Prospects for treatment of paraquat-induced lung fibrosis with immunosuppressive drugs and the need for better prediction of outcome: a systematic review

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Summary

\textbf{Background}: Acute paraquat self-poisoning is a significant problem in parts of Asia, the Pacific and the Caribbean. Ingestion of large amounts of paraquat results in rapid death, but smaller doses often cause a delayed lung fibrosis that is usually fatal. Anti-neutrophil (‘immunosuppressive’) treatment has been recommended to prevent lung fibrosis, but there is no consensus on efficacy.

\textbf{Aim}: To review the evidence for the use of immunosuppression in paraquat poisoning, and to identify validated prognostic systems that would allow the use of data from historical control studies and the future identification of patients who might benefit from immunosuppression.

\textbf{Design}: Systematic review.

\textbf{Methods}: We searched PubMed, Embase and Cochrane databases for ‘paraquat’ together with ‘poisoning’ or ‘overdose’. We cross-checked references and contacted experts, and searched on \url{www.google.com} and \url{www.yahoo.com} using ‘paraquat’, ‘cyclophosphamide’, ‘methylprednisolone’ and ‘prognosis’.

\textbf{Results}: We found ten clinical studies of immunosuppression in paraquat poisoning. One was a randomized controlled trial (RCT). Seven used historical controls only; the other two were small ($n=1$ and $n=4$). Mortality in controls and patients varied markedly between studies. Three of the seven non-RCT controlled studies measured plasma paraquat; analysis using Proudfoot’s or Hart’s nomograms did not suggest that immunosuppression increased survival in these studies. Of 16 prognostic systems for paraquat poisoning, none has been independently validated in a large cohort.

\textbf{Discussion}: The authors of the RCT have performed valuable and difficult research, but their results are hypothesis-forming rather than conclusive; elsewhere, the use of historical controls is problematic. In the absence of a validated prognostic marker, a large RCT of immunosuppression using death as the primary outcome is required. This RCT should also prospectively test and validate the available prognostic methods, so that future patients can be selected for this and other therapies on admission.
Introduction

Pesticide poisoning, particularly intentional self-poisoning, is a significant problem in many parts of the developing world. While organophosphorus pesticides are the most important cause of death and illness, other pesticides are important in particular regions. Paraquat dichloride is a bipyridyl compound that has been widely used as a non-selective contact herbicide since 1962, and ingestion of paraquat is a significant method of self-poisoning in parts of Asia, Pacific islands, and Caribbean.

Paraquat is highly toxic if swallowed as the concentrated product. Ingestion of large amounts is considered to be uniformly fatal, resulting in death from multi-organ failure and cardiogenic shock within 1–4 days. After ingestion of smaller quantities, paraquat is specifically taken up into, and accumulates in, the lung. Subsequent redox cycling and free radical generation triggers a neutrophil-mediated inflammatory response in the lungs, which initiates an irreversible fibrotic process that kills the majority of patients within several weeks.

Therapy has concentrated on reducing paraquat absorption from the GI tract and increasing its elimination. Unfortunately, all proposed interventions have been based on case reports or small case series, and there is no substantiated clinical evidence that either reducing absorption with Fuller’s earth, bentonite, and activated charcoal, or increasing elimination by forced diuresis, haemodialysis or standard haemofiltration, has increased survival.

However, Suzuki and colleagues have suggested that performing haemoperfusion for >10 h increases survival time. A recent study from Koo and others also found that using continuous venovenous haemofiltration in addition to haemoperfusion reduced the proportion of patients dying from acute multiorgan failure, while increasing the proportion dying from respiratory failure. These studies add impetus to the search for therapies to prevent lung fibrosis since they suggest that it may be possible to reduce the paraquat load with extensive haemoperfusion and increase the number of patients potentially able to benefit from such therapies.

Since the principal biochemical mechanism for lung damage is initiated by oxygen free radicals produced by peroxidation, clinicians have tried a number of anti-oxidant treatments in the hope that they might interfere with the process. Unfortunately, none of the studied treatments, including controlled hypoxia, superoxide dismutase, vitamins C and E, N-acetylcysteine, desferroxamine, and nitrous oxide, has been proven to be effective.

Immunosuppressive treatment for paraquat poisoning was first reported by Malone in 1971. This paper quickly stimulated further reports, but there is currently no clear consensus about its efficacy. The first part of this paper reviews ten studies of immunosuppressive treatment for paraquat poisoning.

Seven of these studies used historical control patients, rather than control patients in a parallel group. Historical controls can only be accepted if there are clearly defined (statistical) predictors of prognosis which show that the two patient groups are comparable at baseline. A dramatic improvement in outcome in a sequentially treated group of patients might be regarded as sufficient proof of efficacy if such validated prognostic indicators exist. This is the basis, for example, on which N-acetylcysteine has been accepted as an effective antidote for early paracetamol poisoning without RCT evidence.

In the second part of this paper, we report a systematic search for studies of prognosis in paraquat poisoning, and assess their validity. If validated prognostic indicators exist, they may allow interpretation of the non-randomized trials that use them. Alternatively, if none can be identified, evidence for efficacy of immunosuppression and other new therapies should only be accepted when the data come from RCTs.

Methods

We carried out a systematic search for clinical and prognostic studies by searching PubMed, Embase, and Cochrane databases (last checked 04/11/02), cross referencing from other articles, and contacting experts in the field to identify unpublished studies. All articles that were selected with the text words ‘paraquat’ together with ‘poisoning’ or ‘overdose’ were examined. Articles that could possibly be studies of immunosuppressive regimens or prognostic methods were retrieved to determine if this was the case. The web was also searched using [www.google.com], [www.yahoo.com], and the keywords: paraquat, cyclophosphamide, methylprednisolone, dexamethasone and prognosis (last checked 23/11/02). There were no constraints on quality of the studies. We included case reports if paraquat blood concentrations were determined.
Results
A search of medical databases for clinical studies of immunosuppression in paraquat poisoning revealed eight studies17–24 (Table 1); a search for prognostic methods revealed 17 studies25–42 (Tables 2 and 3). Searches of the internet revealed one further study of immunosuppression;43 a tenth study was presented at a toxicology meeting in 2003.44

Studies of immunosuppression for paraquat-induced lung fibrosis
One study was a randomized clinical trial; seven other studies used historical control groups while two reported case series of one and four patients, respectively. Details of the studies, including selection criteria for patients and controls, are summarized in Table 1 and elaborated below.

The RCT
In 1999, Lin and colleagues published an RCT of pulse methylprednisolone and cyclophosphamide in paraquat poisoning.22 Their paper reported a highly significant improvement in survival in moderate-to-severely poisoned patients randomized to pulse therapy: from 43% (12/28) to 72% (18/22; \( p = 0.008 \)).

The conclusions are, however, complicated by their exclusion of patients dying within 7 days—patients whom they defined as having ‘fulminant’ rather than ‘moderate-to-severe’ poisoning. This demarcation could only be made retrospectively at 7 days when survivors were identified. Their paper did not therefore present an intention-to-treat analysis but one in which 50% of patients were retrospectively excluded because of death from ‘fulminant’ poisoning. Unless it is possible to be certain that the immunosuppressive drugs themselves did not influence the outcome of those patients dying within 7 days, this exclusion is not justified. Reanalysis on an intention-to-treat basis shows an improvement which was not significant at the 0.05 statistical level: from 18% (12/65) to 32% (18/56; \( p = 0.095 \)). This means that the study points towards a benefit of immunosuppressive treatment, but that it was insufficiently powered to detect the effect statistically.

The study is described as a prospective clinical trial with patients randomized to usual or immunosuppressive treatment.22 Due to brevity of reporting, however, it is difficult to determine how the trial was actually performed.46,47 In addition, the start of patient recruitment to this trial (January 1992) predates recruitment of patients to the treatment cohort of their non-randomized study (July 1992).20

Although not stated in the papers, these studies were performed in two different hospitals of the same group in Taipei (J Lin, personal communication).

The authors concluded both this paper and a subsequent letter to the journal with the statement that further double-blind controlled studies are required to determine the efficacy and limitations of pulse therapy.22,48

Non-randomized studies
Study 1
Addo and colleagues reported the results of treating 20 patients with dexamethasone and cyclophosphamide in 1984.17 Compared to their previous 20% survival rate, they reported a much improved rate of 75%. All 20 patients had raised serum creatinine and bilirubin concentrations, suggesting significant exposure. However, exposure was only quantified from the volume of paraquat stated to have been ingested and not via plasma paraquat assays.

Study 2
The same authors subsequently reported their experience with a further 52 patients, presenting 72 patients in all.18 Again, they reported a much higher survival rate, 72% compared to 32%, in patients receiving immunosuppressive therapy compared to historical controls treated with standard therapy.

In response to the criticisms faced by their first study, they retrospectively measured serum paraquat concentrations in 25 patients. Among these patients, the survival rate was 52% (13/25), but six had no detectable serum paraquat (suggesting minimal exposure).49 Therefore, of the 19 patients with proven paraquat exposure, only seven survived (37%) and four of these had blood concentrations which predicted a better than even chance of survival according to the Proudfoot nomogram.

Study 3
Perriens and colleagues subsequently reported their experience of using the Addo regimen of immunosuppression in Suriname.19 They treated 14 patients with usual therapy from March until October 1986 when dexamethasone and cyclophosphamide became available; 33 patients were subsequently treated with Addo’s regimen. They found no difference between the two groups in terms of total mortality (20/33 vs. 9/14; 61% vs. 64%), death from
<table>
<thead>
<tr>
<th>Study</th>
<th>Location, date</th>
<th>Study group</th>
<th>Control group (type)</th>
<th>PQ blood levels</th>
<th>PQ urine levels</th>
<th>Urine DN test</th>
<th>Standard Rx</th>
<th>Immunosuppressive Rx</th>
<th>Patient survival</th>
<th>Control survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Addo</td>
<td>Trinidad, 7/83–1/84</td>
<td>20</td>
<td>NG (Historical)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>GL, FuE, K⁺, MDAC, MgSO₄, forced diuresis</td>
<td>Dexamethasone 8 mg IV, q8h for 2 weeks, then 0.5 mg PO, q8h for 2 more weeks. Cyclophosphamide 1.66 mg/kg IV, q8h to a maximum of 4 g over 4 weeks.</td>
<td>75%</td>
<td>20%</td>
</tr>
<tr>
<td>Addo</td>
<td>Trinidad, 7/83–12/84</td>
<td>72</td>
<td>(Historical)</td>
<td>25/72</td>
<td>No</td>
<td>Yes</td>
<td>GL, FuE, K⁺, MDAC, MgSO₄, forced diuresis Vitamins B and C.</td>
<td>Dexamethasone 8 mg IV, q8h for 2 weeks, then 0.5 mg PO, q8h for 2 more weeks. Cyclophosphamide 1.66 mg/kg IV, q8h to a maximum of 4 g over 4 weeks.</td>
<td>72%</td>
<td>32%</td>
</tr>
<tr>
<td>Perriens</td>
<td>Suriname, 3/86–3/88</td>
<td>33</td>
<td>(Historical)</td>
<td>26/47</td>
<td>No</td>
<td>Yes</td>
<td>GL (&lt; 6 h), Bent, MgSO₄, forced diuresis</td>
<td>Dexamethasone 8 mg IV, q8h for 2 weeks, then 0.5 mg PO, q6h for 2 more weeks. Cyclophosphamide 1.66 mg/kg IV, q8h to a maximum of 4 g over 4 weeks.</td>
<td>39%</td>
<td>36%</td>
</tr>
<tr>
<td>Lin</td>
<td>Taiwan, 7/92–6/94</td>
<td>29 (with dark or navy blue DN test)</td>
<td>(Historical, 7/89–6/91)</td>
<td>No</td>
<td>No</td>
<td>Yes</td>
<td>GL, AC, HP for 8 h.</td>
<td>Methylprednisolone 1 g IV, daily for 3 days. Cyclophosphamide 1 g IV, daily for 2 days.</td>
<td>41%*</td>
<td>18%*</td>
</tr>
<tr>
<td>Vieira</td>
<td>Brasil, NG</td>
<td>25</td>
<td>NG</td>
<td>10</td>
<td>No</td>
<td>NG</td>
<td>HP or HD for 11/25. Details otherwise not given</td>
<td>Dexamethasone 1.5 mg/kg daily for days 1-4, 1 mg/kg daily for days 5-7, then 24 mg daily. Cyclophosphamide 15 mg/kg IV day 1, 10 mg/kg day 2, 7 mg/kg days 3-5, thereafter 5 mg/kg daily, until total dose of 4 g or leukocyte count &lt;3000/mm³.</td>
<td>72%</td>
<td>0%</td>
</tr>
<tr>
<td>Name</td>
<td>Location</td>
<td>Year Range</td>
<td>Controls</td>
<td>Interventions</td>
<td>Outcomes</td>
<td>Treatment Details</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Lin</td>
<td>Taiwan</td>
<td>1/92–12/97</td>
<td>56 (with dark or navy blue DN test)</td>
<td>No</td>
<td>Yes</td>
<td>GL, AC, 2 × HP for 8 h. Methylprednisolone 1 g IV, daily for 3 days. Dexamethasone 8 mg IV, q8h for 2 weeks. Cyclophosphamide 15 mg/kg IV, daily for 2 days.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Botella de Maglia</td>
<td>Spain</td>
<td>?/88–6/00</td>
<td>18</td>
<td>No</td>
<td>No</td>
<td>GL, FuE, AC, MgSO₄, forced diuresis. HP for 9/10 controls, 7/19 on steroids. Vitamins B + C with steroids. One control received dexamethasone.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Garcia</td>
<td>Venezuela</td>
<td>1990s</td>
<td>10</td>
<td>No</td>
<td>No</td>
<td>GL, FuE, AC, MgSO₄, forced diuresis. HP for 9/10 controls, 7/19 on steroids. Vitamins B + C with steroids. One control received dexamethasone.</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Chen</td>
<td>Taiwan</td>
<td>1999</td>
<td>1</td>
<td>Yes</td>
<td>No</td>
<td>GL, AC, Mg citrate. 2 × HP for 8 h. Methylprednisolone 1 g IV, daily for 3 days. Dexamethasone 8 mg IV, q8h for 2 weeks. Cyclophosphamide 15 mg/kg IV, daily for 2 days. Then: Dexamethasone 5 mg IV, q8h for 30 days. Second course of methylprednisolone and cyclophosphamide as above. Survived</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Chomchai</td>
<td>Thailand</td>
<td>2001–2</td>
<td>4</td>
<td>No</td>
<td>No</td>
<td>FuE, Vitamin C 6 g/day Dexamethasone 10 mg q8h IV for 14 days. Cyclophosphamide 1.7 mg/kg IV q8h for 14 days. 100%</td>
<td></td>
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</tbody>
</table>

*Analysis by the present authors according to intention-to-treat.

AC, activated charcoal; Bent, bentonite; DN, dithionite test; FuE, Fuller’s earth; GL, gastric lavage; HD, haemodialysis; HP, haemoperfusion; IV, intravenous; MDAC, multiple dose activated charcoal; NA, not applicable; NAC, N-acetylcysteine; NG, not given; PO, by mouth; PQ, paraquat.
<table>
<thead>
<tr>
<th>Study</th>
<th>Location, date</th>
<th>Patients</th>
<th>Dx</th>
<th>Blood level</th>
<th>Urine level</th>
<th>Treatment</th>
<th>Survival: included (overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UK, NG</td>
<td>16/0</td>
<td>Hx, Urine PQ assay</td>
<td>No</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>2</td>
<td>UK, NG</td>
<td>71/8</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>No</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>3</td>
<td>UK, NG</td>
<td>219/0</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>No</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>4A</td>
<td>France, NG</td>
<td>30/0</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>No</td>
<td>NG</td>
<td>NG</td>
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<tr>
<td>4B</td>
<td>France, NG</td>
<td>53/0</td>
<td>Hx, Urine PQ assay</td>
<td>Yes</td>
<td>No</td>
<td>NG</td>
<td>NG</td>
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<tr>
<td>5</td>
<td>Singapore, 1976–84</td>
<td>14/13 (no Ur PQ assay)</td>
<td>Hx, Body fluid assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>6</td>
<td>Japan, 1985–87</td>
<td>30/0</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>No</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>7</td>
<td>Japan, 1985–87</td>
<td>51/0</td>
<td>Hx, Urine PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>8</td>
<td>Japan, 1981–87</td>
<td>65/95</td>
<td>Hx, Urine PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>9</td>
<td>Thailnad, 1983–88</td>
<td>24/0</td>
<td>Hx and Ex, or PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>10</td>
<td>Japan, late 1980s</td>
<td>18/0</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>11</td>
<td>Guadeloupe, 1987–91</td>
<td>25/0</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>12</td>
<td>Guadeloupe, early 1990s</td>
<td>18/0</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
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<tr>
<td>13</td>
<td>Japan, Australia, NG</td>
<td>128/0</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>14A</td>
<td>Japan, NG</td>
<td>49/3</td>
<td>Hx, Blood PQ assay</td>
<td>Yes</td>
<td>No</td>
<td>NG</td>
<td>NG</td>
</tr>
<tr>
<td>14B</td>
<td>Japan, NG</td>
<td>75/0</td>
<td>Hx, Urine PQ assay</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
</tr>
</tbody>
</table>
lung fibrosis (6/33 vs. 2/14; 18% vs. 14%), or renal failure (24/33 vs. 10/14; 73% vs. 71%).

Serum paraquat concentrations were assayed in 26 consecutive patients: 14 of the usual therapy group and 12 of the immunosuppressive group. Using the nomogram of Hart, they reported that all patients who had a predicted chance of survival <65% died, irrespective of the treatment given (9/14 receiving usual therapy, 10/12 receiving immunosuppression). All patients with predicted survival >65% survived.

Study 4

In 1996, Lin and colleagues reported a study of pulse immunosuppression in 87 patients seen in their hospital between July 1989 and June 1991 (controls) and between July 1992 and June 1994 (patients treated with immunosuppression). They reported a better outcome with immunosuppressive therapy: 12/16 (75%) ‘moderate-to-severely’ poisoned patients survived compared to 5/17 (29%) historical controls. This study was also complicated by their exclusion of patients dying from ‘fulminant’ poisoning.

Only patients with ‘navy blue’ or ‘dark blue’ urine dithionite tests were considered as moderate-to-severely poisoned and therefore given immunosuppression. This practice excluded mildly poisoned patients with a hypothetically good prognosis. Analysing only patients with navy or dark blue urine dithionite tests gave survival rates of 41% (12/29) and 18% (5/28) in the treated and control groups, respectively.

Study 5

A study of 40 patients from Campinas, Brasil, has been reported in abstract format only. Five patients had mild poisoning and were not further studied. Eighteen of 25 patients receiving a reducing course of cyclophosphamide and dexamethasone survived; all ten patients who did not receive immunosuppressive therapy died. Unfortunately, the abstract did not present methodology; most importantly, the method used to determine allocation to immunosuppressive therapy or standard therapy was not stated. The use of paraquat assays in blood or urine, or the dithionite test, was also not detailed.

Study 6

A series of 29 patients treated over 17 years in Valencia, Spain, was reported in 2000. The clinicians started using immunosuppressive drugs in 1988, initially adding them to haemoperfusion, and then stopping haemoperfusion and relying on
<table>
<thead>
<tr>
<th>Study</th>
<th>Prognostic formula for survival</th>
<th>Notes</th>
<th>Validated by authors? (no. of new patients)</th>
<th>Result (spec./sens.)</th>
<th>Tested by others?</th>
<th>Reference papers (no. of patients)</th>
<th>Sensitivity and specificity of proposed cutoff for prediction of death (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wright²⁵</td>
<td>PQ excretion &gt; 1mg/h &gt; 8 h post-ingestion predicts death</td>
<td>Urine PQ assay required</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Proudfoot²⁶</td>
<td>Survivors have plasma paraquat concentrations not exceeding 2.0, 0.6, 0.3, 0.16, and 0.1 µg/ml at 4, 6, 10, 16, and 24 h post-ingestion (Figure 2a)</td>
<td>Applicable up to 24 h. PQ plasma assay required.</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Bismuth⁵⁰ (17, 12 died)</td>
<td>Sensitivity 100% (74–100%) Specificity 100% (48–100%)</td>
</tr>
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<td></td>
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<td></td>
<td></td>
<td>Ragoucy-Sengler ³⁵ (25, 14 died)</td>
<td>Sensitivity 100% (77–100%) Specificity 73% (39–94%)</td>
</tr>
<tr>
<td>Hart²⁷</td>
<td>Graph of plasma concentration on admission vs. time since ingestion generated with contour map lines denoting equal probability of survival (Figure 2b)</td>
<td>Applicable up to 28 h. PQ plasma assay required.</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Perriens ¹⁹ (26, 19 died)</td>
<td>Prediction &lt; 65%: Sensitivity 100% (82–100%) Specificity 100% (59–100%)</td>
</tr>
<tr>
<td>Scherrmann²⁸,³⁹</td>
<td>Survivors have plasma paraquat levels less than ‘c’ µg/l at time point t (h), using the following equation: c = 10⁵/(0.471t-1.302)</td>
<td>Applicable after 24 h. PQ plasma assay required.</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Scherrmann²⁸,³⁹</td>
<td>Urine PQ &lt; 1 mg/ml within the first 24 h predicts survival</td>
<td>Urine PQ assay required</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Fock²⁹</td>
<td>Urine PQ &lt; 0.8 mg/ml within 8 h predicts survival</td>
<td>Urine PQ assay required</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Sawada³⁰</td>
<td>SIPP &lt; 10 predicts survival; SIPP 10–50, death from lung fibrosis; SIPP &gt; 50, death from circulatory failure. SIPP (severity index of paraquat poisoning) = time to treatment (h) x serum PQ concentration (mg/l⁴)</td>
<td>Applicable up to 200 h. Plasma assay required.</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Author</td>
<td>Formula</td>
<td>Requires Blood Gas Assay</td>
<td>WBC Required</td>
<td>Sensitivity</td>
<td>Specificity</td>
<td></td>
<td></td>
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<tr>
<td>Suzuki</td>
<td>Respiratory index (RI) &lt; 1.5 predicts survival. RI = A - aDO₂/P0₂ A - aDO₂ = 713 x FiO₂ - PCO₂ [FiO₂ + (1 - FiO₂)/0.8] - P0₂</td>
<td>Requires blood gas assay</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yamaguchi</td>
<td>Patients with: ( \text{Eq1} &gt; (1500 - 399 \times \log T) ) have a 90% probability of survival; ( \text{Eq1} &lt; (930 - 399 \times \log T) ) have a 3% probability of survival; patients with a value in-between have a 38% probability of survival. ( \log T = \log \text{of time from PQ ingestion to admission.} ) ( \text{Eq1} = [K^+] \times [\text{HCO}_3^-]/[\text{Creatinine}] ) (All values in mEq/l)</td>
<td>Requires basic biochemical assays</td>
<td>No</td>
<td>NA</td>
<td>Yes</td>
<td>Ragoucy-Sengler, Sensitivity 100% (77–100%) Specificity 73% (39–94%)</td>
<td></td>
</tr>
<tr>
<td>Kaojarem</td>
<td>In survivors, the following formula is positive: ( 0.027 \times \text{age (years)} + 0.022 \times \text{ingested volume (ml)} + 0.0002 \times \text{WBC (cells/mm}^3) )</td>
<td>WBC required. Estimate of volume is unreliable</td>
<td>Yes (9)</td>
<td>100%/100%</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Yamashita</td>
<td>U-SIPP (urine severity index of paraquat poisoning) = urine PQ concentration (µg/ml) x time (h) between ingestion and start of intensive therapy. With creatinine clearance &gt; 20 ml/min, patients with U-SIPP &gt; 1250 die from circulatory failure, those with U-SIPP 250–1250 die from lung fibrosis, and those with U-SIPP &lt; 250 survive.</td>
<td>Urine PQ assay required</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ragoucy-Sengler</td>
<td>Chronic alcoholic Caribbean men with gGT &gt; 40 IU/l and mcv &gt; 100 fl have an improved probability of survival. Not quantified.</td>
<td>Requires Hx plus basic biochemical/haematological assays</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Ragoucy-Sengler</td>
<td>( \text{dCreat/dt} &lt; 3.0 ) predicts survival. ( \text{dCreat/dt} = \frac{\text{Creat(T)}}{5} - \frac{\text{Creat(T_0)}}{5} ) where ( T_5 ) is 5 h after ( T_0 ), which can be at any time after the poisoning; ( \text{Creat in } \mu\text{mol/l} )</td>
<td>Time post-ingestion is not required. Requires only basic biochemical assays</td>
<td>No</td>
<td>NA</td>
<td>No</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>

(Continued)
| Study       | Prognostic formula for survival                                                                 | Notes                          | Validated by authors? (no. of new patients) | Result (spec./sens.) | Tested by others? | Reference papers (no. of patients) | Sensitivity and specificity of proposed cutpoint for prediction of death (95% CI) |
|------------|-----------------------------------------------------------------------------------------------|--------------------------------|---------------------------------------------|----------------------|-------------------|------------------------------------|---------------------------------------------------------------------------------
| Ikebuchi   | \( D \) score > 0.1 predicts survival, \( D < -0.1 \) predicts death. \( D = 1.3114 - 0.1617 \ln(T) - 0.5408 \ln(\ln(C/1000)) \) where: \( T \) = time from ingestion (h) \( C \) = plasma paraquat ingestion (\( \mu \)g/ml) | PQ plasma assay required       | Yes (128)                                   | ?                    | No                | NA                                  | NA                                                                            |
| Lheureux   | Survivors have a blood PQ level below a line linking 2 \( \mu \)g/ml at \( \sim 13 \) h and 0.7 \( \mu \)g/ml at \( \sim 75 \) h on a semi-log plot. | Applicable up to 100 h. PQ blood assay required. | No                           | NA                                  | No                              | NA                                  | NA                                                                            |
| Jones      | Probability of survival = \( \exp(\text{logit})/[1 + \exp(\text{logit})] \) \( \text{logit} = 0.58 - [2.33 \times \log(\text{plasma paraquat}) - 1.15 \times \log(\text{h since ingestion})] \) PQ concentration in \( \mu \)g/ml. (See Figure 2a for derived 90% survival curve) | Applicable up to 200 h. PQ plasma assay required. | No                           | NA                                  | No                              | NA                                  | NA                                                                            |
| Hong       | 'Subjects with liver or renal dysfunction or metabolic acidosis had significant risks of fatality' |                                                                               |                             |                       |                   |                                    |                                                                                |

*Units were not given in the paper but are presumed to be mg/l from earlier work. Abbreviations as Table 1.*
immunosuppression alone. They reported a marked improvement with immunosuppressive therapy: an increase in survival from 9% to 44%, particularly in patients reporting the ingestion of <45 ml of 20% concentrate.

However, blood paraquat concentrations were not obtained and the degree of exposure was therefore not known. Of the 22 patients who developed acute renal failure (defined as urine output <400 ml/day and/or serum creatinine >133 \( \mu \text{mol/l} \)), suggesting significant exposure, only three (14%) survived. Similarly, 17/18 patients with acute respiratory failure (\( \text{PaO}_2 < 60 \text{mmHg} \) on room air) died.

**Study 7**

A series of ten ‘moderately to severely poisoned’ patients treated with immunosuppression was reported from Ciudad Bolívar, Venezuela.\textsuperscript{43} Compared to the hospital’s ‘usual 100% fatality rate’ in such patients, the authors reported survival in 8 of 10 patients. They concluded that ‘methylprednisolone and cyclophosphamide are effective in preventing acute respiratory failure…and reducing mortality’.

Paraquat concentrations were available but presented as a mean only, with no indication of time post ingestion for each individual patient’s paraquat level. The mean was stated to be 3.58 ± 0.31, with units ‘\( \mu \text{g/ml} \)’ in the text and ‘pg/ml’ in the abstract. These values seem low: Proudfoot’s paper used a value of 2 mg/l (2 \( \mu \text{g/ml} \)) as a cut-off for survival at 4 h.\textsuperscript{26} These values appear to be 10\textsuperscript{6}-fold lower.

Other features suggest that most patients were not significantly poisoned: leukocyte counts ranged from 4.1 to 16.7 (less than all 72 patients in Addo’s study\textsuperscript{18}), only four developed acute renal failure (two deaths), three of four had normal upper GI endoscopy,\textsuperscript{50} and three of three had completely normal spirometry.

**Study 8**

The Taiwanese group recently reported a single patient who received two courses of pulse immunosuppression for paraquat poisoning.\textsuperscript{24} The patient had a blood paraquat concentration of 3.36 \( \mu \text{g/ml} \) 10 h after ingestion (suggestive of poor prognosis by all nomograms) and developed renal failure requiring haemodialysis. Interstitial lung infiltration was noted on X-ray, and he became hypoxic (nadir \( \text{PaO}_2 \) of 66.6 mmHg, 8.9 Pa, on day 30). The lung fibrosis progressed despite treatment with a course of pulse immunosuppression and 25 days of dexamethasone (see Table 1 for dosage details). However, a second course of pulse immunosuppression, started on day 30, coincided with clinical improvement and he was discharged from hospital on day 41.

**Study 9**

Chomchai and Chomchai have reported in abstract form four Thai patients treated with dexamethasone and cyclophosphamide.\textsuperscript{44} Although blood paraquat levels were not assayed, they were considered moderately-to-severely poisoned on the basis of a history of ingesting 1 g or 20 mg/kg paraquat. Three of four developed both renal failure and hepatitis suggesting significant exposure; however, none developed pulmonary complications and all four survived.

**Prognosis of acute paraquat poisoning.**

The search revealed 18 studies using patient investigations (Tables 2 and 3). Seven and four studies used plasma or urine paraquat concentrations, respectively, for prediction of prognosis; one study used arterial blood gas analysis, and four used fairly simple biochemical and/or haematological assays. One study reported that Caribbean men with a history of chronic alcohol use and raised \( \gamma \text{GT} \) and MCV had a good prognosis, but was unable to quantify it.\textsuperscript{35} A recent study reported an association between renal and liver failure and a metabolic acidosis with poor outcome, but offered no method for distinguishing those who would survive from those who would die.\textsuperscript{42} The treatment given to patients varied both within studies and across studies. Most studies included all eligible patients.

None of these systems have been validated. Only one study tested the proposed method for survival prediction and this was with nine patients. Three prognostic systems were tested by other clinicians, but again they used only small numbers of independent patients (maximum of 79; see Table 3). The largest study, that of Suzuki and colleagues,\textsuperscript{51} compared the accuracy of three different prognostic systems: Proudfoot’s\textsuperscript{26} and Schermann’s\textsuperscript{28} nomograms and the Severity Index of Paraquat Poisoning (SIPP) of Sawada and colleagues.\textsuperscript{30} Although they tested the systems with 79 independent patients, the results are confused by their incorporation of 144 patients from the original papers into the analyses. Since the systems were developed using data from these patients, they cannot be used again to test the system.
Discussion

We were unable to find any study that definitively established the role of immunosuppression in paraquat poisoning. We were also unable to find any properly validated prognostic method that would allow clinicians: (i) to use historical controls in studies of new treatments; and (ii) to predict which patients will die from lung fibrosis, rather than acute multi-organ failure, and therefore possibly benefit from immunosuppressive therapy.

Immunosuppression and lung fibrosis

We found ten studies assessing the effect of immunosuppressive therapy on outcome in paraquat poisoning.

All but two studies reporting more than one patient used historical controls. Using such controls for controlled trials of new interventions, rather than controls treated in parallel, is associated with inflation of evidence for benefit.46,52–54 These studies therefore cannot be considered to provide good evidence of benefit or harm from immunosuppression. A feature of these trials is the great variation in survival rates between different studies (Figure 1).

RCTs are the highest rated form of study for intervention trials. One study was described as a RCT and it reported significant benefit for immunosuppression. Unfortunately, little methodology (as requested by the CONSORT statement46,47) was given in the published paper. It is consequently not possible to assess many elements of trial design and analysis and, in particular, allocation concealment.53

The RCT was not analysed on an intention-to-treat basis. The paper’s analysis thus misses the possibility that the treatment itself may have caused harm (including death) in that arm. An ITT analysis, while suggesting some benefit from immunosuppression, does not confirm benefit to the 0.05 level.45 Despite these problems, some commentators have stated the treatment should be widely used.55,56 We believe this conclusion to be premature and that further RCTs are required (see below).

Future studies of paraquat poisoning using historical controls may be of some value if it is possible to demonstrate that both groups of patients had a similar degree of exposure to paraquat and similar prognoses, in particular their risk of dying from paraquat-induced lung fibrosis. This requires validated prognostic methods.

The single case presented by Chen and colleagues is well characterized, and does suggest that high-dose pulse immunosuppression may be of benefit. Of note, this patient required two courses of immunosuppression 4 weeks apart, in contrast with their RCT in which patients received only one course.

Prognostic methods for paraquat poisoning

We found 18 studies that reported a link between the result of investigations and outcome. Fifteen of these studies proposed a nomogram or formula for predicting outcome. However, just one was tested with new patients by the same authors, and only three appear to have been tested by other researchers. None has been prospectively validated in a large cohort.

The plasma paraquat concentration seems likely to be the most useful marker of exposure and severity (Figure 2).39 A major constraint of this method is the inability of many hospitals in the developing world, where most patients present, to do the assay. Even where the necessary analytical facilities exist, most currently available methods require experience and rigorous quality control to provide reliable results. A properly validated, affordable and robust bedside test of paraquat concentration could make a significant difference.

In the absence of such an assay, the urine dithionite test is often used to estimate the level of exposure. Its validity is questionable since urine paraquat concentration will depend on the individual’s renal function—young people with excellent renal function will initially excrete more paraquat than someone with poor renal function. Patients with poor renal function will have higher urine concentrations at later timepoints. Urine production will also decrease as the poisoning progresses, since paraquat causes renal failure.4,28 Such variation may push the urine paraquat level above or below the threshold for detection.

Scherrmann’s later and larger study of 75 patients with this assay found that 3/21 patients (14%) with a negative or pale blue test result died while 6/54 (11%) of patients with a navy or dark blue test survived.39 Similarly, Hwang and colleagues study found that 5/59 patients (8%) with a negative dithionite assay died, while at least 13/75 patients (17%) with a ‘++ to ++++’ positive result survived.57 The performance of the dithionite test in predicting an adverse prognosis is therefore not sufficiently accurate as to validate the use of historical controls. However, the performance of this simple urine assay may be as good as any single cut-off point of blood concentration in terms of the positive likelihood ratio and it may be useful as an entry criteria for RCTs.
Yamashita published a paper in Japanese in 1989 that reported a Severity Index using urine paraquat levels. He controlled for renal function by including only patients with a creatinine clearance of > 20 ml/min. His formula predicted 6/6 survivors; unfortunately, he did not validate it with other patients and no-one else appears to have used it.

Other methods of prognosis prediction have used the results of biochemical tests such as potassium, bicarbonate and creatinine concentrations. However, most require knowledge of time of ingestion and/or quantity ingested, both often difficult to determine, particularly in those who co-ingest alcohol. One of the attractions of Ragoucy-Sengler's...
proposed system,\textsuperscript{36} based on changes in creatinine concentration over 5 h, is that it is independent of both variables.

Future studies

We believe that a RCT, sufficiently large as to find a 10% absolute difference in all-cause mortality, is urgently required to establish whether high-dose pulse immunosuppression as used by Lin and colleagues is effective in preventing paraquat-induced lung fibrosis. In Lin’s RCT, overall survival in control patients (with exposure shown by a navy or dark blue dithionite test) was 18% (12/65) compared with 32% (18/56) in the treatment arm. In order to be able to detect whether either regimen increases survival from 18% to 28%, with a significance level (alpha) of 5% and a power of 80%, a minimum of 295 patients with significant poisoning (navy or dark blue urine dithionite test) would have to be recruited to each arm of the trial (590 patients in total).

It will be important in this study to also take enough biochemical data (blood and urine paraquat levels, baseline biochemistry, and possibly arterial blood gas, at study entry and 5 h) to prospectively test a number of the proposed prognostic methods.

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Conflicts of interest

MFW is an employee of Syngenta, a manufacturer of paraquat. ME and NAB have accepted hospitality (meals, transport) from MFW to the net sum of around 50 USD and 20 USD, respectively. ME, MFW and NAB are now planning a RCT in Sri Lanka, funded by Syngenta, that will address the question of benefit of immunosuppression in the treatment of paraquat poisoning.

References

Treating paraquat poisoning


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