MEDICAL SCIENCE MONITOR

CLINICAL RESEARCH

e-ISSN 1643-3750
© Med Sci Monit, 2015; 21: 2900-2904
DOI: 10.12659/MSM.894287

Received: 2015.04.01
Accepted: 2015.05.22
Published: 2015.09.28

Prognostic Factors in Cholinesterase Inhibitor Poisoning

Authors' Contribution:
Study Design A
Data Collection B
Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
Literature Search F
Funds Collection G

ABCDEF In O Sun
BC Hyun Ju Yoon
ACDE Kwang Young Lee

Division of Nephrology and Toxicology, Department of Internal Medicine, Presbyterian Medical Center, Jeonju, South Korea

Corresponding Author: Kwang Young Lee, e-mail: kwangpmc@hanmail.net
Source of support: Departmental sources

Background: Organophosphates and carbamates are insecticides that are associated with high human mortality. The purpose of this study is to investigate the prognostic factors affecting survival in patients with cholinesterase inhibitor (CI) poisoning.

Material/Methods: This study included 92 patients with CI poisoning in the period from January 2005 to August 2013. We divided these patients into 2 groups (survivors *vs.* non-survivors), compared their clinical characteristics, and analyzed the predictors of survival.

Results: The mean age of the included patients was 56 years (range, 16–88). The patients included 57 (62%) men and 35 (38%) women. When we compared clinical characteristics between the survivor group (n=81, 88%) and non-survivor group (n=11, 12%), there were no differences in renal function, pancreatic enzymes, or serum cholinesterase level, except for serum bicarbonate level and APACHE II score. The serum bicarbonate level was lower in non-survivors than in survivors (12.45±2.84 *vs.* 18.36±4.73, P<0.01). The serum APACHE II score was higher in non-survivors than in survivors (24.36±5.22 *vs.* 12.07±6.67, P<0.01). The development of pneumonia during hospitalization was higher in non-survivors than in survivors (n=9, 82% *vs.* n=31, 38%, P<0.01). In multiple logistic regression analysis, serum bicarbonate concentration, APACHE II score, and pneumonia during hospitalization were the important prognostic factors in patients with CI poisoning.

Conclusions: Serum bicarbonate and APACHE II score are useful prognostic factors in patients with CI poisoning. Furthermore, pneumonia during hospitalization was also important in predicting prognosis in patients with CI poisoning. Therefore, prevention and active treatment of pneumonia is important in the management of patients with CI poisoning.

MeSH Keywords: Bicarbonates • Cholinesterase Inhibitors • Pneumonia

Full-text PDF: http://www.medscimonit.com/abstract/index/idArt/894287

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Background

Organophosphate (OP) and carbamates (CM) are important insecticides that are used in developing countries [1]. The inhibition of cholinesterase inhibitor activity cause accumulation of acetylcholine at synapses, causing overstimulation and disruption of neurotransmission in both the central and peripheral nervous systems. Such symptoms include tachycardia, hypotension, increased salivation, bronchospasm, and urination [2,3].

The mortality rate of acute cholinesterase inhibitor (CI) poisoning ranges from 10 to 50% [2,4–6], and the annual global number of mortalities is approximately 200 000 [7]. Although plasma or urine OP concentration, cholinesterase activity, APACHE II score, S-100B protein, and C-reactive protein have been correlated with severity and mortality rates in OP poisoning patients [8–11], these laboratory methods are not readily available, and their usefulness remains controversial. Although pneumonia occurs frequently in patient with CI poisoning [12], there is limited data regarding the relationship between pneumonia and CI poisoning.

Therefore, we investigated the mortality rate in patients with CIP and evaluated the prognostic factors affecting this mortality. Furthermore, we examined the usefulness of pneumonia as a prognostic factor.

Material and Methods

Patient selection

We considered for inclusion 102 patients with CI poisoning who visited our hospital between January 2005 and August 2013. We excluded 6 patients who were transferred to other hospitals during treatment or were otherwise lost to follow-up and 4 patients with inhalation exposure. Therefore, 92 patients were included in this study and were divided into 2 groups: survival (n=81) and non-survival (n=11). Patients who survived for longer than 3 months were included in the survival group. The Institutional Review Board at Presbyterian Medical Center approved this study.

Clinical and laboratory information

All data were collected from a retrospective chart review. Acute CI poisoning was defined based on the history of exposure, cholinergic clinical feature, and decreased serum cholinesterase activity. Standardized medical emergency procedures such as gastric lavage, administration of charcoal and intravenous atropine and pralidoxime were conducted to the patients with acute CI poisoning in our center. In our study, the patient with CI poisoning received doses of intravenous atropine from 2 to 5 mg, depending on severity, as assessed by the treating clinician. This was repeated every 10 to 15 min until signs of atropinization were clinically evident (clear chest on auscultation with resolution of bronchorrhea, heart rate of >80 beats per min, systolic blood pressure >80 mmHg, dry axillae, and pupils >2 mm in diameter). The Acute Physiology and Chronic Health Evaluation (APACHE) II scores were obtained on admission. Pneumonia was diagnosed on the basis of a radiographic finding of new and progressive pulmonary infiltrates and at least 2 of the following criteria: body temperature >38°C or <35°C; leukocytosis (leukocyte count, >12 000 cells/mm^3); clinical evidence of suggestive of pneumonia such as purulent bronchial secretions and a decrease in oxygenation. Red cell acetylcholine esterase activity was determined by the modified Ellman method [13,14]. The normal range for red cell acetylcholine esterase activity was 11 188 to 16 698 IU/L in our

Table 1. Baseline characteristics of the 92 patients with CIP.

Characteristics	
Age, years	56.5±17.2
Male, n (%)	57 (62)
Poison	6.6±15
Carbamate, n (%)	19 (21)
Organophosphate, n (%)	72 (79)
Dichlorvos	16
Phospamidon	15
Chlorpyrifos	12
EPN	10
Malathion	4
Methidathion	2
Fenitrthion	2
Monocrotophos	2
Unkown	9
Serum creatinine (mg/dl)	0.90±0.34
APACHE II score (IU/L)	13.54±7.63
HCO_3, (mmol/L)	17.65±4.92
Estimated amount ingested, (mL)	93.13±88.90
RBC cholinesterase, (IU/L)*	7254±4373
Serum pseudocholinesterase, (IU/L)**	2874±2793
Acute respiratory failure, n (%)	53 (58)
Pneumonia	40 (44)
Hospital stay, days	21.10±17.89
Death, n (%)	11 (12)

* The data are available in 79 patients; ** The data are available in 86 patients.

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Table 2. Comparison of clinical characteristics between survivor and non-survivor.

	Survivor (N=81)	Non-survivor (N=11)	P-value
Age, years	56.1±16.6	59.4±22.1	NS
Male, n (%)	51 (63)	6 (55)	NS
APACHE II score	12.07±6.67	24.36±5.22	<0.01
HCO_3, (mmol/L)	18.36±4.73	12.45±2.84	<0.01
Serum creatinine (mg/dl)	0.87±0.30	1.08±0.54	NS
RBC acetylcholine esterase activity, (IU/L)*	7214±4316	7566±5063	NS
Serum pseudocholinesterase, (IU/L)**	3005±2860	1755±1901	NS
Acute respiratory failure, n (%)	42 (52)	11 (100)	<0.01
Pneumonia	31 (38)	9 (82)	<0.01
Hospital stay, days	21.27±18.19	19.82±16.21	NS
Estimated amount ingested, (mL)	88.13±88.78	140.00±80.00	NS

* The data are available in 79 patients; ** The data are available in 86 patients.

Table 3. Multivariate logistic regression analysis.

Variable	B	Relative risk	95% confidence interval	P-value
APACHE II score	0.038	1.457	1.099 1.931	0.009
HCO_3	–0.298	0.743	0.568 0.971	<0.01
Pneumonia	2.462	11.726	1.057 278.46	<0.01

hospital. Plasma cholinesterase activity was measured using a cholinesterase reagent in conjunction with the SYNCHRON LX system (Unicel DxC System, Beckman/Coulter, Fullerton, CA). The normal range for plasma cholinesterase activity was 5320 to 12 920 IU/L in our hospital.

Statistical analysis

All data are presented as mean ± standard deviation unless otherwise specified. The baseline characteristics of patients in the non-survivor and survivor groups were compared using *t* tests, chi-square test, or Fisher's exact test, as appropriate. Multiple logistic regression analysis was applied to predict the outcome after CI poisoning. A p value <0.05 was considered statistically significant. Statistical analysis was carried out using SPSS version 18.0.

Results

Baseline characteristics

The baseline characteristics of the 92 study subjects are presented in Table 1. Of the participants, 51 (62%) were male, and 72 (79%) were cases of OP poisoning. The OP agents responsible for poisoning were dichlorvos (n=16), phosphamidon (n=15), chlorpyrifos (n=12), O-ethyl-O-4-nitrophenyl phenyl phosphonothioate (EPN, n=10), Malathion (n=4), Methidathion (n=2), Fenitrthion (n=2), Monocrotophos (n=2), and unidentified (n=9). Of these, 90 were intentional and 2 were accidental poisoning. The initial mean serum bicarbonate and lipase levels were 17.6 (range, 6–30) mmHg and 103 (range, 13–1387) IU/L, respectively. The mean APACHE II score was 13.54 (range, 1–33). Of the 92 patients enrolled in this study, 53 (58%) experienced respiratory failure requiring mechanical ventilation, and 40 (44%) were diagnosed with pneumonia during hospitalization. Eleven patients (12%) died during the study period. Of these 11 patients, 1 patient was included in the carbamate group.

Comparison of clinical characteristics between survivors and non-survivors

When we compared clinical characteristics between survivors (n=81) and non-survivors (n=11), there were no differences in renal function, pancreatic enzymes, or serum cholinesterase level, except for serum bicarbonate level and APACHE II

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score (Table 2). The serum bicarbonate level was lower in non-survivors than in survivors (12.45±2.84 *vs.* 18.36±4.73, p<0.01). The APACHE II score was higher in non-survivor than in survivors (12.07±6.67 *vs.* 24.36±12.07, p<0.01). All 11 patients who died during the study had acidemia on admission; 6 patients had mixed metabolic and respiratory acidosis and 5 had metabolic acidosis. Respiratory failure requiring ventilator therapy developed more frequently in non-survivors than in survivors (n=11, 100% *vs.* n=42, 52%). The development of pneumonia during hospitalization was higher in non-survivors than in survivors (n=9, 82% *vs.* n=31, 38%). Although there was no difference in hospitalization period between survivors and non-survivors, the hospitalization period was longer in patients with pneumonia than in those without pneumonia (27.05±21.43 *vs.* 16.52±13.06, p=0.005).

Clinical course and prediction of non-survival in CI poisoning patients

Of the 11 patients who died, 7 died due to aggravation of pneumonia, 2 died due to multiorgan failure, 1 died due to acute kidney injury, and 1 probably died due to cardiac arrhythmia. According to univariate analysis, serum bicarbonate concentration, APACHE score, acute respiratory failure, and pneumonia during hospitalization were significant predictors of mortality in patients with OP poisoning. After adjusting for these factors in a multivariate logistic regression analysis, serum bicarbonate concentration, APACHE score, and pneumonia during hospitalization were the most important prognostic factors in OP poisoning (Table 3). When we compared clinical characteristics between pneumonia (n=40) and non-pneumonia (n=52), there were no differences in renal function, pancreatic enzymes, or serum cholinesterase level, except for APACHE II score and mortality rate. In comparison with patients in the non-pneumonia group, the patients in the pneumonia group had higher APACHE II score (16.80±11.03, P<0.05) and higher mortality rate (n=9, 3% *vs.* n=2, 4%, P<0.01).

Discussion

OP and carbamates are acetylcholinesterase inhibitors and are currently used as insecticides in rural Asia. The mortality rate following CI poisoning was reported at up to 50% [2,4–6]. In the present study, the mortality was 12%, which was slightly lower than that of previous reports. We think that this might be due to close monitoring in our intensive care unit (ICU). The policy of management for patients with CI poisoning in our center is admission to the ICU and atropine treatment based on close monitoring of cholinergic symptoms. Although such measures prolong ICU length of stay and increase hospital expenses, they could help increase survival in patients with CI poisoning.

Several prognostic factors for OP poisoning are associated with severity and prognosis, including poisoning severity score, Glasgow Coma Scale score, APACHE II score, Simplified Acute Physiology Score II, S-100B protein, serum cholinesterase activity, and C-reactive protein [8–11]. In this study, serum bicarbonate concentration, APACHE II score, and pneumonia during hospitalization were important prognostic factors in patients with CI poisoning. The APACHE II score has been used as a predictor of poisoning severity, and we also confirmed this finding in our study. All 11 patients who died during the study had higher APACHE II score than those of survivor (12.07±6.67 *vs.* 24.36±12.07, p<0.01). Serum cholinesterase (SChE) activity is often evaluated in OP-poisoned patients; low SChE activity supports the diagnosis of OP poisoning, but a decrease in SChE activity level does not appear to have prognostic value in acute OP poisoning [15,16]. Initial serum cholinesterase level was not different between survivors and non-survivors in our study; however, initial serum cholinesterase level was correlated with APACHE II score. Therefore, we think that serum cholinesterase level is related to clinical severity but not mortality.

The alteration in acid-base status can be developed in acute OP poisoning, and different acid-base status may be detected in acute OP poisoning. Acidosis influences the outcome of patients with OP poisoning [17]. Liu et al. [18] noted that mortality rate varied according to the initial acid-base status in OP poisoning and was highest in patients with mixed acidosis (without acidosis < metabolic acidosis < respiratory acidosis < mixed acidosis). Thus, they reported that acid acid-base status was closely linked with severity of acute OP poisoning and mortality. In the present study, the initial serum bicarbonate level was lower in non-survivors than in survivors (12.45±2.84 *vs.* 18.36±4.73). Of 11 patients who died, 6 had mixed acidosis at admission and 5 and metabolic acidosis.

Pneumonia is a frequently encountered complication in management of CI poisoning because of decreased consciousness and secretion of mucosal fluids. The relationship between CI poisoning and pneumonia is rarely discussed in the literature. In our study, pneumonia during hospitalization was the most important risk factor in predicting the prognosis of patients with CI poisoning. Of the 11 patients who died, 7 died due to septic shock from aggravation of pneumonia. Of these 7, 5 patients had early-onset pneumonia, which occurred within 5 days after admission and was associated with CI poisoning. Wang et al. reported that early-onset pneumonia was a significant risk factor for death in patients with CI poisoning, which was also shown in our study. However, 2 patients were maintained on ventilator care despite termination of atropine treatment and experienced hospital-acquired pneumonia at the 16th and 40th days of admission. Therefore, we think that hospital-acquired pneumonia is also important in patients with CI poisoning.

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Wang et al. reported that respiratory failure was more frequent among those who underwent gastric lavage at peripheral hospitals [12]. In our study, the incidence rate of pneumonia was also higher in patients with gastric lavage at peripheral hospitals than in those with gastric lavage at our hospital, but this was statistically insignificant. Instead, APACHE II score, which was a prognostic factor in this study, was higher in the pneumonia group than in the non-pneumonia group. The APACHE II score is also regarded as a risk factor in development of pneumonia [19]. Therefore, we think that careful respiratory evaluation is needed in CI poisoning patients, especially those with high APACHE II score.

Conclusions

Reliable predictors of prognosis can guide treatment and future clinical research on antidotes and therapies. In this study, the mortality rate was 12%, and serum bicarbonate and APACHE II score were shown to be useful prognostic factors in patients with CI poisoning. Furthermore, pneumonia during hospitalization was also important in predicting prognosis in patients with CI poisoning. Therefore, prevention and aggressive treatment of pneumonia is important in the treatment of patients with CI poisoning.

Declaration of interest

The authors have no conflicts of interest to report.

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