Controversies in treatment of paraquat poisoning

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Paraquat

- A bipyridium herbicide
- Toxicokinetics
  - Rapid absorption: peak plasma level within 1-2 hours
  - Incomplete absorption: 10-30%
  - Distribute to tissues: Lung, Kidney
  - Elimination: 90% eliminated within 12-24 hours via kidney (half-life 10-12 hours)

• Ingestion of paraquat leads to
  - Generation of free oxygen radicals
  - Lipid peroxidation
  - Damaging cell membranes and leading to cell death.
• Paraquat is actively taken up into type II pneumocytes and renal tubular cells.

Clinical classification of severity

- Mild poisoning:
  - Local irritation: vomiting and diarrhea
  - Ingestion of less than 20 mg/kg of paraquat ion
  - Full recovery without sequela
- Moderate to severe:
  - Ingestion of 20-40 mg/kg of paraquat ion
  - GI corrosion, acute tubular necrosis, hepatitis
  - Delayed progressive pulmonary fibrosis
  - Delayed mortality (1-4 weeks) from hyponxia
  - Survivors may have gradual recovery of pulmonary functions over months to years

• Fulminant poisoning:
  - Ingestion of more than 40 mg/kg of paraquat ion
  - Usually die within 1-5 days
  - GI ulceration
  - Acute renal failure, myocardial damage, hepatic failure, pulmonary edema and hemorrhage
  - Multiorgan failure, shock
  - 100% mortality regardless of management
Issues in Management of Paraquat Poisoning

- Supportive and symptomatic care
- Reduction of absorption
- Giving prognosis
- Increase paraquat elimination
- Specific therapy

Supportive and symptomatic care

- Evidence in animals of a relationship between the FiO2 and the severity of the pulmonary damage
  - Animals poisoned with paraquat died more quickly in an O2-enriched atmosphere than did poisoned animals breathing room air
  - Poisoned animals kept in a somewhat hypoxic atmosphere had lower mortality rates than animals kept in room air
- No evidence of adverse effects from oxygen in human
- Supplemental O2 is given when necessary

Reduction of absorption

- From animal experiments, paraquat is absorbed poorly from the stomach and absorbed incompletely (<5%) from the small intestine over a 1-6-h period
- Gastric lavage
- Use of adsorbent
  - Bentonite (sodium montmorillonite)
  - Fuller’s earth (calcium montmorillonite)
  - Activated charcoal

Gastric lavage

- Clark: Feed 4 cats with 62.5 mg/kg paraquat
  - Gastric lavage at 60 minutes after feeding
  - “A marked reduction in the blood paraquat level” between treated and controlled animals
  - Levels were still in toxic ranges
- No evidence of efficacy in human

Adsorbent

- Fuller’s Earth (calcium montmorillonite) and Bentonite (sodium montmorillonite) been shown to be a strong binding agent for paraquat in vitro
- Fuller’s earth and bentonite
  - Reduce plasma paraquat concentrations
  - Reduce mortality in animals when administered after an oral dose of paraquat

| Mortality due to Oral Paraquat when the Adsorbents are Given at Various Times Later |
|---------------------------------|-----------------|-----------------|
| Adsortent | Time after paraquat when adsorbent given (hr) | Paraquat dose and mortality | 200 mg/kg | 300 mg/kg |
| None | --- | 6/6 | 6/6 |
| Activated charcoal | 3 | 6/6 | 6/6 |
| Decaoat | 3 | 6/6 | 6/6 |
| Bentonite | 3 | 6/6 | 6/6 |
| Fuller’s Earth | 3 | 6/6 | 6/6 |
| 6 | 6/6 | 6/6 |
| 9 | 6/6 | 6/6 |

• Smith
• Repeated doses of Bentonite and castor oil/magnesium sulfate mixture at 2-3 hour intervals beginning 4-10 hours after oral administration of 126.65 mg/kg of paraquat
  - 27/29 of control rats died
  - 0/10 of rats treated at 4 hours died
  - 2/10 of rats treated at 10 hours died

Evidences of adsorbents in human
• Vale: Fuller’s earth and charcoal hemoperfusion in 10 cases with paraquat poisoning
  - Only 1 case survived
• Fitzgerald:
  - Survival among 62 patients treated with Fuller’s earth
  - No survival in those with ingestion of more than 30 ml of 20% paraquat
  - Ingestion 5-30 ml
    - 57% survival in patients treated with Fuller’s earth within 6 hours
    - 40% in non-treatment group
  - Fitzgerald GR. J. Irish Med. Assoc.1979;72:149-152

• Fuller’s earth may be beneficial in cases with exposure to paraquat slightly higher than the lethal dose

Activated charcoal and paraquat
• At the time of Clark’s experiment, activated charcoal was assumed not binding to paraquat

• Activated charcoal: low SAC but higher MAC
  - SAC (strong adsorption capacity): quantity of paraquat that can be adsorbed per unit weight of adsorbent before the adsorbent is in equilibrium with a detectable solution concentration
  - MAC (maximum adsorption capacity) maximum quantity of paraquat that can be adsorbed per unit weight of adsorbent
• There is a large variety of MAC among different brands of activated charcoals.

<table>
<thead>
<tr>
<th>Adsorbent</th>
<th>MAC (g of paraquat/100g)</th>
<th>SAC (g of paraquat/100g)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Activated charcoal</td>
<td>&gt;8.0</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Bentonite</td>
<td>6</td>
<td>5</td>
</tr>
<tr>
<td>Fuller’s earth</td>
<td>6</td>
<td>56</td>
</tr>
</tbody>
</table>

Gaudreault: Feed paraquat 200mg/kg in mice

<table>
<thead>
<tr>
<th>Treatment</th>
<th>% survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Control</td>
<td>31</td>
</tr>
<tr>
<td>Activated charcoal and Fuller’s earth</td>
<td>63</td>
</tr>
<tr>
<td>Activated charcoal and magnesium citrate</td>
<td>93</td>
</tr>
</tbody>
</table>

Prevention of absorption

- There is no clear clinical study of benefits of reduction of absorption of paraquat in human.
- On theoretical ground, prevention of paraquat absorption should be helpful only in cases with realistic chance of survival.

Prognosis

- Severity and outcome of paraquat poisoning is determined primarily by the dose ingested.
- However, the quantity ingested is often difficult to determine
  - Altered mental status
  - Vomiting after ingestion
  - Disturbance of gastrointestinal adsorption of paraquat by food

- Measurement of the plasma paraquat concentration can be performed by spectrophotometric and chromatographic techniques with a sensitivity limit <0.1 mg/L.
- Limitations:
  - Lack of availability
  - Clinical demand in emergency situations

Plasma paraquat concentration's relationship to time of ingestion

- In an ideal situation, measuring the plasma paraquat concentration is helpful to
  - Assessing the prognosis
  - Deciding whether to use or withhold aggressive therapy

- A nomogram was initially presented by Proudfoot
- Plasma paraquat concentrations at various times postingestion in 79 poisoned cases
- Those with concentrations below 2.0, 0.6, 0.3, 0.16, and 0.1 mg/L at 4, 6, 10, 16, and 24 h after ingestion, respectively, survived
- Applicable 4-24 hours after the ingestion
Hart with patients ($n = 218$) produced a graph of plasma Paraquat-to-time relationships for 10, 20, 30, 50, 70, and 90% probability of survival. Hart's 50% probability curve correlated well with the predictive line separating survival from death developed by Proudfoot. Applicable up to 28 hours after the ingestion. Hart TB, Nevitt A, Whitehead A. Lancet 1984 Nov 24;2(8413):1222-3.


### A prospective study in 451 cases from Sri Lanka to validate the use of plasma paraquat levels as predictors of death


<table>
<thead>
<tr>
<th>Method</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Positive predictive value</th>
<th>Negative predictive value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proudfoot/Schermann</td>
<td>0.79</td>
<td>0.89</td>
<td>0.92</td>
<td>0.73</td>
</tr>
<tr>
<td>Hart (50% survival line)</td>
<td>0.77</td>
<td>0.92</td>
<td>0.94</td>
<td>0.71</td>
</tr>
<tr>
<td>Jones ($p=0.5$)</td>
<td>0.70</td>
<td>0.93</td>
<td>0.94</td>
<td>0.67</td>
</tr>
</tbody>
</table>

### Urine paraquat

A semiquantitative test. Adding 10 ml of urine to 2 ml of a freshly prepared 1% sodium dithionite in 1 N sodium hydroxide. Positive (blue color change) with presence of paraquat when the urine concentration is about 1.0 µg/ml or more. Good correlation between concentration of paraquat and intensity of the formed blue color. The darker the color, the worse is the patient's prognosis. Scherrmann JM, Houze P, Bismuth C, Bourdon R. Hum Toxicol 1987 Jan;6(1):91-3.
• In a study with 53 cases of paraquat poisoning
• All patients with urinary paraquat concentrations less than 1 µg/ml (no color change), within 24 h of ingestion, survived
• Cases with results more than ++ (navy blue; >10 µg/ml) within 24 h following ingestion have a high probability of death

A study of urine paraquat test as a prognostic predictor


![Urine dithionite test for paraquat](image)

- A study using sodium dithionite test for plasma paraquat as a qualitative test in 233 paraquat poisoning patients
- Blood samples were drawn within 12 hours
- Detection limits: concentration ≥ 2 mg/L
  - Levels above 2 mg/L are associated with high mortality in many studies
  - Patients with a plasma paraquat level < 2.0 mg/L have the potential for recovery with vigorous treatment
  - Sensitivity 0.67
  - Specificity 1.0
  - Positive predictive value 1.0

- Urine should be tested serially for 24 h after ingestion
- An early urinary semiquantitative testing may underestimate the amount of paraquat systemically absorbed

- Although qualitative plasma paraquat concentrations have a greater predictive value, qualitative urine and plasma may contribute to a more rapid evaluation of prognosis with more availability
Enhancement of Elimination

- Concept: To remove paraquat from the circulation and prevent its uptake by pneumocytes
- An animal study demonstrated that the paraquat concentration in severely poisoned pigs decreased with active excretion through the kidneys initially, but the plasma concentration progressively increased later (the rebound phenomena)

Forced diuresis

- Kerr: First forced diuresis in paraquat poisoning cases
- No input volume recorded
- 24 urine output of 11 L with 47 mg of paraquat removed via urine
- Seizure and metabolic alkalosis after initiation of forced diuresis
- Bismuth:
  - Only 1 survival out of 9 cases who could maintain good urine output

Hemoperfusion

- The only method shown to be efficient and to enhance the extracorporeal elimination of paraquat
- Clearance may be as high as 170 ml/min
- Clearance depends on the plasma level, which always decreases rapidly

Hemodialysis

- Hemodialysis clearance of paraquat is insignificant, when compared with the exposed amount
- May be necessary as supportive treatment
Hemoperfusion

- Of 23 paraquat poisoning cases, 15 patients underwent hemoperfusion (HP)
  - 5 survivals
  - 10 died of respiratory failure within 28 days (7.6 +/- 2.9) and 5 survived without pulmonary complications.
- Of eight patients who did not receive HP, six died of respiratory failure
- In one patient, whose paraquat concentration in blood was followed serially, 99% of the paraquat was removed from circulating blood by a single hemoperfusion

- In a study, 21 patients receiving 10 hours or more of hemoperfusion had longer survival times as compared to 19 patients treated with less than 10 hours on the first day
- Hemoperfusion started within 15 hours
- Comparable severity between groups
- No difference in long term survival between the groups (4 of 21 and 5 of 19)

- In a study of 105 patients
  - 50 survivors and 55 nonsurvivors
  - Nonsurvivors ingested significantly more paraquat than survivors (55 +/- 44 mL vs 28 +/- 23 mL)
  - There was no difference in time to hemoperfusion between survivors and nonsurvivors (approximately 11 hours)
- Hemoperfusion was performed for 4 hours
  - Reduction rate was significantly higher in the survivors (80 +/- 20% vs 67 +/- 19%)

- A meta-analysis of 42 cases (35 from literature and 7 observed cases)
  - Sufficient comparative data and hemoperfusion information
  - No patient who had a plasma paraquat level greater than 3 mg/L survived despite charcoal hemoperfusion, no matter when the level was measured
  - Hemoperfusion did not appear to affect survival

- A group of 16 dogs was given a lethal intravenous dose of paraquat.
  - Two out of four dogs hemoperfused 2 hours after poisoning survived.
    - In these survivors, 25% of the paraquat dose was removed by the procedure
  - 10 dogs given charcoal hemoperfusion for 8 hours/day beginning 12 hours after poisoning died

- No systematic study showing that hemoperfusion is efficacious in human
  - Possible causes of failure:
    - Relatively small amount cleared
    - While renal function is still intact, external clearance is smaller than renal clearance
    - When renal failure develops, pulmonary uptake has already occurred

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  - Comparable severity between groups
  - No difference in long term survival between the groups (4 of 21 and 5 of 19)
Specific therapy

- The most widely investigated and applied aspect of specific management is immunosuppressive therapy, especially the regimen consisting of:
  - Cyclophosphamide
  - Corticosteroids
- Concepts: Reduction of pulmonary inflammation and fibrosis using antiinflammatory and immunosuppressive therapy

A repeated pulse regimen

- N = 23 cases of paraquat poisoned patients with predictive mortality > 50% but < 90% by plasma level
- Initial pulse therapy:
  - cyclophosphamide (15 mg/kg/day, i.v., 2 days) and methylprednisolone (1 g/day i.v., 2 days)
  - Followed by dexamethasone 5 mg, i.v., every 6 h until PaO2 > 80 mmHg
- Randomized cases for repeated pulse therapy if PaO2 was < 60 mmHg: 3 days of methylprednisolone and 1 day of cyclophosphamide
- Mortality rate:
  - control 5/7 = 71.4%
  - Study 5/16 = 31.3% (p<0.027)

Anti-inflammatory effect and survival

- A single-blinded randomized clinical trial in 142 paraquat-poisoned patients, pulse therapy reduced mortality in moderate to severe poisoning from 53/65(81.5%) to 38/56(67.9%)
- Pulse therapy included:
  1. 15 g/kg/day of cyclophosphamide for 2 days
  2. 1 g/day of methylprednisolone for 3 days
- All patients also received dexamethasone 30mg/day for 14 days
A meta-analysis

- 12 studies using immunosuppressive therapy in the management of paraquat poisoning
  - Four non-randomized
  - Six non-randomized comparing historical controls
  - Two randomized controlled trials
- The relative risk of immunosuppressive therapy in decreasing mortality with paraquat poisoning
  - 0.55 (95% CI 0.39-0.77) for the non-randomized studies (comparing historical controls)
  - 0.6 (95% CI 0.27-1.34) for randomized controlled studies

Thank you for your attention

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