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
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, Germany) that had polypropylene housing material, activated charcoal adsorbent, a 300 m² 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 (KEPQt1-2) at each time point was calculated according to

\[ KE_{PQ_{t_1-t_2}} (\text{mg}) = uCo_{PQ_{t_1-t_2}} \times UV_{t_1-t_2} \]  

Where \( uCo \) of \( PQ_{t_1-t_2} \) = urinary PQ level and \( UV_{t_1-t_2} \) = timed volume of urine

The renal clearance of PQ (\( KC_{PQ_{t_1-t_2}} \) [mL/min]) was calculated by using PQ level in plasma and urine

\[ KC_{PQ_{t_1-t_2}} (\text{mL/min}) = KE_{PQ_{t_1-t_2}} / \text{AUC}_{t_1-t_2} \]  

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

\[ \text{AUC} = \frac{\left[ pCo_{PQ_{t_1}} + pCo_{PQ_{t_2}} \right]}{2} / (t_2 - t_1) \]  

HP elimination rate of PQ

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

\[ ER = \frac{(A-V)}{A} \]  

Where \( A = \) inlet plasma PQ level and \( V = \) outlet plasma PQ level.

The PQ clearance of HP (HPCPQt1-2) at each time point was calculated according to

\[ HPC_{PQ_{t_1-t_2}} = ER \times BFR \times (1-Hct) \]  

Where BFR = blood flow rate and Hct = hematocrit.

The amount of PQ adsorbed by the cartridges (HPEHPt1-2) at each time point was calculated from the equation

\[ HPE_{PQ_{t_1-t_2}} = HPC_{PQ_{t_1-t_2}} \times \text{AUC} \]  

Values are expressed as mean ± standard deviation. *Time lag means the period between PQ ingestion and arrival to the emergency room of Soonchunhyang Cheonan Hospital.

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           |

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) | PaCO₂ (mmHg) | PaO₂ (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.
Results

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 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 PQ 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
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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.

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