Paraquat Poisoning in Western French Guyana: A Public Health Problem Persisting Ten Years after Its Withdrawal from the French Market

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Résumé

Introduction **>** L'intoxication par le paraquat a quasiment disparu de France métropolitaine avec le retrait du commerce en Europe de cet herbicide intervenu il y a environ dix ans. Néanmoins, en raison de la proximité de pays frontaliers autorisant l'utilisation du paraquat, la situation en Guyane semble différente. Nous avons souhaité rapporter une série de patients intoxiqués par le paraquat admis au service d'accueil des urgences (SAU) du Centre Hospitalier de l'Ouest Guyanais à Saint-Laurent du Maroni, pour attirer l'attention des autorités publiques sur un fléau persistant dans un Département français d'Outre-Mer.

Méthodes **>** Il s'agissait d'une étude rétrospective observationnelle décrivant le tableau clinique, les facteurs pronostiques et l'évolution finale des patients intoxiqués par le paraquat.

Résultats **>** Vingt-six patients intoxiqués au paraquat ont été admis au SAU du 1er janvier 2008 au 31 août 2014. La dose médiane ingérée volontairement de paraquat était de 105 mg/kg (intervalle interquartile, IQR: 359). Dix-huit patients ont été traités par la combinaison de cyclophosphamide / dexaméthasone et dix-sept patients par la N-acétylcystéine, en plus des mesures symptomatiques usuelles. Six patients ont survécu et 20 sont décédés dans un délai médian de 36 h (IQR: 130) après admission. Le décès était lié à une insuffisance circulatoire (65%) ou respiratoire (35%). En analyse bivariée, les facteurs associés au décès étaient ($p < 0,05$) : un âge plus avancé, une dose ingérée plus élevée, la présence à l'admission d'une altération de la fonction rénale, d'une hypokaliémie, d'une acidémie et d'un test au dithionite de couleur bleue marine.

Conclusions **>** L'intoxication par le paraquat persiste en Guyane malgré l'arrêt de sa commercialisation. Il est possible de déterminer dès l'admission la probabilité de décès en se

basant sur des paramètres clinico-biologiques simples. Il devient urgent de proposer aux pays frontaliers de la Guyane d'interdire à leur tour la commercialisation du paraquat pour éradiquer cette intoxication au pronostic toujours aussi sombre.

Mots-clés : Paraquat ; Intoxication ; Pronostic ; Mortalité ; Guyane Française

Summary

Introduction **>** Paraquat poisoning has almost disappeared from metropolitan France following the ban of this herbicide from the European market ten years ago. However, due to neighboring countries still authorizing the use of paraquat, French Guiana seems in a quite different situation. Here we aimed to report a series of patients poisoned by paraquat admitted to the emergency department of the western French Guiana hospital in Saint-Laurent du Maroni, in order to raise awareness of national health authorities on this persistent major issue.

Methods **>** We conducted a retrospective observational study describing the clinical features, the prognostic factors and the final outcome of patients poisoned by paraquat.

Results **>** Twenty-six paraquat-poisoned patients were admitted to the emergency department between January 1, 2008 and August 31, 2014. 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 36 h 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 Guiana 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 now an urgent need to request neighboring countries to ban paraquat with the aim of eradicating this dramatically life-threatening poisoning.

Keywords: Paraquat; Poisoning; Prognosis; Mortality; French Guiana

What was known

- Paraquat poisoning has a very poor prognosis with a mortality rate over 80%.

- Cases of paraquat poisoning have virtually disappeared in metropolitan France since its withdrawal from the market in 2007.

- There is no antidote treatment whose efficacy has been clearly established.

What this study adds

- Paraquat poisoning continues to plague French Guiana despite the withdrawal of this herbicide from the European market.

- The prognosis of paraquat poisoning in French Guiana remains gloomy; it is possible to determine predictive factors on the basis of routine clinical and biological parameters available on admission.

- The authors call for cooperation with French Guiana's neighboring countries in order to address this serious and persistent public health problem.

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 g/L solution for an adult [1-3]. After ingestion, the plasmatic 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 of 20-40 mg/kg, patients rapidly present vomits and ulcerative pharyngeal pain followed by kidney failure and hepatic cytolysis. Secondarily, a progressive alteration of the respiratory function appears, at first due to inflammatory alveolitis with pneumocytes 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 > 1mg/L over 24 h (navy blue or dark blue) is associated with high mortality, unlike paraquaturia < 1mg/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 Guiana. 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 Guiana [1 2]. The aim of this study was to report a series of paraquat poisonings observed in French Guiana and to evaluate their prognosis in a region where management of patients is still done without blood paraquat dosage.

Methods:

We conducted a retrospective study in Western French Guiana 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. 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; hepatic cytolysis by an alanine aminotransferase (ALT) > 1.5 times normal; circulatory failure by a

mean arterial pressure < 65 mmHg and a cardiac rate > 100/min, despite an adequate filling; and respiratory failure by SpO_2 < 90% or PaO_2 < 60 mmHg in ambient 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 a previously described scheme [12,13] was administered in the presence of an identified factor of poor prognosis according to international recommendations [1,4].

The protocol of this study was approved by the local ethical committee at CHOG. 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 test for qualitative variables and Mann-Whitney test 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 received 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 minutes 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 (11h after admission). Paraquaturia was strong, except for one patient who was tended early, 45 minutes 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 hepatic cytolysis in 35%, always associated with kidney failure.

All patients who presented ventilation troubles deceased. During hospitalization, renal function was impaired for all deceased patients versus only two of the six survivors ($p = 0.001$). Hepatic cytolysis was observed for 13 (65%) of the deceased patients 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 constitutes, to 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 following the recommendations for patients care. It therefore clearly supports the need to extend the ban on the marketing of paraquat to French Guiana's neighboring countries. In fact, prohibition of production and then of marketing of paraquat in South Korea in 2011 resulted in a reduction of 10% of suicides and of 46% of herbicides and fungicides poisoning in the years that followed [14].

Our patients were very young in comparison with literature 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 Guiana, 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 Guiana. 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 Chonic Health Evaluation (APACHE II) [16] in order 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 Guiana in the future, in order to predict the prognosis more reliably in the absence of the blood paraquat dosage. In a recent study, a plasmatic 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 study 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.

Conclusion

Paraquat poisonings still remain numerous in French Guiana 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 Guiana, hence other clinical and biological prognostic factors may be used to reliably predict patient's prognosis on admission. In order to decrease the number of deaths, it is urgent to propose to French Guiana's neighboring

countries to ban the marketing of paraquat in order to address this persisting public health challenge.

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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
Median age and IQR (years)	14 (6)	27 (14)	**0,003**
Estimated 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
Digestive troubles, *n* (%)	3 (50)	11 (55)	1
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)	30.5 (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 (7.2)**	**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)	0.64
Activated charcoal, *n* (%)	4 (66)	15 (75)	1
N-acetylcysteine, *n* (%)	2 (33)	15 (75)	0.14
Cyclophosphamide /dexamethasone, *n* (%)	4 (66)	14 (70)	1
Oxygen, *n* (%)	0	0	1
Evolution during hospitalization			

Acute renal failure, *n* (%)	**2 (32)**	**20 (100)**	**0.001**
Hepatic cytolysis, *n* (%)	2 (32)	13 (65)	0.35
Ventilatory disorders, *n* (%)	0	7 (35)	0.15
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 record regarding the exact color.*

****The contributory character of the Yamaguchi index reflects its capability at having predicted on admission the actual clinical evolution of the patient.*