

Paraquat Suicide in a Young Woman: Results of Therapy Directed Against the Superoxide Radical

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The clinical course of a young woman following two separate suicide attempts using the herbicide paraquat is reported. The patient survived an intramuscular injection of paraquat almost asymptotically, but later exhibited a typical fatal course with fulminant proliferative pulmonary fibrosis after an intravenous injection. Fibrosis and death occurred despite a therapeutic regimen based upon a known action of paraquat, the generation of superoxide (O_2^-), using superoxide dismutase, α -tocopherol, and ascorbic acid in conjunction with forced diuresis and prednisone. While treatment failed explanations for the failure of therapy in this case and current therapeutic alternatives are discussed so that they may be considered when future cases are encountered.

Paraquat (methyl viologen, 1, 1'-dimethyl-4,4'-dipyridylium dichloride) is a herbicide which has been responsible for 564 deaths reported to the manufacturer since its introduction in 1958. An estimated 60% of these fatalities were successful suicides. An episode of transient pulmonary edema with kidney and liver dysfunction are often the first symptoms, but they do not ordinarily appear until a day or more after paraquat ingestion. Death usually occurs after one or more weeks and most often is the result of a relentless, fulminant pulmonary fibrosis which is not clinically significant for the first week or longer.

The precise mechanism of the tissue damage produced by paraquat is unknown, but the evidence implicates the reduction products of oxygen as shown in Fig. 1. By accepting electrons from NADPH, cytochrome c reductase [1] and possibly glutathione reductase [2], among others, paraquat can act as an oxidation-reduction couple. Reduced paraquat very rapidly reduces molecular oxygen to its toxic free radical, superoxide (O_2^-) (Fig. 1A) [3]. Superoxide may produce tissue injury by reacting directly with cellular components or by generating other very reactive species of oxygen such as hydroxyl radical (OH^-) and singlet oxygen (1O_2) by the Haber-Weiss reaction [4] (Fig. 1B). Beyond the peroxidation of lipids, and perhaps thiol oxidation, the particular consequences of these species of oxygen in tissues are not well described. The mechanism of toxicity of any of these species of oxygen is not known.

While gastrointestinal absorption may be prevented by the administration of bentonite or Fuller's earth [5], no method exists to limit paraquat absorption from parenteral sites. Tissue binding is rapid and lung even concentrates the compound [6]. Dialysis has not been particularly effective and has shown no advantage over

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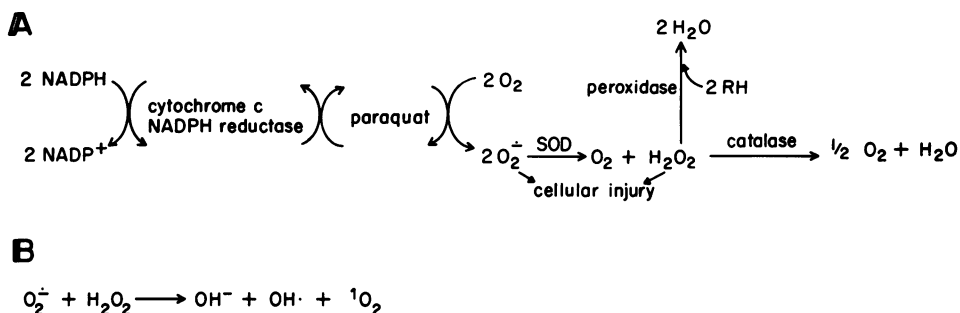


FIG. 1. Generation of toxic species of oxygen with paraquat. *A* shows a possible pathway of electron flow from reduced pyridine nucleotide (NADPH) to superoxide (O_2^-). *B* is the Haber-Weiss reaction generating hydroxyl radical ($\text{OH}\cdot$) and singlet oxygen (${}^1\text{O}_2$). SOD, superoxide dismutase; H_2O_2 , hydrogen peroxide; OH^- , hydroxide.

forced diuresis [7]. Once paraquat is bound to tissues, therefore, major therapeutic efforts must be devised and directed toward the prevention of tissue injury and the ultimate fibrosis.

We report the results of therapy in a case of paraquat poisoning after two suicide attempts, first by intramuscular then by intravenous injection of the compound. The treatment regimen used was designed to interfere with the consequence of superoxide (O_2^-) production by paraquat. While some data concerning the efficiency of similar regimens exist in experimental animals, no published information is available for man.

REPORT OF A CASE

Following the intramuscular injection of about 60 mg of a commercial preparation of the herbicide paraquat into her anterior thighs, a 24-year-old woman was referred for treatment to the Hospital of the University of Pennsylvania. She had attempted suicide many times before, both by self-mutilation and by a variety of drug ingestions. Her history also included frequent episodes of severe asthma, gastrointestinal bleeding from stress ulcers, obesity, schizophrenia, and recent deep vein thrombosis with a documented pulmonary embolus four years previously.

Upon admission the patient complained of abdominal discomfort and had a fever of 102.0° F. Her physical examination and laboratory tests were unremarkable except for blood gases which were consistent with her chronic asthma (pH 7.47, pO_2 89 mmHg, pCO_2 32 mmHg and HCO_3^- 23 meq/l). During this hospitalization a painful erythematous area 4–5 cm in diameter appeared at the injection sites. She developed leukocytosis 20,000 per mm^3 by the fourth hospital day and a low grade fever. No microorganisms were cultured from the urine, cerebrospinal fluid, or blood; her chest x-ray was unremarkable.

Treatment included forced diuresis (680–5075 ml urine output per day) to promote paraquat excretion and ascorbic acid 6.0 grams per day to provide a source of reducing equivalents to allay the oxidizing effect of paraquat. Oral dicloxacillin and probenidol were given to treat a possible staphylococcal cellulitis at the injection site. She returned to the referring hospital on the sixth hospital day and continued to recover uneventfully.

Thirty days after the first paraquat injection the patient procured a commercial paraquat preparation, and injected 2 ml intravenously (550–600 mg). Upon confessing her suicide attempt the next morning she was transferred to the medical service

where therapy was started with a forced diuresis (4000–8000 ml per day) and ascorbic acid, 1 gm four times daily. She complained of epigastric cramping with nausea and vomiting.

Physical examination revealed an occasional respiratory wheeze, moderate ankle edema, and erythematous areas at the sites of the previous paraquat injections. Sixteen hours after injection paraquat was not detectable in serum but was found in the urine. By day 3 she was excreting 4 mg of paraquat per day (Table 1). By the fourth hospital day she developed signs of hepatic and renal toxicity. The creatinine rose to a value of 3.7 mg% on the seventh hospital day, then returned to 0.9 to 1.1 mg% over the next several days. She complained of right upper quadrant pain; the serum lactic dehydrogenase rose to 1300 IU/l serum alanine transaminase (SGOT) level to 92 IU/l and serum aspartate transaminase (SGPT) level to 94 IU/l. Bilirubin and prothrombin time remained normal. The patient developed fever (100.00°) and leukocytosis (20,500) per mm³ on the seventh day without definitive proof of bacterial infection until late in the hospital course.

Ninety hours after the paraquat injection, therapy specifically directed against the consequence of superoxide radical generation was begun. A supply of the enzyme superoxide dismutase was obtained first as the bovine enzyme (Palosein, Diagnostic Data, Inc., Mountain View, California), then as the human enzyme (Ontosein, Worthington Biochemical Corporation, Freehold, N.J.). After obtaining informed consent it was administered at a dose of 5 mg every three hours intramuscularly. Ascorbic acid was raised to 8 gm per day in divided doses and 544 IU α -tocopherol was given intramuscularly twice daily in an attempt to inhibit membrane lipid oxidation. Finally, 20 mg methyl prednisone was given four times daily in an attempt to retard the inflammatory reaction and its potential contribution to the expected pulmonary fibrosis.

Despite this therapy her pulmonary status continued to deteriorate and she was transferred 18 hrs later to the Medical Intensive Care Unit with a pO₂ of 31 mmHg, pH of 7.35, pCO₂ of 32 mmHg, and HCO₃ of 15.2 meq/l. A chest x-ray showed a diffuse bilateral interstitial process consistent with edema. Pulmonary arterial pressure was measured at 45/30 mmHg with a wedge pressure of 5–7 cm. She responded to intubation, 100% O₂, and a positive end expiratory pressure (PEEP) of 5 cm by raising her pO₂ to 66 mmHg. Over the ensuing seven days her fractional inspired oxygen (FIO₂) and PEEP were gradually reduced from 50% and 15 cm to 30% and 0 cm respectively, in order to administer only enough O₂ to maintain adequate peripheral oxygenation, without accelerating the pulmonary toxicity of paraquat. Accordingly she was maintained relatively hypoxic (pO₂ 35–80 mmHg). She also received digoxin, furosemide and theophylline to control volume overload from the forced diuresis, and bronchoconstriction. Ampicillin was given for a possible *E. coli* pneumonia. Urinary excretion of paraquat rose progressively (Table 1) reaching a peak value of 22 mgm/24 hr period two days before death. Pulmonary deterioration continued however and on the 20th hospital day she expired, unable to maintain her pO₂ above 30 mmHg, despite 100% HO₂ and 20 cmPEEP.

At autopsy the lungs were diffusely involved with a pneumonic process with the most dependent portions of the lower lobes less affected. The alveolar spaces were obliterated by florid fibrosis, characterized by proliferation of fibroblasts with loose, light stained collagen. No hyaline membranes were present. The capillaries were patent with the endothelial cell lining preserved. The bronchiolar and alveolar ducts were dilated, and many were filled with red cells as well as numerous hemosiderin-

TABLE I
Urinary Levels of Paraquat

Hospital Day	Concentration (mg/l)	Daily Output (mg/24 hr)
3	1.3	4
6	2.8	16
12	1.0	14
18	1.4	22
Estimated total excretion		280 mg

^a Assayed by reduction with dithionite at 400 nm [23] on 24 hr urine specimens collected on the hospital days noted.

laden macrophages. A mononuclear cell infiltrate was noted. Histologically the pulmonary vasculature was normal (Figs. 2 and 3). No significant abnormalities were seen in the remaining organs.

Tissue levels of paraquat found at autopsy are indicated in Table 2.

DISCUSSION

This patient recovered completely from an intramuscular injection of paraquat only to succumb to a much larger intravenous dose, despite intensive therapeutic efforts. The nearly asymptomatic response to the intramuscular dose is not surprising since muscle binds paraquat, and tissue levels decrease much more slowly in muscle than elsewhere [8,9]. The intravenous dose, however, exhibited the typical course in paraquat poisoning and was not, therefore, apparently influenced by the previous exposure.

The usual clinical course following a fatal dose of paraquat is reflected in this case. Immediately after taking the poison, nausea and vomiting are the only significant symptoms. A few days later, multisystem toxicity with pulmonary edema, kidney failure, and liver dysfunction follow, all of which improve after a few days to a week. Although an occasional patient recovers completely [7,10], most develop pulmonary distress, become hypoxic, require oxygen therapy, and soon die with fulminant irreversible pulmonary fibrosis. The histological picture seen in sections of the patient's lung is typical of that observed in other fatal cases.

Since nausea and vomiting are found in parenteral as well as oral poisonings [7,11], these symptoms are produced by more than the very high concentrations which are in contact with the gastric mucosa after ingestion. Leucocytosis and fever were also seen after both parenteral doses in this case and have been commonly found in previous oral cases [11,12]. The mechanism of these reactions remains unexplained although tissue necrosis may play a role.

Throughout this patient's hospital course she excreted significant quantities of paraquat, a total of approximately 280 mg (Table 1). This high urine output of paraquat would be expected to reflect large tissue stores; however, this was not the case among the tissues assayed (Table 2). From the tissue levels the maximal body burden at death would be much less than 3.0 mg. This data would seem to contradict the urinary levels. To be consistent, either the tissue stores of paraquat must have been exhausted just previous to death, or paraquat must have been sequestered in a tissue which was not available for analysis such as muscle, liver, or skin. Since paraquat excretion is usually biphasic with large quantities excreted within the first twenty-four hours, recovery of an estimated 265 mg of paraquat after the first day is roughly consistent with a total body burden of 550-600 mg paraquat, the amount originally injected intravenously.

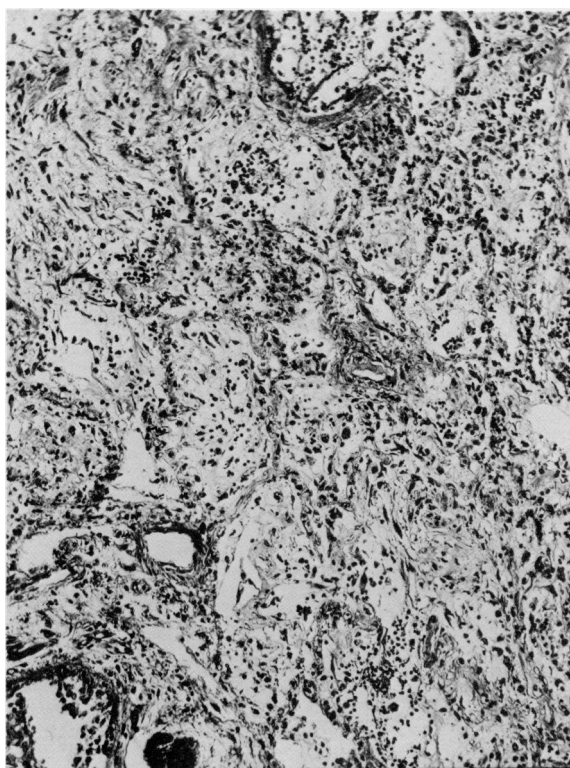


FIG. 2. Diffuse intraalveolar fibrosis (Trichrome 10X).

Therapy in this case was based upon the hypothesis that the generation of superoxide, a known action of paraquat, was also its toxic action, especially in lung. This hypothesis is supported by the dependence of paraquat toxicity on inspired oxygen concentrations [13,14], the finding that superoxide dismutase has a protective effect in paraquat poisoned rats [15], and the similarity of the pulmonary histologic changes seen in oxygen poisoning to those in paraquat poisoning [4]. Superoxide dismutase was given to supplement endogenous superoxide dismutase in order to prevent superoxide from reacting in ways harmful to the cell. Although toxicity studies are not complete, the enzyme has no presently known toxicity [16]. α -tocopherol is a lipid phase antioxidant which protects against lipid peroxidation, a potential consequence of superoxide [4]. In paraquat poisoned rats lipid peroxidation is increased and paraquat is much more toxic in α -tocopherol deficient rats [1]. Ascorbic acid was used to provide aqueous phase reducing equivalents in both the intracellular and extracellular fluid spaces. No reports of the use of such a treatment regimen in man have been published.

There are a number of possible reasons for the failure of the treatment approach in this case. First, the specific therapy was not started until nearly four days after the injection. Certainly by this time extensive, possibly irreversible, damage had occurred. Second, there is no information available on the appropriate dosages of these compounds to use in paraquat poisoning or other analogous situations. However the Michealis constant of superoxide dismutase [18] is, most certainly, much greater than the concentration of superoxide. Thus, even in the presence of paraquat additional enzyme might not have a significant effect; nevertheless a protective effect of the enzyme in paraquat poisoned rats has been observed [15]. Third, it has been shown

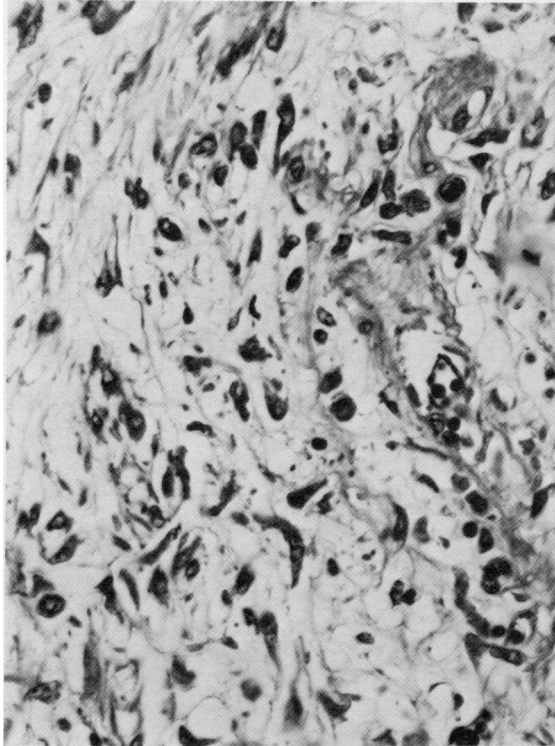


FIG. 3. Alveolar spaces have been obliterated by proliferating fibroblasts with elongated basophilic cytoplasm, large vesicular irregular nuclei, and loose interstitial collagen. Capillaries are patent with preserved endothelial lining (Trichrome 100X).

recently that the lung actively concentrates paraquat [6]. Since administered superoxide dismutase presumably remains in the extracellular space, it may not effectively protect intracellular sites of paraquat action. Fourth, oxygen therapy was required to maintain peripheral oxygenation. Since increasing the fractional oxygen content of inspired air aggravates paraquat injury of lung [13], oxygen therapy, although necessary to maintain life, may have resulted in much more extensive paraquat mediated lung injury. Fifth, it is possible that superoxide is not directly involved in paraquat toxicity in man. Data from studies with *E. coli* suggest mechanisms other than superoxide may be responsible for injury in these organisms [19]. This may represent a second unrelated toxic action of these compounds which is not amenable to treatment directed at dissipation of the superoxide anion.

In future cases of paraquat poisoning other therapeutic possibilities should also be considered. Hemoperfusion, over activated charcoal or a cation exchange resin has reduced serum paraquat concentrations in experimental animals [20]. Paraquat is inactivated by bentonite or Fuller's earth; and gastric lavage and passage of these agents can be a life-saving measure in some cases. Experimental animals have been protected from an otherwise lethal dose with administration of bentonite as long as ten hours after paraquat ingestion [21]. They may also be beneficial when paraquat is taken by other routes. Steroids and cytotoxic agents have been used without marked success [7]; however, a recovery from the proliferative pulmonary fibrosis of paraquat poisoning as well as two therapeutic failures have been recently reported with azathioprine and potassium amino benzoate [10,22,23].

TABLE 2
Tissue Levels of Paraquat

Tissue	Paraquat Concentration ($\mu\text{gm/gm}$)
Spleen	0.01
Vertebral column	0.03
Kidney	0.02
Brain	0.02

^aParaquat was not detected in lung ($<0.01 \mu\text{gm/gm}$), fat, heart, cervix, ovaries, thyroid, urinary bladder, or stomach.

Currently no therapy for paraquat poisoning is uniformly successful and almost all repeated cases have resulted in a fatal outcome even after ingestion of relatively small amounts of the compound [24]. Ideal treatment would inhibit the proliferative pulmonary fibrosis while permitting the recovery of other pulmonary cell types. Until such a therapy is described we are left with absorption, diuresis, or dialysis of paraquat in an effort to recover the compound before irreversible damage is done. To judge whether antioxidants such as those employed in the present case can be of benefit in paraquat poisoning must await a larger sample of reported cases. Furthermore, to enhance any opportunity for success they should be administered as promptly as possible after poisoning occurs to possibly prevent irreversible damage.

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