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Original article

Paraquat Poisoning in Japan : A Hospital-based Survey

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Abstract

Background : Paraquat has been a matter of grave concern around the world, including Japan, in light of high mortality rates and numerous fatalities.

Method : We undertook a cross-sectional survey of pesticide poisoning by collecting data for 6 years, from 1998 to 2003, from 102 hospitals affiliated with the Japanese Association of Rural Medicine. From these cases, we analyzed those with exposure to paraquat.

Results : There were 79 paraquat poisoning cases, including 71 cases of suicide. Of the suicide cases with 5% paraquat and 7% diquat products, more than 80% resulted in suicide deaths. All people who used 24% paraquat products completed suicide. The outcomes of these cases were related to age and volume of ingestion. The prognosis line proposed by Proudfoot in 1979 continues to explain the final outcome of almost all cases even though more than 25 years have passed since it was first proposed. More than 80% of fatalities died within the first three days of ingestion.

Conclusion : Numerous lifesaving methods have been proposed by physicians around the world. However, almost all of these methods treat pulmonary disorders in the sub-acute and subsequent periods and seem unable to effectively decrease mortality rates. It is necessary to take administrative measures to reduce paraquat concentrations in products and, furthermore, to impose strict restrictions on its distribution.

Key words : paraquat poisoning, suicide, hospital-based survey, Japan

Introduction

In Japan, paraquat (Pq), primarily as a 24% Pq product, was first sold as a commonly used herbicide in 1962. However, there were so many deaths with 24% Pq products that restrictions were imposed on their sales, and 5% Pq with 7% diquat (5% Pq+7% Dq) products began to be sold in 1986. However, lowering the concentration of Pq did not lead to an equivalent decline in fatal poisonings, and 5% Pq+7% Dq pesticides have been the cause of poisoning cases in Japan in recent years[1,2].

Some countries, including Sweden, Finland, and Austria, banned sales of Pq products, citing extreme toxicity with no effective treatment strategies available. The US-EPA enforces strict restrictions on the use of Pq products to specified types of spraying. Germany and the Netherlands prohibit the use of Pq, which remains persistently residual in the soil[3].

On the other hand, in countries where the sales of Pq continue, numerous medical investigations have been conducted. For example, the clinical features of Pq poisoning have been discussed and reported by physicians in Korea[4,5], Taiwan[6-8], Sri

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Lanka[9,10], Malaysia[11], and elsewhere in the world [12-14]. Huang et al.[15] expressed concern that Pq poisoning in China may become a grave issue in the near future, given the growing spread of herbicide use.

Under the auspices of the Japanese Association of Rural Medicine, we carried out a series of hospital-based surveys on pesticide poisoning in Japan[16] for six years, from 1998 to 2003. In this report, we will discuss the trends in Pq poisoning in Japan in recent years.

Method

From April 1998 to March 2004 using a protocol established by the Matsushita[17] research group in 1996, we collected data on clinical cases of pesticide poisoning from 102 hospitals affiliated with the Japanese Association of Rural Medicine. Of the 403 cases collected through the survey, there were 79 cases of poisoning with Pq products, including 71 cases of suicide, 5 cases of occupational exposure, and 3 cases of accidental ingestion.

The association between death rates and multiple clinical variables, including age, gender, Pq concentration in the products, amount ingested, urine test results, Pq concentrations in plasma, and clinical data was examined. Pq products were categorized into 24% Pq products, 5% Pq+7% Dq products, and products unknown but confirmed by urine tests or plasma measurement.

Quantities of ingestion were determined by interviews with patients, families and/or the people who found the patients, and classified into three categories - 25 ml or less, 26-50 ml, and more than 50 ml.

The urine test is a fast and useful tool to diagnose Pq poisoning. The results of this test are usually assessed according to five categories -- negative, trace, positive, significantly positive, or extremely positive[18]. In our survey, the physicians who reported the data used three categories--negative, positive, or significantly positive--and those categories were used for this survey.

The clinical dates were defined as follows : Day 1 was the day the patient ingested the Pq product, Day 2 was the following day, and so on.

Pq concentrations in the plasma are often used to predict the outcome of poisonings. Proudfoot[19] proposed a prognosis curve in 1979. Since then, Hart et al.[20], Sawada et al.[21] and Jones et al.[22] have proposed revised prognosis curves. However, these curves are not substantially different from Proudfoot's curve. Consequently, we used the curve originally proposed by Proudfoot as the prognosis curve for comparing concentrations in our cases.

Age groups were compared using Fisher's exact tests and analyzed with SPSS Ver 11. To perform these analyses, ages were divided into two brackets -- 20-59 and 60-89 years old.

Results

The characteristics of the 71 cases are given in Table 1 by gender, age, Pq concentration of the product, amount ingested, and urine test result.

Gender and Age

Twenty-five (81%) of the 31 males and 36 (92%) of the 39 females died. The mortality rate for females was higher, but the difference was not significant.

An analysis by age showed that the number of people in their 70s was largest, followed by the groups with patients in their 50s and 60s. The cases were divided into two age brackets of roughly equal proportions, as shown in Table 1. Twenty-seven (77%) of the 35 people in the 20-59 age bracket and 35 (97%) of the 36 people in the 60-89 age bracket died. The mortality rate of the latter group was significantly higher than that of the overall average.

Products Used for Suicide

Sales of 24% Pq products in Japan were restricted from 1986. In spite of this, eight cases of suicide with these products were reported in

Table 1 Characteristics of Paraquat Poisoning Cases by Ingestion

Characteristics		Recovery	Death	p value*	
Gender	Male	6	25		
	Female	3	36	p=0.138	
	Unknown	1	0		
Age	20-29	1	2	**	
	30-39	1	5		
	40-49	2	6		
	50-59	4	10	p=0.005	
	60-69	0	13		
	70-79	1	18		
	80-89	0	8		
Product	5% paraquat + 7% diquat	9	39	p=0.221	
	24% paraquat	0	8		p=0.071
	Unknown	0	15		
Ingested amount (5% paraquat +7% diquat)	≤25mL	5	4	p=0.657	
	26-50mL	2	2		p=0.003
	>50mL	1	22	p=0.049	
	Unknown	1	11		
Urine test result	Negative	1	1	p=0.544	
	Positive	5	12		p=0.261
	Significantly positive	3	24	p=0.130	
	Unknown	0	25		

* : P value was calculated with Fisher's exact tests.
** : For statistical analysis, ages were classified into two categories - 20-59 and 60-89 years old.

Japan between 1998 and 2003.

Even with 5% Pq+7% Dq products, the sales of which began in 1986, 39 (81%) out of 48 cases resulted in completed suicides.

For Pq poisoning, urine tests and measurements of concentrations in the blood are useful for the identification of the specific poison. There were 15 cases in which Pq poisoning was confirmed in urine tests and/or measurements of concentrations in the blood, although the names of the products were unknown. In all 15 cases, the subjects died.

Quantities of Ingestion

For cases in which quantities ingested were reported by the patients, their families, or the people who found them, there were significant correlations between the volume ingested and the outcome. The death/total numbers and death rates were 4/9 (44%) for 25 ml or less, 2/4 (50%) for 26 to 50 ml, 22/23 (96%) for more than 50 ml.

Urine Test

Using urine tests, there were 2 negative, 17 positive, and 26 significantly positive cases. The mortality rate was 50% for the negative cases, 71% for the positive cases, and 88% for the significantly positive cases. The number of negative cases was small, and this may explain why a statistically significant difference was not found.

Paraquat Concentrations in Plasma

Paraquat concentrations in the plasma were analyzed for 21 patients. In Figure 1, the vertical line represents concentrations in the plasma and the horizontal line shows elapse of time from ingestion to blood sampling. The lozenges represent cases of completed suicide, and the shaded squares denote suicide attempts. Proudfoot

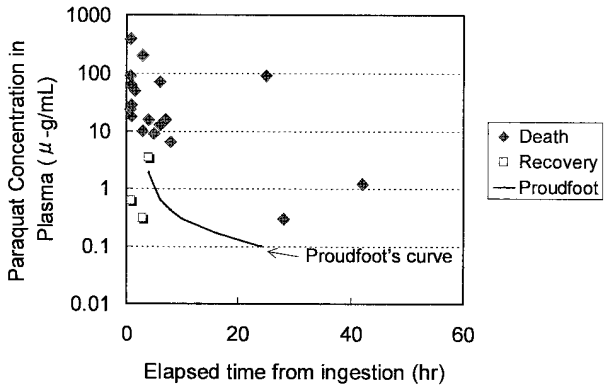

Figure 1 Outcomes and paraquat concentrations in plasma by time from ingestion

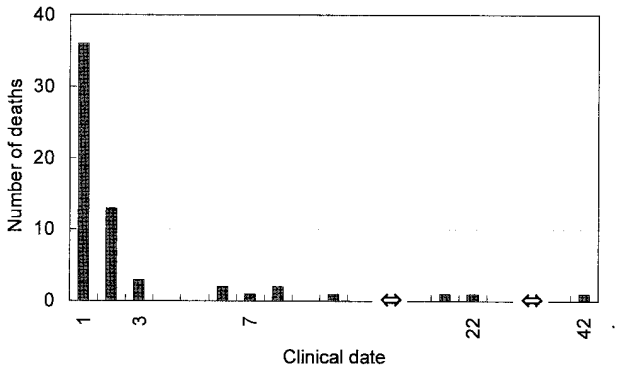

Figure 2 Number of deaths by clincal date

et al. (1979) proposed a prognoses curve for death /recovery, which is represented by the solid curve in Figure 1. Almost all of the deaths in our study are distributed above the curve while the three cases of recovery are either above or below it.

Period between Ingestion and Death

In Figure 2, the number of deaths is represented by clinical date on the horizontal axis. Deaths were concentrated in the first three days, with 36 (58%) on the day of ingestion, 13 (21%) on Day 2, and 3 (5%) on Day 3.

Accidental Ingestion and Occupational Exposure

Three cases of accidental ingestion were reported, and in one case, the person died after ingesting an estimated 40 ml of 5% Pq+7% Dq products.

Five cases of occupational exposure were reported. In four of the five cases, although there was acute poisoning, the patients recovered. In the fifth case, the patient suffered ocular disorder.

Discussion

Mortality rate by Age

The mortality rate of patients 60 years old and over was significantly higher than the rate for those less than 59 years old. This is attributable to differences in physical strength.

Products Used for Suicide

Although sales of 24% Pq products have been prohibited since 1986, eight cases of suicide using these products were reported between 1998 and 2003. This suggests that farming families stored the Pq products for more than ten years. Farmers should be required to relinquish not only Pq products but also all banned pesticide products.

Ingested Volume and Urine Test

All of the patients who ingested more than 50 ml of Pq products died, even when the Pq products had low concentrations. Furthermore, half of the cases in which the patient ingested less than 50 ml resulted in death. Consequently, the switch to products lower in concentrations does not seem to have been effective in preventing suicides.

Even in cases in which the urine test results were negative, death resulted. As a result, prompt treatment is recommended in all cases in which there is the possibility of Pq ingestion, even if the urine test is negative.

Mortality Rate

According to our survey, more than 80% of all suicide attempts using the herbicide Pq ended in death. In contrast, in cases of poisoning with other herbicides, such as glyphosate and glufosinate, the recovery rate was more than 80%. This difference is too drastic to be ignored. Numerous physicians around the world have been researching life-saving methods for those who ingest Pq.

However, the clinical treatment of Pq poisoning has not effectively increased the recovery rate, and the prognosis curve proposed by Proudfoot in 1979 has remained effective since that time. Our cases are represented in Figure 1. Cases ending in death are distributed above Proudfoot's curve, while cases with recovery are either above or below it.

Treatment Methods Proposed for Paraquat Poisoning

Numerous medical investigations and treatments have been tried for Pq poisoning. Almost all of them have included treatments to prevent pulmonary disorders in the subacute and subsequent phases, thus making it possible to increase survival rates during those periods. For example, Lin et al.[8] pointed out that the rate of survival can be raised by using timed treatments of methypredonisolone and cyclophosphamide concurrently with continuous treatments of dexamethasone. Lugo-vallin et al.[23] reported that rates of survival can be increased by using S-carboxymethylsystein for the treatment of Pq poisoning . Ishimaru et al .[24] gave methylpredonisolone to paraquat poisoning patients with decreasing pulmonary compliance. Ichinose et al.[1] argued that fibrosis can be mitigated by eliminating 24% Pq products and instead using 5% Pq+7% Dq products, adding that this mitigation probably stems from the fact that Dq is not as toxic to the pulmonary system as Pq.

In our survey, however, 81% of the deaths caused by Pq poisoning occurred on Day 1 through Day 3, as indicated in Figure 2. Without appropriate measures in the acute phase, it will be impossible to effectively reduce the mortality rate. The urgency of finding effective treatments is further emphasized by the fact that almost all people who ingest in excess of 50 ml of Pq will die.

It is necessary to take administrative measures to reduce Pq concentrations in products and, furthermore, to place harsh restrictions on its distribution[25].

Accidental and Occupational Poisoning

In our survey of data representing six years, only three cases of accidental ingestion were reported, but even among those cases, one person died, because a lethal dose of Pq poisoning is only 10-30 ml of Pq. As a result, administrative measures, such as those just discussed, are highly recommended.

Even occupational exposure to Pq can lead to death, although no such cases were reported in our survey. Kishimoto et al.[26] reported on a case in which the spraying of Pq in a greenhouse led to hepatic and kidney disorders and then respiratory failure resulting in the death of the person spraying the Pq. Wesseling et al.[3] reported that Pq poisoning occurs in Costa Rica and that emphasis must be placed on death such as the kind which arises from percutaneous absorption.

There have also been reports about cutaneous disorders (e.g., Horiuchi's atlas[27]) and ocular disorders[28,29] because of high irritancy and errosiveness to membranes and skin.

To study chronic respiratory disorders, Schenker et al.[30] interviewed and tested the pulmonary functions of farmers who engaged in the spraying of Pq and those who did not. They found many cases in the former group in which chronic coughing and wheezing made the farmers' breath shallow.

Classification of Hazardousness

In Japan, sales of 24% Pq products were banned in 1986, and since that time, 5% Pq+7% Dq products have been widely used instead. Even with low-concentration products, however, ingestion of more than 50 ml is fatal in almost every case.

The International Programme on Chemical Safety[31] classified pesticides into four categories by degree of hazardousness -- extremely hazardous (Class Ia), highly hazardous (Class Ib), moderately hazardous (Class II), and slightly hazardous (Class III). Sales of Class Ia pesticides were prohibited, contributing to decreases in the occurrence of pesticide poisoning around the world.

However, Pq is categorized as moderately hazardous (Class II) because the LD_{50} of Pq is 57 mg/kg for rats[32]. Consequently, in countries where herbicides have never been used before, the severity of Pq poisoning may not be recognized if this classification system is used. In light of the fact that the mortality rate of Pq is high, similar to captafol which is classified as a Class Ia pesticide by reason of its carcinogenesity, Pq should also be classified as extremely hazardous (Class Ia).

Conclusion

Seventy-nine paraquat poisoning cases, including 71 cases of suicide, 3 cases of accidental ingestion, and 5 cases of occupational exposure, were collected in our hospital-based pesticide poisoning survey from 1998 to 2003. Of the cases of suicide with 5% paraquat and 7% diquat products, more than 80% resulted in suicide deaths, and all people who used 24% paraquat products completed suicide. The outcomes of these cases were related to age and volume of ingestion. The prognosis line proposed by Proudfoot in 1979 continues to explain the final outcome of almost all cases even though more than 25 years have passed since it was first proposed. More than 80% of the patients died within the first three days of ingestion. Of the cases in our survey of poisoning due to occupational exposure or accidental ingestion, paraquat was the most hazardous of all pesticides, and there was one fatal case.

The urgency of finding effective treatment is emphasized by the fact that almost all people who ingest paraquat in excess of 50 ml will die. It is necessary to take administrative measures to reduce paraquat concentrations in products and, furthermore, to place strict restrictions on its distribution. In the same way that the International Programme on Chemical Safety classifies captafol as an extremely hazardous pesticide (Class Ia) because of its carcinogenicity, paraquat should be categorized as a Class Ia pesticide in light of its high mortality rate.

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