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Paraquat poisoning in Western French Guyana: a public health problem persisting ten years after its withdrawal from the French market

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Abstract. – OBJECTIVE: Paraquat poisoning has almost disappeared from metropolitan France following its ban from the European market ten years ago. However, due to neighboring countries still authorizing paraquat use, French Guyana seems in a different situation. Here we aimed to report a series of paraquat-poisoned patients admitted to the emergency department of the Western French Guyana Hospital in Saint-Laurent du Maroni, to raise awareness of national health authorities on this persistent major issue.

PATIENTS AND METHODS: We conducted a retrospective observational study describing the clinical features, the prognostic factors and the final outcome of paraquat-poisoned patients admitted to the emergency department between January 2008 and August 2014.

RESULTS: Twenty-six paraquat-poisoned patients were included in the study. The median estimated paraquat dose intentionally ingested was 105 mg/kg (interquartile range, IQR: 359). Eighteen patients were treated with the cyclophosphamide/dexamethasone combination and seventeen with N-acetylcysteine in addition to the usual supportive care. Six patients survived and twenty died within a median 36h delay after admission (IQR: 130). Death was associated with cardiovascular (65%) and respiratory (35%) failure. Based on a bivariate analysis, predictive factors of death included (p≤0.05): advanced age, higher ingested paraquat dose, altered renal function, hypokalemia, acidosis, and dark blue dithionite test, observed on hospital admission.

CONCLUSIONS: Paraquat poisoning still persists in French Guyana despite its withdrawal from the market. It is possible to determine the probability of death on patient admission based on routine clinical and biological parameters. There is an urgent need to request neighboring countries to ban paraquat with the aim of eradicating this dramatically life-threatening poisoning.

Key Words:
Paraquat, Poisoning, Prognosis, Mortality, French Guyana.

Introduction

Paraquat (N, N'-dimethyl-4,4'-bipyridinium dichloride) is a herbicide widely used worldwide because of its low persistence in the environment and its minimal cost[1,2]. Commercialized since 1961, its use was banned by the European Union on July 11, 2007, due to its high toxicity for human beings. Intentional ingestion of paraquat has a poor prognosis, with a mortality rate of 80%, despite all the measures taken to limit its toxicity[3]. The lethal dose is estimated at 35 mg/kg, barely a mouthful of a 200

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g/L solution for an adult[1-3]. After ingestion, the plasma peak is reached within 2 h, followed by tissue redistribution to kidneys, liver and lungs, and renal elimination with a half-life of 12 h. The clinical features are characteristics: after ingesting 20-40 mg/kg, patients rapidly present vomiting and ulcerative pharyngeal pain followed by kidney failure and liver cytolysis. Secondarily, a progressive alteration of the respiratory function appears, due first to inflammatory alveolitis with pneumocyte destruction, then to extensive pulmonary fibrosis, leading to refractory hypoxemia and death in 15-28 days. Conversely, when the ingested dose exceeds 40 mg/kg, death is rapid, within 24-72 h, due to acute circulatory failure. Negative prognostic factors classically described are the ingestion of a dose > 40 mg/kg, on an empty stomach, with esophageal lesions, an impaired renal function, and metabolic acidosis[4-8]. Determination, as early as possible, of plasma paraquat concentration has an excellent prognostic value, with a mortality rate close to 100% for a plasma level > 2 mg/L four hours after the ingestion[3]. However, this test is not available everywhere and in its absence, paraquaturia, appreciated with a semi-quantitative test on dithionite colorimetric strips, permits a rapid and reliable evaluation of the severity of the poisoning[6,9]. Hence, a paraquaturia > 1 mg/L over 24 h (navy blue or dark blue) is associated with high mortality, unlike paraquaturia < 1 mg/L (light blue or colorless). The Yamaguchi index[10] and the Severity Index of Paraquat Poisoning (SIPP)[11], easy to calculate, are equally predictive. While the number of poisonings has significantly decreased in metropolitan French since 2007, it has been growing in French Guyana. Paraquat poisoning thus remains frequent in Saint-Laurent du Maroni, a town on the border with Suriname, where this herbicide is available for sale. From 2008 to 2013, one hundred thirteen calls for paraquat poisoning were collected by the French poison control and toxicovigilance center, nearly half of which originated from French Guyana[12]. The aim of this study was to report a series of paraquat poisonings observed in French Guyana and to evaluate their prognosis in a region where management of patients is still done without blood paraquat dosage.

Patients and Methods

Patients

We conducted a retrospective study in Western French Guyana hospital (Centre Hospitalier de l'Ouest Guyanais – CHOG) in Saint-Laurent du Maroni including all patients admitted to the emergency department from January 1, 2008 to August 31, 2014 for intentional or accidental ingestion of paraquat, verified by at least one positive dithionite urine test. The study protocol was approved by the local Ethical Committee at CHOG. Demographic, clinical and biological data were collected from medical records. The Yamaguchi index[10] was calculated. Renal failure was defined by a glomerular filtration rate (GFR) < 60 mL/min/1.73 m² using Modification of Diet in Renal Disease (MDRD) formula; liver cytolysis by alanine aminotransferase (ALT) > 1.5 times normal; circulatory failure by a mean arterial pressure < 65 mmHg and a cardiac rate > 100/min, despite adequate fluids; and respiratory failure by SpO_2 < 90% or PaO_2 < 60 mmHg at room air. The cause of death was considered to be of respiratory origin if it followed an acute respiratory failure and of circulatory origin in the absence of any associated respiratory disorder. Patient management was left to the discretion of the physician in charge, following the usual recommendations[1,2], but it was solely based on patient history, clinical parameters, the urine dithionite test and Yamaguchi index, the blood paraquat test being unavailable. A cyclophosphamide and dexamethasone combination, according to previously described dosage regimen[12,13] was administered in the presence of any identified factor of poor prognosis according to international recommendations[1,4].

Statistical Analysis

For descriptive analysis, qualitative data are presented as absolute values and percentages and quantitative data as medians and interquartile ranges (IQR). Prognostic factors have been identified comparing data from deceased and survived patients using Fisher's exact tests for qualitative variables and Mann-Whitney tests for quantitative variables. A threshold of $p \leq 0.05$ was considered significant. Analyses have been performed using STATA v13.0®.

Results

Twenty-six patients were included in the study, sixteen females and ten males, aged 24 years old (IQR: 17). Ingestion of paraquat at an estimated dose of 105 mg/kg (IQR: 359) was intentional in all cases. Clinical characteristics and biological data on admission are presented in Table I. Eighteen patients received the cyclophosphamide/dexamethasone combination and seventeen re-

ceived N-acetylcysteine. No patient underwent extra-renal elimination. Six patients survived and twenty patients died within 36 h (IQR: 17, ranging from 11 to 54) after admission. Among the six survivors, three patients presented digestive troubles such as vomiting or abdominal pain on admission, yet none presented oropharyngeal lesions. A patient, who declared having ingested 1 g of paraquat (14 mg/kg), presented with metabolic acidosis and an impaired renal function on admission; however, they promptly receded. Only one patient had a strong paraquaturia. He declared having ingested 2 g of paraquat (43 mg/kg), was rapidly assessed (45 min post-ingestion) and received cyclophosphamide/dexamethasone treatment. His biological parameters remained in the range of normality during all his hospital stay. In the survivors group, no organ failure was found within 24 h after admission. Among the 20 deceased patients, only one presented hypotension on admission (84/48 mmHg): he died precociously (11 h after admission). Paraquaturia was strong, except for one patient who was tended early, 45 min after ingesting 6 g of paraquat (86 mg/kg). This patient presented acute renal failure since the admission and was deceased within 44 h. Renal failure was present in 70% of patients on admission, metabolic acidosis in 25% and liver cytolysis in 35%, always associated with kidney failure. All patients who presented respiratory failure deceased. During hospitalization, renal function was impaired for all deceased patients versus only two of the six survivors (p = 0.001). Liver cytolysis was observed for 13 (65%) of the deceased patien-

Table I. Characteristics on admission, management and occurrence of organ failure during hospitalization of patients admitted for paraquat poisoning depending on the outcome (death or survival).

	Survivors (N = 6)	Deceased (N = 20)	p
Males/females, n (%)	1 (17) / 5 (83)	9 (45) / 11 (65)	0.4
Age (years)	14 (6)	27 (14)	**0.003**
Presumed ingested dose (mg/kg)	17 (20.5)	214 (485)	**0.04**
Clinical characteristics on admission			
Mean arterial pressure (mmHg)	81 (7)	103 (22)	0.1
Temperature (°C)	37,2 (0.5)	36,1 (1.5)	0.1
Gastrointestinal symptoms, n (%)	3 (50)	11 (55)	1.0
Serum potassium (mmol/L)	3,6 (0.7)	2,7 (0.8)	**0.003**
Glomerular filtration rate (mL/min/1,73 m²)	99 (44)	51 (30)	**0.009**
ALT (UI/L)*	27 (1)	31 (25)	0.3
CPK (UI/L)*	315 (168.5)	275 (1317)	0.5
Arterial pH	7.41 (0.03)	7.37 (0.06)	0.3
HCO_3^- (mmol/L)	23.4 (7)	21.0 (11)	**0.04**
$PaCO_2$ (mmHg)	37 (10)	36 (9)	1
PaO_2 (mmHg) in ambient air	118 (19)	111 (88)	0.8
Dithionite test (weak vs. strong paraquaturia), n (%)**	3 (50) / 1 (16)	1 (5) / 18 (90)	**0.008**
Contributory Yamaguchi index, n (%)***	1 (16)	12 (60)	0.2
Treatment during hospitalization			
Gastric lavage, n (%)	3 (50)	13 (65)	0.6
Activated charcoal, n (%)	4 (66)	15 (75)	1
N-acetylcysteine, n (%)	2 (33)	15 (75)	0.1
Cyclophosphamide /dexamethasone, n (%)	4 (66)	14 (70)	1
Oxygen, n (%)	0	0	1
Outcome during hospitalization			
Acute renal failure, n (%)	2 (32)	20 (100)	**0.001**
Liver cytolysis, n (%)	2 (32)	13 (65)	0.4
Respiratory failure, n (%)	0	7 (35)	0.2
Acute circulatory failure, n (%)	0	13 (65)	**0.005**

*ALT, alanine aminotransferase; CPK, creatine-phosphokinase; **Two results of the dithionite test were not included in the analysis due to the imprecision of the records regarding the exact color; ***The contributory character of the Yamaguchi index corresponds to its ability to predict on admission the actual patient's outcome.

ts versus two of the survivors (32%) (p = 0.35). A survivor developed both acute renal failure and hepatic cytolysis, which receded at the end of his hospital stay. He had ingested a high dose of paraquat (43 mg/kg) and the required length of hospitalization was extended by 17 days. Death followed circulatory (65% of patients) or respiratory (35%) failure. In bivariate analysis (Table I), factors associated with death were older age (p = 0.003), a higher ingested paraquat dose (p =0.04), impairment of renal function on admission (p = 0.009), hypokalemia (p = 0.003), a lower alkaline reserve (p = 0.04), and a strong paraquaturia detected with dithionite test (p = 0.008). We did not find a significant association either between the ingested dose and the paraquaturia (p = 0.1), or between the ingested dose and the delay in the occurrence of death (p = 0.2).

Discussion

We report a cohort of 26 patients poisoned by paraquat after intentional ingestion, admitted to CHOG in Saint Laurent du Maroni between 2008 and 2014, which represents, to the best of our knowledge, the largest cohort described in France in the past 30 years. This study confirms the poor prognosis of paraquat poisoning, with a mortality rate of 77%, despite managing the patients according to the recommendations. Therefore, our findings clearly support the need to extend the ban on paraquat marketing to French Guyana neighboring countries. Interestingly, prohibition of paraquat production and marketing in South Korea in 2011 resulted in 10%-reduction in suicides and 46%-decrease in herbicide and fungicide poisonings in the years that followed[14]. Our patients were very young in comparison with the published series, with a predominance of early deaths caused by circulatory failure due to the high doses of paraquat ingested, thereby confirming the circulation, in French Guyana, of concentrated formulations of this banned herbicide. We found the usual prognostic factors, and especially the estimated paraquat ingested dose. However, in this series, a patient who ingested a dose of 6.25 mg/kg died early, the amount that he had actually ingested was probably underreported. Conversely, no significant association was found in our study between the Yamaguchi index and the outcome of patients, whereas this score was used in our center in order to guide the cyclophosphamide/dexamethasone treatment. The plasma paraquat concentration, interpreted according to Proudfoot's or Scherrmann's nomograms, and the SIPP, predict at best the risk of death after paraquat ingestion[3,9,11]; however, they could not be used in French Guyana. Although their usefulness is still under debate, it could have been interesting to calculate usual critical care scores such as the Simplified Acute Physiology Score (SAPS II)[15] or the Acute Physiology And Chronic Health Evaluation (APACHE II)[16] to predict the clinical evolution[17,18]; however, these two scores could not be calculated due to the high number of missing data. The application of the dithionite colorimetric test to plasma appears also promising and this analysis could be introduced in French Guyana in the future, in order to predict the prognosis more reliably in the absence of the blood paraquat dosage. In a recent study, a plasma test turning dark blue corresponded to a plasma paraquat concentration >2 mg/mL, hence systematically predicting death (positive predictive value: 100%) and conversely, a test not turning dark blue was always associated with survival (negative predictive value: 100%)[19]. Our work presents limitations due to its retrospective nature, to the small number of patients, and to the difficulties encountered in the collection of history from patients who often have difficulties speaking French. Because of these limitations, a multivariate analysis of prognostic factors could not be performed.

Conclusions

Paraquat poisonings still remain numerous in French Guyana despite its withdrawal from the market in France 10 years ago, and they still have a severe prognosis. Measurement of plasma paraquat concentration is not available in French Guyana; hence, other clinical and biological prognostic factors may be used to reliably predict patient's prognosis on admission. To decrease the number of deaths, it is urgent to propose to French Guyana neighboring countries to ban the marketing of paraquat in order to address this persisting public health challenge.

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Conflict of Interest

The Authors declare that they have no conflict of interest.

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