

Case series of paraquat poisoning in Tuen Mun Hospital

屯門醫院的「百草枯」中毒個案系列

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Paraquat is highly toxic to human and is widely used in agriculture as a contact herbicide. However, it is easily accessible in agricultural product shops. Seven cases of paraquat poisoning were treated in Tuen Mun Hospital from 1998-2005. The mortality (4 out of 7) was very high. One patient died after oral exposure to paraquat despite immunosuppressive and antioxidant therapies. The mechanism of toxicity and potential new therapies of paraquat poisoning are discussed in the article. (*Hong Kong j.emerg.med.* 2006;13:155-160)

「百草枯」對人體的毒性極高，是農業上被廣泛使用的接觸性除草劑。然而，它很容易從農產品商店中獲得。自 1998 至 2005 年，屯門醫院治理了七宗百草枯的中毒個案，其死亡率極高（七人中四人死亡）。其中一名病者經口部接觸百草枯後死亡，儘管他得到免疫抑制及抗氧化治療。本章討論百草枯毒性的機理及有潛質的新中毒療法。

Keywords: Free radicals, herbicides, immunosuppression, poisoning, pulmonary fibrosis

關鍵詞：游離基、除草劑、免疫抑制、中毒、肺纖維化

Case reviews

Paraquat poisoning is relatively more common in the northwest districts of Hong Kong. The seven cases of paraquat poisoning treated in Tuen Mun Hospital from 1998 to 2005 are summarised in Table 1. The length of hospital stay ranged from 1 to 23 days and four of the patients died during hospitalisation. Five of the cases (1, 2, 4, 5 & 7) had paraquat solution ingested for suicidal attempt. Three cases (1, 5 & 7) had exposure to large amounts (100 ml to 500 ml). These three patients developed pulmonary complications and acute renal failure (ARF), and subsequently died.

Case 5 who ingested a large amount of paraquat solution (200 ml) died even after immunosuppressive and anti-oxidant therapies were tried. She had severe complications. There was excoriation over her oropharyngeal region. Endoscopic examination showed oesophagitis and haemorrhagic gastritis. She developed ARF two days after the exposure, even with charcoal haemofiltration and haemodialysis started on admission and continued throughout the whole period of her hospital stay. She also developed acute hepatic failure with bilirubin level around 600 $\mu\text{mol/L}$. Steroid was given since day 1 and trials of anti-oxidant therapies of deferoxamine and N-acetylcysteine (NAC) were given but there was no recovery of her renal function. She developed acute interstitial pneumonitis and type 1 respiratory failure two days after the exposure and required mechanical ventilation support since day 3. However, she pulled off the endotracheal tube by herself and developed right pneumothorax and pneumomediastinum during spontaneous breathing. A chest drain was then inserted. The pneumonitis

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Table 1. Case summary of paraquat poisoning from 1998 to 2005

Case no.	Date of attendance	Age/sex	Routes of exposure	Amount of exposure	Specific treatment	Complications	Outcome (survival/death)
1	7/3/1998	58/F	Oral	500 ml	GL & FE	ARF (Cr up to 564 $\mu\text{mol/L}$), paralytic ileus & respiratory failure	Death (12 hours after admission)
2	31/3/1999	24/M	Oral	20-40 ml	FE & ST	Renal impairment (Cr 172 $\mu\text{mol/L}$), PF (normal CXR but abnormal lung function test) & painful dysphagia	Survival, renal function recovered without dialysis, refused endoscopic examination
3	25/12/2000	23/M	Oral	~ One mouthful	FE & HD	ARF (Cr up to 700 $\mu\text{mol/L}$ & progressive PF	Death (15 days after admission)
4	16/5/2002	20/M	Oral	Half-spoonful	AC, FE, ST, CH & HD	ARF (Cr up to 400 $\mu\text{mol/L}$) & oropharyngeal erosions	Survival, renal function gradually improved to normal, water soluble contrast study showed no oesophageal involvement
5	21/7/2003	25/F	Oral	200 ml	FE, ST, CH, HD & AOT	Oropharyngeal excoriation, oesophagitis, haemorrhagic gastritis, ARF (Cr up to 600 $\mu\text{mol/L}$), acute interstitial pneumonitis & acute hepatic failure	Death (3 weeks after admission), no improvement of renal function
6	5/12/2004	76/M	Eyes	Few drops	Nil	Nil	Survival
7	13/2/2005	70/M	Oral	100 ml	FE & HP	ARF (Cr up to 337 $\mu\text{mol/L}$) & progressive pneumonitis	Death (3 days after admission)

AC: activated charcoal; AOT: antioxidant therapies; ARF: acute renal failure; CH: charcoal haemoperfusion; Cr: creatinine; CXR: chest X-ray; F: female; FE: Fuller's earth; GL: gastric lavage; HD: haemodialysis; HP: haemoperfusion; M: male; PF: pulmonary fibrosis; ST: steroid therapy.

progressed with refractory hypoxaemia and she died three weeks after admission.

The patient in case 3 accidentally ingested one mouthful of paraquat solution and attended the accident & emergency department (AED) three days after the exposure. He presented with generalised malaise and developed ARF with creatinine up to around 700 $\mu\text{mol/L}$. After two courses of haemodialysis, the creatinine level improved to around 200 $\mu\text{mol/L}$. He was also given steroid therapy. However, he died subsequently with progressive pulmonary fibrosis and type 1 respiratory failure.

Two patients with oral exposure to paraquat survived and the amount of paraquat involved in both cases

were small (case 2 & 4). The patient in case 2 drank 20 to 40 ml paraquat solution for suicidal attempt and developed renal impairment. His renal function recovered spontaneously without dialysis. He also developed pulmonary fibrosis as shown by lung function tests even though his chest X-ray (CXR) was all along clear. He was subsequently transferred to a psychiatric hospital (Castle Peak Hospital) for further management of his mental illness. Case 4 was a young man who attempted suicide by drinking half-spoonful of paraquat solution. He was given activated charcoal in the AED and Fuller's earth after admission. Steroid therapy was also given. He developed ARF with creatinine level above 400 $\mu\text{mol/L}$ even with charcoal haemoperfusion performed soon after admission. His renal function gradually improved to normal in one

week's time with supportive haemodialysis. He did not develop pulmonary complication clinically all along but no lung function test was done. He was subsequently discharged 23 days after admission.

One case of ocular exposure to paraquat survived and the patient was free from systemic complications during the hospital stay (case 6). His eyes were irrigated with normal saline and he was later discharged.

The concentration of paraquat solution ingested in case 5 and 7 was 24% and the concentrations of paraquat involved in the other five cases were not documented. There were no qualitative or quantitative laboratory tests, such as urine dithionite test and serum paraquat assay, performed in all the seven cases.

Discussion

Paraquat is highly toxic to human. The chemical structure of paraquat is 1,1'-dimethyl-4,4'-bipyridinium. It belongs to the group of dipyridyl herbicides. In plants, it disrupts photosynthesis by inhibiting the electron transport chain. It has low environmental toxicity due to rapid deactivation upon soil contact.¹ Another example of dipyridyl herbicides is diquat.² Diquat is uncommon in Hong Kong markets. Paraquat is different from diquat as it is selectively accumulated in the lungs causing pneumonitis and fibrosis. The usual concentration of paraquat solutions available in the market is around 20-40%. Some common brand names of paraquat solution available in Hong Kong and the concentrations are listed in Table 2. Most brands contain only 24% of paraquat dichloride as the active

ingredient. Poisoning with paraquat commonly results in fatal consequences.

Mechanisms of toxicity

Exposure to paraquat can be due to intentional ingestion or occupational exposure, e.g. dermal and eye contact. A dose of 3-6 g is considered to be fatal for adults.¹ So, even a small sip of paraquat may be lethal. The young man in case 3 subsequently died after only a sip of paraquat solution. Paraquat is a water-soluble quaternary ammonium derivative. It is poorly absorbed by the oral route in humans. Around 1-5% of an oral dose is absorbed in the gut. The volume of distribution is 1-2 L/kg.³ It is unbound to plasma proteins. Plasma paraquat concentration exhibits a mean distribution half-life of five hours and a mean elimination half-life of 84 hours.³ Animal studies showed the plasma concentrations of paraquat followed a 2-compartment model with non-linear elimination from the central compartment.⁴ However, it is still controversial whether it is 2 or 3 compartments or even more.

The mechanisms of paraquat toxicity involve the formation of superoxide anions during the 'redox cycling process' which then leads to the formation of other more toxic reactive oxygen species such as hydrogen peroxide and the hydroxyl radical in the presence of NADPH and cytochrome P450 reductase.⁵ In the normal situation, the hydrogen peroxide is detoxified by catalase and glutathione peroxidase in the body. However, if these protective mechanisms are overwhelmed, the resultant oxidative stress will cause cellular damage. The hydroxyl radical, which is formed in the presence of iron, is a more potent oxidant and can induce lipid peroxidation which causes cell membrane damage and cell death.⁶

Table 2. Common brand names and concentrations of paraquat solution available in Hong Kong markets

Brand name	Concentration of paraquat dichloride	Other significant chemicals*
雄獅牌	24%	Nil
除草淨液體殺草劑	24%	Nil
臺灣強力殺草劑® (FORXONE®)	24%	Nil
克蕪踪™ (GRAMOXONE™)	27.6%	Nil

*Paraquat solutions mainly contain paraquat dichloride at different concentrations and some inert ingredients

Clinical features

Poisoning with paraquat can cause multiple organ damage. Paraquat selectively accumulates in the lung where free radicals are formed and lipid peroxidation is induced. The capillary endothelial and epithelial cells of the lung are the main targets of damage. This results in the development of diffuse alveolitis followed by extensive pulmonary fibrosis.^{7,8} The development of pulmonary fibrosis is usually delayed up to 3 to 14 days but progressive. Paraquat can also induce acute tubular necrosis and cause acute renal failure that usually occurs within 24 to 96 hours. Moreover, renal failure can be secondary to hypovolaemia. In our case series, ARF and pulmonary complication occurred sooner in those cases with large amounts of oral exposure. As in case 1, the patient developed ARF and pneumonitis only a few hours after the ingestion of 500 ml of paraquat solution. After ingestion, paraquat can cause burns and haemorrhagic ulcerations of the gastrointestinal (GI) tract. The patient in case 5 had severe GI complications (oropharyngeal excoriation and haemorrhagic gastritis) after ingestion of 200 ml of paraquat solution. For ocular exposure, it can result in protracted opacification of the cornea. The patient with ocular exposure in our case series had only congestion of the conjunctiva and there was no corneal injury. Dermal contact can cause dermatitis. Paraquat is well absorbed from injured skin and severe systemic toxicity with fatal outcomes after dermal exposure had been reported.^{9,10} For the neurological system, paraquat causes cerebral oedema due to its direct toxicity on cerebral blood vessels and indirectly the hypoxia secondary to pulmonary damage. Other toxic effects of paraquat include ventricular arrhythmias, hypotension and cardio-respiratory arrest. The toxicity of paraquat may be enhanced by concomitant alcohol intake¹¹ because animal studies showed ethanol increased the intestinal absorption and tissue distribution of paraquat. The critical fatal plasma concentration of paraquat was lower in the presence of ethanol because of the increased volume of distribution.¹²

Initial management and resuscitation

Patients with paraquat poisoning may develop upper

airway obstruction due to the local toxicity causing oropharyngeal ulceration and oedema. Airway management and adequate ventilation are very important. However, high concentrations of oxygen (O₂) are contraindicated as they will increase the formation of free radicals in the redox cycling of paraquat. The lowest O₂ level possible to limit pulmonary complication should be used. Intravenous fluid supplement should be given to maintain adequate urine output. It is very important to explain the poor prognosis to patient's relatives as the mortality of paraquat poisoning is very high. The most important prognostic indicator is the amount of paraquat absorbed.⁸ According to clinical experience of the prognosis in cases of paraquat ingestion, patients may be asymptomatic or have only GI symptoms if less than 20 mg paraquat ion per kg body weight (less than 7.5 ml of 20% [w/v] paraquat concentrate) are ingested. Recovery is likely for this amount of exposure. Ingestion of 20 to 40 mg paraquat ion per kg body weight (7.5-15 ml of 20% [w/v] paraquat concentrate) will result in pulmonary fibroplasia. Death occurs in most cases but may be delayed 2 to 3 weeks. Rapidly progressive multiple organ damage will occur if more than 40 mg paraquat ion per kg body weight (more than 15 ml of 20% [w/v] paraquat concentrate) are ingested. There will be marked oropharyngeal ulceration. Mortality is up to 100% within 1-7 days.¹³

Investigation

Baseline renal function test and CXR should be obtained initially. The blood paraquat level can help to predict survival with the use of the paraquat normogram.¹⁴ However, blood paraquat assay is not available in most hospitals. The urine dithionite test is useful to estimate the level of exposure. Paraquat reacts with dithionite to form a stable blue radical ion. Colourless or light blue indicates mild poisoning. Navy or dark blue indicates moderate to severe poisoning. However, this test is not accurate because the urine paraquat concentration depends on the renal function and urine production will decrease as poisoning progresses since paraquat causes renal failure. The test will give a false-negative result particularly when the patient's renal function deteriorates.¹⁵

General and new treatment for paraquat poisoning

Once the diagnosis of paraquat poisoning is confirmed, GI decontamination (either Fuller's earth or activated charcoal) should be considered. Fuller's earth is frequently used in paraquat poisoning but it is only available in some hospitals in Hong Kong. An animal study showed no significant difference between the effectiveness of Fuller's earth and activated charcoal on oral absorption of paraquat. It also showed that paraquat absorption from the GI tract was reduced with early administration of these adsorbents. Activated charcoal was still found to be effective in lowering serum paraquat concentration when given more than one hour after the ingestion of paraquat.¹⁶ As the mortality of paraquat poisoning is so high, activated charcoal or Fuller's earth is worth considering in cases with exposure to paraquat for more than one hour. However, GI decontamination may not improve the mortality in cases which present very late or with complications such as ARF or pneumonitis.

For whole bowel irrigation, an animal study showed significant reduction of the plasma paraquat concentration after the initiation of bowel irrigation with polyethylene glycol or Kayexalate with sorbitol when compared with a control group.¹⁷ However, the effectiveness of whole bowel irrigation in humans with paraquat poisoning is not well studied. Extracorporeal elimination techniques, such as haemodialysis/haemoperfusion, have been used worldwide in paraquat poisoning. Human studies have shown haemoperfusion significantly eliminates paraquat from the body.¹⁸ However, these techniques probably do not increase the survival rate in the real situation because the potentially lethal concentration of paraquat may have already been attained in the highly vascular tissue of vital organs and in the pneumocytes when these techniques are initiated.¹⁹ Moreover, paraquat is not dialyzable effectively. Haemodialysis probably has a role only as a supportive treatment for patients who develop renal failure.

Immunosuppressive treatment for paraquat poisoning was first reported in 1971¹⁵ and had been studied for many years. A randomised controlled trial done by Lin

and colleagues for pulse therapy with methylprednisolone and cyclophosphamide in patients with moderate to severe paraquat poisoning showed improvement in survival rates.^{20,21} Their papers reported a highly significant improvement in survival rates in moderate-to-severely poisoned patients randomised to pulse therapy: from 43% (12/28) to 82% (18/22; $p=0.008$). However, there was some bias in the study.¹⁵ Those patients who died within seven days were defined as "fulminant" poisoning and were excluded. Totally 59% of patients (71 out of 121) were excluded. Reanalysis on an intention-to-treat basis showed an improvement but not significant at the 0.05 statistical level: 18% (12/65) to 32% (18/56) ($p=0.095$).¹⁵ The evidence for the effectiveness of immunosuppressive therapies in paraquat poisoning is not yet well established at this stage.

Survival of patients with paraquat poisoning treated with deferoxamine and N-acetylcysteine had been reported in case reports and small studies. The formation of the hydroxyl radical (a mediator of paraquat's toxicity) needs the presence of iron. Deferoxamine has been shown to reduce mortality caused by paraquat in laboratory animals.²² NAC may protect against the toxicity of paraquat by maintaining the intracellular glutathione level.²³ It was shown in an animal study that the lungs of poisoned rats treated with NAC had less oedema and cellular infiltration compared with the control group.²⁴

Recently, survival after single lung transplantation in paraquat poisoning has been reported.²⁵ Surgical therapy may play a role for patients with extensive pulmonary fibrosis in the future.

Conclusion

Although paraquat is not a common agent of poisoning in Hong Kong, the resulting mortality is very high. The mortality is even higher for intentional overdose cases when large amounts are usually ingested. There is no specific antidote for paraquat poisoning and the mainstay of treatment is supportive. Excessive

concentration of oxygen is contraindicated in paraquat poisoning as it will increase the formation of harmful free radicals in the body. Antioxidant and immunosuppressive therapies have been shown to improve survival in animal studies. However, the role of these therapies in humans with paraquat poisoning has not been definitively established at this stage. Further confirmatory human studies are necessary.

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