J Korean Med Sci 2009; 24 (Suppl 1): S156-60
ISSN 1011-8934
DOI: 10.3346/jkms.2009.24.S1.S156

Comparison between Kidney and Hemoperfusion for Paraquat Elimination

The mortality rate of acute paraquat (PQ) poisoning depends on the PQ concentration in the blood. It has been shown that the kidneys eliminate PQ effectively. However, early renal function deterioration is frequently observed in acute PQ intoxication. This study is designed to compare the efficacy of PQ elimination with hemoperfusion (HP) and kidneys, taking into account the functional deterioration of the kidneys. The amount of renal and HP excretion of PQ were measured during the procedure of HP in patients with acute PQ intoxication. The PQ clearance and the actual amount of PQ elimination by the HP cartridge during the HP procedure were 111±11 mL/min (range; 13.2-162.2 mL/min) and 251.4±506.3 mg (range; 4.6-1,655.7) each. While, the renal clearance and actual amount of renal elimination of PQ was 79.8±56.0 mL/min (range; 9.7-177.0) and 75.4±73.6 mg (range; 4.9-245.8). As the creatinine clearance decreased, the PQ elimination by HP was as effective as or more effective than the renal elimination. In conclusion, early HP must be provided for life saving treatment in patients with acute PQ intoxication.

Key Words : *Paraquat Intoxication; Hemoperfusion; Renal Excretion of Paraquat*

Moon-Soo Kang, Hyo-Wook Gil, Jong-Oh Yang, Eun-Young Lee, and Sae-Yong Hong

Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, Cheonan, Korea

Received : 19 August 2008
Accepted : 12 November 2008

Address for correspondence
Sae-Yong Hong, M.D.
Department of Internal Medicine, Soonchunhyang University Cheonan Hospital, 23-20 Bongmyeong-dong, Cheonan 330-721, Korea
Tel : +82.41-570-2121, Fax : +82.41-574-5762
E-mail : syhong@sch.ac.kr

INTRODUCTION

Paraquat (1,1′-dimethyl-4,4′-bipyridium dichloride, PQ) is one of the most widely used herbicides in the world. In humans, intentional or accidental, ingestion of PQ is frequently fatal, resulting from significant lung injury (1). Over the past 30 yr, several methods for modifying the toxicity of PQ have been examined including prevention of absorption from the gastrointestinal tract (2, 3), removal from the bloodstream (4, 5), prevention of accumulation in the lungs (6, 7), scavenging oxygen free radicals (8, 9), and prevention of lung fibrosis (10, 11). Unfortunately, most of these methods have not been effective; the outcome is determined by the degree of exposure to PQ.

The mortality rate after PQ poisoning is strongly affected by the plasma PQ levels as well as the amount of the PQ intake (12-15). Consistent with this, it is clear that hemodialysis (HD) or hemoperfusion (HP) is a critical factor during the initial stages of intoxication. In agreement with previous reports, we recently reported that PQ clearance is more effective with HP than with HD (16). However, there are no reports on the positive effects of HP after PQ poisoning (17-20). Therefore, it is unclear to nephrologists and/or the toxicologist how to eliminate PQ from the system of patients with acute PQ intoxication. We have reviewed previous reports to determine what the specific concerns have been with HP and PQ elimination. We found that the efficacy of HP elimination was not evaluated properly in most prior studies (17-21).

The kidney has been shown to eliminate PQ very effectively, even better than creatinine elimination (22, 23). However, some degree of renal failure is frequently observed with acute PQ intoxication (21-24). This study was designed to determine the efficacy of PQ elimination with HP, taking into account renal elimination, in acute PQ intoxication.

MATERIALS AND METHODS

This study was approved by ethics committee of Soonchunhyang University Cheonan hospital and received a written consent from the subjects and/or their family. Ten patients (6 males and 4 females, between 25 and 70) with acute PQ intoxication were enrolled in this study (Table 1). The ingestion amount of PQ was 153.0±89.3 mL of 23.1% PQ solution and the time lag from PQ ingestion to the emergency room evaluation was 4.5±2.8 hr. The dithionite urine test was strongly positive in all of the subjects. Two patients survived and eight patients within the fifth hospital day. Table 2 summarizes the laboratory findings measured in the emergency room.

The dithionite urine test was carried out in the emergency room, as soon as the patient arrived and was considered to have acute PQ intoxication. All of the patients underwent HP

Table 1. Age, sex, and PQ levels of the subjects at emergency room

Case no	Sex	Age (yr)	Amounts of ingestion (mL)	Time lag (hr)*	Plasma PQ (μg/mL)	Clinical outcome
1	M	68	200	4.0	48.7	Death
2	M	25	200	7.0	8.0	Death
3	F	33	100	5.5	1.2	Survivor
4	F	39	50	2.0	13.7	Death
5	M	50	300	11.0	12.7	Death
6	F	33	30	4.0	1.4	Survivor
7	F	76	250	4.5	21.8	Death
8	M	60	200	2.0	167.0	Death
9	M	47	100	3.0	33.0	Death
10	M	61	100	2.0	30.7	Death

*Time lag means the period between PQ ingestion and arrival to the emergency room of Soonchunhyang Cheonan Hospital.
PQ, paraquat.

Table 2. Laboratory findings of the cases at the emergency room

Case no	WBC (/μL)	Serum BUN (mg/dL)	Serum creatinine (mg/dL)	Amylase (IU/L)	Lipase (IU/L)	$PaCO_2$ (mmHg)	PaO_2 (mmHg)
1	29,980	18.4	1.6	98	56	18.1	114.7
2	18,470	14.1	1.6	192	28	32.6	74.8
3	7,530	6.1	0.3	91	45	31.0	109.4
4	13,380	10.7	0.8	402	52	22.9	135.5
5	19,580	15.0	0.7	218	47	34.5	98.8
6	10,840	10.8	0.4	86	25	34.9	97.2
7	25,990	10.8	0.8	143	21	28.7	74.2
8	15,710	17.1	3.0	171	67	17.4	92.1
9	35,740	8.6	1.2	51	24	19.9	132.3
10	8,980	15.6	0.9	219	76	20.0	62.3

Note that serum creatinine, amylase, lipase, and hypoxia have known as predictive factors for clinical outcome in acute paraquat intoxication.
WBC, white blood cell; BUN, blood urea nitrogen.

as long as the vital signs were stable. HP was carried out through a jugular venous catheter for three hr at a blood flow rate of 200 mL/min. The HP membrane used was an adsorba 300 C, Gambro (Gambro Dialysatoren GmbH Co., KG Hechingen, Germary) that had polypropylene housing material, activated charcoal adsorbent, a 300 m^2 surface area, and cellulose coating material for the adsorbent.

Blood samples for PQ and creatinine were obtained from the arterial and venous lines of the tubing system at time 0, 1 hr, 2 hr, and 3 hr of HP. Urine samples were collected every hour during the HP procedure through a urinary catheter. Plasma and urine samples for the PQ assay were stored at -70°C until high performance liquid chromatography was performed.

Renal excretion of PQ

The amount of renal excretion of PQ ($KE_{PQt_{1-2}}$) at each time point was calculated according to

$KE_{PQt_{1-2}}$ (mg)=uCo of PQt_{1-2} × UVt_{1-2}---------- (1)

Where (uCo of PQt_{1-2})=urinary PQ level and (UVt_{1-2})=timed volume of urine

The renal clearance of PQ ($KC_{PQt_{1-2}}$ [mL/min]) was calculated by using PQ level in plasma and urine

$KC_{PQt_{1-2}}$ (mL/min)=$KE_{PQt_{1-2}}$/AUC t_1-t_2 ---------- (2)

Where AUC is the area under the plasma PQ level-timed curve

AUC=([pCo of PQ {t_1}+pCo of PQ {t_2}]/2)/t_{1-2} (hr) ---- (3)

HP elimination rate of PQ

The PQ extraction ratio (ER) of HP at each time point was calculated according to

ER=(A-V)/A---------- (4)

Where A=inlet plasma PQ level and V=outlet plasma PQ level.

The PQ clearance of HP ($HPCPQt_{1-2}$) at each time point was calculated according to

$HPC_{PQt_{1-2}}$=ER × BFR × (1-Hct)---------- (5)

Where BFR=blood flow rate and Hct=hematocrit.

The amount of PQ adsorbed by the cartridges ($HPE_{HPt_{1-2}}$) at each time point was calculated from the equation (6)

$HPE_{HPt_{1-2}}$=$HPC_{PQt_{1-2}}$ × AUC---------- (6)

Where AUC is the area under the plasma PQ level-timed curve

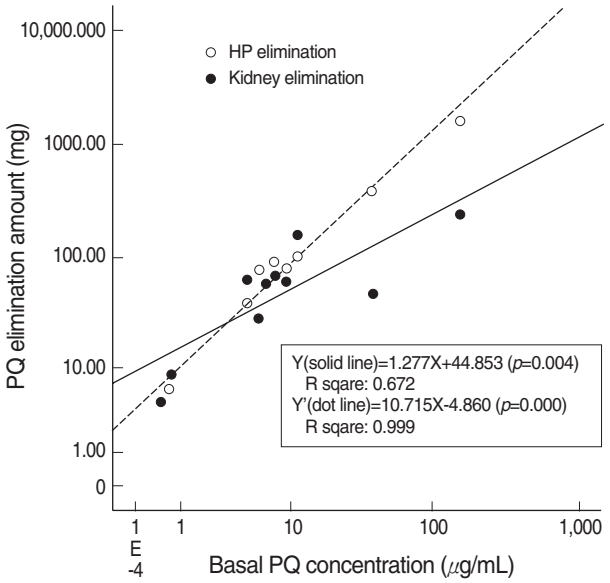

Fig. 1. Comparison between Kidney and HP elimination according to PQ concentration. Note that the intersection of the two lines from the renal and HP elimination equation was at 5.3 μg/mL.
PQ, paraquat; HP, hemoperfusion.

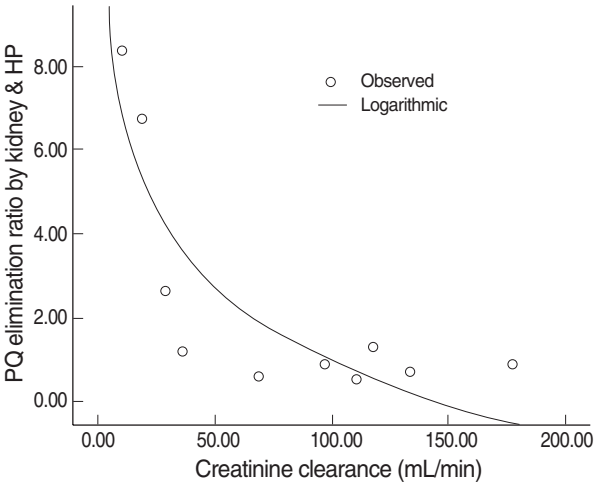

Fig. 2. Comparison between Kidney and HP elimination according to the creatinine clearance. When renal function stays within the normal range, the renal PQ elimination rate is higher than or just as good as the HP. However, as the creatinine clearance decreases, the PQ elimination by HP was more effective than the renal elimination.

Statistical analysis

The results are expressed as means and standard deviation. The significance of the measured differences, between patients with renal failure and those with normal renal function were analyzed by the non-parametric paired t-test. A probability value of $p<0.05$ was considered significant.

RESULTS

HP elimination of PQ

The PQ reduction rate with the HP cartridges was 0.94±0.04 throughout the HP period. The PQ clearance was 111±11 mL/min (range; 13.2-162.2 mL/min) and the actual amount of PQ elimination by the HP cartridge was 251.4±506.3 mg (range; 4.6-1,655.7 mg).

Renal elimination of PQ during the HP

The urine volume during the HP three hours was 3,300±1,600 mL. The overall creatinine clearance was 79.8±56.0 mL/min (range; 9.7-177.0 mL/min) and the PQ clearance was 98.6±53.8 mL/min (range; 13.2-162.2 mL/min). The actual renal elimination of PQ during the HP procedure was 75.4±73.6 mg (range; 4.9-245.8 mg).

Comparison between HP and kidney for PQ elimination

The effect of the plasma PQ level on both the kidneys and HP showed that the renal PQ elimination was higher than that of the HP, in cases with plasma PQ levels lower than 1.0 μg/mL. However, the elimination of PQ was higher with the HP when the PQ level in the plasma was higher than 1.0 μg/mL (Fig. 1).

The effect of the creatinine clearance on the PQ elimination for both the renal and HP clearance showed that as long as the renal function stayed within the normal range, the renal PQ elimination rate was higher or just as good as the HP elimination. However, as the creatinine clearance decreased, the PQ elimination by HP was as effective as or more effective than the renal elimination (Fig. 2).

DISCUSSION

The plasma PQ level changes by unique kinetics, reaching a peak level very early about 60-90 min after ingestion upon disruption of the gastric mucosal barrier (22, 25). Once the peak is reached, the level slopes down rapidly even without extracorporeal elimination (22). Therefore, the toxicokinetics at a given time should be interpreted along with the plasma levels of PQ. A three-compartment model has been proposed for the most accurate description of the PQ distribution: 1) Plasma compartment, 2) Compartment with rapid uptake and removal such as the kidney, and a 3) Slow uptake compartment such as the lungs, reaching a maximum concentration about 4-5 hr after ingestion regardless of the plasma PQ level (22). This model explains the plasma PQ level changes by not only renal excretion factors but also the involvement of other tissue adsorption of PQ.

The efficacy of HP in eliminating PQ is a function of the

reduction rate of the HP cartridge, the blood flow and the plasma levels. In our study, the reduction rate was 0.94 ± 0.04, which showed high efficacy throughout the three hours of HP in all subjects. With an almost constant reduction rate and a fixed value for the blood flow, the main variable factor of the HP for the elimination of PQ appears to depend on the plasma levels of PQ. A linear correlation between the eliminated amount of the PQ and the plasma PQ levels suggests that an earlier initiation of HP, as early as the PQ peak, would be the most effective method for the elimination of PQ.

The frequent deterioration of kidney function after PQ intoxication makes its role in eliminating PQ complicated. In agreement with previous reports (23, 24), the kidney eliminates more PQ than the HP, and can be very effective when the creatinine clearance remains in the normal range (Fig. 1, 2). However, once the renal function begins to deteriorate so does the ability to eliminate PQ (Fig. 1, 2).

Therefore, the efficacy of the kidneys and HP in the elimination of PQ varies depending on a number of factors. The kidney is very effective in eliminating PQ but vulnerable to PQ injury. PQ is metabolized very poorly, and is excreted intact in the urine (26). Renal injury is caused by reactive oxygen species (ROS); their presence progresses very rapidly, causing life threatening clinical features with acute PQ intoxication (27, 28). Deterioration of renal function is frequently observed early in patients with acute PQ intoxication when the PQ level is more than the lethal level (21-24). Therefore, renal protection is critical during the early treatment of PQ intoxication.

The elimination of PQ during HP is limited by the blood flow dynamics which is driven through a jugular venous catheter at a rate of 200-300 mL/min in adults. Keeping in mind both the large PQ distribution volume of 1.0-1.5 L/kg body weight (22, 25) and the very rapid progression of ROS injury with PQ intoxication, the PQ elimination process is pressed for time and blood flow.

In conclusion, our results suggest that early HP must be provided for life saving treatment in patients with acute PQ intoxication, especially in early deterioration of renal function or high plasma levels of PQ.

REFERENCES

1. Smith LL. *Mechanism of paraquat toxicity in lung and its relevance to treatment. Hum Toxicol 1987; 6: 31-6.*
2. Meredith TJ, Vale JA. *Treatment of paraquat poisoning in man: methods to prevent absorption. Hum Toxicol 1987; 6: 49-55.*
3. Okonek S, Hofmann A, Henningsen B. *Efficacy of gut lavage, hemodialysis, and hemoperfusion in the therapy of paraquat or diaquat intoxication. Arch Toxicol 1976; 36: 43-51.*
4. Okonek S. *Hemoperfusion in toxicology. Basic considerations of its effectiveness. Clin Toxicol 1981; 18: 1185-98.*
5. Hampson EC, Pond SM. *Failure of haemoperfusion and haemodialysis to prevent death in paraquat poisoning. A retrospective review of 42 patients. Med Toxicol Adverse Drug Exp 1988; 3: 64-71.*
6. Lock EA, Smith LL, Rose MS. *Inhibition of paraquat accumulation in rat lung slices by a component of rat plasma and a variety of drugs and endogenous amines. Biochem Pharmacol 1976; 25: 1769-72.*
7. Smith LL. *Mechanism of paraquat toxicity in lung and its relevance to treatment. Hum Toxicol 1987; 6: 31-6.*
8. Kitazawa Y, Matsubara M, Takeyama N, Tanaka T. *The role of xanthine oxidase in paraquat intoxication. Arch Biochem Biophys 1991; 288: 220-4.*
9. Suntres ZE. *Role of antioxidants in paraquat toxicity. Toxicology 2002; 180: 65-77.*
10. Lin JL, Leu ML, Liu YC, Chen GH. *A prospective clinical trial of pulse therapy with glucocorticoid and cyclophosphamide in moderate to severe paraquat-poisoned patients. Am J Respir Crit Care Med 1999; 159: 357-60.*
11. Webb DB, Williams MV, Davies BH, James KW. *Resolution after radiotherapy of severe pulmonary damage due to paraquat poisoning. Br Med J (Clin Res Ed) 1984; 288: 1259-60.*
12. Proudfoot AT, Stewart MS, Levitt T, Widdop B. *Paraquat poisoning: significance of plasma-paraquat concentrations. Lancet 1979; 2: 330-2.*
13. Bismuth C, Garnier R, Dally S, Fournier PE, Scherrmann JM. *Prognosis and treatment of paraquat poisoning: a review of 28 cases. J Toxicol Clin Toxicol 1982; 19: 461-74.*
14. Hart TB, Nevitt A, Whitehead A. *A new statistical approach to the prognostic significance of plasma paraquat concentrations. Lancet 1984; 2: 1222-3.*
15. Scherrmann JM, Houze P, bismuth C, Bourdon R. *Prognostic value of plasma and urine paraquat concentration. Hum Toxicol 1987; 6: 91-3.*
16. Hong SY, Yang JO, Lee EY, Kim SH. *Effect of haemoperfusion on plasma paraquat concentration in vitro and in vivo. Toxicol Ind Health 2003; 19: 17-23.*
17. Mascie-Taylor BH, Thompson J, Davison AM. *Haemoperfusion ineffective for paraquat removal in life-threatening poisoning. Lancet 1983; 1: 1376-7.*
18. Van de Vyver FL, Giuliano RA, Paulus GJ, Verpooten GA, Franke JP, De Zeeuw RA, Van Gaal LF, De Broe ME. *Hemoperfusion-hemodialysis ineffective for paraquat removal in life-threatening poisoning? J Toxicol Clin Toxicol 1985; 23: 117-31.*
19. Pond SM, Johnston SC, Schoof DD, Hampson EC, Bowles M, Wright DM, Petrie JJ. *Repeated hemoperfusion and continuous arteriovenous hemofiltration in a paraquat poisoned patient. J Toxicol Clin Toxicol 1987; 25: 305-16.*
20. Koo JR, Kim JC, Yoon JW, Kim GH, Jeon RW, Kim HJ, Chae DW, Noh JW. *Failure of continuous venovenous hemofiltration to prevent death in paraquat poisoning. Am J Kidney Dis 2002; 39: 55-9.*
21. Houzé P, Baud FJ, Mouy R, Bismuth C, Bourdon R, Scherrmann JM. *Toxicokinetics of paraquat in humans. Hum Exp Toxicol 1990; 9: 5-12.*
22. Hawksworth GH, Bennett PN, Davies DS. *Kinetics of paraquat elimination in the dog. Toxicol Appl Pharmacol 1981; 57: 139-45.*
23. Pond SM, Rivory LP, Hampson EC, Roberts MS. *Kinetics of toxic doses of paraquat and the effects of hemoperfusion in the dog. J Tox-*

icol Clin Toxicol 1993; 31: 229-46.
24. Bismuth C, Scherrmann JM, Garnier R, Baud FJ, Pontal PG. *Elimination of paraquat*. *Hum Toxicol 1987; 6: 63-7*.
25. Bennett PN, Davies DS, Hawkesworth GM. *In vivo absorption studies with paraquat and diquat in the dog*. *Br J Pharmacol 1976; 58: 284P*.
26. Murray RE, Gibson JE. *Paraquat disposition in rats, guinea pig and monkeys*. *Toxicol Appl Pharmacol 1974; 27: 283-91*.
27. Chan BS, Lazzaro VA, Seale JP, Duggin GG. *The renal excretory mechanisms and the role of organic cations in modulating the renal handling of paraquat*. *Pharmacol Ther 1998; 79: 193-203*.
28. Van Vleet TR, Schnellmann RG. *Toxic nephropathy: environmental chemicals*. *Semin Nephrol 2003; 23: 500-8*.