

Therapeutic approach to paraquat poisoning.

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Introduction : Paraquat (1,1'-dimethyl-4,4'-bipyridium dichloride) was introduced in 1962 as an effective herbicide that had low chronic toxicity because of its rapid deactivation upon soil contact (1). However, it has since become notorious throughout the world as a potent human poison (2). In spite of the decreasing numbers in the agricultural population of Korea, the incidence of paraquat poisoning is rapidly increasing (3). In humans, intentional or accidental ingestion of paraquat is frequently fatal, as a result of multiorgan failure (4). Ingestion of large amounts is considered to be uniformly fatal, resulting in death from multi-organ failure and cardiogenic shock within 1-4 days (5). After ingestion of smaller quantities, paraquat is specially 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 (5). Over the past 30 years, several methods for modifying the toxicity of paraquat have been examined, including prevention of absorption in the gastrointestinal tract (6), removal from the blood stream (7), prevention of accumulation in the lungs (8), scavenging oxygen free radicals (9, 10) and prevention of lung fibrosis (11). Unfortunately, most of these methods have proven ineffective, with the outcome already determined by the degree of exposure to paraquat. However, in most previous studies the results have been severely compromised by their relatively small sample size, making it hard to detect small changes in the efficiency of the individual treatment modality. The number of patients in such investigation should be large enough to ensure statistical significance in the results. The plasma levels of paraquat have an excellent prognostic value on previous reports (12-15). Patients whose plasma paraquat levels are less than 2.0, 0.6, 0.3, 0.16 and 0.1 mg/L at 4, 6, 10, 16 and 24 hours are likely to survive (15). In this regard, the enhancement of extracorporeal elimination of paraquat seems to be effective treatment because hemoperfusion reduces paraquat levels. Contrary to our expectation, the current consensus is that hemoperfusion does not change clinical outcomes in patients with acute paraquat poisoning (16). There are, in addition, no clinical outcome studies proving that antioxidant therapy changes outcome.

But antioxidant therapy might reduce oxidation injury after paraquat poisoning in pathophysiology, because paraquat injury evokes many oxidant processes that injure many organs. It is unclear why the clinical effect of antioxidant therapy and extracorporeal elimination is below theoretical expectations. In previous reports, all proposed interventions have been based on case reports or small case series, and in most studies the therapy varied. The vigorous therapy, including extracorporeal elimination and antioxidant therapy, may improve the survival of paraquat intoxicated patients. Our center has admitted about 300 paraquat poisoning patients annually (3, 17). Our patients were treated according to uniform treatment protocol. The key to our treatment is as follows. First, fuller's earth was given within 12 hours after paraquat ingestion to reduce absorption in the gastrointestinal tract. Second, intensive extracorporeal elimination therapy, especially hemoperfusion, was performed if the urine paraquat test was positive. Third, intensive antioxidant therapy (N-acetylcysteine, glutathione, vitamin C) was given in the hope

that it may scavenge oxidants. The purpose of this study was to investigate the plasma paraquat level of survivors and non-survivors according to uniform therapy and to examine the upper limit concentration of plasma paraquat for survival and the lower limit concentration that can be told as safe. **Methods:** This study included 375 paraquat poisoning patients who were diagnosed by means of plasma paraquat concentration within 24 hours after ingestion in the Institute of Pesticide Poisoning of Soonchunhyang University Cheonan Hospital, Korea, from January 2005 to December 2006. All patients were treated according to a uniform protocol including extracorporeal elimination and antioxidant therapy. Plasma paraquat concentration was measured by high-performance liquid chromatography. **Results:** The mean age of the paraquat-intoxicated patients was 48.42 ± 6.75 . One hundred ten patients (29.3%) survived. The upper limit of plasma paraquat concentration in survivors was 2.64 at 3 hour. All patients with plasma paraquat level above 3.44 died. The minimum paraquat level of the deaths was very low (0.12 $\mu\text{g/ml}$ at 5 hours; 0.02 $\mu\text{g/ml}$ at 12 hours; 0.01 $\mu\text{g/ml}$ at 24 hours). **Conclusions:** Our data showed that plasma paraquat concentration is good predictor of survivors but is not good predictor of non-survivors in the low plasma paraquat level. **References :** (1). Goldfrank LR, Flomenbaum NE, Lewin NA, Howland MA, Hoffman RS, Nelson LS. Goldfrank's toxicologic emergency, 7th edition, McGraw Hill, 2002: 1396-1402. (2). Eddleston M. Patterns and problems of deliberate self-poisoning in the developing world. *Q J Med.* 2000; 93:715-731.(3). Hwang KY, Lee EY, Hong SY. Paraquat intoxication in Korea. *Arch Environ Health.* 2002; 57:162-166. (4). Vale JR, Meredith TJ, Buckley BM. Paraquat poisoning: clinical features and immediate general management. *Hum Toxicol.* 1987; 6:41-47. (5). Lock EA, Wilks MF. Paraquat. In: Handbook of pesticide toxicology, 2nd edn. San Diego, Academic Press, 2001. (6). Meredith TJ, Vale JA. Treatment of paraquat poisoning in man: methods to prevent absorption. *Human Toxicology.* 1987; 6:49-55. (7). Hong SY, Yang JO, Lee EY, Kim SH. Effect of haemoperfusion on plasma paraquat concentration in vitro and in vivo. *Toxicology and industrial Health.* 2003; 19:17-23. (8). Ross JH, Krieger RI. Structure-activity correlations of amines inhibiting activity uptake of paraquat (methyl viologen) into rat lung slices. *Toxicology and applied Pharmacology.* 1981; 59:238-249. (9). Suntres ZE. Role of antioxidants in paraquat toxicity. *Toxicology* 2002; 180:65-77. (10) Suntres ZE. Role of antioxidants in paraquat toxicity. *Toxicology.* 2002; 180:65- 77.(11). Lin JL, Leu ML, Liu YC and Chen GH. A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat-poisoned patients. *American Journal of Respiratory and Critical Care Medicine.* 1999; 159:357-360.(12). Proudfoot AT, Stewart MS, Levitt T, Widdop B. Paraquat poisoning: significance of plasma-paraquat concentrations. *Lancet.* 1979; 2:330- 332. (13). Hart TB, Nevitt A, Whitehead A. A new statistical approach to the prognostic significance of plasma paraquat concentration. *Lancet.* 1984; ii:1222-1223. (14). Schermann JM, Houze P, Bismuth C, Bourdon R. Prognostic value of plasma and urine paraquat concentration. *Hum Toxicol.* 1987; 6:91-93. (15). Bismuth C, Garnier R, Dally S, Fournier PE, Schermann JM. Prognosis and treatment of paraquat poisoning: a review of 28 cases. *Journal of Toxicology.* 1982; 19:461-474.(16). Hampson ECGM, Pond SM. Failure of hemoperfusion and hemodialysis to prevent paraquat poisoning. A retrospective review of 42 patients. *Med Toxicol* 1988; 3:64-71. (17). Lee EY, Hwang KY, Yang JO, Hong SY. Predictors of survival after acute paraquat poisoning. *Toxicol Ind Health* 2002; 18:201-206.