Systematic Review of Parkinsonian Syndromes in Short- and Long-Term Survivors of Paraquat Poisoning

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Objective: The objective of this study was to assess whether high-dose paraquat exposure was associated with the development of parkinsonism. **Methods:** We carried out a systematic review of all published cases of paraquat toxicity meeting a case-definition of paraquat poisoning and who either recovered or lived for at least 30 days (primary analysis) or lived for 15 to 30 days (secondary analysis). Cases were included if they contained sufficient information to determine whether they had signs of parkinsonism. **Results:** Our search yielded 818 publications containing 83 cases. The primary analysis yielded 70 cases. None manifested signs of parkinsonism. An additional 13 were in the secondary analysis and none exhibited signs of parkinsonism. **Conclusion:** An analysis the world's entire published experience found no connection between high-dose paraquat exposure in humans and the development of parkinsonism.

Paraquat (*N*,*N*′-dimethyl-4,4′-bipyridinium dichloride) is one of the most widely used herbicides worldwide. One concern about its use is that a case-control study from Taiwan, where it is common practice to spray paraquat over rice fields, found a statistically significant association between its use and Parkinson's disease (PD).[1] Several other case-controls studies have found nonsignificant associations between PD and paraquat exposure.[2,3] However, this association has not been verified in other studies[4–7] and has been questioned in a comprehensive review on this topic.[8] Furthermore, many of these studies are confounded by reported associations between PD and working in agriculture, living in a rural environment, exposure to other herbicides and other forms of pesticides, and having water supplied by wells, all of which have been are associated with the development of PD.[8–10]

Despite the number of studies that have been done on this topic, the body of epidemiologic investigations, collectively and individually, are too small and contain too few cases of PD to adequately control for these confounders and thus, their interpretation is likely hampered, even with the best attempts to control for relevant variables, by residual confounding.[8] In addition, these epidemiologic studies use a case-control methodology and are thus vulnerable to recall bias,[11] further compromising the ability to make causal inferences about the relationship between paraquat exposure and the risk of developing PD. Almost all of the epidemiologic studies lack adequate exposure assessments, making the important dose-response analysis impossible or unreliable.

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Given these limitations to the epidemiologic studies on this topic, alternative approaches to human data that may be informative about the possible risk of PD from paraquat exposure are desirable. One such approach derives from paraquat's considerable structural similarity to the chemical 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) (Fig. 1). The latter is formed as a contaminant during the production of the illicit meperidine-like opioid 1-methyl-4-phenyl-4-propionoxypiperidine (known as MPP or "synthetic heroin") if the synthesis reactions are carried out under insufficiently vigorous conditions.[12] MPTP, either in pure form or as a contaminant during the administration of the illicit drug MPP,[13] produces a dose-dependent form of PD that occurs in as short as a few days postexposure in man[14] and animals.[15] MPTP does this by being metabolized by monoamine oxidase B to a product that is toxic to neurons in the substantia nigra pars compacta,[12,14] the part of the brain that is damaged in PD.[16] Animals, and humans, exposed to MPTP exhibit bradykinesia, postural instability, rigidity, and tremor.[17] These clinical signs are considered to be the cardinal features of parkinsonism.[18,19] MPTP-induced parkinsonism is now the primary animal model of PD.[15] Importantly, MPTP causes toxicity to the substantia nigra at doses that do not cause significant systemic toxicity.[18]

Individuals acutely exposed to very high doses of paraquat may develop severe toxicity manifested by acute kidney injury, pulmonary toxicity, corrosive skin and mucus membrane injury, multiorgan system failure and death.[20] Of these, the pulmonary injury is the most discussed in the published literature because paraquat concentrates in the lungs[21,22] and may cause severe, and sometimes fatal, pulmonary toxicity. This occurs either acutely or later in some of those who survive the acute phase of their poisoning but who subsequently develop pulmonary fibrosis.[20] Why this pulmonary fibrosis progresses in some patients, yet resolves in others, is not known.

Given their very close structural similarity, if paraquat does cause PD, it would be expected that it would almost certainly do so in a manner similar to MPTP, and rapid-onset parkinsonism should therefore occur following high-dose paraquat exposure. The hypothesis tested in this study, therefore, is that high-dose paraquat exposure, sufficient to cause significant systemic human toxicity, would be associated with the emergence of features of parkinsonism. On the basis of the earlier-mentioned facts, this study systematically assessed the published world-wide human experience with high-dose paraquat exposure. Specifically, it evaluated cases of acute paraquat poisoning that met an *a priori* case definition including significant objective measures of toxicity, to determine if parkinsonism, or any of its component signs, occurred in these patients.

METHODS

Search Strategy

Our search methodology was aimed at ascertaining all cases of paraquat toxicity published up to July 31, 2010, that might meet an a priori case definition of paraquat poisoning. Four methods were employed to find cases. First, a computerized literature search was done using the search terms paraquat, poisoning, and toxicity. This search utilized the Ovid portal for accessing the National Library of Medicine, EMBase, and the Department of Agriculture's Agricola collections. Secondly, publications were retrieved from the

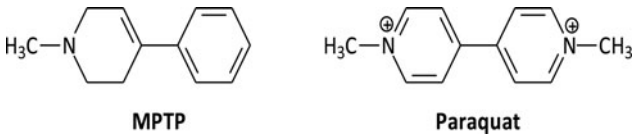

FIGURE 1. Similarity in chemical structure between 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) and paraquat (*N,N′*-dimethyl-4,4′-bipyridinium). Paraquat is usually found as the dichloride salt.

authors' extensive files on paraquat. Publications obtained by these two strategies were reviewed to determine whether they provided clinical information on patients with paraquat poisoning. Third, the references of all publications that were found to contain relevant clinical information were searched for any articles not found by the earlier-mentioned strategies. Lastly, for each article that we found to have clinically relevant information, a further search was done ascertaining any publications that may have subsequently cited that article. Publications identified by this strategy were in 17 different languages. Those potentially containing clinical information were translated into English. All articles were reviewed by physicians subspecialty board-certified in medical toxicology.

Inclusion and Exclusion Criteria

Only fully published cases in medical or scientific journals were included. Cases in other documents or book chapters were excluded because of uncertainty regarding peer review prior to publication. Cases only published in abstract form were excluded because of their lack of sufficiently detailed data.

Cases that fulfilled the a priori case definition of paraquat poisoning (see next) were assessed for one of the four cardinal features of parkinsonism: bradykinesia, rigidity, postural instability, or tremor. Because of these endpoints, cases included in this analysis must have contained sufficient clinical information to determine whether these features were present. Such cases were designated as being neurologically evaluable (referred to herein as "neuroevaluable"). To be considered to be neuroevalauble, cases had to have descriptions provided that indicated that there were no new neurological abnormalities. This was taken to be the case when either a neurological examination was described or a description of a patient recovery was given that indicated that there were no persistent adverse neurological sequelae of paraquat poisoning.

Those cases that did not provide sufficient information to determine whether they developed signs of parkinsonism during the course of their poisoning, at recovery, or at subsequent follow-up, were considered to be nonneuroevaluable. Nonneuroevaluable cases often had clinical descriptions that were restricted to the patient's pulmonary and/or renal status, since these were the major manifestations of most poisonings. Cases that were nonneuroevaluable were excluded from further analysis.

An a priori case definition was developed prior to the assessment of any cases. This case definition was constructed from the well-known clinical features of paraquat poisoning.[19] The case definition incorporated the three major manifestations of paraquat poisoning: pulmonary injury, acute kidney injury, and skin or mucosal corrosive injury. Only patients meeting the case definition of paraquat poisoning were included. To fulfill the case definition, either of the criteria set forth in Table 1 had to be met.

Our primary analysis determined whether neuroevaluable patients who met the case definition of paraquat poisoning and who survived, or lived for at least 30 days, developed any signs of parkinsonism. These cases were designated long-term survivors. We also did a secondary analysis of neuroevaluable patients meeting the case definition who survived for at least 15, but not more than 30, days. Such cases are referred to as short-term survivors. The 15-day period was chosen for two reasons. Most patients who succumb from paraquat toxicity do so in a matter of only a few days.[19] Clinical descriptions of these patients tend to only describe the rapid course of their pulmonary, renal, and multiorgan toxicity. Many of these patients are unconscious or in a medication-induced coma so that they can tolerate being on a ventilator. Secondly, MPTP-induced parkinsonism may be manifested in only a few days postexposure [14] and thus if paraquat were acting in an analogous fashion it would be expected that manifestations of parkinsonism would be seen in this time period.

Data Abstraction

As in the review of all articles, identified cases were assessed by physicians subspecialty board certified in medical toxicology. The data abstracted from all cases are enumerated in Table 2. Interabstractor agreement, determined on 2.5% of the total publications, was 0.9. No discrepancies were identified that changed any of the data used in either the primary or secondary analyses.

Statistics

Differences in the frequency distributions of the factors present in the long-term and short-term survivors were compared by the chi-squared test, with α set at $P < 0.05$.

RESULTS

As shown in Figure 2, the search strategy and case ascertainment strategy identified 818 publications on paraquat toxicity

TABLE 1. Criteria for Fulfilling the Case Definition of Paraquat Poisoning

Cases were considered to have paraquat poisoning if they met either of the following sets of criteria:

1. Have laboratory confirmation of paraquat exposure, and
2. Have corrosive skin or mucosal injury or syndromes of renal or pulmonary injury consistent with paraquat toxicity.

OR

1. Have a history of paraquat exposure, and
2. Have at least two of the following: corrosive skin or mucosal injury, renal injury consistent with paraquat toxicity, or pulmonary injury consistent with paraquat toxicity.

Cases were excluded if laboratory studies done on presentation failed to detect the presence of paraquat.

TABLE 2. Data Abstracted from Each Case

1. Length of survival (if the patient ultimately died)
2. Neuroevaluability
3. Presence or absence of any of the cardinal signs of parkinsonism
4. Age
5. Presence or absence of a paraquat-induced pulmonary syndrome
6. Presence or absence of signs of acute kidney injury or its diagnosis in synonymous terms such as acute renal failure
7. Presence or absence of paraquat-induced corrosive injury to the skin or mucus membranes
8. Whether the paraquat poisoning was due to an attempt at self-harm
9. The specific product ingested

published in medical and scientific journals up to, and including, July 31, 2010. Seven hundred fifty-one of these articles did not have specific patient data or contained insufficient clinical descriptions to make cases discussed neuroevaluable. Most of these publications were animal or laboratory studies, epidemiological investigations, case series, or clinical trials. Sixty-seven articles contained neuroevaluable cases from which 83 individual patients met the case definition of paraquat poisoning. Seventy of these patients were long-term survivors used in the primary analysis; 13 were short-term survivors.

Primary Analysis—Long-term Survivors

Long-term survivors had a mean age of 26 ± 17 years (median 22; range 1 to 68). Sixty-four (91%) of the long-term survivors orally ingested paraquat. Thirty of these were documented suicide attempts. Dermal exposures comprised an additional 5 cases (7%). Fifty-five cases (79%) had a documented paraquat-related syndrome of renal injury, 52 (74%) had clear skin or mucus membrane corrosive chemical injury, and 36 (51%) had a paraquat-induced pulmonary syndrome.

As shown in Table 3, none of the 70 long-term survivors developed bradykinesia, tremor, rigidity, or postural instability.

Secondary Analysis—Short-term Survivors

The 13 patients who survived between 15 and 30 days after paraquat poisoning had a mean age of 30 ± 17 years (median 27; range 1 to 66). All 13 patients orally ingested paraquat. Five (38%) of these were reported to be suicide attempts. The reason for the ingestion was not stated in the other 8 cases. All of the short-term survivors had a paraquat-induced pulmonary syndrome and this was usually the cause of death. Twelve of the 13 patients (92%) in this category also had a renal syndrome characteristic of paraquat toxicity. Skin or mucus membrane corrosive chemical injury was noted to be present in 6 patients (46%).

As shown in Table 4, similar to what was observed in the long-term survivors, none of the 13 short-term survivors developed bradykinesia, rigidity, tremor, or postural instability.

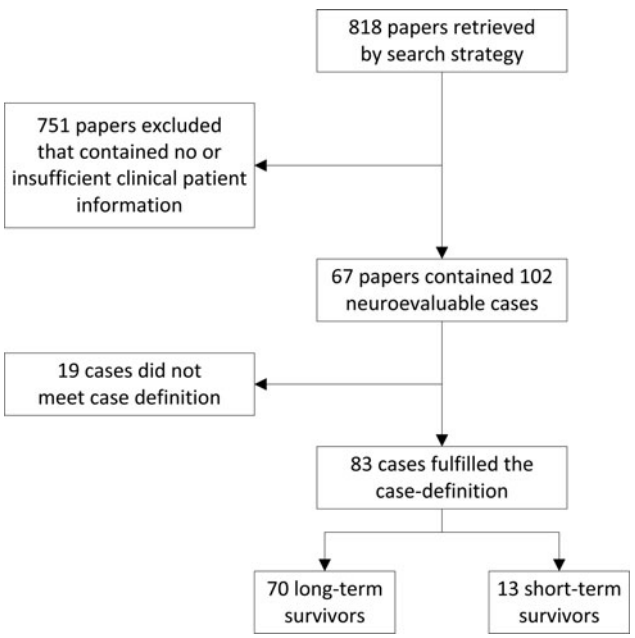

FIGURE 2. Flow chart demonstrating the ascertainment of 93 cases meeting the inclusion criteria from 818 publications identified.

TABLE 3. Clinical Features of 70 Long-term Survivors Meeting the Case Definition of Paraquat Poisoning

Characteristic	Number (%)
Documented suicide attempt	30 (43)
Pulmonary syndrome	36 (51)
Renal syndrome	55 (79)
Skin or mucus membrane corrosive injury	52 (74)
Laboratory confirmation	54 (77)
Exposed by oral ingestion	64 (91)
Exposed dermally	5 (7)
Exposed by inhalation	1 (1.4)
Exposed intravenously	1 (1.4)
Unknown route of exposure	3 (4.3)
Tremor	0 (0)
Rigidity	0 (0)
Bradykinesia	0 (0)
Postural instability	0 (0)

TABLE 4. Clinical Features of 13 Patients Meeting the Case Definition of Paraquat Poisoning and Surviving 15 to 30 Days

Characteristic	Number (%)
Suicide attempt	5 (38)
Pulmonary syndrome	13 (100)
Renal syndrome	12 (92)
Skin or mucus membrane corrosive injury	6 (46)
Laboratory confirmation	12 (92)
Exposed by oral ingestion	13 (100)
Tremor	0 (0)
Rigidity	0 (0)
Bradykinesia	0 (0)
Postural instability	0 (0)

Prognostic Factors

There was no significant difference in the frequency of renal injury in those who survived (79%) and those who did not (90%), or in skin or mucus membrane corrosive injury, which was present in (74%) of survivors and (45%) of those who did not survive. However, paraquat-induced pulmonary injury was associated with a worse prognosis, occurring in (51%) of long-term survivors and (100%) in short-term survivors ($P = 0.003$)

DISCUSSION

The present study was a systematic review of cases of paraquat poisoning conducted with the intention of determining the rate of the development of signs of parkinsonism during the course of their poisoning, recovery, or follow-up. However, we found no cases meeting our case definition where any sign of parkinsonism occurred. This finding provides evidence that high-dose paraquat exposures does not lead to the development of parkinsonism. The approach taken in this study is unique in that it assesses humans acutely exposed to far greater doses of paraquat than they would be exposed to following routine use. Prospectively exposing humans to such toxic doses of paraquat is not feasible. However, cases of paraquat poisoning provide a natural database for the assessment of the effects of high-dose

exposure. Since most toxicological effects are dose-dependent, as are known effects of paraquat, the use of high-dose data provides an excellent opportunity to assess the latter's potential adverse effects.

The cases we evaluated all suffered from considerable toxicity from their paraquat poisoning. Most cases either spent a significant part of the early course of their poisoning in intensive care units or ultimately died. They all had major indicators of paraquat toxicity. Thus, our cases were exposed to very high-doses of paraquat compared with that which workers may be exposed to during routine use. The likelihood of unusually high exposure to paraquat is further heightened by the fact that 35 cases (42%) were documented suicide attempts. Seventy-seven cases (91%) involved patients who ingested paraquat orally and did so in such a way that they had a sufficient dose to cause major toxicity. However, the reason for the ingestion was not documented in many cases. This almost certainly reduced the number of cases that could be classified as suicide attempts. It is very likely that many, if not the majority, of the cases for which the reason for oral paraquat ingestion was not given represent attempts at self-harm. A study that specifically assessed the intent of patients who ingested paraquat orally found that 73% of their cases were due to a suicide attempt.[22]

The presence of pulmonary injury was a significant clinical finding discriminating between short-term survivors, in whom it was prevalent in 100% of the cases, and long-term survivors who exhibited this feature in approximately half the cases ($P = 0.003$). This demonstrates that significant paraquat poisoning with skin and mucus membrane corrosive injury and acute paraquat-induced kidney injury can occur even in the absence of a pulmonary syndrome. Although the latter two characteristics were not statistically significantly more likely to be present in the short-term survivors they were numerically more commonly seen in this group, raising the possibility that our study was underpowered for finding a true difference. Our study was not designed to assess these clinical endpoints as true prognostic factors.

The present study primarily focused on cases that recovered or lived for at least 30 days postexposure. This allowed us to use the longest time periods we could find after the high-dose toxicity. Follow-up periods were for as long as 10 years postpoisoning. However, it was also felt that as a secondary analysis it would be informative to assess patients who died, yet survived for at least 15 days after their exposures. These patients were sicker, with clinical descriptions that primarily focused on their pulmonary, renal, and hemodynamic status. The central nervous system is not a direct end-organ of acute paraquat toxicity and thus the neurological status of these patients tended not to be described in detail. Because of this, a smaller proportion of them were classified as being neuroevaluable. However, because of their degree of injury all of the neuroevaluable short-term survivors met the case definition of paraquat poisoning. This group also represented those who probably had the highest dose exposures. In this population, as in the long-term survivors, there was no indication of the development of features of parkinsonism.

Our study focused on acute high-dose paraquat toxicity because this is probably the most relevant kind of exposure for studying its possible parkinsonism-inducing qualities. If paraquat does cause parkinsonism, the most likely mechanism is that it does so in a manner analogous to MPTP. Acute high-dose MPTP exposures causes parkinsonism within days of exposure in the absence of systemic toxicity involving other organ systems.[14] In our cases, all patients clearly had significant systemic toxicity. Thus, if paraquat were acting in a similar fashion, we would have expected to see some parkinsonian manifestations in the cases we assessed.

There are several reasons that paraquat might not induce parkinsonism despite its very close structural similarity to MPTP. Unlike MPTP, paraquat is ionic (each ion carries a $+2$ charge) and highly water soluble. Except in infant animals with immature blood–brain barriers, it does not appear to accumulate in the brain.[24] Both paraquat and MPTP appear to act by inducing oxidative stress.[25–27] However, MPTP in the brain is metabolized by monoamine oxidase B to the active neurotoxic MPP+ ion,[28] which acts primarily as an inhibitor of mitochondrial energy generation by blocking complex I of the electron transport chain, a mode of action not shared with paraquat.[29] In contrast, paraquat appears to cause injury by redox cycling either in the cytosol or on the cell surface.[30,31] Although at high concentrations paraquat may act as a mitochondrial complex I inhibitor,[29] it is unlikely that it would reach these concentrations during human exposures.

Although this study was designed to assess whether PD has been associated with high-dose paraquat exposure, it did not use PD as an endpoint. Rather, it looked for the broader and more nonspecific endpoint of any feature of parkinsonism. There are many causes of parkinsonism other than PD. Assessing the studied cases for any single feature of parkinsonism was chosen because despite its low specificity, this approach would increase the sensitivity and thus the likelihood of finding even a possible case of PD. Given that we did not find a single case with any feature of parkinsonism, it is clear that none had clinical signs of PD.

In addition to parkinsonism, patients with PD tend to suffer from a number of systemic clinical manifestations such as dementia, visual and cardiovascular abnormalities, gastrointestinal disturbances, sexual dysfunction, and vulnerability to infections. Because these endpoints are nonspecific and occur in a high frequency in the general population, they were not assessed in our study.

This study has several limitations. It was a retrospective analysis and thus, the amount of neurological information available in many cases was limited. This reduced the number of cases that were neuroevalauble. However, it is unlikely that significant new neurologic findings in these patients would go unreported.

The cases evaluated had no direct quantitative assessment of paraquat exposure. In most cases, there was a degree of quantitative information about the dose possibly ingested, but these data were in the form of historical statements by the patients and thus could not be taken to be scientifically accurate. Even in cases where quantitative paraquat levels were available, back extrapolation to ingested or incorporated doses would have been unreliable. However, the patients we evaluated undoubtedly received doses substantially higher than those encountered in routine human use of paraquat. Given the inclusion criteria and case definition that was used, it is likely that most of our patients had very high-dose exposures.

The paradigm upon which this experimental approach rests assumes that if paraquat were a cause of PD, it would act in a manner similar to that of MPTP. However, it is possible that paraquat works by a completely different mechanism. If that is the case, the model of acute high-dose exposures may not be relevant. However, as noted earlier, the existing scientific data strongly point to oxidative stress and redox cycling as the shared mechanism of these two molecules.[25–27] Given this, and the very close structural similarity between them (Figure 1), it is unlikely that paraquat would induce PD by any other mechanism.

The methodology utilized here was intended to be as discriminating as possible in the use of valid case data. We therefore restricted our analysis to fully published cases in medical and scientific journals. This strategy was felt to both allow for the ascertainment of the most detailed data about the cases and to maximize the likelihood that cases were peer reviewed prior to publication. Because our cases were published in a great many different journals, in 17 different languages, and over a period of time dating back to 1969, we could not be absolutely certain that every journal had peer-review procedures in place at the time each article was published. Although cases in book chapters and abstracts were not included in the analyses presented herein, we are unaware of any case, published in a chapter, as an abstract, or in any other form, that reports parkinsonism related to paraquat exposure.

The only case, to our knowledge, of any patient who developed any parkinsonian features and had paraquat exposure was a woman who had a suicidal paraquat ingestion and when evaluated 8 years later was found to have the disease tardive dyskinesia, which was caused by her chronic neuroleptic drug therapy.[23] Neuroleptic medications are used to treat psychiatric disorders and are part of the class of antipsychotic drugs. Tardive dyskinesia is a medication-induced disease caused by upregulation of dopamine receptors in the striatum by neuroleptic medications resulting in parkinsonian manifestations.[32] This patient's tremor was clearly because of her tardive dyskinesia.[22] Tremor is commonly seen in tardive dyskinesia. This disease does not involve the substantia nigra and is very different from PD.[32] This case was not included in our primary analysis because it did not meet the case definition.

Lastly, the total number of cases that we were able to evaluate was 83. If paraquat did induce parkinsonism, but it was a relatively rare event, we might not have been able to detect it with our case series. However, since the various known manifestations of paraquat toxicity were seen repeatedly in our cases (Tables 3 and 4), we would have expected that if parkinsonism was caused by paraquat that too should have been observed. Although our series of 83 patients is relatively small, it does, we believe, constitute the world's experience with cases that met our inclusion criteria.

CONCLUSIONS

Our study was unable to find any documented cases of humans exposed to doses of paraquat sufficient to cause major toxicity that manifested signs of parkinsonism. Because of its chemical similarity to the parkinsonism-inducing drug MPTP, if paraquat did cause this condition, it would almost certainly do it in a similar manner and time frame. The parkinsonism caused by MPTP is due to injury to the substantia nigra pars compacta, the same region primarily affected in PD and the resulting clinical syndrome is almost identical to PD. The fact that high-dose paraquat exposure does not appear to cause this syndrome indicates that it does not appear to be a substantia nigra toxin and thus is unlikely to be a cause of PD.

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