Paraquat Poisoning: case study in an Internal Medicine Service

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Abstract

The authors present a retrospective study of poisoning cases admitted in an Internal Medicine department of a central hospital. This analysis includes a 7.5 years period involving 26 cases, with male gender predominance (16 patients) and ages between 16 and 74 years old. The mean time elapsed between the toxic ingestion and first health care was 1.8 hours if they were admitted in the first 24 hours; three patients arrived later in the hospital. The quantities of poison ingested were variable, but more frequently between 20 and 100 ml. Thirteen in-patients died while the remaining 13 were discharged from hospital in good health (average survival period known of 10 months). The 2 groups were compared and the single prognostic factor was the ingested quantity of Paraquat. Dyspnea, oliguria and jaundice were the clinical manifestations with prognostic value, while values of LDH, AST and pO2 (at admission in the A&E) were also prognostic indicators. Any medical measure seemed to modify the disease course when a high dose was ingested.

Key words: Paraquat, poisoning.

Introduction

Paraquat is a quaternary ammonium bipyridyl herbicide. Its ingestion, whether voluntarily or accidentally, causes severe acute poisoning that is often fatal. Absorption through the skin can also be fatal, but the product is poorly absorbed through inhalation. [1] Previous studies reveal mortality rates of between 56%[2] and 64%.[3]

The mortality and survival rates depend on the toxic dose ingested and absorved:[1]

• If the dose is higher than 50mg/kg (i.e. for an adult weighing 80kg, higher than 20 ml of the paraquat solutions marketed in Portugal), death will occur by multiple organ failure, within 72 hours: renal tubular necrosis, myocarditis, hepatic necrosis, burns of the digestive tract and supra-renal necrosis;

• If the dose is between 30 and 50mg/kg (i.e. between 12 and 20ml), death may occur within 70 days by pulmonary fibrosis; the toxicity is due to the build-up of poison in the pulmonary parenchyma, where free radicals are formed, with lipid peroxidation of the cell membrane and depletion of NADPH, causing diffuse alveolitis followed by pulmonary fibrosis (which is aggravated by oxidants, for which reason oxygen should not be given);

• If it is lower than 30mg/kg, benign poisoning occurs, with the appearance of moderate gastrointestinal alterations, mild or absent hepatic and renal manifestations, and mild pulmonary fibrosis.

According to various works, the most important factor in the prognosis of mortality is the amount absorbed (paraquat poisoning).[1,4] The sodium dithionite test is a qualitative, indirect detection method of detecting paraquat levels in the urine that has with a limit of sensitivity of 0.5mg/ml. The sodium dithionite test is the only regularly requested test in our hospital.

The absence of burns of the digestive tract, and negativity in the sodium dithionite test 24 hours after ingestion, are factors that suggest a good prognosis.[4]

In relation to treatment, [1,4,5,6,7] numerous protocols have been tested, seeking to:

Decrease the absorption of the toxin: Fuller's earth, activated charcoal and resins;

• Increase the elimination: Haemodialysis or hemo

• Interfere in the toxicodynamic: Free radical scavengers (superoxide-dismutase, Glutathione peroxidase, N-Acetylcysteine, vitamins C and E) or inflammatory response inhibitors (corticoids and immunosuppressants).

However, all these measures have had disappointing results.

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TABLE I

General data

Sex	Age (years)	Amounts ingested	Time elapsed	Evolution
F	52	?	1.5 hours	died after 48 hours
F	41	50 ml	3 hours	died after 24 hours
M	70	75 ml	1.5 hours	died after 8.5 hours
F	16	100 ml	6 days	died after 10 days
F	20	100 ml	2 hours	died after 38 days
M	27	100 ml	26 hours	died after 38 hours
M	20	200 ml	2 hours	died after 9.5 days
M	32	200 ml	3 hours	died after 48 hours
M	64	200 ml	1.5 hours	died after 72 hours
M	49	500 ml	?	died after 32 hours
M	19	500 ml	30 minutes	died after 55 hours
M	74	800 ml	?	died after 10 days
M	38	1000 ml	2 hours	died after 24 hours
M	17	10 ml	30 minutes	alive after 3 months
F	40	10 ml	30 minutes	alive after 6 months
F	35	20 ml	30 minutes	alive after 3 months
F	46	20 ml	48 hours	alive after 8 months
F	52	20 ml	30 minutes	alive after 3 months
M	24	25 ml	4 hours	alive after 2 months
M	25	25 ml	4.5 hours	alive after 2 months
F	33	40 ml	?	alive after 1 month
M	21	50 ml	1 hour	alive after 6 months
M	37	50 ml	1 hour	alive after 6 months
M	35	100 ml	1 hour	alive after 60 months
M	58	100 ml	?	alive after 30 months
F	20	200 ml	1.5 hours	alive after 1 month

Since 1993, various experimental therapeutic regimens have been underway with desferrioxamine, immunotherapy[8] (interferons a, b and g cause "in vitro" and "in vivo" inhibition of the production of collagen by the fibroblasts), NADPH repletion, and in selected cases, lung transplant.[4]

With this case study, the authors describe the distribution by sex and age group, the amount of toxin ingested, and the evolution time from the start of medical care; to compare the groups of patients who died with those who survived in terms of distribution by sex and age group, amount ingested, evolution time to medical first aid, clinical, laboratory, imaging and endoscopic manifestations, and evolution; and to look for indicators of severity and factors of prognosis.

Materials and Methods

The clinical processes of patients admitted to the Service III of the HUC for paraquat poisoning, from January 1987 to July 1994 (a period of 7.5 years) were consulted. The data were gathered through a protocol elaborated in advance, and then analyzed. The criteria for diagnosis considered were a positive result in the sodium dithionite test, or the existence of a history of ingestion, accompanied by clinical signs and/or suggestive laboratory alterations.

Two groups of patients were then compared in relation to clinical, laboratory, imaging and endoscopic parameters: those who died during hospitalization, and those who survived and were discharged from hospital. In the analysis of the results, the c^2 and the Student t test were used.

Results (*Table I*)

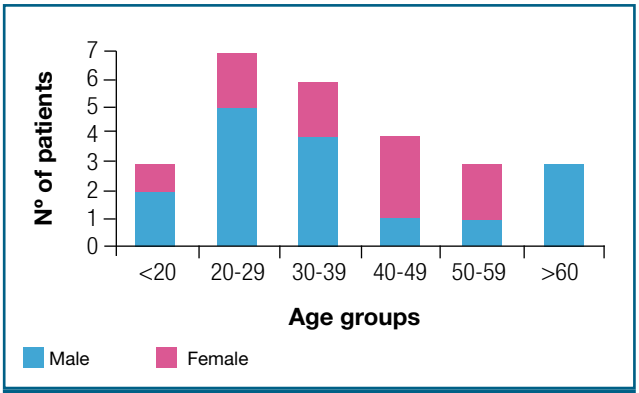
26 cases were observed. The criteria for diagnosis were: positivity in the sodium dithionite test in 23 cases; negativity in the sodium dithionite test in 2 cases, with an evolution time of more than 24 hours, but with the presence of burns of the mouth and oropharynx; and negativity in the sodium dithionite test in 1 case, with an evolution time of one hour, but with burns of the oropharynx and hypoxemia.

Distribution by sex and age group (Fig. 1)

The distribution by sex showed a prevalence of males, with 16 cases (61.5%). The patients were aged between 16 and 74 years (median age 37 ± 16 years), with a slightly higher incidence in the 3rd and 4th decades of life (with 7 and 6 cases, respectively).

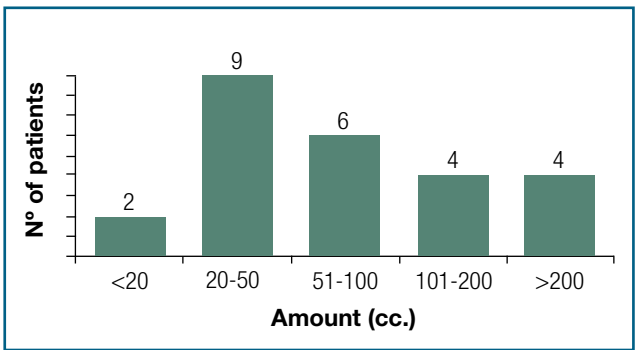
Approximate amounts ingested (Fig. 2)

The amounts ingested were estimated based on data provided by the patients and witnesses, and it was very difficult to know precisely the actual



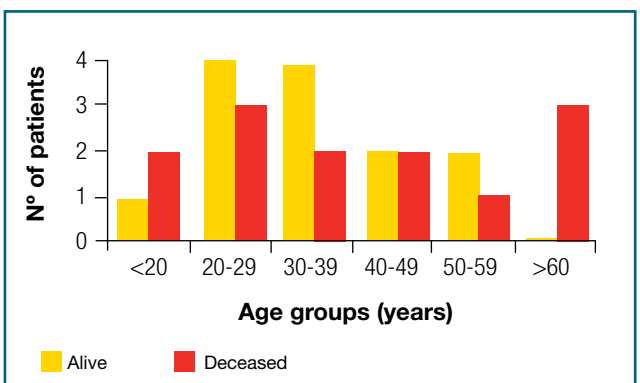
Distribution by sex and age group.

FIG. 1



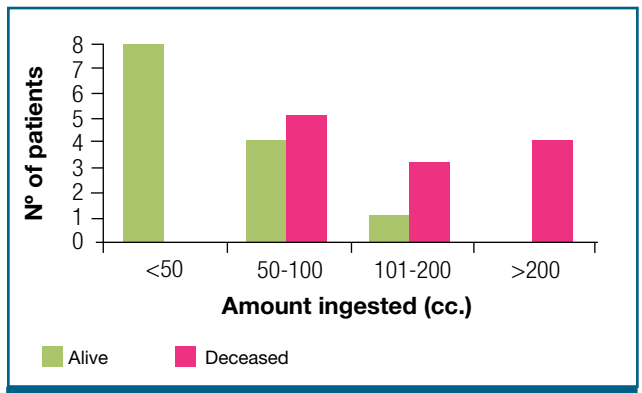
Amount of toxin ingested.

FIG. 2



Distribution of survivors and mortalities by age group.

FIG. 3



Distribution by amount of toxin ingested.

FIG. 4

amount of poison ingested, and whether or not it was diluted.

However, most of the patients (15) had ingested between 20 and 100 ml of the toxin, approximately.

Time elapsed from ingestion of the toxin to medical first aid:

In 5 cases, the time was not known. In 3 cases, the time was more than 24 hours, and in the remaining 18 cases, the time ranged from 30 minutes to 4.5 hours, with a median time of 1.8 hours.

Evolution

During hospitalization, 13 patients died, after an average survival time of 7 days (minimum 24 hours, maximum 38 days).

The remaining 13 were discharged, with clinical and laboratory improvement, and had an average known survival time of 10 months, with a minimum of 1 and a maximum of 60 months (considering, for each case, the last observation registered in the hospital clinical process).

Comparison between the group of patients who died during hospitalization and the group that was discharge with improvement:

Distribution by age group (Fig. 3)

The distribution was similar in the two groups. The average age was slightly lower in the group of survivors (34±12 years) than in the group of mortalities (40±19 years), but the difference is not significant. It is highlighted that the three patients aged over 60 years died.

TABLE II

Clinical manifestations

	Alive	%	Died	%	P
Burns to the mouth/oropharynx	12	0.92	13	1	unknown
Dyspnea	0	0	12	92.3%	<0.00002
Abdominal pain	4	30.7%	5	38.4%	unknown
Fever	5	38.4%	6	46.1%	unknown
Oliguria/anuria	1	7.7%	10	76.9%	<0.002
Jaundice	0	0	7	53.8%	<0.008
Cough with purulent sputum	3	23.7%	2	15.4%	unknown
Oral candidiasis	2	15.4%	2	15.4%	unknown
Hemoptyses	3	23.7%	0	0	unknown

TABLE III

Laboratory alterations

	Total	Alive	%	Died	%	P
Hemoglobin <12 g/dL	4	2	15.4%	2	0,15	unknown
Leukocytes >12 G/L	15	6	46,1%	9	69.2%	unknown
Creatinine >1.1 mg/dL	17	5	38.4%	12	92.3%	<0.02
Creatinine >2.5 mg/dL	12	2	15.3%	10	76.9%	<0.006
Total Bilirubin>3.0 mg/dL	7	0	0	7	100%	<0.008
TGP	13	3	23.0%	10	76.9%	<0.02
pO_2 <70 mmHg	13	4	30.7%	9	69.2%	unknown
pO_2 <60 mmHg	11	3	23.0%	8	61.5%	unknown
pO_2 <50 mmHg	7	0	0%	7	53.8%	<0.008

Relationship between amount ingested and mortality (Fig. 4)

In relation to the amounts ingested, it was seen that these were clearly lower in the patients who survived, with an average of 52±51 ml, than in the patients who died: average of 318±300 ml. This difference is statistically significant (p<0.006). It is also emphasized that all the patients who ingested less than 50 ml survived, while all those who ingested more than 200 ml died. In the intermediate values, there is an overlapping of patients who died and those who survived.

Time elapsed between ingestion and medical first aid

In the group of patients that died, the time was 4.7±7.5 hours, while in the group that survived, it was 5.8±13.4 hours.

Clinical manifestations (Table II)

Of the clinical manifestations found, dyspnea, oliguria and jaundice were statistically relevant for the prognosis, in the patients who later died.

Laboratory values (Table III)

During hospitalization, increased creatinine and TGP, and decreased pO_2, were significant in the patients who died. Comparing the laboratory values on admission to the Emergency Service (*Table IV*), the leukocyte, LDH, TGO and pCO_2 values appear to be indicators of a poor prognosis. However, there is a wide range of overlapping values between the groups.

Radiological manifestations

In the group of survivors, 11 patients did not present radiological alterations, one presented signs of pulmonary fibrosis, and one of pulmonary fibrosis and pleural effusion.

In the group of mortalities, 4 patients did not present radiological alterations, 5 had significant alterations (pneumothorax, atelectasis, pleural effusion or pneumomediastinum, 4 of these patients developing pulmonary fibrosis) and the remaining 4 did not have radiological documentation.

Alterations in the upper digestive endoscopy

Of the patients who survived, 6 did not undergo UDE. Of the remainder, 2 did not present alterations and 5 had ulcers of the esophagus.

Eleven of the patients who did not undergo UDE, and the remaining 2 had oesophagitis.

Therapy (Table V)

The therapies carried out vary greatly, from general

TABLE IV

Laboratory values on admission to the Emergency Service

	Alive	Died	P
Leukocytes	10,300 ± 1,700	18,600 ± 8,200	<0.005
Creatinine	0.9 ± 0.1	2.4 ± 3.4	unknown
TGO	24 ± 7	52 ± 42	<0.04
TGP	19 ± 8	52 ± 56	unknown
GGT	31 ± 20	87 ± 138	unknown
Alkaline Ph.	67 ± 65	61 ± 31	unknown
Total Bilirubin	1.0 ± 0.3	1.6 ± 1.5	unknown
LDH	406 ± 139	592 ± 194	<0.03
CK	91 ± 57	183 ± 169	unknown
pO	98 ± 30	89 ± 26	unknown
pCO	32 ± 6	26 ± 6	<0.03

TABLE V

Therapeutic measures carried out

	Total	Alive	Died
Gastric lavage	22	12	10
Activated charcoal	19	10	9
Sodium sulphate	13	8	5
Hemoperfusion	9	4	5
Corticoids	8	4	4
Fuller's earth	5	3	2
Vitamins	5	2	3
Haemodialysis	2	0	2
Cyclosphosphamide	1	0	1
Gastric lavage + activated charcoal	19	10	9
Gastric lavage + sodium sulphate	13	8	5
Activated charcoal + sodium sulphate	13	8	5

measures (gastric lavage, activated charcoal, sodium sulphate and Fuller's earth) to more aggressive measures (corticoids in high doses, haemodialysis, hemoperfusion and cyclophosphamide). Unfortunately, on the whole, none of the therapies appears to have altered the evolution.

Comments

The mortality rate of 50% may not correspond to the reality, due to the fact that high number of patients who survived was not followed up for very long, after discharge from Hospital (53% at the end of 3 months and 77% at the end of 6 months). If we include the more severe cases who died in the initial hours, while still in the Emergency Service, the mortality rate should be higher still. In previous retrospective studies, Tinoco and cols.[2] studied 25 cases that occurred between 1988 and 1990 in Mexico, of which 64% died. In Brazil, Póvoa and cols.[3] analyzed 25 cases, with a mortality rate of 56%, pulmonary involvement in 96% of the cases, renal in 92%, gastrointestinal in 72%, hepatic in 56% and cardiac in 40% (ranging from minor alterations in the ECG to extensive myocardial necrosis).

No statistically significant differences were found among the mortalities and the survivors in regard to gender, age and time to medical first aid. The fact that all the patients aged over 60 years died is not highly significant, due to the small number of cases. The determining prognostic factor for mortality was the dose ingested (despite the limitations in determining these amounts). This data is in accordance with that reported by Bismuth et al., who observed that the paraquat concentration in the blood in the first 24 hours is the most important factor of prognosis.[4,9]

Of the clinical manifestations studied, dyspnea, oligo/anuria and jaundice, where present, were very bleak factors of prognosis. On admission to the Emergency Services, the average values for leukocytes, TGO, LDH and pCO_2 were also significantly more altered in the patients who died. However, there is an overlapping area of significant values, therefore these parameters cannot be considered as indicators of prognosis in isolated cases.

Regarding the laboratory parameters, the presence, at any time during hospitalization, of creatinine >2.5 mg/dL, total bilirubin >3 mg/dL, increase in transaminases, or hypoxemia <50 mmHg were also ominous factors of prognosis. In other works, [4] it was found that although renal insufficiency develops in the majority of the patients who eventually die, its presence alone did not suggest a worse prognosis. In another study,[9] age, the amount of ingested paraquat and leukocyte count on admission were identified as indicators of a poor prognosis. Yamaguchi et al.[10]

found a direct correlation between mortality rate and kalaemia and the relationship between HCO^3/increase in creatinine and inversely, the interval of time elapsed between ingestion and admission to hospital.

All the patients who developed respiratory insufficiency died. However, 15% of the patients who survived showed radiological signs of diffuse pulmonary fibrosis. In another study[11] involving 42 patients with radiological alterations during the first week after ingesting the poison, 66% of the patients developed lung consolidation, 38% had pneumomediastinum with or without pneumothorax, and 20% had cardiomegaly with narrowing of the upper mediastinum; the manifestations of pulmonary fibrosis began to appear at the end of the first week.

The presence of gastric and/or esophageal ulceration during the first 24 hours after ingestion are confirmation of severe intoxication, while the absence of ulceration indicates a good prognosis.[4] Despite this, in our casuistic, at least 38% of the survivors had ulcerated lesions of the stomach.

None of the therapies instituted in the hospital, even the more aggressive ones, like hemoperfusion, was able to alter the course of the disease. These findings are similar to those of other works.[4,5,6] Recent studies appear to show a decrease in mortality in patients treated with high doses of cyclophosphamide and dexamethasone,[4] but these data have not been confirmed in a comparative study with "standard" treatment with oral absorbents of the toxin and fluidotherapy.[5] Hemoperfusion, lasting 10 hours or more, during the first 24 hours after ingestion of the poison, did not improve the survival rate, but increased the survival time.[6] Lung transplant may be of interest in the patients who survived and presented extensive pulmonary fibrosis.[4]

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