Paraquat is a safe and effective herbicide when used as directed on the label. However, ingestion of significant amounts of the concentrate (usually with the intention of self harm) frequently has a fatal outcome. Measures to limit systemic absorption and enhancing removal of paraquat from the body remain the cornerstone of therapy.

This booklet is structured to emphasise the importance of early recognition and treatment including a flow chart to aid early management of the poisoned patient. A brief synopsis of the mechanism of paraquat toxicity serves as an introduction to other potential treatment options based on the clinical context. The section on laboratory techniques and their availability has been updated and a new section on the interpretation of analytical findings has been added.

This guide aims to present current best practice in the treatment of paraquat poisoning. However, it needs to be emphasised, that the availability of treatment materials varies enormously between countries and primary health care providers need to be familiar with local practices and the availability of laboratory analyses. Where available, poison information centres are an important source of up-to-date information and should be consulted for additional advice and support.

Disclaimer

Although the authors of this booklet have given the advice contained herein in good faith and on the basis of the best and most recent knowledge available at the time of this booklet going to print, no warranty is given or may be implied as to the correctness of the advice nor can any liability be accepted by the authors or Syngenta in respect thereof. Further, the likelihood of success of any treatment will also depend on other extraneous factors over which the authors have no control and which include, for example, the general health of the affected person, the period of time between ingestion and the beginning of the treatment and the quantity of product which has been ingested.
Treatment of Paraquat Poisoning by Ingestion

Diagnosis

- Diagnosis must be made and first aid initiated without delay. This is of utmost importance.

- Diagnosis of paraquat poisoning is often made on circumstantial evidence including:
  1. History of paraquat ingestion – from patients or other observers.
  2. Evidence of paraquat ingestion (suicide note, empty container, residue, odour or colour).
  3. Clinical signs, especially profuse vomiting, burning pain in the mouth, throat or stomach, or ulceration of mucous membranes (which occurs several hours following ingestion).

- Ingestion under certain conditions is unlikely to be serious, including:
  1. Ingestion of plants sprayed with dilute paraquat solution;
  2. Ingestion of soil sprayed with paraquat;
  3. Accidental ingestion of small amounts of spray-strength paraquat solution.

First Aid

- If the patient is conscious, cooperating and not vomiting then administer
  - activated charcoal – 50-100g for adults or 0.5-1 g/kg body weight in children (see also Roberts and Reigart, 2013, Chapter 3).
  - In the absence of activated charcoal and when available, Fuller’s Earth (15% suspension) or Bentonite (7.5% suspension) – 100-150 g for adults or 2 g/kg body weight in children - can be considered as an alternative.

- If there is a suspicion of significant ingestion then arrange IMMEDIATE transfer to hospital following the administration of first aid.

Initial Hospital Management

- Ensure Airway, Breathing and Circulation are intact

- Control vomiting with:
  1. 5HT3 antagonists, e.g. Ondansetron 8mg (5mg/m² in children) by slow i.v. injection or i.v. infusion over 15 minutes, or
  2. Phenothiazine anti-emetics, e.g. prochlorperazine

- Dopamine antagonists such as metoclopramide should be avoided as they may impair therapy for renal support with dopamine.

- Administer:
  - activated charcoal – 50-100g for adults or 0.5-1 g/kg body weight in children,
  - In the absence of activated charcoal and when available, Fuller’s Earth (15% suspension) or Bentonite (7.5% suspension) - 100-150 g for adults or 2 g/kg body weight in children - can be considered as an alternative.

  NOTE: The use of gastric lavage without administration of an adsorbent has not shown any clinical benefit and should be avoided.

- There is no definite indication for the use of cathartics (e.g. sorbitol, mannitol, magnesium citrate, magnesium sulphate) in the management of poisoned patients. If used, a cathartic should be limited to a single dose in order to minimise adverse effects (Position Paper: Cathartics, 2004).

- Rehydrate the patient to optimise renal clearance of paraquat, paying attention to the possibility of fluid overload and electrolyte imbalance.

  NOTE: Forced diuresis is not recommended.

- Do not give supplemental oxygen unless serious hypoxia is present.
Using Laboratory Analysis for Diagnosis

* The practicalities of paraquat analysis vary enormously between countries and it is recommended to consult with local poison information centres or other appropriate health care providers regarding the availability of analytical resources.

• Qualitative confirmation of significant paraquat ingestion
  - urine spot test (alkali and sodium dithionite) as soon as possible (see section on ‘Analytical Techniques’ for details).
  - a negative urine test should be repeated at 6 hours post-ingestion and if this is still negative then serious sequelae are unlikely.

Quantitative measurement in plasma gives an indication of severity and prognosis (the sample must be taken at least 4 hours post-ingestion, and should be stored in plastic, not glass tubes).

Plasma should be analysed rather than serum, because serum paraquat concentrations are approximately 3 fold lower than those in plasma prepared from the same blood sample. If only serum is available results should be interpreted with caution in relation to survival curves.

See section on ‘Analytical Techniques’ for further details.

Clinical Features (based on Lock and Wilks 2010)

• **Mild or subacute poisoning:** <20 – 30 mg paraquat ion/kg body weight.
  - Asymptomatic or mild gastrointestinal symptoms.
  - Renal and hepatic lesions are minimal or absent.
  - An initial decrease of the pulmonary diffusion capacity may be present. Complete recovery would be expected.

• **Moderate to severe acute poisoning:** >20 – 30 but <40 – 50 mg paraquat ion/kg body weight.
  - immediate: vomiting.
  - hours: diarrhoea, abdominal pain, mouth and throat ulceration.
  - one to four days: renal failure, hepatic impairment, hypotension and tachycardia.
  - one to two weeks: cough, haemoptysis, pleural effusion, pulmonary fibrosis with deteriorating lung function.

Survival is possible, but in the majority of cases death occurs within 2 – 3 weeks from pulmonary failure.

• **Fulminant or hyperacute poisoning:** >40 – 55 mg paraquat ion/kg body weight.
  - immediate: vomiting
  - hours to days: diarrhoea, abdominal pain, renal and hepatic failure, gastrointestinal ulceration, pancreatitis, toxic myocarditis, refractory hypotension, coma.

Death from cardiogenic shock and multi-organ failure occurs within 1-4 days.
**General Supportive Measures** *(see flowchart)*

**Early management**
- i.v. fluids – the kidney is the major route of excretion of paraquat and renal function must therefore be closely monitored and optimum function maintained.
- analgesics – aggressive analgesia (e.g. opiates) may be required since patients can have severe pain from oral, oesophageal or abdominal corrosive injury.
- mouth care for ulceration and inflammation.
- patients should be kept nil by mouth if there is a suspicion of oropharyngeal or oesophageal injury. Early insertion of a nasogastric feeding tube should be considered taking care to avoid additional mucosal damage.
- avoid supplemental oxygen unless significant hypoxia exists (oxygen enhances paraquat toxicity).

**Subsequent management**
- analgesia.
- antibiotics for supervening infection.
- supporting renal function with haemodialysis or haemofiltration may be required (see below).
- palliative care is paramount for those with a poor prognosis.
- other specific treatments could be considered depending on the clinical context (see section on ‘Other Potential Treatment’ and obtain advice from a Poison Information Centre).

**Management of acute renal failure**
- Haemodialysis may be considered in patients who develop symptomatic acute renal failure.
- Since the prognosis of such patients is generally poor this procedure is unlikely to change overall outcome (Roberts *et al.*, 2011).

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**Flowchart for the early management of paraquat poisoning**

- **Significant paraquat ingestion suspected on history and/or examination?**
  - Yes: Control of vomiting
    1. Odansetron 8 mg i.v. (5 mg/m²)
    2. Prochlorperazine
  - No: Activated charcoal 50-100g or 0.5-1 g/kg

- **Activated charcoal**
  - 50-100g or 0.5-1 g/kg

- **General early management**
  - i.v. fluids
  - Analgesia
  - Avoid supplemental oxygen if possible

- **Paraquat spot test**
  - Urine or gastric aspirate
  - Repeat at 6 hours
  - neg: Discharge
  - pos: Plasma paraquat level

- **Plasma paraquat level**
  - taken between 5 & 24 hours

- **Supportive management**
  - Analgesia
  - Support renal function
  - Palliative care for those with poor prognosis

- **Survival probability curve**
  - (for prognosis)
Other Routes of Exposure

**Skin**

- If the product is used as recommended on the label and normal hygiene practices are observed, effects on the skin are unlikely. Intact skin is an effective barrier to paraquat absorption under normal circumstances.

- Local Effects
  - concentrated formulations may result in irritation, blistering and potentially full thickness burns which usually develop 1 to 3 days after exposure.
  - brief contact with products diluted for use may cause erythema.
  - nail damage, discoloration (e.g. white spots) or total loss of the nail may occur upon direct contact with the concentrated formulation. Normal nail re-growth follows.

- Systemic toxicity is rare but can occur if there is:
  - prolonged contact, e.g. not washing after being splashed with concentrate; carrying of leaking knapsack sprayers; wearing of clothes soaked in spray;
  - extensive scrotal or perineal contamination;
  - the skin is broken and there is significant exposure;
  - large areas of skin are contaminated with concentrate, even if washed.

**Prevention and treatment**

- Decontaminate as soon as possible by removing contaminated clothes and washing skin thoroughly with soap and copious amounts of water, taking care to avoid abrasion.

- Treat any skin irritation/damage symptomatically with daily review if contaminated with concentrate (as blistering and chemical burns may develop over 1 to 3 days).

- If systemic toxicity is suspected, test urine for paraquat. There is little data for time to peak plasma levels by skin absorption, but if the urine is negative for 24 hours after exposure, systemic toxicity can probably be discounted. If the urine test is positive or if there is any doubt about potential systemic toxicity, obtain a blood sample for paraquat analysis and treat for systemic toxicity as above.

**Eyes**

- Spray dilutions
  - may cause a transient stinging sensation but no damage is expected.

- Concentrated formulations
  - may cause severe inflammation of the cornea and conjunctiva which may gradually develop over 24 hours.
  - loss of corneal and conjunctival epithelium and iritis can occur with the risk of secondary infection and consequent residual corneal scarring.
  - corneal oedema may persist for up to 3-4 weeks with temporary blurring of vision.

**Treatment**

- The eye should be irrigated immediately for at least fifteen minutes with water or saline and a fluorescein stain performed.

- Local antibiotics may be needed to prevent secondary infection.

- If splashed with the concentrate, patients should be reviewed after 24 hours.

- Referral to an ophthalmologist should be considered.
Inhalation

- Paraquat is not volatile but liquid Syngenta paraquat formulations contain an unpleasant 'stenching agent' which may occasionally cause feelings of nausea or headaches.

- Spraying
  - when applied as recommended the spray droplets are too large to be inhaled into the lungs.
  - application as a fine mist may cause some irritation of the upper respiratory tract.
  - local irritation of the nose through spray mist or contact of nasal mucosa with fingers contaminated with paraquat may occasionally cause epistaxis.

Treatment

- No specific treatment is required other than symptomatic for epistaxis. There is no need to perform a urine test as the lungs are not a major route of absorption under normal use according to label instructions.

Background Information

Paraquat’s herbicidal effects were discovered in the late 1950s and the product was first sold in 1962. It is today the world’s second largest selling weedkiller and is registered and used in approximately 85 countries.

It is a fast-acting contact herbicide which is rainfast shortly after application and is rapidly deactivated on contact with soil, having no residual effects in the soil. Its normal use causes no adverse effects on wildlife or the environment. When used as directed on the label it has no known adverse effects on the health of spray operators.

Its many uses in a wide variety of crops have helped to increase the productivity of agriculture in both the developed and developing world. By reducing the need for cultivation it has helped to prevent erosion of soil and assisted in the conservation of soil moisture. It has facilitated the introduction of ‘no-till farming’ or ‘direct drilling’ in which time and energy-consuming soil cultivation have been eliminated.
Mechanism of Toxicity

- Paraquat concentrates in (pulmonary) alveolar type I and II cells via an energy dependant transport system (due to structural similarity of paraquat with naturally occurring polyamines taken up by alveolar cells). Paraquat is actively secreted by the kidney via organic cation transport systems, a process which becomes saturated at higher concentrations leading to accumulation in proximal tubular epithelial cells.

- High concentrations of paraquat, once accumulated into lung or renal cells, results in redox cycling and generation of toxic reactive oxygen species (see diagram). This can overwhelm cellular defence mechanisms and lead to lung damage (acute alveolitis and subsequent pulmonary fibrosis) and renal tubular necrosis.

- Renal failure may occur as a result of direct tubular toxicity and haemodynamic changes. It is an early, but often reversible, feature of paraquat poisoning. Maintenance of renal function is important to reduce plasma paraquat levels and thereby minimise accumulation in lung cells.

- After large doses multi-organ failure can lead to rapid death. At more intermediate doses, the initial lung injury may appear to repair, but then develop into fibrosis. This is characterised by rapid, excessive proliferation and differentiation of fibroblasts, resulting in a loss of pulmonary architecture and interference with gas exchange. Depletion of surfactant and the inflammatory response may also contribute to further toxicity.

- For further details of the mechanistic basis of paraquat toxicity see Dinis-Oliveira et al., 2008, and Lock and Wilks, 2010.

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The Biochemical Pathway of Paraquat Toxicity

Paraquat ion (PQ$^{2+}$)

2NADPH $\rightarrow$ 2PQ$^{2+}$ $\rightarrow$ 2O$_2^*$ then 2O$_2^*$$\rightarrow$ superoxide dismutase (+ 2H$^+$)

Fe$^{3+}$ + OH$^-$ + OH$^-$$\rightarrow$ Fe$^{2+}$

H$_2$O$_2$ + O$_2$$\rightarrow$ 2H$_2$O + O$_2$ catalase

OXYGEN FREE RADICALS

GLUTATHIONE OXIDATION

Structural and enzymatic protein abnormalities

NADPH depletion

LIPID FREE RADICALS

Formed by fatty acids reacting with oxygen free radicals (lipid peroxidation)

Disruption of lipid membrane integrity

Degeneration of membranous organelles (e.g. cell membrane, mitochondria, endoplasmic reticulum, lysosomes)

CELL DEATH AND MULTI-ORGAN DYSFUNCTION / FAILURE
Other Potential Treatments

Enhanced elimination of paraquat

Haemodialysis may be required in patients with acute renal failure, but is not likely to be effective in enhancing the elimination of paraquat from the body.

Haemoperfusion has been postulated as a treatment for many years but its efficacy remains controversial. While charcoal columns are very efficient at removing paraquat from the blood, paraquat is rapidly distributed to other tissues and re-distributes back to the blood relatively slowly. i.e. toxic levels in tissues occur early in the course of the poisoning.

When considering the use of haemoperfusion in paraquat poisoning, note that:

1. Patients who have ingested borderline lethal quantities of paraquat, or have survival probabilities between 20 and 70 percent, and present < 4 hours post ingestion may benefit from haemoperfusion (since the paraquat may not have distributed to the tissues / lungs in toxic quantities and even small differences in the paraquat level may affect survival probability).

2. Patients who have taken many times the lethal dose of paraquat, or have very poor prognosis on survival probability curves, are not helped by haemoperfusion (Hampson and Pond, 1988).

3. There is no evidence that the use of ‘continuous’ haemoperfusion or haemofiltration is life-saving but it may prolong survival (Koo et al., 2002). This may allow the use of other treatment modalities to be considered (see below).

A proposed scheme is to use up to 7 haemoperfusion sessions of 6 – 8 hours duration, started within 4 hours of ingestion and maintained until plasma paraquat levels would be < 0.2 mg/L (Dinis-Oliveira et al., 2008).

Prevention and treatment of pulmonary fibrosis

Patients with moderate to severe intoxication who do not die from early, multi-organ failure often develop progressive pulmonary fibrosis. This leads to respiratory failure and death within a few weeks. Several treatment modalities have attempted to prevent this, the most frequently used being immuno-suppressive therapy.

Cyclophosphamide and steroid therapy

A number of studies have reported a beneficial effect of a combination therapy of cyclophosphamide and steroids. However, these studies have invariably involved small numbers of patients and interpretation is often constrained by methodological and/or analytical problems. In a systematic review on the subject, Eddleston et al. (2003) evaluated 10 clinical studies. Mortality in controls and patients varied markedly between studies. Three of the seven non-randomised studies measured plasma paraquat; analysis using Proudfoot’s or Hart’s nomograms did not suggest that immunosuppression increased survival. The authors concluded that the results could only be regarded as hypothesis-forming rather than conclusive. More recently, Li et al. (2014) evaluated the combined results from 3 randomised controlled trials (RCTs) with a total of 184 patients and concluded that there may have been a beneficial effect of the combined cyclophosphamide/steroid treatment but called for further RCTs.

A large-scale RCT with cyclophosphamide up to 1g/day for two days and methylprednisolone 1g/day for 3 days, and then oral dexamethasone 8mg three-times-a-day for 44 days has now been carried out (trial registration: ISRCTN85372848). 295 patients were randomised to receive immunosuppression (147) or saline/placebo (152). There was no significant difference in inhospital or 3 month mortality rates between the groups. A Cox model did not support benefit from high-dose immunosuppression but suggested potential benefit from the subsequent two weeks of dexamethasone. It was concluded that further research on the use of dexamethasone and other potential treatments was urgently needed (Gawarammana et al., 2012).

Antioxidants

A wide range of therapeutic substances have been studied experimentally. Some have been used in humans, but most of the published work is based on single or a small number of cases (for detailed reviews see Dinis-Oliveira et al., 2008, Lock and Wilks, 2010 and Gawarammana and Buckley, 2011). Furthermore, most therapies have been used in combination, thereby preventing an assessment of single components. The following list includes agents with some experimental evidence of benefit and for which therapeutic preparations are available (doses are based on Dinis-Oliveira et al., 2008):

- vitamin E (300 mg twice daily p.o.) or vitamin C to reduce free radical toxicity;
- N-acetyl cysteine (150 mg/kg over 3h; 300 mg/kg over 24 h for up to 3 weeks) to increase intracellular glutathione;
- desferrioxamine (100 mg/kg over 24 hours) to chelate iron which acts as catalyst in the production of hydroxyl radicals;
- salicylic acid which can scavenge hydroxyl radicals and inhibit the activation of NF-κB.
1. Qualitative confirmation of diagnosis

**TEST TUBE TEST**

- Urine or gastric aspirate can be tested for paraquat using the method based on reduction of the paraquat cation to a blue radical ion in the presence of alkali and sodium dithionite.

- Add alkali, such as sodium hydroxide, to 10 ml of urine or gastric aspirate until the pH is above 9 (approximately half to one teaspoon of sodium bicarbonate can be used as an alternative).

- Add a spatula blade full of sodium dithionite to the alkaline urine or gastric aspirate and mix gently.

  NB. Sodium dithionite can deteriorate on storage so users should ensure that the reagent works effectively preferably by testing a sample known to contain paraquat.

- View the tube against a white background. A blue or green colour in the solution denotes the presence of paraquat and confirms the diagnosis. In the presence of high paraquat concentrations, the solution may turn black, and the test should be repeated with a diluted sample.

- This method can detect concentrations of paraquat in urine down to 2 µg/ml and may be made semi-quantitative if a range of standards are prepared in control urine samples (Widdop 1976; Berry and Grove, 1971). An example of a colour scheme is shown here.

2. Quantitative determination of paraquat

- Paraquat can be quantified in biological samples and various methods are available in specialised laboratories. Contact your local poison information centre or hospital laboratory for further advice.

- Common analytical techniques with varying levels of sensitivity include
  - Second-derivative spectrophotometry (Dinis-Oliveira et al., 2008, Li et al., 2011); lower limit of detection (LOD) = 0.5 - 1 µg/ml.
  - GC-MS (De Almeida and Yonamine, 2007); LOD = 0.05 µg/ml.
  - HPLC fluorescence (Blake et al., 2002); LOD = 0.001 µg/mL after conversion to the dipyridone derivative.
  - LC-Electrospray Ionization-MS (Wang et al., 2011); LOD = 0.0005 µg/mL.

SOLID PHASE EXTRACTION

- Urine, serum or plasma can be tested for paraquat using a method based on *in situ* reduction on a solid phase extraction cartridge (Woollen and Mahler 1987).

- Plasma can block the cartridges so if possible it should be filtered, for example through a 0.45 µm syringe filter (PVDF or nitrocellulose) before performing the test. Serum does not require this pre-treatment unless it is cloudy.

- This test will detect paraquat down to a level of around 0.1 µg/ml with a 2 mL sample. Ideally a positive control should be carried out, at a level of around 0.5 µg/mL.
Measurement of the paraquat plasma concentration over time has proved to be a useful indicator of the prognosis of the intoxication. Many different methods have been proposed based on varying sample sizes and analytical methods, but most have tried to identify a paraquat concentration at a given point in time below which the patient would be expected to survive (‘predictive line’). One example (Hart et al., 1984) is shown here in which the probability of survival is plotted against the paraquat plasma concentration over time.

Based on a sample of 375 patients from one treatment centre in Korea it has been suggested that a significant number of patients with plasma paraquat levels lower than indicated by predictive lines will die (Gil et al., 2008). This was also the conclusion of Senarathna et al. (2009) who prospectively collected data on 451 patients in 10 hospitals in Sri Lanka and tested 5 different published predictive methods in order to determine if any was superior. They found that all methods showed comparable performance within their range of application, but also that all were better at predicting death than survival.

Since paraquat analysis is not available everywhere, at least in a timely fashion, Lee et al. (2002) studied a range of laboratory parameters as possible predictors of survival after acute paraquat poisoning in 602 patients. They found in multiple logistic regression analyses that the probability of survival decreased with higher age and respiratory rate, as well as with increasing white blood cell count, blood urea nitrogen and amylase levels. In a study with 143 patients the predictive value (in terms of a fatal outcome) of serum lactate levels (> 2.95 mmol/L) was superior to that of the Severity Index of Paraquat Poisoning (SIPP) and the Acute Physiology and Chronic Health Evaluation II (APACHE II) scores (Xu et al., 2015). These findings need to be confirmed in larger patient collectives.
References

General advice on treatment of paraquat poisoning


Other references


