EFFECTS OF ETHANOL ON PHARMACOKINETICS AND INTESTINAL ABSORPTION OF PARAQUAT IN ANIMALS

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ABSTRACT — The effect of ethanol on pharmacokinetics of paraquat was studied in rabbits by intravenous (i.v.) bolus injection of ethanol 0.5 g/kg (or normal saline, in the control group) followed by an i.v. dose of paraquat 20 mg/kg. A greater apparent volume of distribution (Vd), faster distribution rate constants and lower peak plasma concentration (P<0.01) of paraquat were observed in the ethanol-treated than that in the control rabbits. The total clearance of paraquat was not significantly different between the two groups. The effect of ethanol on the intestinal absorption of paraquat was estimated by in situ intestinal perfusion technique in rats. The perfusate contained paraquat 50 µg/ml alone or with 1% or 2% ethanol. Inulin 320 µg/ml was added to the perfusate for the measurement of water net flux. The absorption clearance of paraquat as well as the absorption of water increased (P<0.01) about two-fold in the presence of ethanol. The results of this study suggest that ethanol may potentiate paraquat toxicity by increasing intestinal absorption and tissue distribution. The critical lethal plasma concentration of paraquat is supposed to be lower in the presence of ethanol owing to increased volume of distribution.

KEY WORDS : Paraquat, Pharmacokinetics, Ethanol, Drug interaction, Intestinal absorption.

INTRODUCTION

Paraquat (1,1'dimethyl-4,4'-dipyridinium), usually supplied as the dichloride, is a widely used herbicide (Calderbank, 1968). Paraquat can stimulate NADPH oxidation, and subsequently exerts toxicity by the following mechanisms (Bus et al., 1974; Bus and Gibson, 1984; Haley, 1979; Ross et al., 1979): a) reduction of oxygen to a superoxide anion which, in turn, reacts with hydrogen peroxide to produce a hydroxide free radical, and consequently destruct cell membrane by lipid peroxidation ; b) inhibition of DNA synthesis and c) disturbance of NADPH related biochemical reaction such as lipid synthesis. It is extremely toxic and causes a high mortality rate when ingested by man and animals (Haley, 1979; Dasta, 1978; Smith, 1986). The Department of Legal Medicine of our medical college had noticed that acute paraquat intoxication-patients who had ingested para-
quat concomitantly with an alcoholic drink showed a higher mortality rate than those without it (personal communication). A previous study verified that concurrent oral administration of paraquat and ethanol was associated with a higher plasma level of paraquat and a higher mortality in rabbits than with those receiving paraquat alone (Kuo and Yu, 1991). Other studies on animals assessed that ethanol increases the plasma concentration, toxicity and lethality of paraquat after oral ingestion (Kuo, 1988; Kuo and Nanikawa, 1990). An increase in plasma concentration of a drug may result from increase in drug absorption, decrease in elimination, decrease in extravascular distribution and/or a net result of more complicated pharmacokinetic alteration. There has been a vast literature about the effects of ethanol on pharmacokinetics of various drugs (Seixas, 1975; Sellers and Holloway, 1978). Ethanol can potentiate (Kourtopoulos et al., 1983; Mazzanti et al., 1987), inhibit (Said and Strum, 1986; Mansbach, 1983), show concentration-dependent effects on (Middleton et al., 1984) or not influence (Mazzanti et al., 1987) the gastro-intestinal absorption of some substances. Absolutely contrary effects on the gastro-intestinal absorption of theophylline with different concentrations of ethanol has been reported (Koysooko and Levy, 1974). Ethanol also influenced the urinary excretion of other drugs (Kourtopoulos et al., 1983). The effects of ethanol on the gastro-intestinal absorption of paraquat is unclear. The purpose of this study was to elucidate, from the pharmacokinetic point of view, the mechanisms for any ethanol-associated potentiation of paraquat toxicity. By intravenous (i.v.) administration of a drug the factor of gastro-intestinal absorption is excluded, and the drug interaction with regard to absorption and elimination can be discriminated. By comparing the data from i.v. and oral administration, the absorbed dose fraction (Fa) of paraquat and consequently the influence of ethanol on paraquat absorption can be estimated. The influence of ethanol on the intestinal absorption of paraquat is further assessed by an in situ intestinal perfusion study.

MATERIALS AND METHODS

1. Chemicals.
Paraquat and insulin were obtained from Sigma (USA). Anhydrous ethanol and other reagents were purchased from E. Merck (Germany) or Wako (Japan). All reagents are of analytical grade.

2. Animals and treatments.
Pharmacokinetics: Male New-Zealand rabbits, 2.7-3.5 kg were used. The rabbits received a dose of 20 mg/kg paraquat with 0.5 g/kg ethanol or normal saline (control group) by intravenous injection (i.v.) in the right ear vein. Pilot study has shown an intravenous dose of 20 mg/kg paraquat to be non-lethal. Blood samples were obtained from the left ear vein through a catheter, by defined time schedule over the next 23 hr. Plasma was separated, and its paraquat concentration determined as soon as possible; otherwise, it was stored at −20°C until analysis.

Intestinal absorption: Wister rats, 220–250 g, were obtained from The Experimental Animal Center, College of Medicine, National Taiwan University. Drug absorption was investigated by the in situ intestinal perfusion technique of Barr and Reigelman (1970) with certain modifications. Briefly, the animal was anesthetized with pentobarbital solution (3.5%), 1 ml/kg i.p. A small midline incision allowed the gentle exposure of intestine for cannulation. A section of the jejunum and intestine approximately 60 cm long was cannulated with silicone tubings at either end. The cannula at the upper end was connected to a Tygon tubing through which perfusion solution warmed to 37°C and gassed with 95% O2 : 5% CO2 (v/v) was pumped at a flow rate of 1 ml/min using a peristaltic pump (IKA-Werk, Germany). The outflow of the infusate was collected from the other end cannula into a fractional collector. The lumen was cleaned by perfusing warm (37°C) normal saline just prior to dose perfusion. When drug perfusion started, the outflow of the initial 20 min period was discarded. The consequent outflow was collected 15 min per tube for the first four tubes, then 25 min per tube thereafter. During experiment, the exposed intestine was moistened by frequent applications of warm (37°C) saline to a
gauze pad covering the intestine, and kept warm by a small lamp placed over the area. Rats were divided into three groups: (A) treated with paraquat solution (50 μg/ml), (B) paraquat solution (50 μg/ml) with 1% ethanol and (C) paraquat solution (50 μg/ml) with 2% ethanol. All of the dose solution contained inulin (320 μg/ml) for the estimation of water flux. The concentrations of paraquat and inulin in the perfusion solution and outflow were determined.

At the end of the perfusion experiment, a small section from the first 2 cm of the jejunum was prepared for pathological examination. The pieces of intestine were washed with normal saline, then fixed in formalin (10 g per 100 ml), and stained with hematoxylin and eosin. Measurement of the villus height and number as well as crypt height were performed in at least six properly oriented villi and crypts per section. To discriminate between the effect of paraquat and ethanol, another three groups of rats were treated as described above without paraquat in the perfusion solution but with normal saline, 1% or 2% ethanol.

Analytical methods: Plasma concentration of paraquat was determined by HPLC. Plasma (0.2 ml) was deproteinized with 0.2 ml sulfo salicylic acid solution, set for 30 min, then centrifuged. Twenty μl of the clear supernatant was injected to HPLC for analysis. Chromatographic conditions were as follows: column 250 × 3.9 mm packed with micro-Bondapack C18 (Waters, USA), mobile phase methanol(buffer solution, pH 3.0 (15/485, v/v), flow rate 1 ml/min, UV detector 254 nm. The buffer solution was prepared by mixing 9 ml diethylamine and 460 ml 0.005 M sodium-1-heptanesulfonate solution, adjusted to pH 3.0 with phosphoric acid and made up to 485 ml with distilled water.

Paraquat in the perfusion solution was determined by the method of Kuo (1986) with slight modification. In brief, the sample (1 ml) was mixed with 1 ml sulfo salicylic acid solution (5%) and set for 30 min. After centrifugation, 1 ml clear supernatant was diluted with normal saline to make 5 ml. To 2 ml of the diluted solution was added 2 ml alkaline dithionite solution (20 mg/ml in 5 N NaOH) and absorbance at 394 nm was measured.

The concentration of inulin was measured by spectrophotometry (Karino et al., 1982). The sample (0.1 ml) was reacted with 4 ml diphenylamine reagent at 100°C for 30 min, cooled to room temperature, and anhydrous ethanol was added to make up 10 ml; the absorbance was measured at 640 nm. Diphenylamine reagent was prepared by dissolving 1.5 g in 50 ml acetic acid, then adding 30 ml hydrochloric acid.

Accuracy and the reproducibility of all the analytical method have been evaluated by within-day and between-day analysis.

Analysis of data: The intravenous plasma concentration data were fitted to both two- (eq. 1) and three-compartment (eq. 2) models by a nonlinear curve fitting program (PCNONLIN) (Metzler and Weiner, 1986) using standard equations:

\[ C_p = Ae^{-a_1} + Be^{-\beta_1} \]  \hspace{1cm} (1)

\[ C_p = Ae^{-a_1} + Be^{-\beta_1} + Ce^{-\gamma_1} \]  \hspace{1cm} (2)

The AIC test (Yamaoka et al., 1978) was used to judge model suitability.

The water absorption, water net flux (J), paraquat (pq) absorption and its absorption clearance (CLa) were calculated by the following equations:

\[ \% \text{ water absorbed} = 100\% \times \frac{(Q_i-Q_o)}{Q_i} \] \hspace{1cm} (3)

\[ J, \text{ ml/(min-cm)} = \frac{(Q_i-Q_o)}{L} \] \hspace{1cm} (4)

\[ \% \text{ pq absorbed} = 100\% \times \frac{(C_i, pq \times Q_i - Co, pq \times Q_o)}{(C_i, pq \times Q_i)} \] \hspace{1cm} (5)

\[ \text{CLa, ml/(min-cm)} = \frac{(C_i, pq \times Q_i - Co, pq \times Q_o)}{(C_i, pq \times L)} \] \hspace{1cm} (6)

where the C represents concentration; L, the length of the intestine used for the experiment and Q, the flow rate of the perfusion solution. Footnotes “i” and “o” represent initial (flow-in) and flow-out, respectively. The Qo in these equation was estimated from the inulin (inu) concentrations by equation 7.

\[ Q_o = C_i, \text{ inu} \times Q_i / C_o, \text{ inu} \] \hspace{1cm} (7)

RESULTS

1. Reliability of analytical methods.

Paraquat in serum sample was well separated by the HPLC method. A linear relationship between concentration and peak response over the range 0.6–20 μg/ml was obtained. The mean recovery was 98.4 to 100.8%, with a coefficient of variation (C.V.) between 0.9 to 2.8% over the tested concentration range.
The spectrophotometric responses versus concentrations of paraquat (1.25–10 μg/ml) or inulin (1.6–6.4 μg/ml) demonstrate linearity over the tested concentration ranges with the C.V. within 2.7%.

The intraday and the interday precisions for all the analytical methods showed the C.V. less than 3%.

2. Pharmacokinetics.

The mean plasma elimination curves of paraquat observed from control and ethanol-treated rabbits (Fig. 1) were adequately described by a two-compartment model as demonstrated by the AIC values (Table 1). However, except for the central compartment elimination rate constant (k10), the values of the common parameters between the two models are almost equivalent. Animals receiving paraquat with ethanol showed a significantly lower peak concentration (Co), higher volume of distribution (Vd), higher distribution rate constants from central to peripheral compartments (k12) and vice versa (k21) than those receiving paraquat alone (Table 2). Plasma clearance (CLtot) and the area under the plasma elimination curve (AUC) did not significantly differ between the two groups (Table 2). These results indicated that ethanol accelerates and increases the extravascular (tissue) distribution of paraquat. The elimination of paraquat is not significantly changed in the presence of ethanol.

3. Paraquat absorption clearance and Water flux.

The percent dose of paraquat and water absorption after perfusion through intestine is shown in Figure 2. Ethanol enhances the intes-

![Fig. 1. Plasma concentration-time profile of paraquat after i.v. bolus dose 20 mg/kg in rats. Key: () paraquat alone, () paraquat with ethanol 0.5 g/kg.](image-url)

Table 1. Pharmacokinetic parameters of paraquat after i.v. administration in rabbits.

<table>
<thead>
<tr>
<th></th>
<th>Three compartment</th>
<th>Two compartment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Alone</td>
<td>With Ethanol</td>
</tr>
<tr>
<td>A, μg/ml</td>
<td>44.14 (6.89)</td>
<td>16.61 (1.45)</td>
</tr>
<tr>
<td>B, μg/ml</td>
<td>2.83 (36.22)</td>
<td>5.54 (3.28)</td>
</tr>
<tr>
<td>C, μg/ml</td>
<td>0.28 (44.84)</td>
<td>0.13 (4.75)</td>
</tr>
<tr>
<td>α, /hr</td>
<td>1.19 (0.28)</td>
<td>1.73 (0.36)</td>
</tr>
<tr>
<td>β, /hr</td>
<td>0.12 (2.264)</td>
<td>0.08 (0.07)</td>
</tr>
<tr>
<td>γ, /hr</td>
<td>0.012 (5.19)</td>
<td>0.00 (1.38)</td>
</tr>
<tr>
<td>Co, μg/ml</td>
<td>47.25 (2.71)</td>
<td>22.28 (1.49)</td>
</tr>
<tr>
<td>Vd, ml/kg</td>
<td>423.3 (24.33)</td>
<td>897.5 (59.99)</td>
</tr>
<tr>
<td>k21, /hr</td>
<td>0.19 (1.74)</td>
<td>0.05 (0.31)</td>
</tr>
<tr>
<td>k31, /hr</td>
<td>0.006 (5.87)</td>
<td>0.003 (1.47)</td>
</tr>
<tr>
<td>k10, /hr</td>
<td>0.35 (5.48)</td>
<td>0.81 (0.22)</td>
</tr>
<tr>
<td>k12, /hr</td>
<td>0.599 (5.27)</td>
<td>0.53 (2.28)</td>
</tr>
<tr>
<td>AUC, hr·μg/ml</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIC</td>
<td>18.507</td>
<td>2.396</td>
</tr>
</tbody>
</table>

Estimated by fitting the mean plasma elimination curves of six rabbits in each group. In the parentheses are standard errors of curve fitting.
size are shown in Table 4. No significant changes were observed in any of the parameters measured.

**DISCUSSION**

The disposition and elimination of paraquat have usually been described by a three-compartment open model (Hawksworth et al., 1981; Murray and Gibson, 1974; Sharp et al., 1972). The present study showed that the two-compartment model is adequate as demonstrated by the AIC values. However, the results of the common parameters between the two models are comparable.

In both groups, the rate of uptake into the peripheral compartment (k₁₂) was significantly greater than the rate of removal from it (k₂₁), indicating that at equilibrium the amount of paraquat in tissues is more than in plasma. Ethanol accelerates the rate of distribution of paraquat into the peripheral compartment (k₁₂) and vice versa (k₂₁), which implies that ethanol may potentiate the permeability of paraquat through distribution barrier. The mortality of paraquat is well correlated with plasma and tissue concentrations (Proudfoot et al., 1979; Sharp et al., 1972; Levitt and Widdop, 1979). The increases in the distribution volume indicates a decrease in plasma concentration by shifting some paraquat from central to peripheral compartment, which suggests that the drug concentration or the distribution area of paraquat may be increased in some tissues. Consequently, the

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**Table 2.** Pharmacokinetic parameters of paraquat after i.v. administration in rabbits.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Paraquat alone</th>
<th>With alcohol</th>
<th>t value</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC, µg·hr/ml</td>
<td>74.89 (7.76)</td>
<td>50.18 (9.57)</td>
<td>2</td>
<td>N.S.</td>
</tr>
<tr>
<td>alpha t₁/₂, hr</td>
<td>0.62 (0.09)</td>
<td>0.41 (0.08)</td>
<td>1.73</td>
<td>N.S.</td>
</tr>
<tr>
<td>beta t₁/₂, hr</td>
<td>12.85 (3.19)</td>
<td>6.19 (2.29)</td>
<td>1.69</td>
<td>N.S.</td>
</tr>
<tr>
<td>k₁₀, /hr</td>
<td>0.76 (0.20)</td>
<td>0.57 (0.13)</td>
<td>0.8</td>
<td>N.S.</td>
</tr>
<tr>
<td>k₁₂, /hr</td>
<td>0.48 (0.08)</td>
<td>0.94 (0.06)</td>
<td>2.5</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>k₂₁, /hr</td>
<td>0.14 (0.04)</td>
<td>0.66 (0.14)</td>
<td>3.57</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>Vd, l/kg</td>
<td>0.42 (0.05)</td>
<td>0.95 (0.20)</td>
<td>2.63</td>
<td>P&lt;0.05</td>
</tr>
<tr>
<td>Co, µg/ml</td>
<td>53.59 (4.73)</td>
<td>24.01 (3.77)</td>
<td>4.89</td>
<td>P&lt;0.01</td>
</tr>
<tr>
<td>CL, (kg·hr)</td>
<td>0.29 (0.05)</td>
<td>0.48 (0.09)</td>
<td>1.8</td>
<td>N.S.</td>
</tr>
</tbody>
</table>

Data are means (SEM) of six determinations.
N.S. = not significantly different.
Table 3. Paraquat absorption clearance and water net flux from intestinal perfusion solution.

<table>
<thead>
<tr>
<th></th>
<th>Parquat alone</th>
<th>1%</th>
<th>2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>paraquat absorption (F), %</td>
<td>10.2 (1.0)</td>
<td>21.6 (1.2)(^a)</td>
<td>24.5 (2.4)(^a)</td>
</tr>
<tr>
<td>paraquat clearance, (\times 10^{-3}) ml/(min·cm)</td>
<td>1.8 (0.2)</td>
<td>3.7 (0.3)(^a)</td>
<td>4.2 (0.4)(^a)</td>
</tr>
<tr>
<td>water absorption, %</td>
<td>16.9 (1.1)</td>
<td>25.1 (0.8)(^a)</td>
<td>29.1 (1.9)(^a)</td>
</tr>
<tr>
<td>water net flux, (\times 10^{-3}) ml/(min·cm)</td>
<td>2.6 (0.2)</td>
<td>4.0 (0.3)(^a)</td>
<td>4.7 (0.4)(^a)</td>
</tr>
</tbody>
</table>

Data are means (SEM) determined from nine rats. The fluctuation of absorption during 120 min has been averaged within each rat. \(^a\) : P<0.01, significantly different from paraquat alone by one-way ANOVA and Tuckey's test.

Table 4. Mucosal villus height, density and crypt height in jejunum from rats perfused with paraquat, with or without ethanol.

<table>
<thead>
<tr>
<th></th>
<th>Normal saline</th>
<th>Alcohol 1%</th>
<th>Alcohol 2%</th>
<th>Paraquat alone</th>
<th>+ alcohol 1%</th>
<th>+ alcohol 2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Villus height, mm</td>
<td>0.37 (0.02)</td>
<td>0.35 (0.03)</td>
<td>0.36 (0.03)</td>
<td>0.35 (0.03)</td>
<td>0.34 (0.02)</td>
<td>0.34 (0.03)</td>
</tr>
<tr>
<td>Villus number/mm</td>
<td>13.32 (1.86)</td>
<td>12.44 (1.40)</td>
<td>12.76 (1.59)</td>
<td>13.61 (1.41)</td>
<td>13.88 (1.22)</td>
<td>13.81 (1.27)</td>
</tr>
<tr>
<td>Crypt height, mm</td>
<td>0.16 (0.02)</td>
<td>0.15 (0.02)</td>
<td>0.16 (0.03)</td>
<td>0.14 (0.01)</td>
<td>0.14 (0.02)</td>
<td>0.16 (0.02)</td>
</tr>
</tbody>
</table>

Data are means (SEM) of three determinations.

Table 5. Absorption fraction (Fa) and kinetic parameters involving Fa of paraquat\(^a\).

<table>
<thead>
<tr>
<th>Part A</th>
<th>Group I (n=8)</th>
<th>Group II (n=6)</th>
<th>Group III (n=5)</th>
<th>Statistics(^b)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AUC, (\mu g\cdot h/ml)</td>
<td>71.91 (15.15)</td>
<td>98.72 (36.81)</td>
<td>180.59 (46.83)</td>
<td>F = 17.41</td>
</tr>
<tr>
<td>CL/Fa, 1/h/kg</td>
<td>2.93 (0.84)</td>
<td>2.23 (0.67)</td>
<td>1.18 (0.37)</td>
<td>P &lt; 0.01</td>
</tr>
<tr>
<td>Vd/Fa, 1/kg</td>
<td>8.73 (2.44)</td>
<td>5.54 (3.05)</td>
<td>3.52 (2.34)</td>
<td>P &lt; 0.01</td>
</tr>
</tbody>
</table>

Part B

| Fa                      | 0.096 (0.081) | 0.132 (0.088) | 0.241 (0.089)   | 0.036 NS         |
| CL, 1/h/kg              | 0.281 (0.284) | 0.294 (0.284) | 0.291 (0.281)   | NS               |
| Vd' 1/kg                | 0.838 (0.848) | 0.731 (0.848) | 0.848 (0.848)   | 0.171 NS         |
|                         | (0.234 (0.564)| (0.403 (0.564)| (0.403 (0.564)|                 |

\(^a\) : Data are the mean with S.D. in the parentheses.
\(^b\) : By one-way ANOVA.
NS : Not significant.
Part A : Data from oral ingestion study [Kuo and Yu, 1991], Group I, paraquat (200 mg/kg) alone; Group II, with ethanol (1 g/kg); Group III, with ethanol (2 g/kg).
Part B : Estimated by multiplying the Fa values to the CL/Fa and Vd/Fa values in part A.
lowered plasma concentration of paraquat by ethanol should not be interpreted as decreased toxicity; on the contrary, the toxicity of paraquat might be increased inspite of the lowered plasma concentration.

Applying the data of the area under the plasma elimination curve (AUC) from the present study and that from the oral (Kuo and Yu, 1991), the absorption fraction (Fₐ) can be estimated by equation 8 based on the same plasma concentration range and consequently the equivalent clearance of paraquat.

\[ Fₐ = \frac{(AUC_o/Do)}{(AUC_i/Di)} \]

(8)

Where D represents doses, and the footnotes “o” and “i” represent oral and i.v., respectively. Applying the Fₐ values thus obtained to the data CL/Fₐ and the Vd/Fₐ in that report (Kuo and Yu, 1991) in which the Fa value was undetermined, the CL and the Vd of paraquat by oral dosing can be calculated. The results (Table 5) show that absorption of paraquat in rabbits was poor after oral administration, as demonstrated by the low Fa value (9.6%), and was increased 2.5 folds by concomitant ingestion of ethanol (2 g/kg). The Fa value of paraquat alone (control group) thus obtained was in agreement with those of other studies on rats (Murray and Gibson, 1974; Daniel and Gage, 1966) and humans (Steffen and Konder, 1979), and was also in agreement with the absorption ratio observed from the present in situ intestinal absorption study in rats. Ethanol did not significantly influenced the apparent clearance of paraquat after i.v. injection in rabbits. Taking the Fa value into account, the CL of paraquat estimated from oral ingestion also was not significantly altered by concomitant ingestion of ethanol. The CL values thus obtained were again comparable with those obtained from i.v. administration. Paraquat elimination occurs almost totally by renal excretion (Lock, 1979; Daniel and Gage, 1966). The total clearance of paraquat in rabbits, as observed in this study, was comparable with that in dogs (Hawsworth et al., 1981) and rats (Lock, 1979) when those data were normalized against body weights. These comparable results of absorption and clearance suggest that the pharmacokinetics of paraquat are quite similar among creatures. Therefore, the influence of ethanol on paraquat absorption observed from the present study may be applicable for the interpretation of that observed in other animals and humans.

Increases in paraquat and water absorption in the presence of ethanol were parallel. A plausible hypothesis is that the increase in paraquat absorption by ethanol comes from a water-drag effect. A study on the relationship between ethanol and water net flux showed that ethanol (up to 5%) increased water net flux (Koysooko and Levy, 1974). Paraquat, usually available as a dichloride derivative, is very soluble in water. Steffen and Konder (1979) reported that paraquat is poorly absorbed by the gut, and the linearity of absorption over a wide concentration range is consistent with passive transport. These properties suggest that the absorption of paraquat is mainly via water space since the diffusion of paraquat through lipophytic membrane is difficult. Therefore, intestinal absorption of paraquat must be closely related to water flux. The mechanism by which ethanol increases water flux is not determined from this investigation.

Hemorrhagic erosions of the small intestinal villi have been observed in acute but not chronic intragastric administration of 5% ethanol in rats, and the lesions were concentration-dependent (Barona et al., 1974). Chronic ingestion of ethanol revealed shorter villi with fewer villi cells in the jejunum (Barona et al., 1974). Ultra-structural changes were found in cells of the crypts and villi of volunteers after ethanol administration at about 9% concentration (Sellers and Holloway, 1978). The highest concentration of ethanol used in this experiment was 2%, and no significant change was observed in villus length, crypt length or villi cell number. The paraquat alone, or with 1% or 2% ethanol, did not lead to significant changes in those parameters either. Therefore, an increased paraquat absorption in the presence of ethanol did not seem to be from ethanol erosion of the intestine.

Increase in absorption can elevate, while increase in tissue distribution can lower plasma concentration of a drug. The influences of ethanol on plasma concentration of paraquat after concomitant oral ingestion should, therefore, depend on the relative magnitude of the two contrary effects. Evidence showed that influence of ethanol on paraquat absorption exceeded that on paraquat distribution resulting in a net increase in
paraquat plasma concentration (Kuo and Yu, 1991), which implies that the magnitude of increase in tissue concentration of paraquat could be far more than that in apparent plasma concentration.

In conclusion, ethanol may greatly potentiate the toxicity of paraquat and consequently mortality from paraquat intoxication by increasing absorption and tissue distribution of paraquat.

ACKNOWLEDGMENTS

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Effect of ethanol on paraquat kinetics