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Acute Pancreatitis after Carbamate Poisoning

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Purpose: Carbamate insecticides are potent cholinesterase inhibitors capable of causing severe cholinergic toxicity. Use of carbamate rather than organophosphate insecticides has been increasing. Compared with organophosphate poisoning, relatively few studies have investigated carbamate-associated acute pancreatitis. We investigated general characteristics and pancreatitis of carbamate poisoning and the predictors, among those readily assessed in the emergency department.

Methods: We performed a retrospective review of consecutive patients, aged over 18 years, who were admitted between January 2008 and April 2012 to an emergency department (ED) of an academic tertiary care center for treatment of carbamate poisoning. Patients who exhibited poisoning by any other material, except alcohol, were excluded. After application of exclusion criteria, patients were divided according to carbamate-induced pancreatitis and non-pancreatitis groups.

Results: A total of 41 patients were included in this study. Among these 41 patients, the prevalence of acute pancreatitis was 36.6% (15 patients). Initial blood chemistry tests showed a statistically higher glucose level in the pancreatitis group, compared with the non-pancreatitis group (222, IQR 189-284 vs. 137, IQR 122-175 mg/dL, P<0.05). Regarding clinical courses and outcomes, a significantly higher proportion of patients developed pneumonia [10 (66.7%) vs. 6 (23.1%), P<0.05] and had a longer hospital stay (7 days, IQR 6-12 vs. 5 days, IQR 2-11, P<0.05), but no difference in mortality, in the pancreatitis group vs. the non-pancreatitis group. In multivariate analysis, the initial glucose was showing significant association with the presentation of carbamate-induced acute pancreatitis (odds ratio 1.018, 95% confidence interval 1.001-1.035, P<0.05).

Conclusion: Carbamate-induced acute pancreatitis is common, but not fatal. Initial serum glucose level is associated with acute pancreatitis.

Key Words: Pancreatitis, Carbamates, Cholinesterase inhibitors, Lipase

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Introduction

Carbamate and organophosphate are potent cholinesterase inhibitors capable of causing severe cholinergic toxicity following continuous exposure, inhalation, or ingestion. These exposures can occur

after contact with agricultural pesticides, either by intentional self-harm or unintentional use[1-6]. Among these two cholinesterase inhibitors, carbamate is a transient inhibitor which is spontaneously hydrolyzed at the cholinesterase enzymatic site within 24~48 hours; thus, carbamate-induced toxicity tends to be of a shorter duration. As a result, the use of carbamate agents has increased over the last 10 to 20 years, compared with that of organophosphate agents[7].

Toxicity studies have revealed that carbamate poisoning is manifested in primary cholinergic excess and then delayed syndromes similar in organophosphate poisoning, in addition, some cardiac-specific toxicity is also presented[8-15]. Regarding organ-specific damage induced by cholinesterase inhibitors, organophosphate has long been known to increase the acetylcholine sensitivity of the pancreas; histological studies have revealed that organophosphate can cause damage in pancreatic acinar cells, resulting in pancreatitis due to the subsequent increases in pancreatic enzymes[16,17]. However, few studies of carbamate-associated acute pancreatitis have been performed compared to organophosphate poisoning, even though hyperamylasemia and pancreatitis have often been observed in cases of carbamate poisoning[18-26]. The aim of this study was to reveal the prevalence, related risk factors, clinical courses, and outcomes of carbamate poisoning-associated acute pancreatitis.

Methods

1. Study design and population

We performed a retrospective review of consecutive patients, aged over 18 years, who had been admitted between January 2007 and April 2012 to an emergency department (ED) of an academic tertiary care center for treatment of carbamate poisoning.

Carbamate poisoning was confirmed by patient or guardian statements, verification of the agent by an emergency physician who entered the pesticide information into a poisoning information database, and serum levels of pseudo cholinesterase (pseudo-CE). Daily pseudo-CE follow-up was performed throughout the duration of the study until symptoms of cholinergic excess disappeared. Patients were excluded if they exhibited chronic pancreatic disease or poisoning by any other material, with the exception of alcohol.

During the study, gastric lavage was performed and activated charcoal was given to patients if the poisoning ingestion was suspected to be recent or potentially lethal. Additionally, atropine was continuously infused if the patient exhibited cholinergic toxicity, until respiratory secretion and bronchus constriction were alleviated.

2. Data collection

A poisoning information database, laboratory data, and radiologic images [including plain chest x-rays and abdominal computed tomography (CT) scans] were reviewed to collect patient information. Data collected included patient sex and age, ingested amount of carbamate, cause of poisoning, elapsed time from poisoning to arrival at the ED, route of poisoning, initial Glasgow Coma Scale (GCS) score, blood pressure, hourly urine output. The arterial blood gas analysis (including pH and lactate), white blood cell count, electrolytes (sodium, potassium), creatinine (Cr), aspartate aminotransferase (AST), alanine aminotransferase (ALT), amylase, lipase and pseudo-CE were also collected. Information regarding gastric lavage, administration of activated charcoal, the cumulative dose of atropine within the initial 24 hours, the CT grade of acute pancreatitis (if a CT scan was taken), and the organ-specific disorders and outcomes were also recorded.

3. Study definitions

The poisoning route was classified as either oral or non-oral (including continuous exposure or inhalation). If poisoning occurred by the oral route, the ingested amount was defined as follows: 'a little or a spoon' was defined as 5 cc, 'a mouthful' was presumed to be 25 cc, 'a small cup' was presumed to be 100 cc and 'a bottle' was presumed to be 300 cc.

Pancreatitis was defined by an amylase level more than three times greater than the normal value (≥ 400 U/L) or a lipase level more than 400 U/L, according to values obtained during the hospital stay[27,28]. During the study period, amylase values were routinely checked when patients exhibiting symptoms of intoxication were admitted. Lipase values were routinely monitored when the amylase level increased more than two times over the normal value, and daily follow-up was performed until lipase values began to decrease.

The CT severity index (CTSI) score was calculated based upon the degree of necrosis, the amount of inflammation, and the presence of fluid collection[29]. In accordance with hospital protocols, all abdominal CT scans were interpreted by the same radiologist who had performed the scan during the study period.

During the hospital stay, organ-specific disorders, such as respiratory failure requiring mechanical ventilation, shock (defined as a systolic blood pressure 〈90 mmHg), pneumonia, acute kidney injury (AKI, defined as an increase in serum Cr levels to more than twice the baseline level, or a urine output of 〈0.5 ml/kg/h for ≥12 hours), decreased consciousness (defined as a GCS score 〈15) were evaluated within the initial 72 hours of patient admission.

The outcome factors which were monitored included the length of stay (in days) in the intensive care unit (ICU), the total length of the hospitalization period, and mortality (death or moribund discharge).

4. Data analysis

Nominal data are presented as frequencies and percentages. Continuous variables are presented as means and standard deviation (means±SD) or medians and interquartile range (IQR), after investigating for normality using the Shapiro-Wilk test. Comparisons between two groups (carbamate-induced pancreatitis vs. non-pancreatitis) were performed using the Chi-square test or Fisher' s exact test for categorical variables, and the t-test or the Mann-Whitney U test for continuous variables. Multiple logistic regression was used to determine whether the variables of interest were associated with carbamate-induced acute pancreatitis. A P-value 〈0.05 was considered to indicate statistical significance. Analysis was performed using IBM SPSS software, version 20.0 (SPSS, Inc., Chicago, IL, USA).

Results

1. Patient characteristics

A total of 41 patients were included in this study. The cohort included 23 men (56.1%), whose ages ranged from 32 years to 85 years (mean, 57±15 years). The median elapsed time from poisoning onset to ED arrival was 145 minutes (IQR 81-317), and 33 (80.5%) patients exhibited intoxication caused by oral ingestion, the median amount of which was 100 cc (IQR 40-150). Among these patients, 24 (58.6%) exhibited intoxication caused by self-harm. Among patients with carbamate intoxication, the prevalence of acute pancreatitis was 36.6% (15 patients).

The pancreatitis and non-pancreatitis groups were statistically different regarding oral route intoxication and poisoning amount [15 (100.0%) vs. 18 (69.2%), P=0.018; 150 cc (100~200) vs. 50 cc (25~100), P〈0.001]. According to initial arterial blood gas analysis, the levels of serum lactate were significantly different between the pancreatitis and non-pancreatitis groups (median 4.35, IQR 1.77-6.01 vs. median 3.01, IQR 1.65~5.23 mmol/L, respectively; P=0.040). Initial blood chemistry tests also revealed a statistically higher glucose level in the pancreatitis group, compared with the non-pancreatitis group (median 222, IQR 189-284 vs. median 137, IQR 122-175 mg/dL, P=0.006). No other differences were observed between any of the other measurements, including factors related to the poisoning itself (elapsed time from poisoning to ED, intention, co-ingestion of alcohol), treatment factors (gastric lavage, charcoal administration, atropine use) or any other initial laboratory values (pH, WBC, CRP, sodium, potassium, Cr, AST, ALT, or pseudo-CE) between the two groups (Table 1).

2. Lipase and pseudo-CE patterns following carbamate-induced acute pancreatitis

In the carbamate-induced acute pancreatitis group, the median lipase levels within the initial 24 hours, from 24 to 48 hours, and from 48 to 72 hours were 904 (IQR 302-1566), 336 (IQR 134-855) and 326 (IQR 95-1063) U/L, respectively (Fig. 1). The median pseudo-CE levels within the initial 24 hours, from 48 to 72 hours, and from 48 to 72 hours were 1941 (IQR 1,234-3,365), 3,499 (IQR 1,484-6,912) and 5,732 (IQR 4,134-7,816) (Fig. 2).

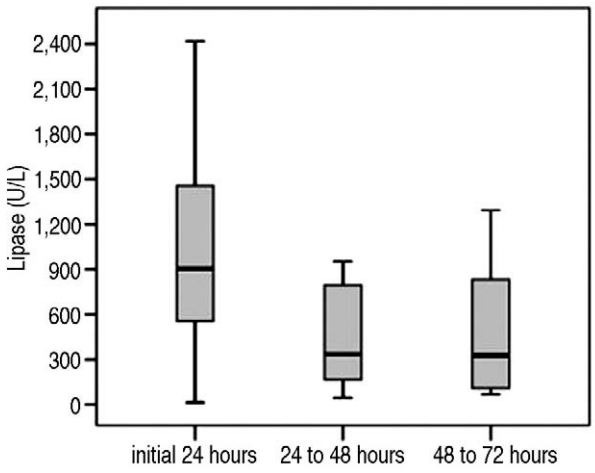

Fig. 1. Lipase pattern following carbamate-induced acute pancreatitis.

3. Predictors of carbamate-induced acute pancreatitis

Multivariate analysis revealed that only one factor, the initial serum glucose was associated with carbamate-induced acute pancreatitis (odds ratio 1.018, 95% CI 1.001-1.035, P=0.039). The co-ingestion with alcohol, administration and cumulative atropine dose within the initial 24 hours, initial lactate level, and initial pseudo-CE level were not associated with the development of acute pancreatitis (Table 2). The area under the receiving operating characteristic (AUC)

Table 1. Comparison of clinical variables between the carbamate-induced pancreatitis and non-pancreatitis groups

Characteristic	Total	Pancreatitis Group (n=15)	Non-pancreatitis Group (n=26)	*P*-value
Age (years)	57±15*	54±15*	59±16*	0.323
Male	23 (56.1)	6 (40.0%)	17 (65.4%)	0.115
Elapsed time from poisoning to ED (min)	145 (81-317)†	111 (38-233)†	191 (109-378)†	0.136
Oral route	33 (80.5)	15 (100.0)	18 (69.2)	0.018
Amount (cc)	100 (40-150)†	150 (100-200)†	50 (25-100)†	<0.001
Intentional poisoning	24 (58.5)	11 (73.3)	13 (50.0)	0.195
Co-ingested with alcohol	15 (36.6)	7 (46.7)	8 (30.8)	0.460
Gastric lavage	25 (61.0)	10 (66.7)	15 (57.7)	0.742
Charcoal administration	26 (63.4)	11 (73.3)	15 (57.7)	0.502
Cumulative atropine dose in the initial 24 h (mg)	20 (0-36.5)†	25 (4-40)†	14 (0-34.8)†	0.345
Initial laboratory findings				
pH	7.37 (7.33-7.42)†	7.35 (7.29-7.42)†	7.39 (7.33-7.42)†	0.337
Lactate (mmol/L)	4.35 (1.77-6.01)†	5.46 (4.33-6.17)†	3.01 (1.65-5.23)†	0.040
WBC (cells/mL)	12,520 (9,270-16,765)†	13,900 (10,360-17,860)†	11,785 (8,275-13,928)†	0.183
CRP (mg/dL)	0.30 (0.29-0.39)†	0.30 (0.29-0.44)†	0.30 (0.29-0.37)†	0.654
Sodium (mmol/L)	142 (140-144)†	141 (139-147)†	142 (140-143)†	0.920
Potassium (mmol/L)	3.6±0.5*	3.5±0.5*	3.7±0.5*	0.195
Cr (mg/dL)	0.8±0.3*	0.7±0.3*	0.8±0.3*	0.504
Glucose (mg/dL)	170 (123-220)†	222 (189-284)†	137 (122-175)†	<0.001
AST (U/L)	33 (27-46)†	35 (27-127)†	33 (25-43)†	0.365
ALT (U/L)	24 (17-35)†	29 (17-58)†	22 (17-30)†	0.128
Pseudo-CE (U/L)	2,869 (1,475-5,167)†	1,940 (1,234-3,365)†	3,759 (1,711-6,478)†	0.054

* Means±standard deviation, †median (interquartile range), ED: emergency department, WBC: white blood cell count, CRP: C-reactive protein, BUN: blood urea nitrogen, Cr: creatinine, AST: aspartate aminotransferase, ALT: alanine aminotransferase, CE: cholinesterase

curve that described the sensitivity and specificity of isolated serum glucose for different cutoff levels was 0.819 (0.671~0.967) (Fig. 3). The optimum cutoff to predict acute pancreatitis has been identified at 189 mg/dL, with respective values of 80.0% for sensitivity and 84.6% for specificity.

4. Clinical course and outcome of carbamate-induced acute pancreatitis

In the pancreatitis group, the median peak value of lipase was 1,111 (IQR 749-15,496) U/L, and the median peak day of lipase was day 1 (IQR 1-1). Eight (53.3%) of 15 patients in the pancreatitis group received abdominal CT scans; all of these scans yielded a CTSI score of 0. In both groups, the median lowest day of pseudo-CE was day 1 (IQR 1-2).

To compare the clinical courses between the two groups, we analyzed the lowest value of pseudo-CE, the day with the lowest pseudo-CE, and the development of organ-specific disorders such as respiratory failure, shock, pneumonia, decreased consciousness and AKI. The lowest pseudo-CE value was significantly lower in the pancreatitis group compared with the non-pancreatitis group (median 1,502, IQR 1,156-2,732 vs. median 3,053, IQR 1,574-5,973 U/L, P=0.019). Furthermore, significantly more disorders (pneumonia, decreased consciousness) developed in the acute pancreatitis vs. the non-pancreatitis group [10 (66.7%) vs. 6 (23.1%), P=0.009; 14 (93.3%) vs. 13 (50.0%), P=0.006]. The development of other disorders (respiratory failure, shock, AKI) was not significantly different between the two groups.

Outcome variables were also compared between the two groups. The total hospitalization length was significantly longer in the pancreatitis group vs. the non-pancreatitis group (median 7 days, IQR 6-12 vs. median 5 days, IQR 2-11; P=0.009), whereas the length of stay in the ICU and mortality were not significantly different between the two groups (Table 3).

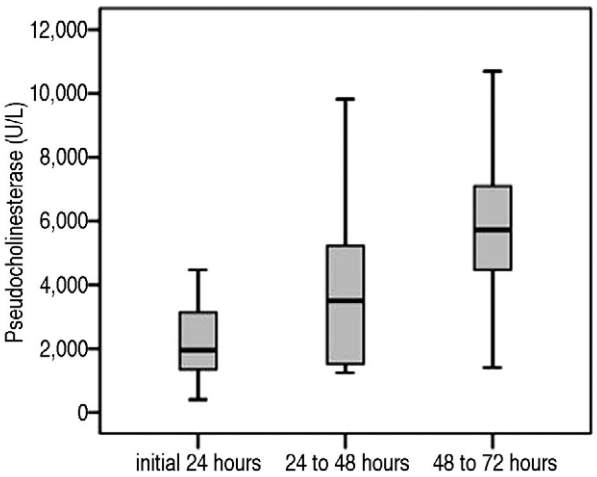

Fig. 2. Pseudo cholinesterase pattern following carbamate-induced acute pancreatitis.

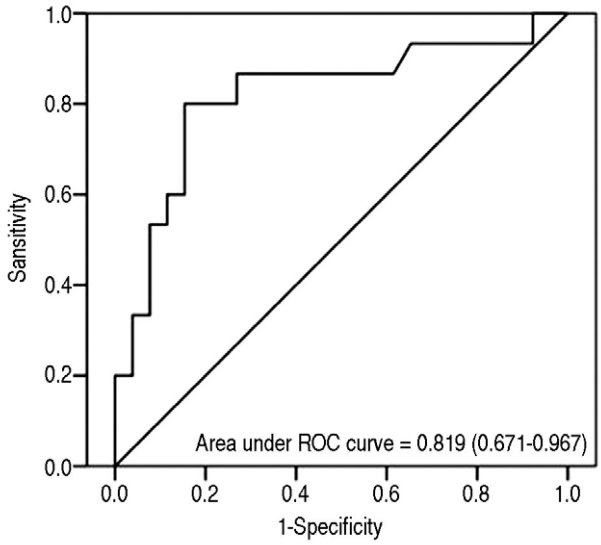

Fig. 3. Serum glucose receiving operating characteristic (ROC) curve predicting a acute pancreatitis.

Table 2. Multivariate analysis of association factors and their relationships to acute pancreatitis

Potential predictors of acute pancreatitis	Odds ratio	95% CI	*P*-value
Co-ingestion with alcohol	1.417	0.257-7.810	0.689
Cumulative dose of atropine within the initial 24 h	0.991	0.958-1.025	0.590
Initial lactate	1.089	0.698-1.699	0.706
Initial glucose	1.018	1.001-1.035	0.039
Initial pseudo-CE	1.000	1.000-1.000	0.992

CI: confidence interval, CE: cholinesterase

Table 3. Comparison of clinical courses and outcomes between the carbamate-induced pancreatitis group and the non-pancreatitis group

Clinical course and outcome	Total	Pancreatitis group (n=15)	Non-pancreatitis group (n=26)	*P*-value
Initial amylase (U/L)	94 (54-244)*	245 (123-733)*	76 (49-144)*	<0.001
Lowest value of pseudo-CE (U/L)	2,699 (1,403-4,053)*	1,502 (1,156-2,732)*	3,053 (1,574-5,973)*	0.019
Day with lowest pseudo-CE (day)	0 (0-1)*	0 (0-1)*	0 (0-1)*	0.612
Peak value of lipase (U/L)		1,111 (749-15,496)*		
Day with peak lipase (days)		0 (0-0)*		
CT severity index (if CT was taken, n=8)		All 0		
Organ-specific disorders during the initial 72 h				
Respiratory failure requiring ventilator care	21 (51.2)	11 (73.3)	10 (38.5)	0.052
Shock (SBP<90 mm Hg)	4 (9.8)	3 (20.0)	1 (3.8)	0.130
Pneumonia	16 (39.0)	10 (66.7)	6 (23.1)	0.009
Decreased consciousness (GCS score <15)	27 (65.9)	14 (93.3)	13 (50.0)	0.006
AKI	3 (7.3)	2 (13.3)	1 (3.8)	0.543
Total length of hospitalization (days)	6 (3-11)*	7 (6-12)*	5 (2-11)*	0.009
ICU stay length (days)	2 (0-6)*	4 (2-6)*	2 (0-5)*	0.094
Mortality	2 (4.9)	1 (6.7)	1 (3.8%)	1.000

* Median (interquartile range), CE: cholinesterase, CT: computed tomography, SBP: systolic blood pressure, GCS: Glasgow Coma Scale score, AKI: acute kidney injury, ICU: intensive care unit

Discussion

In our study, a large percentage of patients (36.6%) developed carbamate-induced acute pancreatitis. Until now, few studies have investigated the overall prevalence of carbamate-induced acute pancreatitis. Organophosphate poisoning studies by Sahin et al., Weizman et al., and Lee et al. revealed incidences of acute pancreatitis from 7.4 to 29.4%[20,30,31]. The diagnostic criteria for acute pancreatitis and the population target ages were slightly different, but our study revealed that acute pancreatitis is more common with carbamate intoxication than those previous organophosphate poisoning studies. Further study will be needed.

In acute pancreatitis, the level of serum lipase normally reaches its maximum level within 24 hours, and returns to a normal level between 8 to 14 days[32]. Similarly, in our study of carbamate-induced acute pancreatitis, the peak median lipase level was observed within the initial 24 hours; however, lipase levels returned to normal much more quickly than in general acute pancreatitis. As a cholinesterase inhibitor, carbamate can cause increased sensitivity to acetylcholine in the pancreas, resulting in the development of pancreatitis due to the increased activity of pancreatic enzymes. However, this effect should be transient, since carbamateis spontaneously hydrolyzed from the cholinesterase enzymatic site. That is why our results revealed that the pseudo-CE level which reflects the cholinesterase effect was lowest within the initial 24 hours, and recovered during the period from 24~72 hours. And this pseudo-CE pattern exhibits a negative correlation with the level of lipase. Thus, we hypothesize that these characteristics of carbamate could affect this pattern of lipase level what begins to decline earlier than general acute pancreatitis.

Some activated pancreatic enzymes (phospholipase, elastase, trypsin, etc.) and cytokines (tumor necrosis factor, platelet activating factor) released into the circulation from an inflamed pancreas could potentially mediate metabolic complications, including hyperglycemia[33,34]. Moreover, a previous study concluded that special attention should be paid to glucose homeostasis and the special risks of patients with diabetes and organophosphate intoxication[35]. Likewise in our study, hyperglycemia was significantly associated with the pancreatitis group. Thus, we

could suggest that patients with carbamate-induced acute pancreatitis require careful monitoring to control their blood glucose levels.

Some case studies have revealed that acute pancreatitis resulting from carbamate intoxication can manifest itself in severe forms, such as pancreatic ascites, accumulation of intrapancreatic fluid, necrotic hemorrhagic pancreatitis, and pancreatic pseudocyst formation[22-26]. However, no studies have yet investigated the general clinical course of carbamate-induced acute pancreatitis. In our study, organ-specific disorders of carbamate intoxication such as decreased consciousness and pneumonia that could be affected by cholinergic toxicity are more often found with acute pancreatitis. And, in contradiction with previous reports, forms of severe acute pancreatitis (CTSI score $\geq$6) were not observed, even though intoxication was from occurred with various kinds of carbamate (16 methomyl, 12 cabofuran, 2 fenobucarb, 1 carbosulfan, 8 unrecorded subtypes). For example, a case about methomyl intoxication, even exhibited a lipase level greater than 25,000 U/L; however, an image reading of the patient's CT scan revealed a CTSI score of 0. Moreover, the non-severe forms of acute pancreatitis were loosely related to mortality and length of ICU stay in our study.

Our study did have some limitations; for instance, our study was retrospective in nature and performed only at a single center. Thus, abdominal CT scans were not taken for all acute pancreatitis patients. However, the indications for obtaining an abdominal CT scan included clinically severe abdominal pain and elevated lipase levels; these indications could minimize missing of severe form pancreatitis. We also concede that our study was possibly subject to selection bias, since it was a single center study, and the patients accessing the center may represent a different population than the population accessing hospitals in general. In response to this concern, we argue that our institution contains a regional emergency center that has the ability to provide acute poisoning care; moreover, the center used in this study had a relationship between pre-hospital health care systems and medical direction during the study period, so most of the patients exhibiting carbamate poisoning in the region were presumably admitted to the center.

Conclusions

Carbamate-induced acute pancreatitis is frequent, but is generally associated with a good prognosis. The factor most closely associated with the acute pancreatitis is the hyperglycemia.

Declaration of Interests

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

Ethics approval

This study was approved by the Institutional Review Committee of Wonju College of Medicine, Yonsei University.

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