Intoxication by organophosphates: Prognostic evaluation on 143 patients

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Abstract

Organophosphate pesticides intoxication is a serious clinical condition often life threatening in patients admitted to ICUs. In our experience, severity scores as APACHE II, SAPS I and TISS, although useful in this context, they are not effective whilst predicting a fatal outcome. After reviewing 143 files of admitted patients in a Medical Emergency Unit using an appropriate statistic methodology, two hazard scores were defined using clinical, laboratorial and therapy elements: the first – Score 1 – estimated on admission, the second – Score 2 – estimated throughout the admission period. Score I patients were classified in three groups (Score 1<19 – mortality: 4%; Score I between 19 and 33 – mortality: 30%; Score 1 > 33 – mortality: 94%). Using the second score – Score 2 – enable to define two groups of high value prognosis (Score 2 <14 – mortality: 4%; Score 2>=14 – mortality: 78%). To use this score to determine the prognosis has achieved 93% sensitivity and 87% specificity. Both scores (1 and 2) correlated better with the final outcome than with APACHE II, SAPS I and TISS. Score 2 has enhanced Score 1 predictive ability, enabling to reclassify patients whose final prognosis was intermediary, and showing as accurate predictions in 89% of a total of evaluated patients.

Organophosphates [OF] are substances with anticholinesterase activity, used as farming pesticides.[1,2]

Accidental exposure while manufacturing or use, as well as its use with suicidal intent (due to its easy access in our country) are in the basis of acute and chronic intoxication conditions.

The severity of acute intoxication due to Organophosphates [OF] relies on multiple factors, from those inherent to the characteristics and nature of the toxic agent involved, to those related with the intoxicated individuals. Therefore, it is known that progression tends to be worst in alcoholic, undernourished patients, in those with suicidal intent, in those whose clinical condition progresses to coma, seizures, breathing failure, kidney failure and aspiration of the gastric content into the respiratory tree. The same way, progression can be influenced by early implementation of the right therapies. If extreme cases are excepted, and by all the exposed reasons, it becomes problematic to issue a diagnosis on the first few days of an acute intoxication condition. The severity scoring systems used in routine work of Intensive Care Unit,[3,4,5] determined in the first twenty four hours, can be insensitive while evaluating the condition severity and predicting mortality. This study intended a better definition of the main characteristics of the admitted patients by organophosphates intoxication aiming to ascertain its vital prognosis value. The results obtained were related with the values determined in the severity scores usually more used in the Intensive Care Units (APACHE II, SAPS I and TISS).

Material and Methods

143 patients admitted by organophosphates intoxication were evaluated retrospectively for 3 years (from 1989 to 1991) in the Medical Emergency Unit of Sao Jose Hospital. Clinical and laboratorial endpoints evaluated focused specific manifestations and complications of organophosphates intoxication, as well as clinical situations deemed relevant for the prognosis. It was not possible to determine some variable in the total of patients. However, the amount of incomplete data was always small compared to the sample total in all assessed variables.

Two risk scores were built from clinical and laboratorial data which has most deteriorate the prognosis (one at the point of admission in 99 of the 143 patients with complete data to build the initial score and the other throughout the clinical evolution in the Unit in 138 patients).

In a total of 98 from 143 patients it was possible

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to obtain complete data in the first 24 hours to build APACHE II, SAPS I and TISS scores. The death risk was estimated to Apache II with a recommended equation by Knaus.[3]

Fischer and x^2 with continuity correction methods were used to assess the contingency tables. The prognosis importance of each variable was quantified according to the odds ratio estimate. To ascertain the score corresponding to items of Index 1 and 2, it was applied a variation of discriminatory analysis with a ponder approximation of odds ratio value, in function of the predictive value of each variable. P <0,05 was considered statistically significant.

Results

Population characteristics

For 3 years (1989 to 1991) 143 patients with organophosphates intoxication were admitted to the Medical Emergency Unit in a total of 5701 patients (2,5% of cases). Among 143 patients, 84 were of male gender (59%). The average age was 42 years old (SD 19 years).

APACHE II score system average in the 98 patients evaluated was 1 among 17 (between 1 and 39; SD 9). In the SAPS I score it was found an average value of 11 (from 2 to 34; SD 6). In the TISS score, the average was 24 (from 12 to 38; SD 5), 22 among the 98 patients (22%) were classified in Cullen Class II and 76 (78%) in class III. The mortality rate by organophosphates intoxication was of 34% (49 among 143 patients) being 37% the hospital rate. The mortality rate anticipated for the 98 patients with complete information to estimate the APACHE II Score – 29% - was slightly less than the real one. Mortality was higher in the male gender (3 of all 84 men – 39% - and 16 of all 59 women – 27%). The average age of admitted men by organophosphates intoxication (44 years old; SD 19 years) was slightly higher than women (38 years old; SD 18 years – P < 0,10). The average age of the 33 deceased men (55 years; SD 19 years) was slightly higher to the 16 deceased women (39 years old; SD 21 years; P <0,05).

Of the 94 non deceased patients, 89 were transferred from the Unit to other hospital services and five patients were discharged. Mortality after transfer or discharge was too reduced (3%) and was not assessed in this study. The admission period for organophosphates intoxication patients in the Medical Emergency Unit changed from 1 to 48 days (average: 8 days in admission). The average admission period for deceased patients was slightly less (8 days; SD 7 days; average: 5 days; 1-36 days) than the patients transferred or discharged (11 days; SD 10 days; average: 7 days; 1-48 days).

TABLE I

Therapy before admission	%
Previous treatment before MEU admission	83
Gastric wash	73
Atropine	71
Activated charcoal	69
Nasogastric intubation	59
Endotracheal intubation	48
Ubidoxime	47

It was possible to ascertain the previous suicidal attempt, in 29 of the 73 patients with complete information (40%). There was a reference to previous psychiatric disease in 43 of the 69 patients with psychiatric anamnesis data (62%).

In most patients it was not possible to determine accurately neither the amount of toxic ingested nor the time elapsed since admission to the Unit reason why these endpoints were not analyzed. In 90%of cases, it was possible to know precisely the product name; 70% of toxic agents belonged to the toxicity class I (DL50 < 50 mg). The organophosphates intoxication more used in the intoxication was parathion (class I) in 50% of total cases. The product class had no significant statistic influence in mortality.

The most frequent intoxication route was the oral route being mentioned in 121 out of 132 patients (92%). The intoxication was voluntary in 118 of 130 patients with found data (91%).

Around 83% of patients arrive in the Unit with on-going therapy (Table I). Once the vast majority of patients had already undergone previous treatment before the admission, the effects of such therapy were not tested in those measures in the prognosis.

Clinical and laboratorial values in ICU admission

The depression of consciousness (51%), breathing failure (37%) and fasciculation (36%) made up the most frequent clinical manifestations (Table II).

TABLE II

Clinical manifestations	%
Changes of Consciousness	51
Breathing failure	37
Fasciculation	36
Deep coma (Glasgow score <5)	21
Hypothermia (Axillary temp. < 35,0º C)	13
Previous cardiorespiratory arrest	11
Myoclonia	7
Seizures	4

TABLE III

Laboratory	%
Cholinesterase <3.000 U/L	73
Leukocytosis (>10.000/µL)	68
Serial amylase > 200 U/L	65
HCO3 < 22mM	62
TGO > 40 U/L	39
Glucose > 200 mg/dL	29
pH < 7,35	27
Urea > 45 mg/dL	11

Analytically, it was detected, at the time of admission in the Medical Emergency Unit lower values than normal (< 3.000 U/l) of serial cholinesterase in 73% of patients. Several laboratorial endpoints were altered highlighting the pH, the leukocyte count, HCO_3, serial amylase, urea and TGO (Table III).

Mortality rate on admission - Score 1

It was possible to get complete date to build a prognosis score at the time of admission [Score 1] in 99 out of 143 patients (Table IV). Among the many studied variables those that deteriorated significantly the prognosis were selected. X^2 and odds ratio values were used to each one of the variable in the mortality assessment pondering then those values according to the positive and negative of each variable. Finally, it was achieved a score to allocate to each one of the Score 1 variable, by approximation with two significant numbers.

Stratifying the 99 patients in 3 groups, according to the severity score it was found a score with a high prognosis value (Table V). The high risk group (Score 1>33) has shown a high positive predictive value (94%) and negative (84%), and high specificity (99%) on assessing the mortality risk.

TABLE IV

Score 1 Clinical and laboratorial status on admission	Mortality Predictive V + %	Mortality Predictive V - %	Score
Male gender > 60 years old	79	74	+10
Oral route intoxication	33	100	+10
Seizures	83	68	+5
Previous cardiorespiratory arrest	73	70	+4
Hypothermia (Temp. <35,0 C)	69	75	+3
Deep Coma (Glasgow Score <5)	66	75	+2
Breathing failure	49	74	+1
Myoclonia	70	68	+1
Cholinesterase <3.000 U/L	41	86	+10
HCO3 <14,0 mom	90	71	+10
Transaminase GO > 100 U/L	60	70	+6
pH < 7.30	73	74	+5
Glucose > 260 mg/dL	70	73	+4
Urea > 45 mg/dL	60	70	+2
HCO3 > 21,0 mM	18	51	-2
pH> 7,44	17	55	-3

The mortality of the low risk group (Score 1 <19) was 4% (Int. Conf. P < 0,05: 0 -11%). This value was in contrast with a 94% mortality (Int. Conf. P < 0,05 : 82 – 100%) in the high risk group (Score 1>33). The mortality in the intermediate risk group (Score 1 between 19 and 33, inclusive) was 30% (Int. Conf. P <0,05 : 15-45%).

Correlation with APACHE II, SAPS I and TISS

The score obtained in the Medical Emergency Unit in 99 patients – Score 1 – was correlated better with the prognosis that APACHE II and SAPS I – estimated in a total of 98 patients, different from the 99 patients used to build Score 1. However, the 2 groups did not differ

TABLE V

	Deceased	Transferred /discharges	Total
Score 1 <19	2	43	45
Score 1 to 19 to 33	11	26	37
Score 1 > 33	16	1	7
Total	29	70	99

TABLE VI

	Deceased	Transferred /discharges	Total
Apache < 9	1	19	20
Apache 9 to 24	20	36	56
Apache > 24	15	7	22
Total	36	62	98

TABLE VII

	Deceased	Transferred /discharges	Total
Saps < 8	3	34	37
Saps de 8 a 13	13	18	31
Saps > 13	20	10	30
Total	36	62	98

significantly one from the other, in the assessed variable. Such scores have enabled to stratify in a similar way, patients in different risk groups although with a lower predictive power (Table VI, VII and VII).

Score 1 Validation

As 44 patients were excluded of the Score 1 calculation, an important evaluation error could happen, it was validated the selected group of 99 patients (patients with the complete data to Score 1 estimate) comparing with 44 patients excluded by incomplete data. No statistically significant differences occurred among the group of patients with complete data (N=99), and the excluded patients group (N=44) in any of the variable used to get Score 1.

Clinical laboratorial evolution during admission

During admission several clinical complications have

TABLE VIII

	Deceased	Transferred /discharges	Total
TISS < 27	15	48	63
TISS from 27 to 30	7	13	20
TISS > 30	14	1	15
Total	36	62	98

TABLE IX

Clinical-laboratorial alterations	%
Hypokalemia (K+ <3,5 mEq/L)	70
Pneumonia	57
Hyponatremia (NA < 135 mEq/L)	49
Rabdomyolisis	43
Anemia (Hgb<10,0 gr/dL)	40
Acute kidney failure	34
Aspiration pneumonia	32
Infection with bacterial isolation	31
Arrhythmia	26
Changes in liver function	21
Shock	20
Atropine intoxication	20
ARDS	6
Sepsis	3

TABLE X

Therapy	%
Atropine	86
Parenteral feed	59
Mechanic ventilation	58
Atropine maximum dosage above 25 mg/h	50
Dopamine	31
Isoprenaline	13
Dobutamine	12
Noradrenaline	6

TABLE XI

Score 2 Clinical and laboratorial status on admission	Mortality Predictive V + %	Mortality Predictive V - %	Score
Male gender ≥ 60 years old	79	73	+2
Cholinesterases lower value <2500 U/L	42	94	+2
Atropine maximum dosage <10mg/h	10	49	-2
Atropine maximum dosage <5mg/h	61	76	+1
Mechanical ventilation	57	97	+8
Dopamine therapy	78	86	+4
Dobutamine therapy	82	72	+2
Isoprenaline therapy	89	74	+2
Noradrenaline therapy	89	69	+4
ARDS	100	70	+4
Arrhythmias	65	76	+1
Acute kidney failure	59	79	+1
Deep Come Glasgow Score≤ 5	59	89	+2

occurred highlighting the hydroelectrolytical changes and infection (Table IX). In most patients intensive therapy interventions were necessary namely ventilation, nutrition and vasopressure support (Table X).

Clinical laboratorial evolution and mortality rate – Score 2

It was possible to get complete data on building a second prognosis score aiming to evaluate the clinical progression during the Unit admission. Such score [Score 2] was estimated in 138 of the 143 patients (Table XI).

Stratifying the 138 patients in 2 groups according to the severity score built – Score 2 – it was reached a high predictive value of the final prognosis (sensitivity = 93%; specificity = 87% - Table XII). Such score was estimated from changes occurred throughout the admission period.

The mortality in the low risk group (Score 2 < 14) was 4% (Int. Conf. P. <0.05: 0-8%). This value contrasted with a 78% mortality (Int. Conf. P. < 0.05: 66-89%) in the high risk group (Score 2>=14).

Two scores usefulness: Score 1 + Score 2

Score 2 has reinforced the predictive power of Score 1 estimated when entering the Unit in 99 of the 143 patients enabling to reclassify intermediary prognosis patients (Table XIII). Using 2 scores together, the prognosis anticipation has proven itself accurate in 88 of the 99 assessed (89%).

Discussion

The epidemiological dimension of acute organophosphate intoxication is not perfectly known.

In 1972, WHO estimated in 500 000 the number of annual cases, being lethal around 1%. In 1977, nine countries notified 20,640 deaths in the sequence of acute intoxication.

In 1983, the Economic and Social Commission for Asia and the Pacific evaluated the yearly incidence in two million cases, with a 2% mortality (40.000 fatal cases)[6].

In Portugal, the real dimension of this problem is not determined[7,8,9]. However, the situation is common in most emergency services; intensive care units are usually only requested for the treatment of sicker patients. In the Medical Emergency Unit of Hospital S. José were received 354 patients with acute intoxication by organophosphates between 1986 and 1988, having been 28% the mortality in the unit.

The clinical condition of acute intoxication, made up by symptoms and signs of muscarinic stimulation, nicotine (in the neuromuscular plate), associated to irritation or depressive activity of the central nervous system, is usually well identified, mainly if associated to the knowledge of exposure to a toxic product. However, the clinical presentation is often olygosymptomatic and unspecific [1,6,7,10,11,12]

The proof of diagnosis by detection and determination of organophosphates concentrations in the biological factors is made difficult due to pharmacokinetics reasons and hurdles related with methodology of laboratorial diagnosis. To reduce the activity of acetyl-cholinesterase (c. red cells) and Butyl cholinesterase (serial c.) is the biochemistry marker used to supplement the clinical diagnosis. However, the wide normal range as well as the evident lack of parallelism among the measurable activities and those verified in the different tissues and organs (with pathogenic relevance), make these determinations not very sensitive or specific [6,10,11,12,13,14,15].

TABLE XII

	Deceased	Transferred /discharges	Total
Score 2< 14	3	81	84
Score 2> 14	42	12	54
Total	45	93	138

TABLE XIII

		Deceased	Transferred /discharges	Total
Score 1 < 19	Score 2 < 14	0	43	43
	Score 2 ≥ 14	2	0	2
Score 1 From 19 to 33	Score 2 < 14	2	17	19
	Score 2 ≥ 14	9	9	18
Score 1 > 33	Score 2 < 14	0	1	1
	Score 2 ≥ 14	16	0	16
Total		29	70	99

The natural history of intoxications caused by organophosphates is troublesome. Admitted patients in an apparently less severe condition and responding to small dosage of atropine in the first few days of admission, evolve subsequently in an unfavorable manner, even in the absence of infectious complications, common in intensive care units. Others, in a critical clinical condition at the beginning progress well, dispensing the ventilator support and antidote administration. The reasons of such unpredictability are not at all investigated but surely the chemical heterogeneity of many of the used pesticides, the ingestion of other toxics, the idiosyncrasies, the comorbidity effect, the precocity and correction of all resuscitation measures, and the intoxicated patient guided therapy will not be strange to them.

The early admission in an Intensive Care Unit seems to have a favorable influence in the prognosis due to the monitoring and therapy means available[16]. Such effect was not included in any of the defined score, reason why the lead time bias can influence the outcome, in this as in other stratification systems.

The current study intended to obtain a value of prognosis discrimination in variables made by clinical and laboratorial signs, and by therapy approaches; these were selected in accordance with the impressions of Medical Emergency Unit experience in this chapter. His target was to build a tool of initial and sequential severity ponderation, enabling eventually the early detection of complications and its timely treatment. It can still provide an input to the knowledge of the natural history of this serious condition.

In spite of excluding for incomplete data a significant number of patients to build Score 1 (44 of 143 patients), we think the bias introduced in this determination would not be important as none of the comparison made between the group of patients used in Score 1 (n=99) and the group excluded (n=44) has revealed significant statistically differences.

The severity scores [Score 1 and Score 2] obtained from assessed data enabled a strict evaluation of the prognosis. Score 1 was higher than Apache II and SAPS I to determine the mortality rate on admission at the Unit. Possibly and comparing with APACHE II, inaccuracies occurring from the use of quotes to diagnosis subgroups, whose selection is not always accurate [17]

The value of certain variables influencing the prognosis in a more specific way, as the male gender or the level of serial cholinesterase, would have increased the predictive power of two obtained scores. Some variables showing a deep physiological change, as in the case of serial pH and bicarbonate, were naturally correlated with an unfavorable outcome. The predictive power of the variable glucose ≥ 260 mg/dL, also surprising, it will have in its origins several possible influences: pre-existing diabetes mellitus, dextrose serum administration, nicotinic effect, direct toxic action on the Langerhans cells, acute pancreatitis, change on the glucidic metabolism in the critical patient (Diabetes of Injury or Stress Diabetes) [18].

The use of a second score (Score 2) has enabled a better prognosis precision in the admission period.

The identification of complications as pneumonia, rabdomyolosis, acute kidney failure and shock, as well as to use measures as total parenteral feed, inotropic support with vasopressing support, mechanic ventilation [19,20] and high doses of atropine[21] verify the severity of patients treated in the Medical Emergency Unit.

The evolution and improvement of this system severity evaluation, depend on the calibration and the use of a statistic study of a multivariate analysis, only possible after an application to a sample of di-

mensions well above to the one used as basis to the current study. ■

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