Paraquat is a safe and effective herbicide when used as directed on the label. However, exposure to toxic doses of paraquat (largely with suicidal intention) is often fatal, despite aggressive medical intervention. Early recognition, and attempts at removal of paraquat from the body remain the cornerstone of therapy.

In recent years there has been little change in the general management of paraquat poisoning, but this booklet is structured in a way to emphasise the importance of early recognition and early treatment. It also includes a section on the mechanism of paraquat toxicity, a flowchart to aid early management and an update on the latest laboratory techniques (and their availability). The booklet has been jointly produced by members of the Health Assessment and Environmental Safety Department of Syngenta and the Medical Toxicology Unit, Guy’s & St Thomas’ Hospital NHS Trust, London, UK.

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.

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 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.
- 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 with intractable vomiting, or inflammation 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 a mouthful of spray-strength paraquat

**First Aid**

- If the patient is not vomiting then administer:
  - activated charcoal - 100g for adults or 2 g/kg body weight in children or,
  - A purgative should also be used, e.g. mannitol or magnesium sulphate
- If there is a suspicion of significant ingestion then arrange IMMEDIATE transfer to hospital following the administration of first aid.

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**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 either:
  - activated charcoal - 100g for adults or 2 g/kg body weight in children
- NOTE: The use of gastric lavage without administration of an adsorbent has not shown any clinical benefit.
- A purgative should also be used, e.g. mannitol or magnesium sulphate
- 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

• Qualitative confirmation of significant paraquat ingestion
  - urine spot test (alkali and sodium dithionite) as soon as possible (test kits can be obtained via your local Syngenta office or by e-mail to ctltestkitsupply@syngenta.com).
  - 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 a measure 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 details

Clinical Features (based on Lock and Wilks 2001)

• **Mild or subacute poisoning:** <20 – 30 mg paraquat ion/kg body weight.
  - Asymptomatic or vomiting and diarrhoea.
  - 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:** >40 – 55 mg/kg 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, convulsions.
  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.
- **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
- 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)

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

**Significant paraquat ingestion suspected on history and / or examination**

**Vomiting?**
- **Yes**
  - Control of vomiting
    1. Ondansetron 8mg iv (5mg/m² in children)
    2. Prochlorperazine

- **No**
  - Charcoal 100g or 2 g/kg

**General Early Management**
- i.v. fluids
- analgesia
- avoid supplemental oxygen if possible

**Paraquat Spot Test - urine or gastric aspirate**

**Plasma paraquat level** *(taken between 5 and 24 hrs)*

**Supportive Management**
- analgesia
- support renal function
- palliative care for those with poor prognosis
Other Routes of Exposure

**Skin**

- If the product is used as recommended 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 (e.g. ‘Gramoxone 100’) 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 regrowth 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.
  - skin is broken and there is significant exposure.
  - large areas of skin 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, 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 level and treat for systemic toxicity as above.

**Eyes**

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

- Formulations concentrates
  - may cause severe inflammation of the cornea and conjunctiva which may gradually develop over 24 hours.
  - loss of corneal and conjunctival epithelium and even mild 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 all 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 but there are no reports of serious systemic toxicity from inhalation. Local irritation of nose and throat may occasionally cause epistaxis. Contact of nasal mucosa with fingers contaminated with paraquat may also cause nose bleeds.

**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.

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**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 well over 100 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 properly used it has no 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 dependent transport system (due to structural similarity of paraquat with naturally occurring polyamines taken up by alveolar cells).

- High concentration 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 and subchronic) 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.

The Biochemical Pathway of Paraquat Toxicity

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

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

  - $\text{Fe}^{3+} + \text{OH}^- + \text{OH}^- \rightarrow \text{Fe}^{2+}$ ("Fenton" reaction)

  - $\text{H}_2\text{O}_2 + \text{O}_2 \rightarrow 2\text{H}_2\text{O} + \text{O}_2$

  - 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 (eg. cell membrane, mitochondria, endoplasmic reticulum, lysosomes)

- Cell death and multi-organ dysfunction / failure
Other Potential Treatments

Enhanced elimination of paraquat

Peritoneal dialysis or haemodialysis may be required in patients with acute renal failure, but they are ineffective in enhancing the elimination of paraquat from the body.

Haemoperfusion has been postulated as a treatment for a number of 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 redistributes 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 within a few hours (probably < 6-10 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. The use of ‘continuous’ haemoperfusion is probably not life-saving but may prolong survival. This may allow the use of other treatment modalities to be considered (e.g. lung transplantation, see below) (Suzuki et al., 1993).

Prevention and treatment of pulmonary fibrosis

Patients with moderate intoxication who do not die from early, multiorgan 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.

Cyclophosphamide and steroid therapy

Several studies have looked at the use of cyclophosphamide and steroid therapy. Addo and Poon-King (1986) claimed a 72% survival rate in 72 patients treated with cyclophosphamide (5 mg/kg/day to a maximum total of 4 g) and dexamethasone (8 mg eight-hourly over two weeks). However, the plasma paraquat data of 25 patients showed that 7 survivors had no measurable paraquat levels, and of the other 18 only the six patients with the lowest plasma concentration survived. Lin et al., (1999) reported results of a prospective, randomised study of pulse therapy with cyclophosphamide (1g/day over 2 days) and methylprednisolone (1g/day over 3 days) in 142 patients. Seventy-one patients died from fulminant poisoning within one week, and cyclophosphamide did not make any difference. In the group of moderately to severely poisoned patients, only 4/22 patients treated with cyclophosphamide died, compared to 16/28 in the control group. Plasma paraquat concentrations were not available, but the authors stated that there was no difference in severity of poisoning between the two groups based on the urine dithionite test. However, the beneficial effects of the cyclophosphamide-dexamethasone regime have been disputed and in a prospective study Perriens et al., (1992) did not find any difference in mortality between 14 patients who had received standard treatment and the 33 patients who had received high-dose cyclophosphamide and dexamethasone. A final answer regarding the usefulness of this therapy can therefore not been given at this stage.

Radiotherapy

Radiotherapy has been suggested to decrease the number of fibroblasts (very radiosensitive) in the lung, and hence decrease fibrosis. However, there is no conclusive evidence that it improves survival.

Lung transplantation

Although lung transplantation has been tried in several cases, success has been reported in only one (Walder et al., 1997). This was performed 5 weeks after the initial presentation (the patient was supported with mechanical ventilation during this time until a donor was found). Supportive treatment also consisted of haemodialysis until no paraquat was detected in the plasma or dialysate.

Other agents

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 a detailed review see Lock and Wilks, 2001).

Agents which have been used clinically include:
- antioxidants (vitamins C and E) and superoxide dismutase to reduce free radical toxicity
- N-acetyl cysteine to increase intracellular glutathione
- desferrioxamine to chelate iron which acts as catalyst in the production of hydroxyl radicals
- propranolol to block paraquat uptake into the lung
- inhaled nitric oxide to improve pulmonary gas exchange
1. Qualitative confirmation of diagnosis

1.1 TEST TUBE TEST

- Urine or gastric aspirate can be tested for paraquat using the method based on reduction of 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. Once opened and exposed to air/moisture sodium dithionite can deteriorate on storage so users should ensure that the reagent works effectively preferably by testing a sample known to contain paraquat. Sodium dithionite packed in foil sachets supplied in test kits has a shelf-life of at least 10 years.**

- View the tube from above 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).

1.2 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). A more sensitive version of this test using the reagents provided in the test kits is detailed below.

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

- Mix approximately 1g portions of sodium bicarbonate and sodium dithionite with 10 mL water and allow to settle.
- Urine is made alkaline by addition of approximately 0.5g of sodium bicarbonate to 5 mL urine.
- Transfer 2 mL plasma, serum or alkalised urine to a 1 mL/100mg silica SPE cartridge, and allow the sample to percolate through into the bed (the preferred cartridge is Bakerbond Cat No 7086-01, an alternative is Varian Bond-Elut 14102010).
- Using a syringe fitted on to the top of the cartridge with an adapter, apply gentle pressure to force the rest of the sample through the cartridge.
- Wash the cartridge with an equal volume of water, keeping the flow rate low.
- Add approximately 0.2 mL of the dithionite solution to the cartridge and apply very slight pressure to ensure that the liquid penetrates to just below the top frit. Do not allow the cartridge to dry out.
- A blue band immediately below the top frit of the cartridge indicates the presence of paraquat and confirms the diagnosis.
- 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.

2. Quantitative determination of paraquat

2.1. SPECTROPHOTOMETRY FOLLOWING SOLID-PHASE EXTRACTION AND REDUCTION WITH SODIUM DITHIONITE

- Plasma or serum samples are first filtered as described in section 1.2. Bond-Elut cyanopropyl cartridges (100mg 1 mL reservoir, Varian) are pre-conditioned successively with two column volumes of methanol, 0.1M HCl and 0.1M ammonia solution. The cartridges are fitted with 15 mL reservoirs and the patient plasma, serum, blank or spiked plasma (5 mL) is applied and drawn through by attaching the cartridges to a vacuum manifold until the cartridges are dry. The cartridges are rinsed with 1 mL 0.1M ammonia until they are dry and then paraquat is eluted with 0.8 mL 0.1M HCl into a test tube. Concentrated ammonia (0.025 mL) and sodium dithionite (0.1 mL 0.23M in 4M NaOH) are added. After vortexing the solutions are poured into disposable semi-microcuvettes (1 mL) and the absorbance scanned from 490 to 385 nm. The absorbance difference (A395-A460) is used to determine the paraquat concentration.
A standard curve is prepared in the range 0.05 - 1 µg/mL paraquat ion. Higher concentrations in unknown samples may be determined by taking a smaller amount of plasma sample. The lower limit of quantitation of the assay is 0.045 µg/ml based on a 5 mL sample.

The method is also applicable to urine which must be alkalinised (0.025 mL concentrated ammonia to 5 mL urine) and centrifuged prior to addition to the cartridge.

2.1. HPLC FLUORESCENCE

Paraquat can be measured in plasma or urine down to 0.001 µg/mL by fluorescence HPLC after conversion to the dipyridone derivative (Blake, et al 2002).

3. Advice on paraquat analysis

Syngenta CTL can provide advice on analysis of paraquat in biological samples via the e-mail address ctltestkitsupply@syngenta.com


