สารศิริราช
SIRIRAJ HOSPITAL GAZETTE

จัดพิมพ์โดยอนุมัติคณะกรรมการคณะแพทยศาสตร์ศิริราชพยาบาล
Published Under the Auspices of the Faculty of Medicine, Siriraj Hospital

ปีที่ 56, ฉบับที่ 4, เมษายน 2547	Volume 56, Number 4, April 2004

Treatment of Paraquat Poisoning with Cyclophosphamide / Dexamethasone Combination : The First Two Years Experience at Siriraj Hospital

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Abstract : **While the mortality rate from paraquat is high, a proven treatment for paraquat poisoning is still lacked. In this article, we describe the outcome of the first two years of implementing a treatment protocol containing cyclophosphamide and dexamethasone for paraquat poisoning at Siriraj Hospital. Treatment group was studied by a retrospective review of cases at Siriraj Hospital with significant paraquat poisoning in 2002-2003. Significant ingestion means ingestion of 1gram total or 20 mg/kg or positive urine dithionite test for paraquat. All patients with significant ingestion received treatments with a regimen consisting of enteral administration of a single dose of Fuller's earth solution and a 14-day course of intravenous cyclophosphamide plus intravenous dexamethasone plus intravenously vitamin C. Survival rate was compared with historical controls that included searchable cases with significant paraquat poisonings admitted to Siriraj Hospital who were treated only with Fuller's earth or Bentonite, vitamins B and C and supportive care. From January 2002 to November 2003, there were 6 cases of significant paraquat poisoning presented to Siriraj Hospital. The survival rate of treatment group is 83.3% as judged by presence without life-threatening signs at 4 weeks after the ingestion. Nine cases of significant paraquat poisoning were identified from Siriraj Hospital's searchable medical records from 1994-1997 and were enrolled as controls. All control cases died within 12 days, six from fulminant paraquat poisoning and the remaining from moderate to severe poisoning. The use of immunosuppressive agents known for its ability to treat inflammatory lung disease such as cyclophosphamide and dexamethasone presents a viable alternative to an otherwise serious and untreatable poisoning.**

Key words : paraquat, herbicide, cyclophosphamide

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เรื่องย่อ : **ประสบการณ์สองปีแรกในการรักษาภาวะพิษจากยาปราบวัชพืชพาราควอทด้วยยาไซโคลฟอสฟาไมด์และเดกซาเมธาโซนที่โรงพยาบาลศิริราช**

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สารศิริราช 2547; 56: 163-170.

ภาวะการเกิดพิษจากยาปราบวัชพืชพาราควอทเป็นภาวะการเกิดพิษที่มีอัตราการเสียชีวิตสูงมาก แต่ในปัจจุบันยังไม่มีวิธีการรักษาใดเป็นที่ยอมรับว่าได้ผลดี บทความนี้เป็นรายงานผลการรักษาผู้ป่วยรับประทานสารพาราควอท วิธีการรักษาประกอบด้วย ไซโคลฟอสฟาไมด์และเดกซาเมธาโซนนาน 14 วัน ซึ่งเริ่มใช้ที่ร.พ. ศิริราช ปีพ.ศ. 2545 ข้อมูลของผู้ป่วยกลุ่มที่ได้รับการรักษาได้จากการทบทวนเวชระเบียนของผู้ป่วยที่รับประทานพาราควอทอย่างมีนัยสำคัญที่มีการปรึกษาหน่วยพิษวิทยา โรงพยาบาลศิริราช ช่วงปี พ.ศ. 2545 - 2546 การรับประทานพาราควอท อย่างมีนัยสำคัญหมายถึงการรับประทานพาราควอทในขนาด 1 กรัม หรือ 20 มิลลิกรัมต่อกิโลกรัมของน้ำหนักตัว หรือมีการตรวจปัสสาวะหาพาราควอทด้วยวิธีไดไธโอไนต์ได้ผลบวก ผู้ป่วยทุกรายได้รับการรักษาด้วยการบริหารฟุลเลอร์เอิธทางปากหนึ่งครั้ง และการรักษาด้วยไซโคลฟอสฟาไมด์และเดกซาเมธาโซนและวิตามินซีทางหลอดเลือดดำนาน 14 วัน ข้อมูลที่ใช้ในการเปรียบเทียบได้แก่การรอดชีวิตโดยไม่มีภาวะคุกคามต่อชีวิตที่เกี่ยวข้องกับพิษพาราควอทที่เวลา4 สัปดาห์หลังการรับประทานพาราควอท กลุ่มเปรียบเทียบได้จากการทบทวนเวชระเบียนผู้ป่วยในโรงพยาบาลศิริราชที่รับประทานพาราควอทอย่างมีนัยสำคัญและได้รับการรักษาด้วยการบริหารฟุลเลอร์เอิธทางปาก วิตามิน ซี และ/หรือ บี และการรักษาประคับประคอง ระยะเวลาระหว่างปี พ.ศ. 2545-2546 มีผู้ป่วยรับประทานพาราควอทอย่างมีนัยสำคัญ 6 รายและอัตราการรอดชีวิตเท่ากับร้อยละ 83.3 กลุ่มเปรียบเทียบมีผู้ป่วย 9 รายและทุกรายเสียชีวิตก่อนวันที่ 12 หลังการรับประทานพาราควอท โดย 6 รายเป็นภาวะพิษแบบรุนแรงมาก และ 3 รายเป็นภาวะพิษแบบปานกลางถึงรุนแรง การรักษาด้วยไซโคลฟอสฟาไมด์และเดกซาเมธาโซนอาจเป็นทางเลือกในการรักษาภาวะพิษพาราควอทที่ได้ผล โดยเฉพาะอย่างยิ่งเมื่อเทียบกับวิธีรักษาแบบเดิมที่ไม่ได้ผล

INTRODUCTION

Poisoning by the herbicide Paraquat is commonly found in agricultural countries like Thailand. According to the statistics from Ramathibodhi Poison Center, paraquat is the most commonly implicated substance, accounting for 20% of all poisoning deaths in Thailand during the year 2000[1]. However, despite such statistics, there is yet no proven method for treatment of patients with paraquat poisoning. Therefore, patients continue to be treated on a symptomatic basis, having been justified by the lack of clearly effective treatment.

In Siriraj Hospital, a university-based tertiary care hospital in Bangkok, Thailand, a regimen consisting of cyclophosphamide and dexamethasone has been used to treat patients with significant paraquat ingestion since January 2002. Before such time, cases of paraquat poisoning at Siriraj Hospital were treated with supportive and symptomatic care and may include a regimen containing vincristine and dexamethasone. The present regimen was implemented based on ethical and medico-legal reasons. In this article we report the outcome of the first two years, in terms of survival and adverse effects,

of implementing such protocol at Siriraj Hospital. Moreover, we report results of a survey conducted among a group of Thai practicing physicians to evaluate their experience in treating paraquat poisoning and decision to manage a scenario of significant paraquat poisoning.

MATERIALS AND METHODS

We retrospectively reviewed data from all patients consulted to the Clinical Toxicology Services of the Department of Preventive and Social Medicine and the Department of Pediatrics at Siriraj Hospital during the period of January 2002 to December 2003. Patients presenting with the history of paraquat ingestion all received gastrointestinal decontamination with 150 milliliters of 15% Fuller's Earth Solution. Patients were then categorized into poisoning risk groups based on their ingestion history and urine test. "Significant ingestion" is defined by a dose of ingestion that is larger than 1 gram (approximately 4 milliliters of 27.6% paraquat) or 20 mg/kilogram body weight or positive urine dithionite (blue color) test performed any time after the ingestion. Patients determined to have significant ingestion received treatment with 5 mg/kg/day of cyclophosphamide intravenously (in 3 divided doses) plus 40 mg/ day of dexamethasone (10 mg or 0.15 mg/kg body weight intravenously every 6 hours) and 6 grams of vitamin C per day intravenously for 14 days. No dosing adjustments were made for alteration in renal or liver function during the time of therapy. All patients' clinical parameters were monitored through out the treatment, including renal function, liver enzymes, complete blood count, pulse oximetry and chest x-ray. Patients were scheduled for a follow up appointment two to four weeks after their hospital discharge to confirm survival and to check for possible toxicity of paraquat and adverse effects of treatment.

Control group was obtained by reviewing cases of paraquat ingestion that did not receive any treatment with any immunosuppressive agents (vincristine, corticosteroid and dexamethasone) from all available Siriraj Hospital's medical records. Clinical data collected included clinical manifestation, renal and liver function tests, urine paraquat test, treatment received, the clinical course and final patient outcome. Permission to retrieve and to review medical records in this study was granted by the Dean of the Faculty of Medicine at Siriraj Hospital.

To evaluate the experience and clinical decisions of physicians regarding the management of paraquat poisoning in their practices, we administered a short questionnaire to a group of physicians attending a continuous medical education course "Updates in Internal Medicine 2003: Emergencies in Internal Medicine" at Siriraj Hospital in November 2003. Contents of the questionnaire included current practice status, experiences in caring for patients with paraquat poisoning (number of cases) and knowledge regarding methods of treatment in managing a scenario of a patient who presents 2 hours after ingestion of 30 ml of 27.6% paraquat. The treatment options in the questionnaire included gastric lavage, Fuller's earth or Bentonite, activated charcoal, vitamin C, vitamin E, N-acetylcysteine, methylprednisolone, dexamethasone, cyclophosphamide and vincristine.

Definitions: Amounts of ingestion are estimated based on the volume of ingestion and the concentration of paraquat ingested. Onsets of treatment are the times when the gastrointestinal decontaminations were first performed. Severity of clinical course is classified according to clinical severity stages as described in discussion. Pulmonary toxicity is defined by presence of progressive generalized crepitations or progressive infiltrations from chest radiography or hypoxia (oxygen saturation less than 95% at room air), when other causes for example, pneumonia, can be excluded. Survival is defined as presence for the follow up without any life-threatening abnormality related to paraquat poisoning at 4 weeks or more after the ingestion.

RESULTS

From January 2002 to December 2003, there were 9 cases of paraquat poisoning presenting to the Clinical Toxicology Services at Siriraj Hospital, of which six were identified based on history as significant ingestions. Of these, 5 were confirmed by a positive urine dithionite test (Table 1). Four out of 5 patients were males who ingested paraquat in

Table 1. Description of cases of paraquat poisoning consulted to the Toxicology service during the years 2002-2003 who were treated with the cyclophosphamide- dexamethasone regimen.

Patient	Age (Years)	Gender	Amount of ingestion (Gram)	Dithionite test	Onset of treatment (Hours)	Peak creatinine (mg/dL)	Peak AST (IU/L)	Pulmonary toxicity	Survival status / Day of death after ingestion	Severity of clinical course	Complications of treatment	Motive for ingestion
1	35	Male	7	Positive	48	3.5	35	No	Yes	Moderate to severe	None	Suicide
2	2	Female	0.9	Not tested	120	0.9	28	No	Yes	Moderate to severe	None	Accidental
3	26	Male	7	Positive	12	4.5	26	No	Yes	Moderate to severe	None	Suicide
4	29	Male	14	Positive	20	5.3	58	Yes	No Day 21	Moderate to severe	None	Suicide
5	34	Male	14	Positive	30	2.7	32	No	Yes	Moderate to severe	Hair loss, Acne	Suicide
6	50	Male	14	Positive	2	1.6	130	No	Yes	Moderate to severe	None	Suicide

Table 2. Description of historically control cases of paraquat poisoning hospitalized in Siriraj Hospital from 1994-1997 who were not treated with immunosuppressive therapy.

Patient	Age (Years)	Gender	Amount of ingestion (Gram)	Dithionite test	Onset of treatment (Hours)	Peak creatinine (mg/dL)	Peak AST (IU/L)	Pulmonary toxicity	Survival status / Day of death after ingestion	Treatment	Severity of clinical course	Motive for ingestion
7	19	Female	14	Positive	2	6.0	252	Yes	No / Day 2	Vitamin B & Vitamin C	Fulminant	Suicide
8	17	Female	8	Positive	2	11.0	200	Yes	No / Day 10	Vitamin C	Moderate to severe	Suicide
9	40	Female	40	Positive	2	3.3	650	Yes	No / Day 1	Vitamin B & Vitamin C	Fulminant	Suicide
10	20	Female	8	Positive	6	5.4	2080	Yes	No / Day 2	Vitamin B & Vitamin C	Fulminant	Suicide
11	50	Male	14	Positive	2	4.1	43	Yes	No / Day 3	Vitamin B & Vitamin C	Fulminant	Suicide
12	60	Male	14	Positive	6	3.5	455	Yes	No / Day 2	Vitamin B & Vitamin C	Fulminant	Suicide
13	25	Male	8	Positive	6	4.0	122	Yes	No / Day 12	Vitamin B & Vitamin C	Moderate to severe	Suicide
14	25	Male	8	Positive	1	5.0	800	Yes	No / Day 2	Vitamin B & Vitamin C	Fulminant	Suicide
15	29	Male	4	Positive	3	5.8	216	Yes	No / Day 11	Vitamin B & Vitamin C	Moderate to severe	Suicide

Table 3. Summary of survival rates and average ingested dose.

	Treatment group		Control group	
	Survival rate (%)	Average dose (Gram)	Survival rate (%)	Average dose (Gram)
Moderate to severe poisoning	100	9.48	0	6.67
All cases	83.3	9.48	0	13.11 (9.75*)

*The average ingested dose of controls, excluding patient 9, who had an extremely large ingestion.

Table 4. Results from the survey among attendees of the Updates in Internal Medicine 2003 Course.

Experience in caring patients with paraquat poisoning	
- No experience	16 (21.05%)
- Less than 5 cases	47 (61.84%)
- More than 5 cases	13 (17.11%)
Decision to treat a patient with significant paraquat poisoning with	
- Gastric lavage	68 (89.47%)
- Fuller's earth or Bentonite	70 (92.11%)
- Activated charcoal	19 (25.0%)
- Vitamin C	43 (56.58%)
- Vitamin E	18 (23.68%)
- N-acetylcysteine	10 (13.16%)
- Methylprednisolone	6 (7.89%)
- Dexamethasone	33 (43.42%)
- Cyclophosphamide	8 (10.53%)
- Vincristine	7 (9.21%)

suicidal attempts. Onsets of treatment varied from 1 hour to 5 days after the ingestion. All patients developed marked gastrointestinal effects, including oral and orophraryngeal ulcers, nausea, vomiting and abdominal discomfort, most of which subsided within one week. All of the patients, except for the 2-year-old child, developed acute renal failure. None of the patients who had acute renal failure required dialysis and creatinine levels normalized by the end of the second week after the ingestion. All 6 patients had elevation of liver enzymes that were no more than four times the upper normal limits and did not manifest any other signs of fulminant paraquat poisoning. All the patients completed the 14-day course of treatment with cyclophosphamide and dexamethasone without any adverse effects. Patients were discharged from the hospital with normal physical examination, renal function tests, liver function tests, and pulse oximetry measurements and chest radiography. Upon follow up, all patients appeared to be in good state of health. Patient 5 reported acne on his back and gradual but total loss of his scalp hair, starting on day 17 after the ingestion. At 8 weeks after the ingestion, his skin lesion recovered completely and his scalp hair grew well. On day 20 after the ingestion, 2 days after being discharged from the hospital, patient 4 ingested another dose of approximately 14 grams of paraquat. He rapidly developed progressive dyspnea and coughs and presented at Siriraj Hospital six hours

Table 5. Studies of immunosuppression in paraquat poisoning using 2-week cyclophosphamide and dexamethasone regimens.

Study	Study group (cases)	Control group (cases)/type	Exposure assessment	Control treatment	Immunosuppressive treatment	Treatment survival rate	Control survival rate	Significance of difference
Addo(8)	20	Unspecified number / historical	Dose Dithionite test	GL, FE, MDAC, $MgSO_4$, forced diuresis	Control treatment + Cyclophosphamide 5 mg/kg/IV day for 14 days Dexamethasone 24 mg/day IV for 14 days	75%	20%	Significant
Addo(9)	72	61 / historical	Dose Dithionite test	GL, FE, MDAC, $MgSO_4$, forced diuresis, vitamin B and C	Control treatment + Cyclophosphamide 5 mg/kg/IV day for 14 days Dexamethasone 24 mg/day IV for 14 days	72%	32%	Significant
Perriens(11)	33	14 / historical	Dose Dithionite test	GL, Bentonite, $MgSO_4$, forced diuresis	Control treatment + Cyclophosphamide 5 mg/kg/IV day for 14 days Dexamethasone 24 mg/day IV for 14 days	39%	36%	Not Significant
Our series	6	9 / historical	Dose Dithionite test	FE, vitamin B and C	FE + vitamin C + Cyclophosphamide 5 mg/kg/IV day for 14 days Dexamethasone 40 mg/day IV for 14 days	83.3%	0%	Significant

GL, gastric lavage; FE, Fuller's earth; MDAC, multiple dose activated charcoal

after the ingestion. Physical examination revealed tachycardia, tachypnea and generalized crepitations in both lung fields. In addition, hypoxia was found by arterial blood gas (SaO_2 85% at FiO_2 1.0). His clinical course rapidly deteriorated into severe hypotension and the patient expired before any treatment for paraquat poisoning could be initiated.

The review of Siriraj Hospital's searchable electronic medical records revealed 14 cases of paraquat poisoning that did not received immunosuppressive treatment between January 1994 to December 1997. Nine cases fulfilled the criteria for significant ingestion based on history and were included in the historical control group (Table 2). The male to female ratio was 5/4. The ingested dose ranged from 4 to 40 grams and resulted in positive urine dithionite test in all cases. Treatment was initiated within 6 hours after the ingestions, and included gastrointestinal decontamination using Fuller's earth or Bentonite, vitamin B and vitamin C. All the patients experienced severe gastrointestinal symptoms and developed significant renal failure, hepatitis and pulmonary toxicity. All the historical controls died while they were in the hospital. Six out of the nine historical controls developed fulminant poisoning and died because of multiorgan failure within day 3 after the ingestion. The remaining three patients gradually developed progressive dyspnea, pulmonary infiltration and hypoxia. Finally their clinical course ended by intractable hypoxia no later than day 12 after ingestion. The survival rates and average ingested doses are summarized in table 3.

Of the 130 attendees of the Updates in Internal Medicine 2003 course, 76 responded to the questionnaire. All the responders were doctors of medicine and were in clinical practice. Table 4 summarizes answers of these physicians.

DISCUSSION

Estimation of dose ingested has long been used as the method for determining severity of paraquat poisoning, being classified into three clinical stages[2-4].

Stage 1 or mild poisoning occurs with ingestion of less than 20 mg of paraquat per kg body weight. Patients may be asymptomatic or experience gastrointestinal symptoms such as gastrointestinal erosions, nausea and vomiting and diarrhea. There is no systemic toxicity in this stage. Patients in stage 1 usually have complete recovery[2].

Stage 2 or moderate to severe poisoning results from ingesting 20-40 mg of paraquat per kg body weight. In addition to gastrointestinal symptoms that are found in stage 1, acute renal failure and hepatitis may develop. All untreated patients develop pulmonary fibrosis. Mortality rate for this stage varies from 60-100%[2]. Patients in stage 2 are the target group where treatment with immunosuppressive regimen has been proposed to alter clinical outcome[5].

Stage 3 or fulminant poisoning is associated with ingestion of 40 mg or more of paraquat per kg body weight. Patients in this stage experience marked gastrointestinal ulceration and severe nausea and vomiting. Acute renal failure, severe hepatitis, acute non-cardiogenic pulmonary edema and hypotension quickly follow. Death due to multiorgan failure occurs within 5-7 days after the ingestion and mortality rate is 100% regardless of treatment[2].

Since paraquat poisoning is associated with exceptionally high mortality, our inclusion criteria for 'significant ingestion', using the cut off of at least 1 gram or 20 mg/kg or positive dithionite test is designed to include all cases with stage 2 or stage 3 poisoning. Patients were only categorized into stage 3 retrospectively, after their clinical course of multiorgan failure became apparent within day 7 after the ingestion[5]. From a study reported by Schermann whereby 53 patients with acute paraquat ingestion were tested for urine paraquat by semi-quantitative dithionite and quantitative radioimmunoassay methods and were followed for clinical outcome without any anti-oxidant or immunosuppressive therapy, positive dithionite test correlated with urine concentration of paraquat above 500 microgram/liter. The positive dithionite test results within 24 hours after the ingestion have 100% sensitivity, 68% specificity and 85% positive predictive value for fatal, either stage 2 or stage 3, paraquat poisoning[6]. In addition to high sensitivity and specificity, urine dithionite test is also rapid (5-10 minutes) and has easy applicability in community hospitals and emergency departments. In our series, all the patients with positive dithionite tests developed stage 2 or 3 poisoning.

In our series, patients treated with immunosuppressive regimen had survival rate of 83.3%. However, it should be noted that patient 4 in the treated group died because of acute fulminant paraquat poisoning from re-ingestion of paraquat. Therefore, the survival rate of the treated group in our series is actually 100% if only moderate to severe poisoning are considered (excluding patient 4). The 0% survival rate in our control group is in concordance with other reported series. According to the previous studies, the survival rate of patients with moderate to severe paraquat poisoning who did not receive any specific treatment other than gastrointestinal decontamination, antioxidants (vitamin C and E and N-acetylcysteine), varies from 0-36%[5,7-11]. The overall survival rate of 83.3% in our treatment group is at least comparable with survival rate of 32-80% from previous reports using cyclophosphamide-containing immunosuppressive regimens[5,7-11]. Studies by Addo found statistically significant increased survival among patients with significant paraquat ingestion[8,9], while another study by Perriens did not[11] (Table 5). The disagreement between these studies demonstrates the lack of evidence-based treatment for paraquat poisoning.

Since a randomized controlled trial for the treatment of significant paraquat ingestion is not ethically feasible, comparing the outcomes of our current regimen with historical control serves to place our study's outcome in perspective. As the data is obtained retrospectively, definitive exposure to paraquat could not be quantified by serum or urine paraquat levels, making the estimation of paraquat dose based on the ingested amount alone a somewhat presumptive maneuver. However, serum and urine paraquat concentrations are not widely available for clinical practice and have not been reported as a decision-making tool for treatment in any institution.

Adverse effects found in our treated cases, including acne and transient alopecia, are similar to

those from previous reports[11]. There has been no report of serious adverse effects, for example, hemorrhagic cystitis and leucopenia, associated with treatment of paraquat poisoning with either the 14-day cyclophosphamide plus dexamethasone regimen[8,9,11] or the pulse therapy with cyclophosphamide plus methylprednisolone[5,10,12].

Results from the survey (Table 4) among practicing physicians give us some insight about the treatment of paraquat poisoning that is currently in practice in Thailand. Most of the responders had some experience in managing cases with paraquat poisoning. Treatment options chosen by the physicians in the questionnaire, except the gastrointestinal decontamination, had been demonstrated to be obsolete and would not expect to effect clinical outcomes. In contrast, the immunosuppressive therapies (cyclophosphamide, methylprednisolone and vincristine) were not given in the actual practice, most likely owing to the unfamiliarity of the physicians to the drugs and the fear of adverse effects.

From the outcomes of ours and other's previous studies, coupled with the extremely unfavorable experience with the non-immunosuppressive treatment in the past and the relatively benign adverse effects being reported, we would like to encourage practicing physicians in Thailand to treat patients with paraquat poisoning with the cyclophosphamide plus dexamethasone regimen. Indication for the treatment can be determined by the ingestion history, in combination with the urine dithionite test, which is reasonably accurate and is available for urgent decisions even in community hospitals.

CONCLUSION

Our first two years experience with the cyclophosphamide plus dexamethasone regimen in treatment of paraquat poisoning has a satisfactory outcome, especially when compared to the outcomes from historical controls from our institution. Therefore, the Medical Toxicology Service at Siriraj Hospital will continue its practice using this viable alternative to an otherwise serious and untreatable poisoning and would like to encourage treatment with the regimen for medical practice in Thailand.

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