

Spectrum of corrosive esophageal injury after intentional paraquat or glyphosate-surfactant herbicide ingestion

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Background: Data on the spectrum of corrosive injury to the esophagus after paraquat or glyphosate-surfactant ingestion are sparse in the literature and confined to case studies and brief reports. Therefore, this study aimed to examine the clinical features, degrees of esophageal injury, and clinical outcomes after paraquat or glyphosate herbicide ingestion, and sought to determine what association, if any, may exist between these findings.

Methods: We performed an observational study on 47 patients with paraquat or glyphosate ingestion who underwent endoscopic evaluation over a period of 11 years (2000–2011).

Results: Corrosive esophageal injuries were classified as grade 1 in 14 (glyphosate-surfactant) and three (paraquat), grade 2a in nine (glyphosate-surfactant) and 18 (paraquat), and grade 2b in one (glyphosate-surfactant) and two (paraquat) patients. No patients had grade 0, 3a, or 3b esophageal injuries. Therefore, the severity of corrosive injury was more severe in the paraquat group ($P = 0.005$). After toxin ingestion, systemic toxicity occurred, with rapid development of systemic complications in many cases. Neurologic complications occurred more frequently in the glyphosate-surfactant group (29.2% versus 0%, $P = 0.005$), although respiratory failure (4.2% versus 34.8%, $P = 0.008$), hepatitis (12.5% versus 52.2%, $P = 0.004$), and renal failure (20.8% versus 52.2%, $P = 0.025$) developed more frequently in the paraquat group. Patients with glyphosate poisoning had shorter hospital stays than patients with paraquat poisoning (13.3 ± 15.1 days versus 26.8 ± 10.2 days, $P = 0.001$). Nevertheless, there was no significant difference in mortality rate between the glyphosate-surfactant and paraquat groups (8.3% versus 13.0%, $P = 0.601$). We ultimately found that patients with grade 2b esophageal injury suffered from a greater incidence of respiratory (100.0% versus 5.9%, $P = 0.001$) and gastrointestinal (66.7% versus 11.8%, $P = 0.034$) complications than patients with grade 1 injury, regardless of herbicide type.

Conclusion: Paraquat and glyphosate are mild caustic agents that produce esophageal injuries of grades 1, 2a, and 2b only. Our data also suggest a potential relationship between the degree of esophageal injury and systemic complications.

Keywords: paraquat, glyphosate-surfactant, poisoning, suicide, esophageal injury

Introduction

Because of the ease of access, intentional ingestion of paraquat¹ occurs commonly in Taiwan. Paraquat is a widely used bipyridyl contact herbicide with a good safety record when used properly. However, the lethal toxicity of this compound always results in a high mortality rate. There are three degrees of severity for paraquat poisoning following ingestion.² Mild poisoning initially induces oral irritation and gastrointestinal upset but eventually results in a complete recovery. Moderate to severe poisoning typically results in acute renal failure, whereas in severe cases, acute hepatitis is followed by

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either pneumonitis or pulmonary fibrosis, which often results in death after 2–3 weeks. Finally, acute fulminant poisoning results in death within a week due to multiple organ failure and cardiovascular collapse.² Many treatment modalities have been developed for paraquat poisoning, including adsorbents, hypo-oxygenation, lung radiotherapy,³ prolonged extracorporeal detoxification,⁴ and lung transplantation. However, the efficacies of these therapeutic methods remain uncertain.

At our hospital, all patients with paraquat poisoning are treated using a standard detoxification protocol.^{1,5–10} This protocol consists of repeated pulses of methylprednisolone and cyclophosphamide followed by prolonged dexamethasone therapy. Using this practice, the respiratory function and blood oxygen concentrations in most patients returned to near-normal levels in 3–6 months.¹¹ Notably, there is no specific antidote for paraquat intoxication.¹²

Glyphosate-surfactant is a broad spectrum, nonselective herbicide that is extensively used in agriculture in Taiwan. The glyphosate-surfactant herbicides available on the agrochemical market in Taiwan are formulated commercial products that contain isopropylamine salt of glyphosate, variable amounts of surfactant, and water.¹³ The ingestion of glyphosate-surfactant is reported to cause significant toxicity, including oral irritation, gastrointestinal upset, renal and hepatic impairment, respiratory distress, pulmonary edema, shock, and disturbance of consciousness.¹⁴ The mechanism of toxicity of glyphosate-surfactant formulations in humans is unclear,¹⁴ because both the herbicide and surfactant may contribute to toxicity. It is also unknown whether mixing glyphosate with a surfactant could enhance the toxicity. Nevertheless, there is no available antidote for glyphosate-surfactant poisoning, and its management is principally symptomatic and supportive.¹⁴

Data on the spectrum of corrosive injury to the esophagus after paraquat^{6,15–19} or glyphosate-surfactant^{20–24} ingestion are sparse in the literature and confined to case studies and brief reports. There have been occasional reports of severe damage to the esophagus; however, the location, extent, and severity of the damage have not been clearly defined. The use of paraquat has been questioned and discussed for decades by international and national regulatory bodies as well as nongovernmental organizations, and many countries have banned its use;²⁵ as a result, few related studies have been published. Therefore, this observational study examined the clinical features, degrees of esophageal injury, and clinical outcomes after paraquat or glyphosate-surfactant ingestion, and sought to determine what association, if any, may exist between these findings.

Materials and methods

Ethics statement

This retrospective observational study complied with the guidelines of the Declaration of Helsinki and was approved by the medical ethics committee of Chang Gung Memorial Hospital. Because of the retrospective nature of this study, institutional review board approval (99-1073B) was obtained and the informed consent of the risk of endoscopic examinations and treatment modalities provided by all patients on their initial admission was used. Moreover, all individual information was securely protected (by delinking identifying information from the main dataset) and made available only to the investigators. All of the data were analyzed anonymously, and all primary data were collected according to the Strengthening the Reporting of Observational Studies in Epidemiology guideline. This policy was based on a previous publication.²⁶

Patients

Here we performed a retrospective observational study on all patients with paraquat or glyphosate-surfactant poisoning admitted to the Chang Gung Memorial Hospital over a period of 11 years (2000–2011). Only patients with paraquat and glyphosate ingestions for whom endoscopic evaluations were performed were included in the study.

Diagnosis of paraquat or glyphosate-surfactant poisoning

A presumptive diagnosis of paraquat poisoning was based on exposure history, clinical effects, and physical and laboratory examinations (especially urine sodium dithionite screening test).^{1,5–10} The urine sodium dithionite reaction was dependent on reduction of paraquat by sodium thionite under alkaline conditions to form stable blue-colored radical ions. The generation of a strong navy or dark blue color generally indicates significant paraquat ingestion and often indicates a poor prognosis. Nevertheless, the urine test was used as a paraquat screen, and a confirmatory diagnosis of paraquat poisoning was only possible by checking blood paraquat levels using a spectrophotometer (Hitachi, Tokyo, Japan). Similarly, the diagnosis of glyphosate-surfactant poisoning was based on exposure history, clinical effects, and physical and laboratory examinations.¹⁴

Inclusion and exclusion criteria

All patients >18 years of age diagnosed with either paraquat or glyphosate-surfactant poisoning at Chang Gung Memorial Hospital between 2000 and 2011 were eligible

for inclusion in this study. Patients with paraquat poisoning were excluded from this study if they were <18 years or if the paraquat exposure was dermal or intravascular. They were also excluded if they did not have detectable paraquat levels in their urine and blood (despite suspicion of exposure) or had major comorbidities such as cancer, heart, lung, renal, or liver disease. Similarly, patients with glyphosate-surfactant poisoning were excluded from this study if they were <18 years or if they had major comorbidities such as cancer, heart, lung, renal, or liver disease.

Paraquat or glyphosate-surfactant detoxification protocol

The protocol^{1,5-10} includes gastric lavage with a large amount of normal saline followed by active charcoal administration, charcoal hemoperfusion, and pulse therapies of cyclophosphamide and methylprednisolone followed by dexamethasone therapy as well as repeated glucocorticoid and cyclophosphamide pulse therapies in cases of hypoxemia. Similarly, glyphosate-surfactant patients were intensively treated by gastric lavage with a large amount of normal saline followed by active charcoal administration. As mentioned, there is no antidote available for glyphosate-surfactant poisoning, and its management is mainly symptomatic and supportive.¹⁴

Endoscopic examination and grading

After an overnight fast, upper gastrointestinal endoscopy was performed using a standard flexible endoscope. Injury to the upper gastrointestinal tract was reported as described by Zargar et al: grade 0, normal findings; grade 1, edema, hyperemia of mucosa; grade 2a, friability, blisters, hemorrhaging, erosions, whitish membranes, exudates, and superficial ulcerations; grade 2b, grade 2a plus deep discrete or circumferential ulcerations; grade 3a, small scattered areas of multiple ulcerations and areas of necrosis (brown-black or grayish discoloration); and grade 3b, extensive necrosis.²⁷

Definitions of clinical events

Neurologic complications were defined if a patient experienced a seizure with a disturbance of consciousness. Cardiovascular complications were defined as patients suffering from hypotension, shock, or arrhythmia. Respiratory failure was defined as intubation. Gastrointestinal bleeding episodes were recorded as hematemesis, melena, or hematochezia. Acute renal failure was documented if serum creatinine increased to >1.4 mg/dL (normal 0.4–1.4 mg/dL). Acute hepatitis was documented when

serum alanine aminotransferase was >70 U/L (normal 0–36 U/L) or when total bilirubin was >3.0 mg/dL (normal 0–1.3 mg/dL).

Statistical analysis

Data are expressed as the mean \pm standard deviation or number and percentage in parentheses unless otherwise stated. All analyses were performed using IBM Statistical Package for the Social Sciences version 20 software (IBM, Armonk, NY, USA). Data were routinely tested for normality of distribution and equality of standard deviations before the analysis. For comparisons between patient groups, the Student's *t*-test was used for quantitative variables, whereas the Chi-square or Fisher's Exact test was used for categorical variables. The criterion for significance was the 95% confidence interval to reject the null hypothesis.

Results

Table 1 outlines the patient characteristics at baseline. We found that patients with glyphosate-surfactant poisoning were older (56.8 ± 17.6 years versus 36.4 ± 13.8 years, $P < 0.001$) but received endoscopic examinations sooner (4.4 ± 6.9 days versus 9.3 ± 6.4 days, $P = 0.016$) than patients with paraquat poisoning. Otherwise, there were no significant differences in other baseline variables between the two groups.

As shown in Table 2, corrosive esophageal injuries were classified as grade 1 in 14 (glyphosate-surfactant) and three (paraquat) patients, grade 2a in nine (glyphosate-surfactant) and 18 (paraquat) patients, and grade 2b in one (glyphosate-surfactant) and two (paraquat) patients. No patients had grade 0, 3a, or 3b esophageal injuries. The severity of corrosive injury was greater in the paraquat group than in the glyphosate-surfactant group ($P = 0.005$).

After toxin ingestion, systemic toxicity occurred with the rapid development of systemic complications in many cases (Table 3). Neurologic complications occurred more frequently in the glyphosate-surfactant group (29.2% versus 0%, $P = 0.005$), although respiratory failure (4.2% versus 34.8%, $P = 0.008$), hepatitis (12.5% versus 52.2%, $P = 0.004$), and renal failure (20.8% versus 52.2%, $P = 0.025$) developed more frequently in the paraquat group.

Patients with paraquat poisoning were intensively treated using a standard detoxification protocol (Table 4). In contrast, patients with glyphosate-surfactant poisoning received the best supportive medical care. Patients with glyphosate poisoning stayed in hospital for a shorter duration than patients with paraquat poisoning (13.3 ± 15.1 days versus 26.8 ± 10.2 days, $P = 0.001$). Nevertheless, there

Table 1 Baseline characteristics of patients with paraquat or glyphosate-surfactant poisoning who underwent endoscopic evaluation (n = 47)

| Variable | Glyphosate-surfactant (n = 24) | Paraquat (n = 23) | Chi-square | P-value |
|---|--------------------------------|-------------------|------------|-----------|
| Male, n (%) | 16 (66.7) | 13 (56.5) | 0.512 | 0.474 |
| Age, years | 56.8 ± 17.6 | 36.4 ± 13.8 | | <0.001*** |
| Intentional, n (%) | 20 (83.3) | 18 (78.3) | 0.195 | 0.659 |
| Diabetes mellitus, n (%) | 3 (12.5) | 0 (0) | 3.071 | 0.080 |
| Hypertension, n (%) | 1 (4.2) | 0 (0) | 0.979 | 0.322 |
| Serum paraquat level, µg/mL | | 1.3 ± 2.2 | | |
| Interval from poisoning to detoxification treatment, days | 0.2 ± 0.4 | 0.6 ± 0.8 | | 0.057 |
| Interval from poisoning to endoscopy, days | 4.4 ± 6.9 | 9.3 ± 6.4 | | 0.016** |
| White blood cell count/mm ³ | 12,258 ± 5,102 | 10,426 ± 4,148 | | 0.185 |

Notes: **P < 0.01; ***P < 0.001.

was no significant difference in mortality rates between the glyphosate-surfactant and paraquat groups (8.3% versus 13.0%, $P = 0.601$).

Our findings suggested that the magnitude of corrosive esophageal injury (a local complication) might be associated with systemic complications regardless of herbicide type (Table 5). For example, patients with grade 2b esophageal injuries suffered from greater incidences of respiratory failure (100.0% versus 5.9%, $P = 0.001$) and gastrointestinal bleeding (66.7% versus 11.8%, $P = 0.034$) than patients with grade 1 injuries.

Discussion

As mentioned, data on the spectrum of corrosive injury to the esophagus after paraquat ingestion are sparse in the literature and confined to case studies and brief reports.^{6,15–19} In 1978, Ackrill et al¹⁵ reported two fatal cases of esophageal perforation due to paraquat ingestion. The striking feature noted in these two cases was total ulceration of the esophageal mucosa, but the stomach was spared. Whether the lack

of gastric ulceration was due to the type of epithelium, the presence of acid or mucus, or other local factors is unknown. Mui and Epp¹⁹ did a retrospective study of 38 paraquat-induced upper gastrointestinal tract injury cases during the period of 1986–1989. Fifty-three sessions of endoscopy were performed. The endoscopic assessments of buccal, esophageal, and gastric lesions were classified into grades I, II, III, and IV according to injury severity. A total of five, six, ten, and 17 patients, respectively, were classified in these four different groups. Grade I lesions were lesions confined to the oral or pharyngeal mucosa only. Grade II lesions were lesions in the oral cavity combined with focal esophageal lesions. Grade III lesions were defined as any form of oral and diffuse esophageal lesions but without gastric lesions. Grade IV lesions consisted of any combination of oral and esophageal lesions accompanied by gastric lesions. Patients with grade III or IV injury had a worse

Table 3 Systemic complications after paraquat or glyphosate-surfactant ingestion (n = 47)

| Variable | Glyphosate-surfactant (n = 24) | Paraquat (n = 23) | Chi-square | P-value |
|-------------------------------------|--------------------------------|-------------------|------------|---------|
| Neurologic complications, n (%) | 7 (29.2) | 0 (0) | 7.882 | 0.005** |
| Cardiovascular complications, n (%) | 3 (12.5) | 1 (4.3%) | 1.002 | 0.317 |
| Acute respiratory failure, n (%) | 1 (4.2) | 8 (34.8) | 7.111 | 0.008** |
| Gastrointestinal bleeding, n (%) | 4 (16.7) | 3 (13.0) | 0.122 | 0.727 |
| Acute hepatitis, n (%) | 3 (12.5) | 12 (52.2) | 8.508 | 0.004** |
| Acute renal failure, n (%) | 5 (20.8) | 12 (52.2) | 4.997 | 0.025* |

Notes: *P < 0.05; **P < 0.01.

Table 2 Spectrum of corrosive esophageal injury (local complication) after paraquat or glyphosate-surfactant ingestion (n = 47)

| Corrosive esophageal injury | Glyphosate-surfactant (n = 24) | Paraquat (n = 23) | Chi-square | P-value |
|-----------------------------|--------------------------------|-------------------|------------|---------|
| Grade, n (%) | | | 10.434 | 0.005** |
| 0 | 0 (0) | 0 (0) | | |
| 1 | 14 (58.3) | 3 (13.0) | | |
| 2a | 9 (37.5) | 18 (78.3) | | |
| 2b | 1 (4.2) | 2 (8.7) | | |
| 3a | 0 (0) | 0 (0) | | |
| 3b | 0 (0) | 0 (0) | | |

Note: **P < 0.01.

Table 4 Treatments and outcomes after paraquat or glyphosate-surfactant ingestion (n = 47)

| Variable | Glyphosate-surfactant (n = 24) | Paraquat (n = 23) | Chi-square | P-value |
|--|--------------------------------|-------------------|------------|-----------|
| Gastric lavage, n (%) | 6 (25.0) | 14 (60.9) | 6.182 | 0.013* |
| Activated charcoal and magnesium citrate, n (%) | 10 (41.7) | 9 (39.1) | 0.031 | 0.859 |
| Glucocorticoid and cyclophosphamide pulse therapy, n (%) | 0 (0) | 23 (100.0) | 47.000 | <0.001*** |
| Charcoal hemoperfusion, n (%) | 0 (0) | 19 (82.6) | 33.280 | <0.001*** |
| Length of hospital stay, days | 13.3 ± 15.1 | 26.8 ± 10.2 | | 0.001** |
| Mortality, n (%) | 2 (8.3) | 3 (13.0) | 0.274 | 0.601 |

Notes: *P < 0.05; **P < 0.01; ***P < 0.001.

prognosis than those with grade I or II injury. The authors also found that buccal mucosal erosion, ulceration, hemorrhage, and pseudomembranous formation were identified in the esophagus and stomach as the injury process progressed. Gastric erosion was an ominous endoscopic sign related to a high mortality rate.¹⁹ Valiante et al¹⁶ later described a victim of severe panesophagitis and localized erosive hemorrhagic gastritis after accidental oral diquat exposure during work. Subsequently, Tanen et al¹⁷ also reported a case of esophagitis after the ingestion of a diluted diquat solution. Furthermore, Singh et al¹⁸ presented two lethal cases of caustic esophageal burning after paraquat ingestion.

In our preliminary study,⁶ 16 of 1,410 paraquat subjects who underwent endoscopies at Chang Gung Memorial Hospital between 1980 and 2007 were retrospectively analyzed. Corrosive esophageal injuries were classified as grade 1 in eight patients, 2a in five patients, and 2b in three patients. No patients had grade 0, 3a, or 3b esophageal injuries. After paraquat ingestion, systemic toxicity occurred with rapid development of hypoxia, hepatitis, and renal failure in many cases. Hypoxia occurred in one (12.5%), five (100%), and three (100%) patients with grades 1, 2a, and 2b esophageal injury, respectively. More patients with hypoxia had grades 2a and 2b than grade 1 esophageal injury ($P < 0.05$). The nadir partial pressure of oxygen in the arterial blood was lower in patients with grades 2a and 2b than in those with grade 1 esophageal injury ($P < 0.05$). Therefore, it was

concluded that paraquat was a mild caustic agent because it produced only grades 1, 2a, and 2b esophageal injury after ingestion.⁶ The findings also showed a potential relationship between degree of hypoxia, mortality, and degree of esophageal injury.⁶

Similarly, there are only a few reports^{20–24} in the literature regarding the corrosive outcomes of glyphosate-surfactant ingestion. In 1991, Talbot et al²¹ reported that ingestion of glyphosate-surfactant caused gastrointestinal erosion and hemorrhage in 66% and 8% of patients, respectively. Moreover, Tominack et al²² reported that irritation of the oral mucosa and gastrointestinal tract was the most frequent effect after glyphosate-surfactant ingestion. Another study²⁰ revealed that corrosive esophageal injury was present in 68%, gastric injury in 72%, and duodenal injury in 16% of patients. There were no grade 3 injuries after glyphosate-surfactant ingestion. There were recent case reports of extensive burns and ulceration of the oral cavity after accidental exposure²⁴ as well as gastric mucosa hemorrhage and small intestine dilatation after deliberate ingestion.²³

Neurologic complications occurred more frequently in the glyphosate-surfactant group than in the paraquat group (29.2% versus 0%, $P = 0.005$). Studies have shown that after glyphosate ingestion, consciousness disturbances of 12%–32.9% occur.^{21,28} The mechanisms involved in paraquat-induced or glyphosate-surfactant-induced brain damage are unclear. Experimental research demonstrated a role of

Table 5 Association between local and systemic complications after paraquat or glyphosate-surfactant ingestion (n = 47)

| Variable | Corrosive esophageal injury | | | Chi-square | P-value |
|-------------------------------------|-----------------------------|-------------------|------------------|------------|---------|
| | Grade I (n = 17) | Grade 2a (n = 27) | Grade 2b (n = 3) | | |
| Neurologic complications, n (%) | 2 (11.8) | 4 (14.8) | 1 (33.3) | 0.936 | 0.626 |
| Cardiovascular complications, n (%) | 1 (5.9) | 2 (7.4) | 1 (33.3) | 2.567 | 0.277 |
| Acute respiratory failure, n (%) | 1 (5.9) | 5 (18.5) | 3 (100.0) | 14.606 | 0.001** |
| Gastrointestinal bleeding, n (%) | 2 (11.8) | 3 (11.1) | 2 (66.7) | 4.590 | 0.034* |
| Acute hepatitis, n (%) | 3 (17.6) | 11 (40.7) | 1 (33.3) | 2.563 | 0.278 |
| Acute renal failure, n (%) | 3 (17.6) | 12 (44.4) | 2 (66.7) | 4.536 | 0.104 |

Notes: P-value represents a comparison between patients with grade 2b and grade I corrosive esophageal injury. *P < 0.05; **P < 0.01.

oxidative stress and reactive oxygen species in paraquat-induced neurotoxicity that seemed to be mediated by both mitochondrial and endoplasmic reticulum stress pathways.²⁹ Several molecular mechanisms including redox cycling, mitochondrial electron transport chain inhibition, and activation of nicotinamide adenine dinucleotide phosphate oxidases have been proposed as potential sources for reactive oxygen species formation, particularly for the accumulation of superoxide anion. However, the exact molecular targets being regulated by oxidative stress and reactive oxygen species in response to paraquat remain elusive.²⁹ Basic glyphosate-surfactant-induced neurotoxicity research is still lacking.

The mortality rates for glyphosate-surfactant and paraquat poisoning were 8.3% and 13.0%, respectively ($P = 0.601$). Theoretically, glyphosate-surfactant cases should have lower mortality rates after ingestion than paraquat cases. Unlike paraquat, glyphosate-surfactant is claimed to be a very toxicologically and environmentally safe herbicide.³⁰ Nevertheless, glyphosate-surfactant contains toxic substances in its commercial formula. Every glyphosate product is composed of three parts, ie, the parent acid, salt, proprietary components (surfactants, defoamers, and other compounds), and water.¹⁴ Notably, the proprietary components are listed as inert ingredients on product labels, and manufacturers are not required to provide information about these components. Following a standard detoxification protocol, the overall in-hospital mortality rate after paraquat ingestion was found to be 54%.¹ Therefore, the lack of significant mortality in paraquat cases may be explained by the limited recruitment of patients into this study due to lack of endoscopic data.

It has been suggested that the magnitude of corrosive esophageal injury (a local complication) might be associated with systemic complications regardless of herbicide type (Table 5). As mentioned, our preliminary data⁶ revealed a potential relationship between degree of hypoxia, mortality, and degree of esophageal injury after ingestion of paraquat. Similarly, the study by Chang et al²⁰ reported that white blood cell count, amount of glyphosate-surfactant, length of hospital stay, and occurrence of serious complications were markedly increased in the group that had grade 2 esophageal injuries than in the other groups. Therefore, the analysis suggested that severity of esophageal injury might be predictive of systemic complications.²⁰

In conclusion, paraquat and glyphosate-surfactant are mild caustic agents that produce only grade 1, 2a, and 2b esophageal injuries. Our data revealed a potential relationship between degree of esophageal injury and systemic complications. Nevertheless, the small patient population, small number of endoscopies, lack of information

on blood glyphosate and surfactant concentration, and a relatively short follow-up period limit the certainty of our conclusions. As such, further studies are warranted.

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Disclosure

The authors report no conflicts of interest in this work.

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