
# International Journal of Pharmacology

ISSN 1811-7775

science alert

ansinet
Asian Network for Scientific Information

International Journal of Pharmacology 7 (6): 732-735, 2011
ISSN 1811-7775 / DOI: 10.3923/ijp.2011.732.735


# N-acetylcysteine a Novel Treatment for Acute Human Organophosphate Poisoning

[1]S. Shadnia, [1]S. Ashrafivand, [2]S. Mostafalou and [2]M. Abdollahi
[1]Department of Clinical Toxicology, Loghman Hakim Hospital Poison Center,
Faculty of Medicine and Toxicological Research Center,
Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2]Faculty of Pharmacy and Pharmaceutical Sciences Research Center,
Tehran University of Medical Sciences, Tehran, Iran

**Abstract:** Since oxidative stress markers are increased in Organophosphates (OPs) toxicity, the efficacy of the antioxidant N-acetyl-L-cysteine (NAC) as an adjunct therapy to atropine and pralidoxime for acute OPs toxicity was evaluated. Twenty-four adult subjects with acute OP toxicity were included in a randomized single blind controlled trial on the use of intravenous NAC. Among included subjects, twelve were randomized to receive NAC and the rest did not receive NAC. The results showed that the needing to atropine but not pralidoxime was reduced in NAC group. The duration of hospitalization was reduced in the NAC group. Addition of NAC to current treatment protocol of acute OPs poisoning is recommended.

**Key words:** Organophosphate, N-acetyl cysteine, poisoning

## INTRODUCTION

Organophosphate (OP) compounds are cholinesterase inhibiting chemicals used mainly as pesticides and nerve agents. They are the most widely used pesticides today and the most common cause of pesticide poisoning than any other chemical class of pesticides in Iran (Shadnia *et al*., 2007a). It is estimated that the incidence of pesticide poisonings in developing countries has doubled during the last decade of nineteenth century (WHO, 1997), so that OPs have been reported as the third most common cause of poisoning and one of the principal causes of poisoning-related mortality in Iran (Shadnia *et al*., 2007a; Moghadamnia and Abdollahi, 2002).

Their main mechanism of toxicity is inhibition of Acetylcholinesterase (AChE) resulting in an accumulation of the neurotransmitter acetylcholine and the continued stimulation of acetylcholine receptors. Thus, the goal of treatment of OP toxicity is to block the cholinergic stimulation that is usually achieved by administration of high doses of atropine and the use of oximes as an enzyme reactivator. Imbalance of the other neurotransmitters including Gama Amino Butyric Acid (GABA) or catecholamines are involved in OP poisoning (Gupta, 2006). Among all pathogenic elements, oxidative stress has been under attention of many studies in the recent years (Abdollahi *et al*., 2004; Soltaninejad and Abdollahi, 2009; Soltaninejad *et al*., 2007; Teimouri *et al*., 2006).

Glutathione (GSH) as a ubiquitous thiol-containing tripeptide is involved in numerous processes which are essential for normal biological functions, such as detoxification of electrophilic xenobiotics and free-radical scavenging. Considering induction of oxidative stress by OPs, several studies proposed that a drug like N-acetyl-L-cysteine (NAC) which could increase the GSH content and act as a reductant, would improve the tolerance to OP toxicity (Pena-Llopis *et al*., 2003a, b). Our previous study indicated that administration of NAC in rats with subchronic exposure to diazinon has beneficial effects in reactivation of AChE and reversal of oxidative stress biomarkers (Shadnia *et al*., 2007a). Also, since respiratory failure is one of the common demonstrations of OPs poisoning and regarding known efficacy of NAC and other antioxidants in management of lung disorders, we expected to see positive effects of NAC in OP poisoning (Mousavi *et al*., 2010; Soltan-Sharifi *et al*., 2007). Thus in the present study, we aimed to examine how administration of NAC as an adjunctive may decrease toxicity of OP in intoxicated patients.

## MATERIALS AND METHODS

This study was a randomized single blind clinical trial which was conducted in the Intensive Care Unit (ICU) of Loghman Hakim Hospital Poison Centre (LHHPC) over a 12-month period.

Adult patients (≥12 y/o) with confirmed acute OP toxicity and no history of diabetes, cardiovascular,

**Corresponding Author:** Mohammad Abdollahi, Faculty of Pharmacy and Pharmaceutical Sciences Research Center, Tehran University of Medical Sciences, Tehran, Iran

respiratory, renal and hepatic failure and no advanced medical management for OP poisoning in any medical centre before admission in LHHPC were recruited in the study. A written informed consent obtained from their attending relative. Establishment of the diagnosis in all cases was based on the history of exposure, clinical manifestations and other circumstantial evidence such as availability of a poison bottle or a label found by the relatives that brought to hospital. Plasma Cholinesterase (PChE) level was used to confirm the acute exposure to OPs and as a measure of severity of poisoning on admission.

On admission, a full history and examination were carried out. Venous blood samples were obtained for full biochemistry analyses. Patients were randomly assigned (1 to 1 patient) to either NAC as adjunctive treatment to parenteral atropine and pralidoxime or control to receive the routine treatment for acute OP toxicity which consists of parenteral administration of atropine and pralidoxime.

NAC was obtained as 10 mL ampoules containing 20% w/v NAC from hospital pharmacy. NAC was given by intravenous (iv) infusion at a dose of 140 mg $kg^{-1}$ as a loading dose and then followed by 70 mg/kg/4 h for 17 doses, as the safety of this regimen of NAC therapy has been proven in the acute and or complicated acetaminophen poisoning (Pajoumand *et al*., 2003).

Atropine and pralidoxime were administered as standard protocols (Aaron, 2007). All the patients received gastric decontamination and supportive and conservative treatments by the same medical personnel of ICU. The patients were followed until discharge from the hospital or death.

The patients' information including gender, age, therapeutic interventions, laboratory tests and PChE and outcome from the medical records were collected. Data were kept confidential in all stages of the study. A detailed multiple variable database was formed and data were analyzed with StatsDirect software and expressed as Mean±SD for numerical or as frequency for categorical variables. Chi-Square test was used for statistical comparison of qualitative variables. The normal distribution of quantitative variables was tested by Kolmogorov-Smirnov test. The statistical comparison was done with Mann-Whitney U-test for nonparametric variables and independent student t-test for parametric variables. The p-values of 0.05 or less were considered to be statistically significant. Primary outcome measures were: the extent of needing to atropine and pralidoxime. Secondary outcome measures included duration of hospitalization and mortality rate. The protocol of the study was approved by the Regional Ethics Committee.

## RESULTS

During the study period, 24 patients with acute OP toxicity (15 men, 9 women), with the mean age of 31.1±15.8 years (median 28 years, range 14-90 years) were studied. Of these, 12 patients were randomized to receive NAC beside routine treatments and 12 received just routine treatments without NAC. There was no difference between 2 groups regarding age and sex of the patients (Table 1). In all of the patients, the cause of acute poisoning was intentional oral ingestion of OPs. There was no statistical difference between the mean of PChE level (KU $L^{-1}$) in treatment (326.5±101.3) and control (340.3±92) groups on admission time. The levels of activity of PChE were in the normal range on the time of discharge in both groups (Table 1). The duration of hospitalization in treatment and control groups were 2.7±1.1 and 5.3±2.2 days, respectively (p = 0.003, Table 1). NAC treatment decreased duration of hospitalization to 50.9% of control group. The mean of atropine dose per day of hospitalization was 9.1±7.2 and 38.9±28.8 mg in treatment and control groups, respectively (p = 0.002). Treatment with NAC decreased the rate of atropine needing to 23.4% of control group. Although, no significant difference was observed between the total doses of pralidoxime that was administered in 2 groups (p = 0.81) (Table 1).

Table 1: Demographic and outcome measures of patients received or not received NAC

| Parameters | All patient (n = 24) | Treatment group (n = 12) | Control group (n = 12) | p-value |
|---|---|---|---|---|
| | Mean±SD (Range) | | | |
| Age (Year) | 32.1±15.8 (14-90) | 27.6±11.8 (15-52) | 34.6±18.8 (14-90) | 0.16 |
| Sex | | | | |
| Male | 15.0 | 7.0 | 8.0 | 1.00 |
| Female | 9.0 | 5.0 | 4.0 | |
| Plasma cholinesterase activity (normal = 1900-3500 KU $L^{-1}$) | 333.4±94.9 (135-540) | 326.5±101.3 (211-540) | 340.3±92 (135-475) | 0.73 |
| Mean daily dose of atropine (mg) | 24.0±25.6 (2-96) | 9.1±7.2* (2-28) | 38.9±28.8 (4-96) | 0.002 |
| Total dose of pralidoxime (g) | 9.2±4.8 (2-20) | 8.9±4.5 (2-16) | 9.4±5.3 (2-20) | 0.81 |
| Duration of hospitalization (day) | 4.0±2.2 (1-9) | 2.7±1.1* (1-5) | 5.3±2.2 (2-9) | 0.003 |
| Outcome | | | | |
| Survived | 19.0 | 11.0 | 8.0 | 0.32 |
| Non-survived | 5.0 | 1.0 | 4.0 | |

Data are Mean±SD. *The difference between treatment and control groups is statistically significant

The mortality rate was 20.8% (5 of 24 cases), with 1 fatal case in the treatment group and 4 fatal cases in the control group. Although, treatment with NAC caused a decrease in the rate of mortality but it was not statistically significant ($p = 0.32$) (Table 1).

## DISCUSSION

This study evaluated the effects of NAC as an adjunct therapy to atropine and pralidoxime for the treatment of acute OPs toxicity. The results indicate that NAC has beneficial effects in the treatment of acute OPs toxicity evidenced by reduction in the mean atropine dose per day and duration of hospitalization. This is supported by our recent animal study which indicated benefit of NAC in diazinon-induced toxicity (Shadnia *et al*., 2007b).

Regarding the potential of OPs in inhibition of carboxylic ester hydrolases within the body, the most prominent clinical manifestations in acute and or chronic toxicity result from the inhibition of ChE (Aaron, 2007; Pajoumand *et al*., 2004; Shadnia *et al*., 2009) but oxidative stress is another main mechanism of action of OPs that leads to depletion of antioxidant reservoirs and also ChE inhibition (Shadnia *et al*., 2005; Soltaninejad and Abdollahi, 2009) and can be cause of further consequences like hyperglycemia (Rahimi and Abdollahi, 2007). Therefore, NAC by increasing intracellular glutathione levels and direct scavenging of reactive oxygen species causes its benefit. In explanation of cellular mechanisms, it is known that muscarinic acetylcholine receptors regulate cellular responses through calcium release from intracellular stores and thus accumulation of the neurotransmitter acetylcholine and continued stimulation of muscarinic receptors may result in metabolic calcium disorders. Intracellular hypercalcemia may facilitate formation of oxidative stress, which may inactivate the thiol-dependent calcium pump, which in turn, aggravates the hypercalcemia (Karami-Mohajeri and Abdollahi, 2010). Therefore, NAC likely by reducing oxidative stress ameliorates the signaling pathways related to muscarinic receptors and thus decreases the needing to atropine.

As shown in the present study, NAC had no effect on the total amount of pralidoxoime. This can be explained by the fact that in intoxicated patients on admission time, their PChE were already scavenged by the OPs and some were inhibited irreversibly.

Considering the high mortality rate and high expenses of admission in hospitals in OP-intoxicated cases in one hand (Abdollahi *et al*., 1999) and the low price and availability of NAC (Nikfar *et al*., 2011) as well as its remedial effects in improvement of OPs toxicity on the other hand, it can be concluded that adding NAC to current treatment protocol of acute OP toxicity in human may confer benefit in management of OP poisoning. Of course, small sample size was an inevitable limitation of this study and thus performing a multicentre randomized clinical trial to evaluate the exact role of this novel treatment in larger group of patients is recommended.

## ACKNOWLEDGMENT

This study was supported by a grant from Toxicological Research Center of Shahid Beheshti University of Medical Sciences. The Authors wish to thank nurses of ICU of Loghman Hakim Hospital Poison Center, especially Mrs. S. Bana-Jafari, Mrs. M. Rezvani and Mrs. B. Barari for their assistances.

## REFERENCES

Aaron, C.K., 2007. Organophosphates and Carbamates. In: Haddad and Winchester's Clinical Management of Poisoning and Drug Overdose, Shannon, M.W., S.W. Borron and M.J. Burns (Eds.), Saunders-Elsevier, Philadelphia, USA., pp: 1171-1185.

Abdollahi, M., A. Ranjbar, S. Shadnia, S. Nikfar and A. Rezaie, 2004. Pesticides and oxidative stress: A review. Med. Sci. Monit., 10: 141-147.

Abdollahi, M., N. Jalali, O. Sabzevari, S. Nikfar and M. Fallahpour, 1999. Pesticide poisoning during an 18 month period (1995-1997) in Tehran, Iran. Iranian J. Med. Sci., 24: 77-81.

Gupta, R.C., 2006. Toxicology of Organophosphates and Carbamate Compounds. 5th Edn., Elsevier Academic Press, Boston; Amsterdam. Chapter 30, ISBN: 0120885239 9780120885237, pp: 411-422.

Karami-Mohajeri, S. and M. Abdollahi, 2010. Toxic influence of organophosphate, carbamate and organochlorine pesticides on cellular metabolism of lipids, proteins and carbohydrates: A systematic review. Hum. Exp. Toxicol., 30: 1119-1140.

Moghadamnia, A.A. and M. Abdollahi, 2002. An epidemiological study of acute poisonings in northern Islamic Republic of Iran. Eastern Mediterr. Health J., 8: 88-94.

Mousavi, S., M. Mojtahedzadeh and M. Abdollahi, 2010. Place of iron chelators like desferrioxamine and deferasirox in management of hyperoxia-induced lung injury: A systematic review. Int. J. Pharmacol., 6: 326-337.

Nikfar, S., M. Khatibi, A. Abdollahi-Asl and M. Abdollahi, 2011. Cost and utilization study of antidotes: An Iranian experience. Int. J. Pharmacol., 7: 46-49.

Pajoumand, A., N. Jalali, M. Abdollahi, S. Shadnia, 2003. Successful treatment of acetaminophen overdose associated with hepatic failure. Hum. Exp. Toxicol., 22: 453-458.

Pajoumand, A., S. Shadnia, A. Rezaie, M. Abdi and M. Abdollahi, 2004. Benefits of magnesium sulfate in the management of acute human poisoning by organophosphorus insecticides. Hum. Exp. Toxicol., 23: 565-569.

Pena-Llopis, S., M.D. Ferrando and J.B. Pena, 2003a. Fish tolerance to organophosphate induced oxidative stress is dependent on the glutathione metabolism and enhanced by N-acetylcysteine. Aquat. Toxicol., 65: 337-360.

Pena-Llopis, S., M.D. Ferrando and J.B. Pena, 2003b. Increased recovery of brain acetylcholinesterase activity in dichlorvos-intoxicated European eels *Anguilla anguilla* by bath treatment with N-acetylcysteine. Dis. Aquat. Organ., 55: 237-245.

Rahimi, R. and M. Abdollahi, 2007. A review on the mechanisms involved in hyperglycemia induced by organophosphorus pesticides. Esticide Biochem. Physiol., 88: 115-121.

Shadnia, S., A. Okazi, N. Akhlaghi, G. Sasanian and M. Abdollahi, 2009. Prognostic value of long QT interval in acute and severe organophosphate poisoning. J. Med. Toxicol., 5: 196-199.

Shadnia, S., E. Azizi, R. Hosseini, S. Khoei and S. Fouladdel *et al*., 2005. Evaluation of oxidative stress and genotoxicity in organophosphorus insecticide formulators. Hum. Exp. Toxicol., 24: 439-445.

Shadnia, S., H. Esmaily, G. Sasanian, A. Pajoumand, H. Hassanian-Moghaddam and M. Abdollahi, 2007a. Pattern of acute poisoning in Tehran-Iran in 2003. Hum. Exp. Toxicol., 26: 753-756.

Shadnia, S., M. Dasgar, S. Taghikhani, A. Mohammadirad, R. Khorasani and M. Abdollahi, 2007b. Protective effects of alpha-tocopherol and N-acetyl-cysteine on diazinon-induced oxidative stress and acetylcholinesterase inhibition in rats. Toxicol. Mechanisms Methods, 17: 109-115.

Soltan-Sharifi, M.S., M. Mojtahedzadeh, A. Najafi, M.R. Khajavi and M.R. Rouini *et al*., 2007. Improvement by N-acetylcysteine of acute respiratory distress syndrome through increasing intracellular glutathione and extracellular thiol molecules and antioxidant power: Evidence for underlying toxicological mechanisms. Hum. Exp. 26: 697-703.

Soltaninejad, K. and M. Abdollahi, 2009. Current opinion on the science of organophosphate pesticides and toxic stress: A systematic review. Med. Sci. Monit., 15: RA75-90.

Soltaninejad, K., S. Shadnia, M. Afkhami-Taghipour, R. Saljooghi, A. Mohammadirad and M. Abdollahi, 2007. Blood β-glucuronidase as a suitable biomarker at acute exposure of severe organophosphorus poisoning in human. Hum. Exp. Toxicol., 26: 963-966.

Teimouri, F., N. Amirkabirian, H. Esmaily, A. Mohammadirad, A. Aliahmadi and M. Abdollahi, 2006. Alteration of hepatic cells glucose metabolism as a non-cholinergic detoxication mechanism in counteracting diazinon-induced oxidative stress. Hum. Exp. Toxicol., 25: 697-703.

WHO, 1997. Guidelines for poison control. World Health Organization, Geneva, pp: 3-10.