Multiple logistic regression analysis of plasma paraquat concentrations as a predictor of outcome in 375 cases of paraquat poisoning

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Summary

Successful prediction of who may survive paraquat poisoning can prevent inappropriately aggressive treatment in those who have little hope of survival and those only minimally poisoned. We examined case records of patients admitted to one poisoning treatment unit over the last 5 years, and the English and French language literature on paraquat poisoning. Data were recorded from all patients where outcome and timed plasma paraquat concentrations were present. Of 375 patients (113 M, 62 F, 200 unknown), mean age 38.3 years (range 1–87 years), 49 had evidence of renal toxicity, and 41 received haemodialysis or charcoal haemoperfusion; 61 developed pulmonary sequelae; and 44 had lesions in the upper gastrointestinal tract. Median time from ingestion to death in the 241 deaths reported was 270 h (range 3–720 h). We plotted log(plasma paraquat concentration) against log(h since ingestion). The predicted probability of survival for any specified time and concentration was exp(logit)/(1 + exp(logit)), where logit = 0.58–2.33 × log(plasma paraquat)–1.15 × log(h since ingestion). This equation may be helpful in predicting who will survive after ingestion of paraquat up to at least 200 h after ingestion, and can now be used as a research tool for studies on efficacy of treatment of paraquat poisoning.

Introduction

Paraquat remains a major cause of death in developing countries, such as Pakistan and Sri Lanka, although deaths also occur in the UK each year. Although there are few efficacious therapeutic options for the management of paraquat poisoning, it is important to be able to predict who will survive, so that inappropriately aggressive techniques, such as haemodialysis, are not used in those who have no hope of survival, and to advise patients and relatives of the likely outcome. Similarly, minimally-poisoned patients may be protected from unnecessarily aggressive treatment.

Proudfoot examined 79 cases of paraquat poisoning, and related outcome to plasma paraquat concentrations on admission and the ingestion to sampling interval. This has guided therapy, at least in the UK, for the last two decades; however, the numbers in this study were relatively small, the separation between patients who died and those who survived in the first 5 h after ingestion was not clear, and no patients presenting >24 h after ingestion were included. However, some patients seek medical help only once they have developed symptoms of poisoning, which is often later than 24 h.

Our aim was to examine all the clinical records of patients under our care with paraquat poisoning, and all the cases reported in the world literature, in
order to produce a more data-intensive survival curve and one that was valid beyond 24 h after ingestion.

**Methods**

We examined the case records of patients admitted to the poisons ward in Edinburgh Royal Infirmary over the last 5 years, and the world literature on paraquat poisoning. Medline and Medline were searched using the terms ‘intoxication or poisoning, or overdose’ to link with ‘paraquat or herbicide or pesticide’. Only English or French language publications could be included for logistical reasons.

Data were as recorded from all papers in which outcome data and timed plasma paraquat concentrations were given. Sometimes this required reading data from photocopied enlargements of graphical information. Duplication of case data between publications was excluded by examining acknowledges of other data sources on papers and by closely matching patient criteria (i.e. age, sex, plasma paraquat concentration, and time since ingestion) between all publications. When there was any doubt about duplication, the data was entered only once for analysis.

When serial plasma paraquat concentrations were available from a single patient, the first result available to the clinician was used. The theoretical basis for this approach comes from the observation that when multiple samples were taken for paraquat estimation, ‘peak plasma paraquat concentrations’ had been reached before the first samples were drawn, even when the interval between ingestion and sampling was as short as 2 h. This is also important, as data for this study have been collected before elimination methods have been used, although in any case, their efficacy is highly questionable.

Plasma paraquat concentrations related to time since ingestion in patients who survived and those who died were plotted using GraphPad (Prism 1996, Version 2.01). Multiple logistic regression analysis was performed to provide a line that fitted the data and predicted survival or death, using a standard statistical program (SPSS Version 4.01, 1994).

**Results**

Data were collected from papers in English or French languages. A list of those omitted from the study, either inaccessible because of language or with unavailable data, is available on request. We identified 375 cases (113 men, 62 women, and 200 of unidentifiable sex), of mean age 38.3 years (range 1–87 years). They included patients from Australia, Belgium, France, the French West Indies, Germany, Holland, Israel, Japan, South America, Taiwan, Trinidad and Tobago, the UK, and the USA. Preparations taken included 10%, 12%, 20% and 24% paraquat. In 106 cases the route of exposure was noted: one intravenous, one oral, five dermal and, 99 by mouth. Several were severely poisoned: 49 had evidence of renal toxicity, of whom 41 eventually received haemodialysis and/or charcoal haemoperfusion; 61 developed pulmonary sequelae and in six, supplemental oxygen was given; 18 patients had evidence of hepatic injury; 44 had lesions of the upper gastrointestinal tract; seven patients developed circulatory failure. The median time from ingestion to death in the 241 deaths reported was 270 h (range 3 to 720 h).

A plot of the logarithm of the plasma paraquat concentration versus the logarithm of the time since ingestion is shown in Figure 1. A logistic regression of survival using both these variables gave significant independent effects for each ($\chi^2 = 95.3$ for plasma concentration and $\chi^2 = 13.5$ for time, both $p < 0.001$).

To calculate a predicted probability of survival for any specified time and concentration, a formula was derived based on the logistic regression coefficients:

$$ \logit = 0.58 - 2.33 \times \log(\text{plasma concentration of paraquat}) - 1.15 \times \log(\text{h since ingestion}) $$

Predicted probability of survival $= \exp(\logit) / [1 + \exp(\logit)]$

(all logarithms in these formulae are to base 10).

**Discussion**

Paraquat poisoning remains a significant world-wide cause of morbidity and mortality. There have

<table>
<thead>
<tr>
<th>Table 1 Clinical details recorded for paraquat-poisoned patients</th>
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<td>Survival</td>
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<td>Pulmonary complications</td>
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<tr>
<td>Age</td>
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<td>Pre-existing disease</td>
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<td>Haemoperfusion/haemodialysis</td>
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<td>Circulatory failure</td>
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<td>Time from ingestion to death</td>
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<td>Degree of hepatic injury</td>
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<td>Other substances taken</td>
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been several previous attempts to predict survival in patients poisoned with paraquat using plasma paraquat concentrations and/or clinical criteria.\textsuperscript{3,38,42,46,49,59–61} By far the most useful and in widest use, despite the limitations discussed above, has been the survival curve produced by Proudfoot.\textsuperscript{3,49}

Several probability survival curves based on a larger number of patients ($n = 218$) were provided by Hart,\textsuperscript{58} but similarly, the data did not extend beyond 28 h after ingestion of paraquat. In the non-exponential mathematical survival curve produced by Scherrman,\textsuperscript{38} data were included up to 360 h after ingestion, but this curve was based on only 30 patients. Ikebuchi\textsuperscript{61} performed multivariate analysis on data from 128 poisoned patients in order to assess the severity of paraquat poisoning. As a result, the TIP or toxicological index of paraquat was developed. However, only 21 patients who survived were included in this study.

We report a new relation between plasma paraquat concentration and time, which may be helpful in predicting who will survive after ingestion of paraquat up to at least 200 h after ingestion (Figure 1). Although a line has been drawn in Figure 1 to separate the fatal and non-fatal cases, it can only act as a guide, and prognosis may be influenced by several factors, including individual sensitivity to paraquat\textsuperscript{58} and inaccuracies in assessment of the ingestion-presentation interval.

One patient appears anomalous (Figure 1), a 52-year-old man with a past history of alcoholism and seizures who had ingested ‘one glass of herbicide’ and who died in spite of a very low concentration of paraquat: 0.0024 mg at 13 h after ingestion.\textsuperscript{40} We could find no obvious explanation for this anomaly, unless the patient gave the time from ingestion incorrectly or a laboratory error occurred.\textsuperscript{40} Despite intensive supportive care and treatment with fuller’s earth and haemodialysis, he died as a result of cardiovascular shock and acute renal failure, having developed the characteristic corrosive gastrointestinal tract lesions of paraquat toxicity.\textsuperscript{40} Thus, the data on this patient have been included in the analysis.

Use of the survival curve (Figure 1) is not intended to replace the initial qualitative screening test, which is performed by adding a knifepoint of sodium dithionite and a knifepoint of sodium bicarbonate to a urine sample taken within 24 h of ingestion of paraquat.\textsuperscript{38,62} However, if the patient presents $>24$ h after ingestion, the qualitative urine test is not reliable and should not be used.\textsuperscript{38} In that event, plasma paraquat concentrations may be used, together with Figure 1, to help predict survival.

The logistic regression using both time and plasma paraquat concentration as variables gave very highly significant independent effects for each as predictors of survival. This quantifies what is apparent from Figure 1, namely that patients with a given concentration of paraquat have a better chance of survival if they have only recently taken it, and at any time after ingestion, the prognosis is better the lower the plasma concentration. Use of the logistic regression equation allows us to predict the probability of survival for any specified time and paraquat concentration. Whilst calculation looks quite complicated, it is remarkably easy to do on a pocket calculator. It could be used to draw in contours of constant probability on the plot, and these would be straight lines parallel to the one already shown in Figure 1. For example, a contour for a 50% chance of survival would correspond to a logit of zero, giving a line
defined by:
\[
\log(\text{concentration}) = 0.25 - 0.49 \times \log(t)
\]

Those patients near the survival line (Figure 1) might be anticipated to be those most likely to benefit from therapeutic intervention; a prospective multicentre study should evaluate whether measures which have been previously used for gut decontamination, such as activated charcoal\(^{12,63,64}\), or for elimination\(^{14,22,30,37}\), will alter outcome. There are many reports of the ineffectiveness of such strategies, but the patients have not been sufficiently standardized according to risk to allow valid comparisons between studies or groups of patients. As the absorption of paraquat peaks at 2 h after ingestion, and irreversible fixation of paraquat into the alveolar cells occurs within the first 4 h, any technique designed to increase elimination of absorbed paraquat must be instituted as early as possible in order to remove toxicologically significant quantities,\(^{64}\) and most elimination methods, such as haemoperfusion and haemodialysis, appear to remove only a very small proportion of absorbed paraquat.\(^{65}\) When renal function is conserved, elimination by the kidney is 3–10 times more efficient than haemoperfusion.\(^{65}\) It is therefore possible that methods for enhancing elimination may prove ineffective.

Reduction of morbidity and mortality of poisoning by paraquat also relies on methods designed to prevent ingestion of significant amounts of toxin. This includes limiting the supply of concentrates, the addition of stenching and emetic agents, and adequate labelling and public awareness of the hazard.\(^{63}\)

In conclusion, prognosis in acute paraquat poisoning is largely determined by the time between ingestion and plasma paraquat concentrations before treatment. This curve that we have described (Figure 1) and the logistic equation associated with it have extended the original Proudfoot data\(^{2}\) to later times and have provided a relatively simple mathematical way of calculating the risk of death. This can now be used as a research tool for studies on the efficacy of treatment of paraquat poisoning. It is also important that the new survival curve is now validated prospectively, to determine its specificity and sensitivity for predicting outcome in patients poisoned with paraquat.

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References


