Clinical Presentation and Outcomes of Intentional Paraquat Ingestion in a Hospital at Northern Philippines from 2011 to 2013

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Abstract

Introduction: Acute paraquat (PQ) poisoning is associated with high case fatality rate. Following a report of 108 cases of poisoning from 2011 to 2013, the distribution, sale, and use of PQ was recently prohibited in the Philippines. However, there still is a need to gather additional information on the manifestations of PQ poisoning in the Philippines. Hence, this study aimed to identify the clinical presentation and outcomes of cases of PQ poisoning seen in a hospital at northern Philippines.

Case presentation: Nine cases of oral PQ poisoning from 2011 to 2013 were included in this series. All cases were intentional. Majority (88%) of the patients were females. Seven of the nine (77%) cases were from Baggao, Cagayan, a nearby agricultural town. Mean age was 30 (range 21-47). Initial presenting symptoms were vomiting, difficulty in swallowing, abdominal pain and gastrointestinal bleeding. Of the nine cases, four died (44%) in the hospital. Three (33%) survived without complications. Long-term outcomes of the remaining two cases (22%) were unknown. All patients who eventually died developed dyspnea during their hospital stay, and subsequently went into acute respiratory failure. Azotemia and leukocytosis were also recorded among those who died.

Discussion: High mortality rate among PQ poisoning patients can be attributed to the absence of antidote and the unsatisfactory outcomes of post-exposure management.

Conclusion: Mortality rate for this series was 44%, and all died of progressive respiratory failure. Gastrointestinal toxicity was universal in the nine reported cases. Azotemia and leukocytosis were the other significant findings observed among the cases of fatal poisoning.

Keywords: paraquat, herbicide, ingestion, poisoning, case report

Introduction

Paraquat (PQ, 1,1'-dimethyl-4,4'-bipyridinium dichloride) is a potent herbicide and is considered the leading single agent causing death from pesticide poisoning worldwide.[1,2]

Fulminant poisoning or ingestion of 50-100 ml of PQ (20% solution) causes multiorgan failure followed by death within hours to a few days. Ingestion of smaller amounts causes toxicity in the lungs and kidneys with death occurring in two to three weeks from respiratory failure.[1-5] Overall, the mortality rate for PQ poisoning is reported to be more than 50%.[1,2] This is largely attributed to the absence of antidote and the unsatisfactory outcomes of post-exposure management even in non-fulminant cases.[4]

In 2017, a bill prohibiting the distribution, sale and use of PQ was filed in the Philippine House of Representatives[6] in response to increasing incidents of PQ poisoning in the Philippines, including 108 cases reported by the Benguet Provincial Health Office from 2011 to 2013.

There is a need, however, to further elucidate the manifestations of PQ poisoning in the Philippine setting. This present report of nine cases, therefore aimed to identify the clinical presentation and outcomes of cases of PQ poisoning seen in a tertiary teaching hospital in northern Philippines from 2011 to 2013.

Methods

This study was conducted at the Cagayan Valley Medical Center, a 500-bed Department of Health-accredited, tertiary teaching hospital in northern Philippines. A number of agricultural towns are part of the catchment area of the regional medical center.

We reviewed the medical records of nine consecutive patients admitted in the service ward due to PQ ingestion from 2011 to 2013. The following data were abstracted from the retrieved medical charts: age and sex, place of origin, time elapsed from ingestion to emergency department (ED) consult, clinical presentation and outcomes.

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Table I. Clinical presentation and outcomes of the reported nine cases of paraquat ingestion

Case	Age/Sex	Amount (mL)	Time elapsed from ingestion to ED consult (hours)	Presenting symptom	Dyspnea	Leukocytosis	Azotemia	Initial management	Outcome
1	47/F	60	12	dizziness, epigastric pain, hematemesis	Present	Present	Present	ACC, PPI	Died
2	27/F	45	4	vomiting	Present	Present	Present	ACC, PPI	Died
3	46/F	60	12	epigastric pain, dysphagia	Present	Present	Present	ACC, PPI, hydrocortisone	Died
4	31/F	30	12	vomiting and loose stools	Absent	Present	Absent	ACC, PPI	Survived[1]
5	37/F	15	96	hoarseness of voice, dysphagia	Absent	Absent	Present	PPI	Survived[2]
6	29/F	30	7	abdominal pain, vomiting	Present	Present	Absent	ACC, PPI, dexamethasone	Died
7	30/F	15	20	epigastric pain, vomiting	Absent	Absent.	Absent	ACC, PPI, dexamethasone	Survived[1]
8	27/M	10	4	dizziness, abdominal pain	Absent	Absent	Absent	ACC, PPI, dexamethasone	Survived[2]
9	21/F	30	168	hoarseness of voice, dysphagia, oral cavity exudates	Absent	Absent	Present	PPI, dexamethasone clindamycin	Survived[2]

ACC: activated charcoal with cathartic, PPI: Proton Pump Inhibitor
[1] Long-term outcome unknown, [2] No complications

Case Presentation

The clinical presentation and outcomes of the nine cases included in this series are summarized in Table I.

Demographic data summary

All cases were intentional. Eight of the nine (88%) cases were female. Mean age was 30 (range 21-47). Seven of the nine (77%) cases were from Baggao, Cagayan, a nearby agricultural town.

Case 1

A previously well 47-year-old female from Baggao, Cagayan consulted at the ED, 12 hours after intentionally-ingesting approximately 60 mL of PQ (20% solution). Upon ingestion, patient complained of dizziness followed by epigastric pain and an episode of vomiting amounting to one-half cup of blood-streaked vomitus.

At the ED, patient was conscious, coherent and not in cardio-respiratory distress. The vital signs were as follows: blood pressure of 110/80 mmHg, cardiac rate of 79 bpm, respiratory rate of 19 and temperature of 37°C. No pallor or jaundice was noted. Breath sounds were clear. Examination of the abdomen revealed tenderness on the epigastric area upon deep palpation and no melena or hematochezia was noted on rectal examination. There were no skin lesions and neurological examination was normal.

Nasogastric tube was inserted. Lavage with activated charcoal and cathartic (castor oil) was done. Patient was given omeprazole 40 mg intravenously once a day.

Laboratory results were as follows: Hemoglobin: 128 g/L (NV 120-160), Hematocrit 0.39 (NV 0.38-.47), Platelets 863 x 10^9 (NV 150-400), White blood cells (WBC) 47 x 10^9 (NV 4.5-11) (Neutrophil 95.2, Lymphocyte 1.3, Eosinophil 0.1, Monocyte 3.54). Creatinine 117.7 umol/L (NV 53-115). AST and ALT were not done. Chest radiograph showed no infiltrates. Electrocardiogram was normal.

On her first hospital day, epigastric pain persisted with episodes of dyspnea. The difficulty of breathing progressed on her second hospital day and the patient eventually went into respiratory failure, three hours prior to her demise and she was subsequently intubated. Cardiopulmonary arrest followed and patient expired despite attempt to resuscitate.

Case 2

Four hours after intentionally-ingesting approximately 45 mL of PQ, a previously well 27-year-old female from Baggao, Cagayan was brought to the ED. Patient had one episode of vomiting upon ingestion.

Patient was conscious and coherent but in respiratory distress. Patient was normotensive (BP 120/80), with a cardiac rate of 89 beats per minute, regular, tachypneic at 26 breaths per minute and afebrile. Chest examination was normal. Examination of the heart was also unremarkable. Jaundice and other skin changes were absent. Initial management comprised of administration of activated charcoal and parenteral omeprazole at the dose of 40 mg once a day.

Laboratory examination results were as follows: Hemoglobin 161 g/L (NV 120-160), Hematocrit 0.49 (NV 0.38-.47) Platelets 307 x 10^9 (NV 150-400) WBC 45.90 x 10^9 (NV 4.5-11) (Neutrophil 91.1, Lymphocyte 2.6, Eosinophil 0.1, Monocyte 4.7, Basophil 1.5). Creatinine 218 umol (NV 53-115) AST and ALT were not done. Chest radiograph showed no infiltrates. Electrocardiogram was normal.

At the ward, patient developed progressive respiratory failure leading to endotracheal intubation and eventually

went into cardiopulmonary arrest, six hours after hospital admission and 10 hours after PQ ingestion.

Case 3

A 46-year-old female from Baggao, Cagayan with no known co-morbidities was brought to the ED complaining of epigastric pain and dysphagia. The patient intentionally ingested PQ amounting to approximately 60 mL, 12 hours prior to consult and subsequent admission.

Patient was conscious, coherent and not in cardio-respiratory distress. Vital signs were within normal limits. Pertinent findings in the physical examination were note of erythematous oropharyngeal mucosa and the presence of epigastric tenderness on palpation. No jaundice, adventitious breath sounds, or neurologic deficits was noted.

Laboratory examination results were as follows: Hemoglobin 127 g/L (NV 120-160), Hematocrit 0.38 (NV 0.38-.47) Platelet 469 x 10^9 (NV 150-400) WBC 22 x 10^9 (4.5-11) (Neutrophil 89.6, Lymphocyte 7.7, Monocyte 2.2, Eosinophil 0.2, Basophil 0.3.) Creatinine 264.92 umol (NV 53-115) AST and ALT were not done Chest radiograph showed no infiltrates. Electrocardiogram was normal.

Lavage with activated charcoal and cathartic (sodium sulfate) was done. Patient was given omeprazole 40 mg intravenously once a day.

Esophagogastroduodenoscopy (EGD) was performed revealing erosive gastritis with no evidence of bleeding. Omeprazole was continued.

Patient was seen by the psychiatry service. She was diagnosed with major depressive disorder and started on duloxetine.

The dysphagia and epigastric pain resolved after seven days and the patient insisted to be discharged against medical advice. Two days after discharge, patient was brought back to the ED in severe respiratory distress with a respiratory rate of 38 breaths per minute. She was intubated at the ED. Hydrocortisone 100 mg IV every six hours was started. Patient went to cardio-pulmonary arrest and eventually expired 15 hours after readmission due to progressive respiratory failure.

Case 4

A 32-year-old female from Baggao, Cagayan, who ingested approximately 30 mL of PQ, four hours prior consulted at the ED due to the chief complaint of loose stools. Patient complained of several episodes of vomiting and loose stools upon ingestion of the herbicide.

At the ED, patient was conscious, coherent and not in cardio-respiratory distress. The vital signs were within normal limits. Oral mucosa was moist. Skin turgor was good. Examination of the abdomen revealed no tenderness. Yellow watery stool was noted on rectal examination. Physical findings of the heart, lungs, skin and central nervous systems were normal.

Supportive therapy with activated charcoal and intravenous omeprazole was given.

Laboratory results were as follows. Hemoglobin: 132 g/L (NV 120-160), Hematocrit 0.39 (NV 0.38-.47), Platelet 437 x 10^9 (NV 150-400), WBC 22.5 x 10^9 (NV 4.5-11) (Neutrophil 69.9, Lymphocyte 23.2. Monocyte 6.9). Creatinine 60 umol/L (NV 53-115). AST 33 U/L (NV 14-59) and ALT 22 U/L (9-72). Chest radiograph showed no infiltrates. Electrocardiogram was normal.

Patient was seen by the psychiatry service and was diagnosed with impulse control disorder.

Resolution of diarrhea was noted on the second hospital day and the patient requested to be discharged. Patient was advised to come back for follow up check but did not comply. Long-term outcome for this case was thus unknown.

Case 5

A previously well 32-year-old female from Baggao, Cagayan, intentionally ingested approximately 15 mL of PQ, four days prior to consult at the ED and presented with hoarseness of voice and dysphagia.

At the ED, patient was conscious, coherent and not in cardio-respiratory distress. The vital signs were within normal limits. There was note of oropharyngeal congestion, but the rest of the physical examination was unremarkable.

Nasogastric tube as inserted but lavage with activated charcoal and cathartic was not done. Patient was given a stat dose of omeprazole 40 mg intravenously and then once a day thereafter.

Laboratory results were as follows. Hemoglobin: 150 g/L (NV 120-160), Hematocrit 0.43 (NV 0.38-.47), Platelets 448 x 10^9 (150-400), WBC 9.41 x 10^9 (NV 4.5-11) (Neutrophil 55.9, Lymphocyte 26.8 Monocyte 16.3, Eosinophil 0.7, Basophil 0.3). Creatinine 244 umol/L (NV 53-115). AST and ALT were not done. Chest radiograph showed no infiltrates. Electrocardiogram was normal.

EGD was performed with note of oropharyngeal and esophageal injury. Then the patient was discharged after six hospital days with complete resolution of symptoms. Patient was seen on follow-up and had no evidence of complication.

Case 6

A previously well 29-year-old female from Baggao, Cagayan, complaining of abdominal pain and vomiting was rushed to the ED, seven hours after intentionally ingesting approximately 30 ml of PQ.

At the ED, patient was conscious, coherent and not in cardio-respiratory distress. The vital signs were within normal limits. The physical examination was unremarkable.

Control of vomiting was done by giving of metoclopramide and then lavage with activated charcoal was subsequently performed. Intravenous omeprazole was also given.

Laboratory results were as follows. Hemoglobin: 128 g/L (NV 120-160), Hematocrit 0.379 (NV 0.38-.47), Platelets 468 x 10^9 (NV 150-400), WBC 17.4 x 10^9 (4.5-11) (Neutrophil 89.7, Lymphocyte 6.8, Monocyte 3.3). Creatinine 71.8 umol/L (NV 53-115). AST 33 U/L (NV 14-59) and ALT 29 U/L (NV 9-72). Chest radiograph showed no infiltrates. Electrocardiogram was normal.

At the ward, the abdominal pain resolved on her first hospital day. The patient insisted to go home against medical advice on her third hospital day. Patient was sent home on oral omeprazole.

Five days after discharge, the patient complained of dyspnea. Progression of dyspnea prompted relatives to bring the patient back to the hospital. Patient was in severe respiratory distress at the ED. Patient was intubated and started on dexamethasone 8 mg IV every six hours.

Laboratory results were as follows. Hemoglobin: 115 g/L (NV 120-160), Hematocrit 0.33 (NV 0.38-.47), Platelets 665 x 10^9 (NV 150-400), WBC 36.5 x 10^9 (4.5-11) (Neutrophil 83.9, Lymphocyte 9,5, Monocyte 6.7). Creatinine 103 umol/L (NV 53-115). Liver enzymes were not done. Chest radiograph was normal. Electrocardiogram was normal. Patient eventually expired 10 hours upon readmission due to progressive respiratory failure.

Case 7

A thirty-year-old woman was brought to the ED 20 hours after ingesting 15 ml of PQ. Patient complained of epigastric pain and vomiting. At the ED, patient was conscious, coherent and not in cardio-respiratory distress. The vital signs were within normal limits. The physical examination was unremarkable.

Lavage with activated charcoal and cathartic (sodium sulfate) was done. Patient was given omeprazole 40 mg intravenously once a day. Patient was given dexamethasone 8 mg IV every six hours.

Laboratory results were as follows. Hemoglobin: 123 g/L (NV 120-160), Hematocrit 0.370 (NV 0.38-.47), Platelets 369 x 10^9 (NV 150-400), WBC 7.8 x 10^9 (4.5-11) (Neutrophil 47.3, Lymphocyte 29.5, Monocyte 6.9, Eosinophil 16.0). Creatinine 71.8 umol/L (NV 53-115). AST and ALT was not done. Chest radiograph showed no infiltrates. Electrocardiogram was normal.

Patient was discharged after four hospital days with complete resolution of symptoms. Patient was sent home on oral dexamethasone to complete two weeks. Patient was advised to come back for follow up check but did not comply. Long-term outcome for this case is thus unknown.

Case 8

A previously well 27-year-old male from Alcala, Cagayan intentionally ingested approximately 10 ml of PQ with one and half bottle of gin, four hours prior to admission. Patient complained of dizziness and epigastric pain at the ED.

Patient was conscious, coherent and not in cardio-respiratory distress. The vital signs were within normal limits. The physical examination was unremarkable.

Initial management included lavage with activated charcoal and giving of omeprazole 40 mg IV once a day and dexamethasone 8 mg IV every six hours hours.

Laboratory results were as follows. Hemoglobin: 128 g/L (NV 120-160), Hematocrit 0.370 (NV 0.38-.47), Platelets 369 x 10^9 (NV 150-400), WBC 6.9 x 10^9 (4.5-11) (Neutrophil 57.3, Lymphocyte 29.5, Monocyte 6.9, Eosinophil 16.0). Creatinine 89.28 umol/L (NV 53-115). AST 26.9 U/L (NV 0-40) and ALT 19.10 U/L (NV 0-41). Chest radiograph showed no infiltrates. Electrocardiogram was normal.

Patient was seen by the psychiatry service and was diagnosed with impulse control disorder.

Patient was discharged asymptomatic after three hospital days. Patient was sent home on oral omeprazole and dexamethasone to complete two weeks. Patient was advised to come back for follow up check but did not comply. Patient was contacted after four weeks through telephone and there was no evidence of complication.

Case 9

A previously well 21-year-old female from San Mariano, Isabela intentionally ingested approximately 20 mL of PQ one week prior to consult at the ED and presented with hoarseness of voice and dysphagia.

At the ED, patient was conscious, coherent and not in cardio-respiratory distress. The vital signs were as follows: blood pressure of 120/80 mmHg, cardiac rate of 88 bpm, respiratory rate of 22 and temperature of 36.8 degrees

Celsius. There was note of whitish exudates in the oral cavity extending to the pharyngeal walls.

Patient was given a stat dose of omeprazole 40 mg intravenously and then once a day thereafter. Patient was also started on dexamethasone 8 mg IV every six hours and clindamycin 600 mg IV every six hours.

Laboratory results were as follows. Hemoglobin: 114 g/L (NV 120-160), Hematocrit 0.316 (NV 0.38-.47), Platelets 270 x 10^9 (150-400), WBC WBC 5.96 x 10^9 (NV 4.5-11) (Neutrophil 54.9, Lymphocyte 36.3 Monocyte 7.1, Eosinophil 1.4, Basophil 0.3). Creatinine 522 umol/L (NV 53-115). AST 26 U/L (NV 14-59) and ALT 36 U/L (NV 9-72). Chest radiograph showed no infiltrates. Electrocardiogram was normal.

EGD was performed with note of caustic injury to the oral cavity, pharynx and distal third of the esophagus.

Patient was discharged after four hospital days with complete resolution of symptoms. Patient was sent home on oral omeprazole and dexamethasone to complete two weeks. Patient went on follow up check with no evidence of complication.

Outcome summary

Of the nine cases, four died (44%) in the hospital. Three (33%) survived without complications. Long-term outcomes of the remaining two cases (22%) were unknown. All patients who eventually died developed dyspnea during their hospital stay and subsequently went into acute respiratory failure. Azotemia was also recorded among those who died (3/4, 75%), suggestive of a probable multi-organ failure as a cause of death. Five of the nine patients also manifested with leukocytosis and four of whom died (80%).

Discussion

We reported nine cases of PQ poisoning with 44% case fatality rate.

Regardless of the amount ingested, the initial presenting symptoms of oral PQ poisoning in this series refer to the involvement of the gastrointestinal system. Symptoms noted after exposure were vomiting, difficulty in swallowing, abdominal pain, loose stools and gastrointestinal bleeding. Erosive injury along the alimentary tract was documented in the patients who underwent EGD. These findings are consistent with the observation previously reported in literature that gastrointestinal toxicity is universal among PQ poisoning patients.[2]

Manifestations of fatal acute PQ poisoning, however, are dose-dependent.[1-5] As previously mentioned, ingestion of 50-100 ml of PQ (20% solution) causes multiorgan failure followed by death without hours to a few days. Ingestion of smaller amounts causes toxicity in the lungs and kidneys with death occurring in two to three weeks from respiratory failure.

Quantitative plasma determination taken within four hours from ingestion is considered the most reliable predictor of mortality.[4, 5, 7-10] A semi-quantitative urine dithionite test is another useful test to ascertain prognosis as survival is expected if the test is negative.[9] Concentration assays, however are not available in the Philippines. Consequently, in this series, amount ingested were only estimates as reported in the medical history. There was a trend towards poorer outcomes with higher doses, however. The four patients who died ingested more than 30 ml.

The development of dyspnea and subsequent acute respiratory failure were observed in all patients who died. The absence of which seemed to favor better prognosis. This is consistent with what was previously noted in literature. Death from severe PQ poisoning primarily results from progressive pulmonary fibrosis secondary to diffuse alveolar damage leading to acute respiratory distress syndrome (ARDS) as documented in the autopsy of patients who died of PQ poisoning.[1,2,3] The respiratory failure seen in the four patients who died, however, can only be presumptively attributed to progressive pulmonary fibrosis because no autopsy was performed. Furthermore, due to rapid progression of the respiratory distress, documentation of ARDS by arterial blood gases and serial chest radiographic imaging was not done.

Increased serum creatinine was also noted among three of the patients who died. This is expected because PQ is eliminated unchanged in the urine.[11] Acute kidney failure is a recognized complication of PQ poisoning and often accompanies acute lung injury in moderate to severe cases.

Leukocytosis has also been reported in the literature as another surrogate marker for multi-organ damage and probable predictor of survival.[12] PQ causes a significant increase in the total number of white blood cells. No evidence of leukocytosis over time may be indicative of a lesser degree of PQ exposure or absorption, a greater degree of PQ excretion, or a lower vulnerability to PQ toxicity. Five of the nine patients included in the series manifested with leukocytosis and four of whom died in the hospital.

The literature[1,2,3,4,12] also reported liver injury and metabolic acidosis in PQ poisoning but this was not seen among the patients reviewed due to the lack of documentation of liver tests and arterial blood gases.

High mortality rate among patients of PQ poisoning is largely attributed to the absence of an antidote[4] and the lack of standards of care in post-exposure management. Common treatments with absorbents, radiotherapy,

hemodialysis and hemoperfusion have been disappointing in reducing mortality.[1,2,3] Variations in the post-exposure management of PQ ingestion due to the lack of a standardized hospital treatment protocol was highlighted in our experience with the nine patients included. Hence, there is a need to assess the applicability of new treatment modalities in the local setting.

Pulse immunosuppressive therapy in the management of lung injury due to severe PQ poisoning seems promising. A Cochrane systemic review[13] of three small RCTs (164 participants) reported that moderate to severe PQ poisoning patients treated with glucocorticoids and cyclophosphamide on top of standard care had a lower risk of death than those receiving standard care only. A subsequent review[14] that included two additional non-randomized control trials reported the similar results but also reported that pulse immunosuppressive therapy also caused more leukopenia than the controls. The relative high cost of pulse immunosuppressive therapy, however, limits the applicability of such intervention locally.

Conclusion

Mortality for this series was 44%, and all died due to progressive respiratory failure. Gastrointestinal toxicity was universal for the reported PQ poisoning patients. Azotemia and leukocytosis were the other significant findings observed among the cases of fatal poisoning.

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