratory values, amylase was most closely correlated with lipase. In contrast, peak levels of amylase were not correlated with renal tests, direct bilirubin, CPK

and LDH, and HA patients had a lower renal test value and serum bilirubin value. Given these results, the increased amylase levels in our patients might not have been caused by renal failure or biliary obstruction. Circulating pancreatic enzymes are removed by the reticulo-endothelial system in the body, and the liver is suspected to be a major organ for amylase removal[35,36]; liver damage is also suspected to play a role in inducing pancreatic hyperenzymemia[3,37]. In our results, the amylase level was mildly correlated with AST. Although toxic materials after self-poisoning can injure acinar cells and serum amylase was released into the blood stream, we believe that decreased liver metabolism of serum amylase in patients with an injured liver may lead to an accumulation of these enzymes in some patients with HA.

The limitations of this study are as follows: First, it was a retrospective and registry-based study. Some of the data, such as abdominal pain consistent with AP, were collected by chart reviews and were likely to be inaccurate. Second, while all self-inflicted intoxicants were included, the number of cases of each substance may be too small. A study with a larger scope may have yielded more concrete results. Third, adverse drug effects are generally dose-dependent (i.e., the duration and concentration of exposure to the drug). We were unable to ascertain the exact drug dose, which is a potential weakness of this study. In addition, further evaluations for AP, such as measurements of amylase iso-enzymes, were not performed in the HA patients. Thus, our results should be interpreted cautiously.

Conclusion

In our study, HA occurred rarely in self-poisoning patients. Pesticide and multiple-drug use were independent predictors of HA in these patients, whereas sedative use was negatively associated with an elevated amylase level. The peak amylase levels were correlated with lipase levels and AST levels. Although cautious interpretation is required, most patients with HA were asymptomatic, and in our cohort, none of the HA patients was ultimately diagnosed with AP.

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