

## پیشرفت‌های اخیر در درمان مسمومیت با حشره‌کش‌های فسفردار آلی

مهدی بلالی \*

### چکیده:

سموم فسفردار آلی به میزان وسیعی در دفع آفات نباتی و هم به عنوان عوامل اعصاب در جنگ‌های شیمیایی مورد استعمال قرار گرفته‌اند. حشره‌کش‌های فسفردار بطور فراوان وارد کشور شده و متأسفانه اغلب بدون کنترل در دسترس افراد قرار می‌گیرند. بهمین دلیل مسمومیت حاد با این سموم بویژه نوع عمدی بسیار شایع بوده به نحوی که ۲۵۰ نفر (۲۱/۸٪) از مسمومین بستری بیمارستان امام رضا (ع) مشهد را در سال ۱۳۷۳ شامل گردیده‌است.

سموم فسفردار آلی با مهار آنزیم کولین استراز موجب وقفه هیدرولیزاستیل کولین و در نتیجه احتباس این ماده در پایانه‌های عصبی می‌گردد که این خود باعث تحریک گیرنده‌های موسکارینی و نیکوتینی می‌شود. آثار تحریک گیرنده‌های موسکارینی با سولفات آتروپین و تحریک گیرنده‌های نیکوتینی با اکسیم‌ها مانند پرایدوکسیم و ابیدوکسیم درمان می‌شود. با وجود تجویز و نوع پادزهر یادشده مرگ و میر ناشی از سموم فسفردار آلی نسبتاً زیاد (حدود ۱۰٪) گزارش شده‌است.

در مورد اثر درمانی سولفات آتروپین در مسمومیت با سموم فسفردار آلی از قدیم اتفاق نظر وجود داشته‌است اما در خصوص میزان و نحوه تجویز این پادزهر از اوائل دهه هشتاد میلادی با توجه به تجربیات درمان مسمومین مشهد و تأیید آن از سوی جامعه علمی بین‌المللی با تزریق مقادیر زیاد آتروپین تا حد مسمومیت خفیف از میزان مرگ و میر سموم فسفردار آلی کاسته شده‌است.

اکسیم‌ها به عنوان فعال‌کننده آنزیم کولین استرازو کنترل آثار نیکوتینی مسمومیت با حشره‌کش‌های فسفردار آلی مورد استفاده واقع شده‌اند. تجربیات بالینی در درمان مسمومیت با حشره‌کش‌های فسفردار آلی مسمومین مشهد و گزارش محققین از سری لانکا (مجله لانست شماره ۳۳۹ سال ۱۹۹۲) مؤید عدم تأثیر اکسیم‌ها در سیر بهبودی این مسمومیت می‌باشد. پرونده بالینی ۳۱۷ بیمار مسموم با حشره‌کش‌های فسفردار آلی که طی سالهای ۷۳-۱۳۷۱ در بخش مسمومین بستری شده بودند مورد مطالعه قرار گرفت. در بیمارانی که اکسیم دریافت کرده بودند یک وابستگی مثبت و معنی‌داری بین مقدار این دارو و طول دوره بستری ( $P < 0/001$   $r = 0/625$ ) و میزان مرگ و میر ( $P < 0/01$ ) مشاهده گردید. این نتایج نشانگر اثرات سوء و عدم تأثیر درمانی اکسیم‌ها در درمان مسمومیت حشره‌کش‌های فسفردار آلی می‌باشد. تأیید نهائی این نتایج مستلزم انجام یک تحقیق آینده‌نگر کنترل شده بالینی می‌باشد که خوشبختانه در دست انجام است.

۲- ترکیب اورگانو فسفات  
۴- اکسیم

کلید واژه‌ها: ۱- مسمومیت با آفت‌آکش  
۳- استیل کولینستراز

\* بخش مسمومین بیمارستان امام رضا (ع) - دانشگاه علوم پزشکی مشهد

# RECENT ADVANCES IN TREATMENT OF OP PESTICIDE POISONING

M.Balali-Mood\*

M.Shariat

## ABSTRACT

*Organophosphate (OP) compounds have largely been used as pesticides and also as nerve agents in Chemical Wars. OP pesticides have frequently been imported and freely available to the public without usage control. Therefore, OP poisoning, mainly intentional type, is very common; and accounts for 21.8% (250 patients) of the total admission to the hospital between 21 March 1994 and 20 March 1995.*

*OP compounds induce accumulation of acetyl choline by inhibition of acetyl cholinesterase leading to the stimulation of muscarinic and nicotinic receptors. Muscarinic effects are counteracted successfully by atropine sulfate, but the therapeutic effects of oximes on nicotinic receptors and cholinesterase reactivation have not been observed in clinical practice. Clinical observations of the author and a report from Sri Lanka (Lancet 339,1992), indicates no therapeutic effects of oximes in OP poisoning. Case notes of 317 Treatment Centres between 21 March 1993 and 20 March 1995 were studied.*

*There were significant positive correlations between the oxime doses and either hospitalization days ( $r=0.625$ ,  $p<0.001$ ) or mortality rate ( $=0.718$ ,  $p<0.01$ ).*

*It seems that oximes had no therapeutic effects on OP pesticide poisoning. However, a prospective investigation is currently undertaken to confirm this hypothesis.*

**Key Words:** 1) Pesticide Poisoning                      3) Acetylcholinesterase  
2) Organophosphate (OP) compound      4) Oxime

---

\* Poisons Treatment Centre, Imam Reza Hospital, Mashhad University of Medical Sciences, Mashhad, I.R.Iran

## INTRODUCTION

Organophosphates (OP) have been used mainly as pesticides and also as nerve agents in chemical wars. OP pesticides have been imported, distributed and used in this country without proper control. Therefore, poisoning particularly suicidal attempts with these chemicals are very common and accounted for 250 (21/8%) admissions to the Poisons Treatment Centre and 25 (38%) deaths in the year of 1994.

Op inhibits cholinesterase enzyme and thus acetylcholine accumulates at nerve ending and stimulates muscarinic and nicotinic receptors. Muscarinic stimulation is reduced by atropine sulphate. Oximes have been used for relief of nicotinic stimulation and cholinesterase reactivation<sup>(2)</sup>, but the mortality rate is still around 10%<sup>(3)</sup>. The effects of atropine sulphate have long been established, although the dosing regimens were different. Based on clinical experience, the proposed high doses of atropine by Mashhad Poisons Treatment Centre are now universally approved. The following mechanisms for oximes have been reported<sup>(4)</sup>:

1) Dissociation of phosphorylated binding of the enzyme and OP.

2) Direct attack of oxime at free molecule of OP.

3) Antimuscarinic effects

Based on clinical experience at Mashhad Poisons Treatment Centre and a report

from Sri Lanka<sup>(5)</sup>, oximes revealed no significant therapeutic effects on OP poisoning. Over the past few years, there has been shortage of oximes and thus most of the OP cases were treated by atropine alone. It was aimed to compare the cases treated by atropine with those who have received oxime as well. Therefore, the case notes of the OP patients who were treated at the centre between 21 March 1992 and 21 March 1995 were investigated.

## PATIENTS & METODS

Case notes of all patients with OP pesticide poisoning who were hospitalised for more than three days were reviewed. Relevant parameters such as age, sex, clinical features, serum cholinesterase activity (estimated spectrophotometrically using Behring kit), atropine and oxime doses, hospitalisation days and outcome of treatment were recorded. The data were processed by FoxPro program and analysed by Statistical Package for Social Sciences (SPSS). Comparisons were made by Student-t. Pearson and Chi-Square tests.

## RESULTS

A total of 317 case notes of OP poisoning including 114 males (36%) and 203 females (64%) with a mean $\pm$ SD age of 25 $\pm$ 14(1-80) years were reviewed. Apart from accidental cases in seven children (2.2%), the remainder were self-poisoning. the most

frequent age group was 16-20 years (107 cases) as shown in figure 1. Seasonal distribution revealed 32% in spring, 22% in summer, 25% in autumn and 21% in winter with no significant differences between them. Based on oxime therapy, 185(58%) patients were treated by atropine and oximes and 132 (24%) were treated by atropine alone. There were no age and sex differences between the two groups. Main clinical conditions on admission were pulmonary edema, coma and convulsions that were observed in 28, 28, and 16 patients of the oxime group compared with 16, 15 and 13 patients of the atropine alone group, respectively. There were no statistically significant differences between them.

Oximes were given as obidoxime (158 patients), pralidoxime (24 patients) and mixture of both (three patients) with a dose of 0.25 to 38g ( $3.5 \pm 4.2$ g) based on severity of poisoning (Fiurre 2). Atropine was given based on the severity of intoxication in the doses ranging from 16 to 4650 ( $314 \pm 567$ ) mg in the oxime group compared with 13 to 1685 ( $205 \pm 214$ ) mg in the group receiving atropine alone. The atropine dose difference between the two groups was significant ( $P < 0.05$ ).

Serum cholinesterase (SChE) activities of the patients were all lower than normal on admission and were less than 200U/L in 46% of the patients (Normal value  $> 2000$ U/L). There was a good relationship between the clinical severity and

reduction of SChE. Reactivations of the enzyme during treatment were different in each group as shown in figures 3 and 4. SChE reactivation was even quicker in the group receiving atropine alone compared to the oxime group, although the difference was not statistically significant (figure.5)

Hospitalization days in the oxime group were 4 to 19 ( $6.7 \pm 2.9$ ) days. There was a significant positive correlation between the hospitalisation days and oxime doses ( $r = 0.5149$ ,  $P < 0.001$ ) as shown in figure 6.

Mortality rate in the group of atropine alone was 6(4.5%), whereas in the oxime group was 15 (98.1%) patients. The mortality rate in the obidoxime subgroup was 12(7.6%) and in the pralidoxime subgroup was 3(13%) as shown in figure 7. However, there were no statistically significant differences between the groups. There was a small number of patients in the pralidoxime subgroup, thus, statistical analysis between the subgroups was not carried out.

## DISCUSSION & CONCLUSION

Since the clinical finding on admission of the oxime group was not significantly different from the group of atropine alone, thus the two groups were comparable clinically. However, atropine doses used in the oxime group were significantly higher than the group of atropine alone. It seems that first of all the oxime group patients were more severely intoxicated than the group of atropine alone, secondly the use of oximes

did not reduce the atropine doses as previously reported<sup>(4)</sup>. Similar hospitalisation days of the two groups suggest similar severity of intoxication. The significant positive correlation between the hospitalisation days and oximes particularly the obidoxime group may also have two different explanations: First, those patients who had received more obidoxime were more intoxicated. Second, the adverse effects of obidoxime have more morbidity and thus more hospitalisation days.

SChE reactivations were similar in both groups. It appears that oximes did not increase the reactivations previously reported<sup>(6,7,8)</sup>.

## REFERENCES

1) De Silva HJ, et al. Does Pralidoxime Affect Outcome of Management in Acute Organophosphate Poisoning, *Lancet*, 339:1136-8, 1992.

2) Ellenhorn MJ, Barceloux DG, Medical Toxicology, Elsevier, New York, pp 1070-78, 1988.

3) Gelman CR & Rumack BH (eds): DRUGDEX(R) Information System, MICROMEDEX, Inc., Dever, Colorado, Vol 75, 1993.

4) Haddad LM, Organophosphate and Other Insecticides, In: Clinical Management of Poisoning and Drug overdose, Haddad LM and Winchester JF(eds), W.B. Saunders Company, USA, pp 1080, 1990.

5) Jahnsen MK, Vale JA, Marrs TC &

The dose and duration of oxime therapy in Sri Lanka<sup>5</sup> Study were evaluated in sufficient by the European colleagues<sup>9</sup>. In the present study, we did not find any significant difference between the low and high doses of oximes.

Mortality rate was slightly higher in the oxime group than in the atropine alone. It can be concluded that oximes particularly obidoxime had no therapeutic effects on acute OP poisoning. However, a prospective double blind clinical trial is currently undertaken to investigate more carefully about the therapeutic effects of oxime in OP poisoning.

Meredith TJ, Pralidoxime for Organophosphorus Poisoning, *Lancet* 340: 64, 1992.

6) List of approved pesticides in Iran. Publication of Agriculture department, Tehran, 1994-1995.

7) Minton NA, Murray VSG, A Review of Organophosphate Poisoning, *Med Toxicol*, 3:350-75, 1988.

8) Rumack BH & Spoerke DG (eds): POISINDEX (R) Information System. MICROMEDEX, Inc., Denver, Colorado, Vol 75, 1993.

9) Thompson DF, Thompson GD, Greenwood RB, et al, Therapeutic dosing of Pralidoxime Chloride, *Drug Intell Clin Pharm*, Jul-Aug; 21(7-8): 590-3, 1987.