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Sodium Bicarbonate and N-Acetyl Cysteine in Treatment of Organophosphorus Poisoning Cases: A Randomized Controlled Clinical Trial

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Abstract

Introduction: Organophosphorus poisoning (OPP) is an important health problem in many parts of the world particularly in developing countries. However, the treatment did not change since many years, despite the increasing complications and case fatalities of the exposure. From the clinical experience, some pharmacologic agents had proved useful in improving the outcome and decreasing the complications of this exposure.

Aim: This study was conducted to test the efficacy of N-acetyl cysteine; the famous antioxidant, and of blood alkalization by sodium bicarbonate in improving the outcome of OPP cases.

Methods: Seventy patients of OPP were given N-acetylcysteine (NAC) and $NaHCO_3$ together with classic treatment of OPP. Serum Malondialdehyde (MDA), Glutathione peroxidase (GPx), pH, plasma butyrylcholinesterase were measured and compared of a matched group of patients, who received classic treatment only, on presentation and after 24 hours of classic treatment only.

Results: There were no significant differences between the two groups of study in initial levels of MDA, GPx, pH, plasma butyrylcholinesterase that turned highly significant after 24 h of treatment and observation. There was a highly significant difference (P=0.001) in length of hospital stay (LOS) between the two groups. No adverse effects for the supplements were observed.

Conclusion: NAC and sodium bicarbonate are affordable agents and are very helpful in improving the outcome in OPP and decreasing LOS.

Keywords: N-acetyl cysteine; Sodium bicarbonate; Organophosphorus poisoning; Treatment; New modality

Introduction

Organophosphorus compounds are organic compounds containing phosphorus. They are used primarily in pest control as an alternative to chlorinated hydrocarbons that persist in the environment. They are highly effective against insects, however, toxic to humans [1].

Among the commonly used organophosphates are parathion, malathion, methyl parathion, chlorpyrifos, diazinon, dichlorvos, phosmet, fenitrothion, tetrachlorvinphos and azamethiphos. Malathion is the most commonly used organophosphate insecticide in the United States (US). Forty organophosphate pesticides are registered in the US, with at least 73 million pounds used in agricultural and house-hold settings [2].

Organophosphorus poisoning is an important cause of mortality and morbidity in developing countries. It is responsible for about 3 million poisoning cases and 200,000 deaths per year and responsible for at least 5 million deaths over the last three decades. Despite that, no new modalities are actively approached and studies on new therapies of this type of toxicity are still scarce [3].

Organophosphorus (OP) pesticides poisoning can result from occupational, accidental or intentional exposure. Both organophosphorus (OP) and carbamate insecticides are acetylcholinesterase (AChE) enzyme inhibitors. This results in accumulation of acetylcholine (ACh) at autonomic and some central synapses and at autonomic postganglionic and neuromuscular junctions. This produces the characteristic features of OP poisoning [4].

With OP insecticides (but not carbamates), "aging" of the AChE enzyme may also occur due to partial dealkylation of the serine group at the active site of AChE. The recovery of the enzyme activity requires synthesis of new enzyme in the liver. Moreover, OP poisoning may be complicated by 'Intermediate Syndrome'. This is shown by relapse after apparent resolution of cholinergic symptoms. It manifests by muscle paralysis particularly in upper-limb muscles, neck flexors, and cranial nerves, about 24-96 h after OP exposure and is often associated with the development of respiratory failure [5].

Another complication of OP poisoning is the OP-induced delayed neuropathy. It results from phosphorylation and subsequent aging of at least 70% of neuropathy target esterase (NTE). Cramping muscle pain in the lower limbs, distal numbness, and paresthesia, followed by progressive weakness, depression of deep tendon reflexes in the lower limbs and, in severe cases, in the upper limbs. The therapeutic

combination of oxime, atropine, and diazepam is well established in the treatment of OP insecticide poisoning. However, there has been controversy as to whether oximes improve morbidity and mortality in human poisoning. The explanation may be that the solvents in many formulations are primarily responsible for the high morbidity and mortality; oximes would not be expected to reduce toxicity in these circumstances even if given early and in appropriate dose [6].

This reflects the need for new antidote approach for OP pesticide therapy. Very few studies suggest benefit from new treatments such as Sodium bicarbonate and N-acetyl cysteine, and larger trials are needed [7].

Aim of the Work

This study was conducted to assess efficacy of sodium bicarbonate and N-acetyl cysteine in treatment of organophosphorus-poisoning cases. This aims in broader terms to approach new modalities for treatment of organophosphorus poisoning and to reduce morbidity/mortality of that common toxic exposure.

Subjects and Methods

This is a prospective randomized controlled clinical trial that was carried out on 140 patients diagnosed of poisoning of organophosphorus compounds. The patients were attending to the Toxicology Unit in Mansoura Emergency Hospital in the period from June 2014 to August 2015.

Patients were divided into 2 groups of 70 patients each; a control group that received classic treatment regimen of organophosphorus poisoning and a second group that received, in addition to the classic treatment, the N-acetyl cysteine and sodium bicarbonate.

N-acetyl cysteine was given in a dose of 400 mg/day [8] and sodium bicarbonate was given in a dose of 2-5 mEq/kg IV infusion over 4-8 h. Subsequent doses should be based on patient's acid-base status until reaching the target arterial pH of 7.50 (range 7.45-7.55) [9].

Patients age ranged from 16- 57 y. Sixty four (64) were female and 76 were male. Median age of females was 28 y (range 16–51 y). Median age for males was 32 y (range 18-57 y). Excluding patients with concomitant other diseases, e.g. liver disease, kidney or respiratory diseases and cases with any drugs intakes were also excluded.

Patients' severity of intoxication ranged from mild to severe degrees. The selection of patients to receive the additional treatments plus conventional treatment, or the conventional treatment only was done by simple random sampling.

The study was approved from the local ethical committee and informed written consents were obtained from all subjects included in this study. Forms of the approval and the consent are included later.

Diagnosis of organophosphorus poisoning was made on the basis of history and clinical manifestations. Five common clinical manifestations of OP poisoning have been selected as parameters (miosis, increased secretions, diaphoresis, bronchospasm, bradycardia) each to be assessed on a 3 point scale varying from 0-2. Poisoning can then be graded as mild (score 0-3), moderate (score 4-7) or severe (score 8-11) whit the patient first presentation. Increased secretions include salivation, lacrimation, urination, diarrhea and vomiting [10].

Other manifestations include smell of pesticides or solvents, and reduced butyrylcholinesterase or acetylcholinesterase activity in the blood [10].

Patients with severe organophosphorus poisoning show reduced consciousness and poor respiration. The major differential diagnosis is carbamate poisoning, which is clinically indistinguishable [11].

Many organophosphorus pesticides are more potent inhibitors of butyrylcholinesterase than they are of acetylcholinesterase. So, butyrylcholinesterase assays can be used to detect exposure to an organophosphorus or carbamate pesticide [10].

Treatment of cases after exposure includes resuscitation of patients and giving oxygen, a muscarinic antagonist; atropine in a dose of 0.01-0.03 mg/kg, fluid therapy in the form of normal saline 0.9% in a dose of 10-20 ml/kg, and an acetylcholinesterase reactivator (an oxime that dephosphorylate acetylcholinesterase rendering the enzyme active again). The oxime; Toxogonin is given in a dose of 3-7 mg/kg. This continued for 24 h and better to be done in an intensive care unit (ICU). Respiratory support is given as necessary. The patient is usually vomiting, so gastric decontamination is not needed. If it will be done, it should be considered only after the patient has been fully resuscitated and stabilized. Continuous observation is mandatory, adjustment of atropine and oxime needs should be done. Worsening respiratory function because of intermediate syndrome, and recurrent cholinergic manifestations may occur with fat-soluble organophosphorus [12].

The patients were monitored in intensive care unit (ICU) and compared for clinical status and routine laboratory tests including Arterial blood gases (ABG) and serum electrolytes. Blood samples were withdrawn by simple venipuncture at the time of arrival of the patient and 24 hours after beginning treatment for assay of MDA and GPx.

Materials

Drugs: the following drugs were used.

1- N-acetylcysteine: "Acetylcysteine sachets" each contains 200 mg acetylcysteine. It is produced by Sedico pharmaceutical Company, 6th October City, Egypt.

2- $NaHCO_3$: Egypt Otsuka pharmaceutical Co., SAE. Ampoules of 25 ml, 8.4% Sodium bicarbonate for intravenous infusion.

Kits:

1- Malondialdehyde was assayed by kits purchased from Bio-diagnostic Chemical Co., Egypt (Cat. No. MD 2529), using spectrophotometer (Model Metrolab 1600 DR, Serial Number 071216D39, Argintine) with wavelength adjusted at 534 nm.

2- Glutathione peroxidase (GPx) was assayed by kits purchased from Biodiagnostic Chemical Co., Egypt (Cat. No. GP 2524), using spectrophotometer (Model Slim, Serial Number 327288, Italy) with wavelength adjusted at 340 nm.

3- Butyrylcholinesterase assay kits of Sigma Aldrich (Cat. No. C1057).

Methods: Blood samples of 2 ml were withdrawn from the patients by simple venipuncture under sterile conditions. The serum was separated by centrifuging the blood sample at 3000 rpm for 5 min. Following which the serum MDA was measured using the method of Walker and Shah [13].

Glutathione peroxidase was measured by Spectrophotometer (Model Slim, Serial Number 327288, Italy) with wavelength adjusted at 340 nm. While buturylcholinesterase was measured by spectrophotometric assay of BChE titrimetrically in a 50.4 ml reaction mixture containing 4 mM butyrylcholine, 1, 600 mM $MgCl_2$, 100 mM NaCl, and 30–60 units BChE at pH 8 and 37°C.

Statistical analysis

Data was tabulated, coded then analyzed using the computer program SPSS (Statistical package for social science) version 17.0. Descriptive statistics were calculated in the form of mean ± standard deviation (SD) and Median, IQR (interquartile range). In the statistical comparison between the different groups, the significance of difference was tested using one of the following tests:

Student's t-test (Unpaired): Used to compare between mean of two different groups of numerical (parametric) data.

Mann Whitney U test: Used to compare between two different groups of numerical (non-parametric) data.

Student's t-test (Paired): Used to compare between mean of two related groups of numerical (parametric) data.

Wilcoxon signed rank test: Used to compare between two related groups of numerical (non-parametric) data.

Spearman correlation coefficient test was used correlating different parameters. A P-value<0.05 was considered statistically significant.

Results

Table 1 represents socio- demographic data & circumstances of poisoning in the cases of the study and the control groups.

	Control group (n=70)	Treated group (n=70)	P-value
Age			
≤ 25 yr. n. (%)	22 (31.43%)	24 (34.29%)	0.56
>25 yr. n. (%)	48 (68.57%)	46 (65.71%)	
Residence			
Rural n. (%)	38 (54.29%)	39 (55.71%)	0.98
Urban n. (%)	32 (45.71%)	31 (44.29%)	
Gender			
Male n. (%)	35 (50.00%)	37 (52.86%)	0.99
Female n. (%)	35 (50.00%)	33 (47.14%)	
Occupation			
Farmer n. (%)	37 (52.86%)	35 (50.00%)	0.25
Non-farmer n. (%)	33 (47.14%)	35 (50.00%)	
Mode of Poisoning			
Intentional n. (%)	29 (41.43%)	27 (38.57%)	0.89
Accidental n. (%)	22 (31.43%)	22 (31.43%)	
Occupational n. (%)	19 (27.14%)	21 (30.00%)	
Route of Exposure			
Ingestion n. (%)	27 (38.57%)	24 (34.29%)	0.91
Inhalation n. (%)	30 (42.86%)	30 (42.86%)	
Dermal contact n. (%)	13 (18.57%)	16 (22.86%)	
Severity of Toxicity			
Mild	24 (34.29%)	18 (25.71%)	0.78
Moderate	24 (34.29%)	28 (40.00%)	
Severe	22 (31.42%)	24 (34.29%)	

Table 1: Socio- demographic data & Circumstances of Poisoning in the Cases of the Study and the Control groups.

Table 2 represents the values of serum MDA, GPx, pH and LOS in the two groups of the study on presentation and after 24 h of treatment and observation.

	Control group			Treated group			P-value
	Median	Percentile 25	Percentile 75	Median	Percentile 25	Percentile 75	
MDA-On Presentation	6.15	5.08	8.11	6.11	4.22	8.15	0.66
MDA-After 24 h	12.78	10.75	15.54	3.09	2.14	3.56	<0.001
Serum GPx-On Presentation	7503.83	6248.4	8596.07	7258.36	5621.4	8321.7	0.67
Serum GPx-After 24 h	7593.09	7258.36	9265.47	8745.95	6640.2	10254.33	0.004
pH-On Presentation	7.3	7.23	7.33	7.3	7.25	7.33	0.96
pH-After 24 h	7.34	7.33	7.34	7.44	7.43	7.45	<0.001
LOS	48	36	54	24	20	24	<0.001

Table 2: Serum MDA, GPx, pH and LOS in the two groups of the study on presentation and after 24 h of treatment and observation. MDA: Malondialdehyde, GPx: Glutathione peroxidase enzyme, LOS: Length of hospital stay, P: Probability, P-value significance when <0.05, Test used: Mann-Whitney U.

			Serum GPx-After 24 h	Plasma Butyrylcholinesterase-After 24 h	pH-After 24 h	LOS
Control group	MDA-After 24 h	r	-0.143	-.330-**	-.337-**	.665**
		P	0.237	0.005	0.004	0
	Serum GPx-After 24 h	r	1.000	0.052	-0.021	-.239-*
		P		0.668	0.862	0.047
	Plasma Butyrylcholinesterase-After 24 h	r	0.052	1.000	0.214	-.243-*
		P	0.668		0.076	0.043
	pH-After 24 h	r	-0.021	0.214	1.000	-0.173
		P	0.862	0.076		0.151
Treated group	MDA-After 24 h	r	0.190	-.256-*	-.301-*	.669**
		P	0.116	0.033	0.011	0
	Serum GPx-After 24 h	r	1.000	-.276-*	-.239-*	.301*
		P		0.021	0.047	0.011
	Plasma Butyrylcholinesterase-After 24 h	r	-.276-*	1.000	.248*	-.291-*
		P	0.021		0.039	0.014
	pH-After 24 h	r	-.239-*	.248*	1.000	-0.208
		P	0.047	0.039		0.084

Table 3: Correlation between different parameters in the two groups of the study after 24 h of treatment and observation. P: Probability, P significance when ≤ 0.05, r: Correlation, **Correlation is significant at the 0.01 level (2-tailed), *Correlation is significant at the 0.05 level (2-tailed).

Discussion

Organophosphorus poisoning is the cause of thousands of deaths and morbidity in all parts of the world particularly in developing countries. The case-fatality ratio for pesticide poisoning is around 10-20% even when the standard antidotes (atropine, oximes and benzodiazepines) is given. Oxygen and artificial ventilation may be needed. Due to the wide range of toxic effects, patients may require extra modalities of treatment, in addition to the poison-directed antidote therapy. There is shortage in verifying new treatments for organophosphorus poisoning [5].

Improved medical management of organophosphorus poisoning should result in a reduction in worldwide deaths from such an exposure [10].

In this study, N-acetyl cysteine and sodium bicarbonate were tried for treatment of acute organophosphorus-poisoned patients together with the classic antidote regimen. This was compared with a matched group of patients who were treated with the classic antidote regimen only without these additional therapies. Diagnosis of cases was based on history, clinical manifestations and laboratory investigations of reduced serum cholinesterase levels of 50% or less than average range of the enzyme. The patients were observed for 24 h and clinical and laboratory outcomes were recorded.

	Control group		Treated group		P-value
Plasma Butyrylcholinesterase	Mean	± SD	Mean	± SD	
On Presentation	2565.29	840.45	2628.12	899.08	0.67
After 24 h	3207.44	802.82	5147.7	1245.64	<0.001

Table 4: Plasma Butyrylcholinesterase in the two groups of the study on presentation and after 24 h. P: Probability, P-value significance when<0.05, Test used: Student's test (Unpaired).

There was found no significant difference between the two groups in the levels of serum MDA, GPx and pH at the time of presentation (Table 1). Also, there was no significant difference in plasma Butyrylcholinesterase was 50% or more, less than normal in both groups at the time of patient presentation and there was no significant difference between them (Table 2).

The differences between the two groups of the study in all of the above parameters were returned highly significant 24 h after treatment (Tables 1 and 2).

These results go with Shadnia et al. [14] who tried NAC in oroganphosphate-poisoned patients and found that the need to

atropine but not pralidoxime was reduced in NAC group. The investigators explained the findings by the role of NAC in reduction of organophosphate-induced oxidative stress. The investigators also found that the duration of hospitalization was reduced in the NAC group. The authors recommended NAC to be added to current treatment protocol of acute OPs poisoning [14].

Yurumez et al. [15] had tried NAC in mice administered with an acute high dose of fenthion poisoning and found clear improvement of survival rates in NAC-supplemented group. The investogators measured MDA and GPx in all mice and found significant improvement in NAC-supplemented group, also. The authors concluded that NAC has not only prophylactic but also therapeutic activity in fenthion poisoning and recommended to do researches to explore the exact mechanism of NAC protective effect in organophosphate poisoning [15].

Abdollahi and Karami-Mohajeri [16] believed that oxidative stress could be an important component of the mechanism of organophosphate (OP) compounds toxicity [16].

Buckley et al. [17] highlighted the need for new remedies like sodium bicarbonate for pesticide poisoning. They believed also that the response the public health and research perspectives towards this poisoning is inadequate, as pesticides poisoning is the cause of many fatalities and deaths in many parts of the world [17].

Roberts et al. [18] believed that plasma alkalinization would be beneficial in treatment of acute organophosphorus poisoning, but recommended to describe the dose and regimen by doing further research in this respect [18].

Husain et al. [19] believed also in the therapeutic/prophylactic value of sodium bicarbonate for the treatment of organophosphate poisoning and decreasing its complications like the OPIDN (Organophosphorus-induced delayed neuropathy) [19].

Table 3 showed that there were no significant correlation between the measured parameters in the control group after 24 h, while in the treated group, there were found highly significant and significant correlation between serum MDA, GPx and pH when with length of hospital stay (LOS). There was also a significant correlation between the level of plasma butyrylcholinesterase in the treated group and the LOS (Table 4).

All of these results suggest the great correlation between oxidative stress and the mechanism and outcome of organophosphorus poisoning.

These findings go with Eddleston and Chowdhury [7] who stated that antioxidants and sodium bicarbonate are amongst the many affordable pharmacologic products that can greatly improve the distressing organophosphate toxicity. The authors recommended many clinical trials to be conducted, so helpful agents can be licensed for routine clinical use in the settings of organophosphate poisoning [7].

Recommendations and Take-home Message

Organophosphorus poisoning constitutes a major clinical and public health problem across the developing world.

The clinical care of patients with organophosphorus (OP) insecticide poisoning has little improved over the last six decades.

N-acetyl cysteine and sodium bicarbonate proved to be effective in improving the outcome of cases of OPP and in decreasing the length of hospital stay of these patients, with no major adverse effects of these medications.

Larger randomised controlled trials should be made, so affordable and already licensed antidotes may find their place in routine clinical care.

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