ISSN: 0975-8585

Research Journal of Pharmaceutical, Biological and Chemical Sciences

Demographics, Clinical Characteristics, Treatment and Outcomes of Acute Organo-Phosphorous Pesticide Poisoning From South India.

Puppala Geetika Krishna[1], Thunga Girish[1]*, Chekka Manasa[1] , Sudha Vidya Sagar[2], Sureshwar Pandey[3] , Vijayanaryana K[1], Sreedharan N[1], and Prasanna Kumar Shetty[1].

[1]Department of Pharmacy Practice, Manipal College of Pharmaceutical Sciences, Manipal University, Manipal- 576104, Karnataka, India.
[2]Department of General Medicine, Kasturba Hospital, Manipal University, Manipal-576104, Karnataka, India.
[3]Department of Pharmaceutics, School of Pharmacy, The University of West Indies, St.Augustine, Trinidad and Tobago.

ABSTRACT

Organophosphate poisoning is a major clinical problem causing 200,000 deaths annually. Case fatality of intentional-poisoning in developing countries is as high as 10-20%, due to the high toxicity of available pesticides, and lack of proper evidence for the use of standard treatments. This study is aimed to review the demographics, characteristics, treatment and outcomes of OP poisoning. Patients with clinical diagnosis of acute OP poisoning, admitted between February 2009 and November 2012 were followed prospectively. Chronic exposures of OP, unknown or mixed poisons were excluded. In 256 subjects, Mean age was 33.44 ± 13.55 years, Males constituted 53.5%. Maximum poisons belonged to WHO class I toxicity, most common was Methyl Parathion. Median pseudocholinesterase level was 290±1987 (median ± IQR). Severity at the time of admission was assessed using GCS: 12± 6 (median ± IQR), PSS: 2± 1 (median ± IQR) and APACHE-II scores: 17± 27 (median ± IQR). Higher the severity of poisoning lower was the cholinesterase level. 232 (91%) patients received gastric lavage. 62 (24.2%) received atropine and glycopyrrolate. 230 (89.8%) received pralidoxime. There was no significant effect of gastric lavage or charcoal administration on the outcome. Hospitalization duration was reduced in atropine and glycopyrrolate group compared to atropine alone.

Keywords: OP Poisoning, demographics, treatment, outcomes, pralidoxime, glycopyrrolate.

Corresponding author

ISSN: 0975-8585

INTRODUCTION

Organophosphates were introduced in 1854 and have been used extensively as pesticides, petroleum additives and warfare agents since then. Their toxicity was first reported in 1931[1]. OP poisoning has been a major challenging health problem worldwide. The global incidence of OP poisoning is estimated as 3,000,000 cases per year and the mortality as 200,000 a year. Almost 99% of these deaths occur in developing nations [2, 3]. Also, death due to intentional poisoning is more common than unintentional poisoning [4].

India being an agriculture dominant nation, use of pesticides and poisoning due to them is highly prevalent here. Most cases are reported from south or central India.The state of Andhra Pradesh reported the highest rate of pesticide poisoning in India [3]. The high fatality rate of OP poisoning in the developing countries could be due to the availability of highly toxic pesticides (WHO class I toxicity) [4]. Lack of hospital or transport facilities in the vicinity, reduced care-giver to patient ratio and unavailability of the antidote can also be the cause [5]. OP poisoning is the major cause of morbidity and mortality especially in patients admitted to the intensive care unit (ICU). In hospital based studies of India, mortality rates associated with pesticides have been reported to be as high as 50–70%. A study conducted in south India reported that OP poisoning accounted for 12% of ICU admission and 29% of total poisoning admissions [6]. This fatal situation might be due to delay in diagnosis or inefficient management. Key to efficient treatment is proper knowledge on the type of compound, presentation, and timely management of the poisoning.

The demographical component of the OP poisoning patients plays important role in the patient management. Even though several studies are available in the literature with respect to demographical details of OP poisoning patients, limited studies are available with respect to southern Indian population. Moreover, majority of the pesticides used in this region are either banned or not used in developed countries. Furthermore, there have not been any documented systematic studies on these compounds done previously in this locality. Epidemiological data plays an important role in the identification of target population affected and will also help in usage of this data in designing strategies both at the level of clinicians and hospital administrators for policy decisions. This section mainly focuses on the demographical details of OP poisoning patient including age, occupation, type of compound consumed and treatment with outcome.

Objectives

To study the demography, clinical characteristics, severity, treatment and outcomes of patients admitted for acute organophosphorus poisoning in a tertiary care hospital in South India.

METHODOLOGY

The study was designed to be prospective and observational. The approval for the study was obtained from the University Ethical Committee (UEC/26/2009). The inpatient files of 256 patients, admitted in the Emergency department of the hospital from February 2009-November 2012, with a clinical diagnosis of Acute Organophospharus Poisoning were reviewed prospectively. Patients admitted due to acute ingestion of carbamates, organochlorines, acetanilide derivatives or a mixture of the pesticides other than OP compounds; patients admitted with unknown poisoning; patients who had a history of chronic occupational exposure of OP poisoning and patients with history of mixed poisoning were excluded from the study.

Data was collected from the Medical records of the patients admitted to the emergency wards using specifically designed Case Record Form (CRF) which recorded the patients' demographic details like age, sex, and occupation, personal history, medical history, medication history, type of pesticide consumed, route of exposure, quantity of pesticide consumed, laboratory parameters, treatment chart, condition at discharge, number of ventilation days and number of hospitalization days. A suitably designed Informed Consent form prepared in English and translated to Kannada was used to obtain consent initially from patient's legally acceptable representative and then from patient after complete recovery. The CRF and Informed Consent Form was validated and checked for suitability and quality by physician. Adverse drug reaction (ADR) reporting form and ADR documentation form were also included to carry out the study. Severity of poisoning was assessed twice during hospital stay. First assessment was carried out at the time of admission with help of physician. Various scales like Glasgow coma scale (GCS Scale), Acute Physiology and Chronic Health Evaluation

Scale (APACHE scale), Poison Severity Scale (PSS scale) were employed in the assessment of severity. The second clinical status and severity assessment was done at the time of discharge.

For data analysis, Statistical Package for Social Sciences (SPSS) version 20.0 was used. Categorical data was presented as frequencies with percentages and was analyzed by Chi-square test. Continuous data was presented as Mean ± Standard deviation or median and inter quartile range (IQR). The difference in mean values of comparative groups was analyzed using chi square test. A p value less than or equal to 0.05 was considered to be statistically significant.

RESULTS

During the year June 2009 to December 2012, a total of 509 patients were admitted in the emergency ward for the management of acute OP poisoning. Among them 256 patients were enrolled for the study based on the inclusion criteria. All the patients were enrolled in the study after taking informed consent.

The mean age of the study population was found to be 33.44 ± 13.55 years and majority of them belonged to the age group of 21-30 years (n=97 (37.9%). Gender wise distribution showed that majority of them were males who constituted 53.5% of the study population. Majority of poisonings were intentional (97.7%). Severity of the subjects at the time of admission was assessed by using GCS (median ± IQR ,12(6)), PSS (median ± IQR ,2(1)) and APACHE-II scores (median ± IQR , 17(27)) in ICU as a baseline. Among the study population, 10.5% (n=27) of the patients were hypertensive, followed by 5.1% (n=13) of the patients who had both diabetes and hypertension. 2% (n=5) of the patients had only diabetes. Other details are mentioned in Table 1.

Table 1: Demographic characteristics of OP poisoning patients

Demographic Parameter	No. of patients (n = 256)
Mean age ± SD (in years)	33.44 ± 13.55
Gender Male Sex, n (%)	 44 (52.4%)
Social Habits Alcoholic, n (%) Smoking, n (%)	 124 (48.8%) 140 (54.68%)
Details of OP exposure Suicidal, n (%) Quantity of pesticide consumed (Median ± IQR) in mL Pre-Hospitalization Period (Median ± IQR) in hours	 250 (97.7%) 50 (67.5%) 2 (2%)
Severity Assessment Median GCS (IQR) Median APACHE-II Score (IQR) Median PSS (IQR)	 12 (6%) 17 (27%) 2 (1%)
Co-Morbid illness Hypertension, n (%) Diabetes, n (%) Hypertension and Diabetes, n (%)	 27 (10.5%) 5 (2%) 13 (5.1%)

Majority of admissions were due to consumption of WHO-class Ia (extremely hazardous chemical) type of OP pesticides. It accounted for 49.2% of the total admissions of OP poisoning. Other details are given in Table 2.

Table 2: Type of pesticide consumed (According to WHO classification of pesticides)

Type of pesticide consumed	No. of patients (n = 256)
Extremely hazardous	49.2%
Highly hazardous	14.3%
Moderately hazardous	32.9%
Slightly hazardous	2%
Unknown	1.6%

ISSN: 0975-8585

Among the different OP compounds consumed, methyl parathion contributes to 32.8% of the total OP admissions during the study period. Other details are mentioned in Table 3.

Table 3: List of different OP compounds consumed by the patients

OP compounds	No. of patients (n = 256)
Unknown	11 (4.3%)
Monocrotophos	24 (9.4%)
Clorpyrifos	66 (25.8%)
Methyl parathion	84 (32.8%)
Triazophos	8 (3.1%)
Parathion	7 (2.7%)
Quinalphos	20 (7.8%)
Phorate	7 (2.7%)
Edifenphos	5 (2.0%)
Malathion	7 (2.7%)
Dimethoate	9 (3.5%)
Fenthion	6 (2.3%)
Profenofos	1 (0.4%)
Ethion	1 (0.4%)

Among the study population majority of them were agriculturists [n=89 (34.8%)] followed by household [n= 57 (22.3%)]. Details are given in the Table 4.

Table 4: Comparison of occupation with incidence of OP poisoning

Occupation	No. of patients (%) N = 256
Agriculturist	89 (34.8%)
Household	57 (22.3%)
Student	20 (7.8%)
Business	49 (19.1%)
Labour	36 (14.1%)
Government employee	3 (1.2%)
Fisherman	2 (0.8%)

The clinical characteristics of OP poisoning patients mainly included miosis (n=240, (93.8%)) followed by bradycardia (n=167, (65.2%)) and fasciculation (n=126, (49.2%)). The median pseudo cholinesterase level for the study population was found to be 290±1987 (Median ± IQR) in IU. Other details are mentioned in Table 5.

Table 5: Clinical Characteristics of OP poisoning patients

Patient clinical characteristics	No. of patients (%) N = 256
Miosis	240 (93.8%)
Bradycardia	167 (65.2%)
Emesis	45 (17.57%)
Salivation	76 (29.8%)
Intermediate Syndrome	25 (9.7%)
Fasciculation	126 (49.2%)
Median Pseudo cholinesterase level ± IQR IU	290± 1987

Clinical Severity Indices

OP poisoned patients were categorized into 3 groups based on the Initial GCS score as mild (GCS 13-15), moderate (9-12) and severe (less than or equal to 8) at the time of admission. Out of 256 patients, 76 had GCS less than 8, 77 patients had GCS 9-12 and 103 had GCS 13-15.

According to PSS score patients were categorized into four groups based on the severity of poisoning at the time of admission as mild, moderate, severe and fatal. In the study population out of 256 patients, 12

belonged to severe, 134 belonged to moderate and 110 belonged to mild severity group. There were no patients in the fatal group. Other details are mentioned in Table 6.

Table 6: Categorizing the patients according to severity

Severity	GCS [No. of patients(%)] N = 256	PSS [No. of patients (%)] N= 256
Severe	76(29.7%)	12(4.7%)
Moderate	77(30.1%)	134(52.3%)
Mild	103(40.2%)	110(43.0%)

The study population was categorized into 3 different groups based on their Glasgow coma score and their median AChE level. They were compared by Kruskal-Wallis test which showed that median AChE level of three different severity groups varied significantly ($p<0.006$). Higher the severity of the poisoning lower was the cholinesterase level. Details are presented in Table 7.

Table 7: Severity of OP poisoning and AChE level. Values are in Median ± IQR

GCS Category	AChE level (Median ± IQR) [Normal range: 5,000-13,000 IU]
Severe	180.5 ± 826.5
Moderate	481 ± 1967.5
Mild	869 ± 2755.5

Initial GCS severity was compared with outcome of the study population. There was a significant (at $p=0.05$) increase in trend of mortality with increase in the severity of poisoning. Details are presented in Table 8.

Table 8: GCS and outcome

Category of GCS	Outcome			
	Unknown	**Recovery**	**Sequel**	**Fatal**
Severe(≤8)	0	52 (68.4%)	3 (3.9%)	21(27.7%)
Moderate(9-12)	1(1.3%)	58 (75.3%)	6(7.8%)	12 (15.6%)
Mild(13-15)	2 (1.9%)	85(82.5%)	6(5.8%)	10 (9.7%)

Values are in frequency & percentage. Data was analyzed by Chi square test for trend ($p<0.05$)

Initial PSS severity was compared with outcome of the study population. There was a significant (at $p=0.05$) increase in trend of mortality with increase in the severity of poisoning. Details are presented in Table 9.

Table 9: PSS and outcome.

Category of PSS	Outcome			
	Unknown	**Recovery**	**Sequel**	**Fatal**
Mild	0	11 (91.7%)	0	1(8.3%)
Moderate	2 (1.5%)	108 (80.6%)	9(6.7%)	15 (11.2%)
Severe	1(0.9%)	76 (69.1%)	6(5.5%)	27 (24.5%)
Fatal	0	0	0	0

Values are in frequency & percentage. Data was analyzed by Chi square test for trend ($p<0.05$)

Among the study population, 233(91%) patients received gastric lavage at initial stage of therapy. Only 68(26.6%) patients received activated charcoal every 6th hourly for 1-2 days. All the patients received atropine as antidote, while 62 (24.2%) patients received atropine and glycopyrrolate. A total of 135 (52.7%) patients were on ventilator support. PAM therapy was administered to 230 (89.8%) patients. Atropine was administered in different dosage regimens. A bolus dose of 5mg followed by continuous infusion or continuous infusion of atropine without bolus dose at different infusion rates like 5ml, 8ml and 10ml per hour was administered. The mean atropine requirement for the study population was 1458.99 ±3112.3mL. Similarly

glycopyrrolate was administered along with atropine in 62(24.2%) patients as a bolus injection of 1ml every hour. The mean glycopyrrolate requirement for the study population was 14.99 ± 37.58mL. Pralidoxime was administered in 230 patients, i.e. (89.8%) of the study population. Details are mentioned in Table 10.

Table 10: Overall treatment analysis of OP poisoning patients

Treatments	No. of patients (n (%)) N = 256
Gastric lavage	233 (91%)
Activated charcoal	68 (26.6%)
Ventilator support	135(52.7%)
Atropine	194 (75.8%)
Atropine and Glycopyrrolate	62 (24.2%)
PAM	230 (89.8%)
Mean atropine consumed ± SD (in mL)	1458.99 ±3112.3
Median atropine consumed (IQR)	375(1145.25)

The outcome analysis of the study subjects showed that 195 (76.2%) of them recovered, 15(5.9%) of them were sequel and 43(16.8%) of them expired. The mean hospitalization period and ventilator period of study population was found to be 10.21± 6.33 and 3.09 ± 4.05 days respectively. Details are mentioned in Table 11.

Table 11: Overall outcome analysis of OP poisoning patients

Outcome	No. of patients (n (%)) N = 256
Unknown	3(1.2%)
Recovery	195(76.2%)
Sequel	15(5.9%)
Mortality	43(16.8%)
Mean Hospitalization period ± SD	10.21± 6.33
Median Hospitalization period (IQR)	9 (5)
Mean ventilator period ± SD	3.09 ± 4.05
Median Ventilator period (IQR)	1(5)

Among the study population, 233 people received gastric lavage and 23 people were not treated with gastric lavage. Outcome analysis of these groups showed no significant effect of gastric lavage in OP poisoning patients unless at the initial stage of poisoning. There is no significant difference in the outcome between the two groups. The recovery rate was found to be good in patients without gastric lavage when compared to patients with gastric lavage as highlighted in table 12.

Table 12: Gastric lavage and outcome analysis by chi-square test and p<0.05

	Outcome			
	Unknown	**Recovery**	**Sequel**	**Mortality**
Gastric lavage	3(1.3%)	174(74.7%)	15(6.4%)	41(17.6%)
No gastric lavage	0	21(91.3%)	0	2(8.7%)

Among the study population, 68 people received charcoal and 188 people were not treated with charcoal. Outcome analysis of these groups showed no significant effect of charcoal administration in OP poisoning patients unless at the initial stage of poisoning. There is no significant difference in outcome between the two groups as shown in table 13.

Table 13: Charcoal administration and outcome analysis by chi-square test and p<0.05

	Outcome			
	Unknown	**Recovery**	**Sequel**	**Mortality**
Charcoal administration	1 (1.5%)	54 (79.4%)	4 (5.9%)	9 (13.2%)
No charcoal administration	2(1.1%)	139(74.7%)	11(5.9%)	34(18.3%)

Among 256 patients, 194 patients received only atropine and 62 patients received atropine and glycopyrrolate combination. Outcome of these two groups were analyzed in terms of primary outcome and secondary outcome. Primary outcome included percentage of mortality, percentage of recovery and percentage of sequel. Secondary outcome included duration of hospitalization days, duration of ventilation days, incidence of intermediate syndrome and percentage of adverse reactions of atropine. Outcome analysis of these groups showed that there was no significant difference in percentage of recovery and percentage of mortality; however, there was reduction in hospitalization days and incidence of adverse drug reactions of atropine in atropine and glycopyrrolate group when compared to atropine group alone as shown in table 14.

Table 14: Effectiveness of atropine and glycopyrrolate combination in OP poisoning pa

	Atropine Alone N=194	Atropine + Glycopyrrolate N=62	p value
Primary Outcome			
Mortality	31 (16%)	12 (19.4%)	
Sequel	12 (6.2%)	3 (4.8%)	p<.0.166
Recovery	149 (76.8%)	46 (74.2%)	
Unknown	2 (1%)	1 (1.6%)	
Secondary Outcome			
Duration of Ventilation (in days)	3.1±4.08	3.08±4.22	
Duration of Hospitalization(in days)	10.4±6.4	7.6± 4.12	
Incidence of Intermediate Syndrome	25(12.8%)	10 (16.1%)	
Adverse Drug reactions of Atropine	65.6%	28.2%	

DISCUSSION

Pesticide poisoning is a significant problem in South India. OP compounds are the most common cause of deaths due to intentional-poisoning. Patients in our study belonged to productive age (mean age 33.44 ± 13.55 years) group and majority of them were males (53.5%). An Indian study by Nilamadhab showed similar results with the mean age of 31.5 ± 12.37 years and majority of poisoning was observed in males[7]. Another study by Rao et al, showed that about two third of the patients admitted in Warangal due to acute exposure of OP poisoning were less than 30 years and males predominated over females[3.] However, in a study carried out in Turkey by Avni et al. showed females predominance among the acute exposure of OP compounds with a mean age of 22.19 ±/9.2 years [8].

Our study showed that majority of admissions was due to consumption of methyl parathion which belongs to WHO Ia category. In a similar study in South India by Rao et al., showed that majority of the cases were admitted due to ingestion of WHO class Ib pesticides and monocrotophos contributed to major portion among them.[3] A study in Srilanka by Hoek &Flemming reveled that majority of cases admitted were due to WHO II type of pesticides [9].

In the present study majority of patients admitted due to OP poisoning were agriculturists. A similar result was found in a study by De Alwis LB in Sri Lanka which showed that 75% of total poisonings occurred in agriculturists.[10] Another study by Gannur etal., (2008) showed that 37.8% of the total OP poisoning occurred among agricultural workers [11].

Among the severity indices GCS was found to be the most predictable and precise in assessing the initial severity and prognosis in OP poisoning. Moreover GCS is easy to perform, and does not require complex physiologic parameters and laboratory methods [12]. Comparing the GCS with AchE in our study population showed higher the severity of the poisoning, lower was the cholinesterase level. But in literature we were not able to find studies that correlated GCS with cholinesterase levels.

Comparing the Clinical Severity indices with outcome, our study showed that mortality rate increased with reducing GCS. Similarly comparing the outcome with PSS, the mortality rate increased with higher severity when compared to mild and moderate severity cases. Similar studies carried out by Sungurtekin etal., 2006 reported that there was a significant correlation between the mortality and scoring scales systems, like APACHE II, GCS, APACHE III and SAPS II scores [13]. Another study by Bilgin etal., concluded that APACHE II and

SAPS II scores had similar impacts in predicting the outcome; however, GCS system has superiority over the other systems in being easy to perform, and not requiring complex physiologic parameters and laboratory methods [12].

Treatment analysis showed that majority of patients received gastric lavage 232 (91%) at initial stage of therapy. However 62 (24.2%) patients received atropine and glycopyrrolate. A total of 135 (52.7%) patients received ventilatory support. PAM therapy was administered to 230 (89.8%) patients. Gastric lavage is the first intervention and most common form of decontamination for OP poisoned patient on presentation to hospital. In our study we observed that the recovery rate was found to be good in patients without gastric lavage when compared to patient with gastric lavage. The probable reason may be late presentation of patients to the hospital. However there are very few RCTs or observational studies of sufficient quality carried out to evaluate the role of gastric lavage in OP poisoning [14,15] Similarly outcome analysis of activated charcoal showed that there was no significant effect of charcoal administration on OP poisoning patients. A randomized control trial of multidose activated charcoal compared with single dose did not find any beneficial effect in OP poisoning patients [14].

Atropine is the main antidote in the management of OP poisoning. In our study group all the patients received either atropine alone or atropine in combination with glycopyrrolate for the management. Among 256 patients, 194 patients received only atropine and 62 patients received atropine and glycopyrrolate combination. Outcome of two groups were analyzed in terms of percentage of mortality, percentage of recovery, duration of hospitalization days, duration of ventilation days and incidence of intermediate syndrome. We observed that no significant difference was observed in terms of percentage of mortality or percentage of recovery between the two groups. But we observed that there was a reduction in duration of hospitalization period in atropine and glycopyrrolate group when compared to atropine alone. The reduction in hospitalization period was probably due to reduction in ADRs of atropine in these patients due to addition of glycopyrrolate. Similar observations by Bardin and Van Eeden demonstrated that both arm was equally effective, except for a fewer respiratory infections cases in the glycopyrrolate group [16]. A similar study conducted by Arendse R and Irusen E showed beneficial effect of combination therapy of atropine and glycopyrrolate over atropine alone. But in this study the toxicity of atropine remained unchanged even on addition of glycopyrrolate as additional therapy in the management [17].

CONCLUSION

Pesticide self- poisoning is a major health problem in India mostly affecting the agricultural population. OP poisoning is responsible for most suicidal deaths in Southern part of India. Majority of them were males belonging to the age group of 21-30 years. Majority of the people consumed WHO Ia category of pesticide with intentional harm. Majority of them received GI decontamination followed by atropine and few patients received glycopyrrolate with atropine in combination. Based on the severity of poisoning, different patients received different regimens of pralidoxime. Outcome analysis of OP poisoning with different treatment regimen showed that gastric lavage and activated charcoal did not show any significant benefit in the patient's outcome. Addition of glycopyrrolate with atropine improves the quality of treatment with reduction in number of adverse drug reactions of atropine

ACKNOWLEDGEMENTS

We thank Manipal College of Pharmaceutical Sciences and Kasturba Medical College, Manipal University for supporting the study.

REFERENCES

[1] Sinha P, Sharma A. Med J Indones 2003; 12: 120-6.
[2] WHO. Public health impact of pesticides used in agriculture. World Health Organization; Geneva: 1990
[3] Rao S, Venkateswarlu CH, Eddleston M. Trop Med Int Health 2005; 10(6): 581–588.
[4] Eddleston M, Eyer P, Dawson H. Lancet 2008; 371: 597–607.
[5] Ahmed SM, Das B, Nadeem A, Samal RK. Indian J Anaesth 2014;58(1):11-17.
[6] Peter JV, Cherian AM. Anesthesia Intensive Care 2000; 28: 11-21.
[7] Nilamadhab K. Ann Gen Psychiatr 2006; 5: 17.

[8] Avni SH, Idris S, Filiz A. Hum Exp Toxicol 2003;22(7):349-53.
[9] Hoek W, Flemming K. Clin Toxicol (Phila) 2006;44(3):225-31.
[10] De Alwis LB. Forensic Sci Int 1988;36(1-2):81-9.
[11] Gannur DG, Maka P, Reddy N. Indian J Forensic Med Toxicol 2008 ;2(1): 3-11
[12] Bilgin TE, Camdeviren H, Yapici D, Doruk N et al. Toxicol Industr Health 2005; 21:141-46
[13] Sungurtekin H, Gurses E, Balci C. Clin Toxicol (Phila) 2006;44(2):121-6.
[14] Davies JOJ, Eddleston M, Buckley NA. QJM 2008;101(5):371-9.
[15] Bhattarai MD. Managing self-poisoning. BMJ 2000;320(7236):711.
[16] Bardin PG, Eeden SF. Crit Care Med 1990;18:956–60.
[17] Arendse R, Irusen E. Hum Exp Toxicol 2009; 28(11):715-20.