Detoxification of Paraquat Poisoning: Effects of Alkylsulfates and Alkylsulphonates on Paraquat Poisoning in Mice and Rats

Teruo Tsuchiya, Takamasa Yoshida, Atsumune Imaeda, Tadashi Kihö, and Shigeo Ukaı

Gifu Prefectural Hospital, Noishiki 4-chome, Gifu 500, Japan and Gifu Pharmaceutical University, Mitahora-higashi 5-chome, Gifu 502, Japan. Received August 15, 1994; accepted December 5, 1994

The study revealed that high molecular polyvinyl sulfate (PVP) or sulfonate (PVS), and low molecular alkylsulfonates (NaO,S(CH2)nSO3Na, n=2–5: EDS, TDS, BDS and PDS) can alleviate acute toxicity of the herbicide, paraquat dichloride (PQ) in mice. Their activity as antidotes and the mode of the action varied depending on molecular size. The survival rate for mice receiving PQ at 200 mg/kg alone was increasingly improved when the dose of antidotes was increased from 8 to 10 times the dose of PQ; all the test compounds, except EDS (70% survival), achieved a survival rate of 100%. When test compounds were orally dosed to mice in a mixture with PQ, they improved LD50 of PQ alone. With the low molecular compounds EDS, TDS, BDS and PDS, the value increased to about 2 to 3 times (300–458 mg/kg) over that of PQ alone (140 mg/kg). With high molecular PVS and PVP, the combination reached about a 7-fold (900–1000 mg/kg) increase in LD50 value. The formation of lipid peroxide in lungs of rats due to PQ tended to be suppressed by concomitant administration of carbohydrate sulfate (DS and GS). PVP, BDS and TDS were more effective in depressing synthesis of lipid peroxide than DS or GS in the lungs, although BDS and TDS were less effective in suppressing PQ absorption from the rat small intestine than DS, GS or PVP. The results of these experiments indicate that the main mechanism for the detoxification of a high molecular alkylsulfate or sulfonate, and a low molecular alkylsulfonate must be suppression of PQ absorption from the intestine, similar to that of carbohydrate sulfate. In addition, a low molecular alkylsulfonate (BDS and TDS) was also proved to be significantly effective in suppressing the formation of lipid peroxide in the lungs.

Key words paraquat detoxification; polyvinylsulfate; polyvinylsulfonate; alkylsulfonate; lipid peroxide; active oxygen

Paraquat, 1,1-dimethyl-4,4-dipyridylidylidium salt, has a potent action as a herbicide, but is potentially toxic. Suicides involving paraquat and accidental deaths due to its ingestion by mistake or its incorrect use have been reported. To prevent such deaths, a commercial preparation of paraquat dichloride (PQ) with less toxic content has replaced paraquat. An herbicidal preparation is currently used with a low percentage of PQ and less toxic diquat and containing an emetic and a blue dye. But accidents regarding PQ have still not been eliminated in Japan. The excretion of PQ from the body is the best way to treat PQ poisoning. This is commonly done by gastrointestinal lavage, blood perfusion, or hemodialysis. There is no specific antidote which neutralizes PQ.

As part of our investigation on detoxification of PQ poisoning, we examined and reported the effectiveness of a wide variety of water soluble sodium carbohydrate sulfates; dextran sulfate (DS), sucrose sulfate (SS) and glucose sulfate (GS), capable of trapping cations for activity to alleviate the effect of PQ poisoning in mice and rats. In the preceding paper, we proposed that the alleviating effect of carbohydrate sulfate on PQ poisoning was dependent on the proportion of sulfate groups in the carbohydrate molecule, regardless of its molecular size. To confirm the counteracting effect of the sulfate group and its related sulfonate group on the acute toxicity of PQ, this paper deals with alkyl sulfates or sulfonates having short and long alkyl chains instead of carbohydrate compounds.

One group includes water soluble potassium polyvinyl sulfate (PVP) and sodium polyvinyl sulfonate (PVS) which have high molecular weight alkyl groups other than sugars.

The other group includes the low molecular weight compounds disodium pentane-1,5-disulfonate (PDS), disodium butane-1,4-disulfonate (BDS), disodium propane-1,3-disulfonate (TDS), disodium ethane-1,2-disulfonate (EDS), sodium octanesulfonate (OS), sodium isethionate (ISA) and sodium methyl sulfate (MS). Chemical features necessary for the activity to lessen PQ poisoning and the mechanism of the action are also discussed.

MATERIALS AND METHODS

Animals and Reagents Male mice of the ddY strain (4 weeks old) and two age groups of male Wistar rats (5 and 9 weeks) were purchased from Japan SLC Co., Ltd. (Hamamatsu). They were used after fasting for 12 h. PQ was the generous gift of Zeneca K. K. DS (molecular weight ca. 3300, S-content 18%), and GS (S-content 21%) were offered by Meito Sangyo Co., Ltd. PVP (molecular weight ca. 243000, S-content 19.0%), ISA (S-content 21.6%) and OS (S-content 14.8%) were purchased from Nacalai Tesque Co., Ltd. PVS (molecular weight ca. 19500, S-content 24.6%) and MS (S-content 23.9%) were purchased from Aldrich Chemical Co., Ltd. BDS (S-content 24.4%) and EDS (S-content 27.4%) were purchased from Tokyo Kasei Co., Ltd. TDS (S-content 25.8%) and PDS (S-content 27.4%) were synthesized by the method of Pethybridge and Tabra. ELISA kit was a gift from Zeneca Central Toxicology Laboratory, Cheshire England.

Preparation of TDS and BDS To synthesize TDS, trimethylene dibromide was added dropwise to a hot aqueous solution supersaturated with sodium sulfite. The mixture was refluxed until the oily layer disappeared, and
then was filtered. After concentration, the filtrate was cooled for crystallization. The crystals were dissolved in distilled water. After addition of hydrobromic acid, the solution was heated to decompose unreacted sodium sulfide, and then neutralized with sodium hydroxide. To the solution was added barium bromide to precipitate barium sulfate, which was removed by filtration. The filtrate was evaporated under reduced pressure at 60°C. Crystals thus obtained were recrystallized from methanol. The crystals were separated by filtration and dissolved in water. The solution was applied to a glass column (42.6 mm x 450 mm) packed with an ion-exchange resin of Amberlite CG-120 [H⁺]. TDS was eluted from the column with distilled water; the eluate was collected until it became neutral. The pooled eluate was neutralized with sodium hydroxide and evaporated to dryness under reduced pressure. The residue was used as TDS. PDS was synthesized with pentamethylene dibromide in place of trimethylene dibromide in a similar way.

Preparation of Aqueous Solutions to Treat Animals

Alkylsulfates (PVP, OS and MS), alkylsulphonates (PVS, PDS, BDS, TDS, EDS and ISA), carbohydrate sulfates (DS and GS) and PQ were dissolved in distilled water. These solutions were administered through a stomach tube, 7 cm long and 2 mm in diameter.

Experiments to Assess Doses Necessary for Alleviating PQ Poisoning

Mice were orally treated with PQ at 200 mg/kg alone or simultaneously with an oral dose of one of PVP, PVS, PDS, BDS, TDS, EDS, OS, ISA or MS. Five doses ranging from 400 to 2000 mg/kg were used for each compound in this study. The survival rate on the 14th day after PQ treatment was determined. Each treatment group consisted of ten animals.

Experiments to Assess Detoxification Effects of Treatment with Antidotes Given Different Periods after PQ Ingestion

Ten mice orally receiving PQ at 200 mg/kg were treated orally with a dose of PVP, PVS, PDS, BDS, or TDS at 2000 mg/kg immediately, 10, 20, 30 or 60 min after the treatment with PQ. A 14-d survival rate for each treatment group was calculated with 10 animals.

Effects on Acute Toxicity of PQ (LD₅₀)

Mice were treated orally with an aqueous mixture of PQ and one of PVP, PVS, PDS, BDS, or TDS in different ratios between 1:0.5 and 1:4. Each group consisted of ten mice. LD₅₀ values for PQ were calculated by the Litchfield Wilcoxon method based on the number of animals alive 72 h after the treatment.

Effects on Small Intestinal Absorption of PQ as Assessed by an in Situ Recirculating Perfusion Method

Nine week old rats were anesthetized with ether and the abdomen opened. A 100 ml portion of physiological saline containing 5 mg of PQ and 50 mg of one of the study compounds (PVP, BDS or TDS) was introduced into the intestine from the proximal cut end made in the proximal part of the duodenum and removed from the other cut end in the distal part of the ileum, to allow continuous circulation of the solution. A peristaltic pump placed between the two ends was used to pump the solution into the intestine at a flow rate of 5 ml/min. Four sample solutions were withdrawn at 30 min intervals during the perfusion experiment, and PQ in each solution was determined by colorimetry. Before the perfusion study the intestine was rinsed with about 50 ml of physiological saline. The solution was kept at 37°C during the perfusion. Phenolphthalein, which is not absorbed from intestine, was added to each solution to offset change in its volume due to absorption or secretion of water.

Effects on Excretion of PQ and Formation of Lipid Peroxide in Organs

Effects of DS, GS, PVP, BDS and TDS were investigated in 5 week old rats. The animals were orally treated simultaneously with PQ at 50 mg/kg and one of the test compounds at 500 mg/kg. Feces and urine excreted after the treatment were collected using metabolism cages, and amounts of PQ excreted over periods of 6, 12 and 24 h and 2, 3, 4, 5, 6, 7, 10 and 14 d after the treatment were determined. The animals were killed 14 d after the treatment immediately following the last collection of feces and urine. The lungs, kidneys, and liver were removed and the lipid peroxide in these organs was separately determined. Each group consisted of 5 rats.

Determination of PQ and Lipid Peroxide

PQ in Feces: A portion of feces was suspended in 10 volumes (i.e., 10 ml per gram) of 5 n sulfuric acid, and the mixture was heated for about 2 h, neutralized with sodium hydroxide, and centrifuged. The supernatant was analyzed by ELISA. PQ in Urine: The total volume of urine was adjusted to 50 ml with distilled water and then centrifuged. The urine supernatants were adjusted to pH 10.5 using 1 M sodium carbonate. PQ in the supernatant was adsorbed on a Sep-Pak C18 column and eluted with acetic methanol. The solution was evaporated to dryness and then dissolved in 500 ml mobile phase. The concentration of PQ in the solutions was determined by HPLC. HPLC measurements were made using Hitachi Model 655 equipment with a Hitachi 638 variable wavelength detector set at 286 nm and a JASCO Finepak SIL C18 column. The mobile phase of 1 contained sodium phosphate monohydrate 0.75 g, methanol 100 ml, diethylamine 10.3 ml and 13.5 ml of 85% phosphoric acid in distilled water. The flow rate was 0.8 ml/min and the column was maintained at 50°C.

PQ Concentrations in Perfusion Solution: Sample solutions withdrawn during the in situ absorption experiment were made alkaline with sodium hydroxide. After addition of sodium hydrosulfite, the absorbance of the solution was measured at 600 nm.

Concentrations of Lipid Peroxides in Organs: Organs isolated from rats were separately homogenized in 0.85% sodium chloride solution in 1 mm Tris-HCl buffer (pH 7.8), and the homogenate was centrifuged at 4°C and 15000 x g for 15 min. A portion of the supernatant was analyzed for lipid peroxide at 532 nm by the thiobarbituric acid (TBA) method modified by Okawa et al. The concentration of lipid peroxide in each organ was expressed in terms of malondialdehyde.

Statistical Analysis

Data were expressed as the mean value ± standard error. Statistical analysis of the TBA value data (see Table 4) was performed using Duncan's multiple comparison test. The significance of differences between means (see Figs. 1—3) was performed using Student's t test.
RESULTS

The survival rates (14 d) of mice treated orally with PVP, PVS, PDS, BDS, TDS, EDS, OS, ISA or MS immediately after an oral dose of PQ at 200 mg/kg are listed in Table 1. PVP and PVS had the most potent activity among the test compounds in alleviating PQ poisoning as did the carbohydrate sulfates DS, SS and OS. Of mice treated with these compounds at 1200 to 2000 mg/kg, 90 to 100% were alive. This group was followed by PDS, BDS and TDS. With the second group, the detoxification activity assessed in mice receiving PQ at 200 mg/kg tended to increase as the dose was increased from 400 to 2000 mg/kg or from 2 to 10 times the dose of PQ. EDS was somewhat less active than the above two groups, and failed to increase the survival rate beyond 70% at any dose. ISA allowed only 10 to 30% of the animals to survive, and OS and MS were completely ineffective. These results indicated that active compounds have to have more than one sulfate or sulfonate group per molecule in the low molecular compounds and that the activity tended to increase with the molecular weight. Effects of timing of the treatment on the activity were studied with PVP, PVS, BDS, PDS, BDS and TDS, all of which proved considerably active. As shown in Table 2, the survival rates were the highest when they were dosed immediately after dosing of PQ. The longer the interval was, the lower the rate was.

Detoxification activity in mice was next assessed in terms of change in LD_{50} value for PQ. As shown in Table 3, within the dose ratio range of 1:0.5 to 1:4 of PQ to the test compound, the LD_{50} value increased as the relative dose of the test compound increased. When mice received a high molecular weight compound such as PVP or BDS at the ratio of 1:4, the LD_{50} value was about 7 times (900 to 1000 mg/kg) greater than the value measured in mice receiving PQ alone. When mice received a low molecular weight test compound such as BDS, PDS or TDS with PQ, in contrast, the respective LD_{50} values were 420, 458 and 429 mg/kg, about 3 times greater than the LD_{50} for PQ alone. With EDS which failed to alleviate PQ toxicity up to 100% survival, the LD_{50} value was improved only up to 300 mg/kg, a value about two-fold that for PQ alone.

The value of LD_{50} for PQ ion toxicity has been reported to be similar in mice (104 mg/kg) and rats (95-150 mg/kg). We also previously observed a similar behavior in two species for the alleviating effect of carbohydrate sulfate on PQ toxicity. Therefore, rats were used in the experiments on fecal and urinary excretion, intestinal absorption during in situ perfusion, and lipid peroxide in lungs, kidneys and liver for PQ and test compounds.

An absorption study by an in situ recirculating perfusion method was performed in small intestine of ether-anesthetized rats using 100 ml of physiological saline containing 5 mg/dl of PQ alone or in combination with 50 mg/dl of one of the study compounds (PVP, BDS and TDS). The effects of the compounds on the rate of absorption (mean ± S.E.) of PQ are as shown in Fig. 1. When PQ alone was perfused for 180 min, 13.4 ± 1.0% of its amount in the solution was absorbed. This rate decreased to 3.7 ± 0.5% in the presence of PQ, and to about 10% if the PQ solution contained BDS or TDS (9.6 ± 0.7% or 10.1 ± 0.7%, respectively). The high molecular weight PVP suppressed the absorption significantly, as did DS and GS and all were more active in the suppression than the low molecular weight alkylsulfonates BDS and TDS.

Fecal and urinary excretion of PQ in rats is shown...
in Figs. 2 and 3, respectively. Irrespective of type of treatment, most (nearly 90%) of the cumulative PQ detected in feces was excreted within the first 24 h after PQ administration. Excretion continued at very low levels until 7 d after the administration. No PQ was detected on the 8th day or later. In rats receiving PQ alone, 56.7% (mean ± S.E.: 3.06 ± 0.16 mg) of the dose was excreted into the feces over 14 d. In rats receiving PQ in combination with PVP, BDS, or TDS, the rates increased to 72.7% (4.00 ± 0.44 mg), 71.0% (3.62 ± 0.19 mg) and 69.1% (3.63 ± 0.41 mg), respectively. When PQ was given with one of these compounds the increase was somewhat lower than that of DS or GS.\(^{11}\) Thus, it was suggested that all these compounds enhance fecal excretion of PQ. In animals receiving PQ alone, 7.2% (387.5 ± 38.4 μg) of the dose was excreted in the urine over the same period. The rate was decreased to 0.6% (33.3 ± 5.5 μg), 3.0% (159.8 ± 42.5 μg) and 2.6% (132.5 ± 20.1 μg) in animals receiving PQ with PVP, BDS and TDS, respectively. The reduced urinary excretions indicate that these compounds suppress intestinal absorption of PQ because essentially all the absorbed PQ is excreted into the urine and little into the bile.\(^{24}\) The degrees of the suppression of urinary excretion well agree with those demonstrated in the above in situ absorption experiment.

Concentrations of lipid peroxide in various organs determined 14 d after the treatment in various groups of rats are shown in Table 4. In animals receiving PQ alone, the lipid peroxide concentration (TBA value: mean ± S.E.) in the lungs, as expressed in terms of malondialdehyde, was 123.7 ± 25.4 nmol/g. In rats receiving PQ in combination with any of the study compounds (DS, GS, PVP, BDS or TDS), the TBA value in lungs tended to decrease compared with that in animals receiving PQ alone. In rats receiving PVP, BDS or TDS, this decrease was significant. The TBA values were practically normal, particularly in the lungs of rats receiving low molecular alkylsulfonate such as BDS and TDS. The TBA value in the liver was significantly lower in animals receiving PQ with BDS than PQ alone. In kidneys, the TBA value due to PQ alone did not decrease significantly in any 

![Fig. 1. Absorption of PQ from Small Intestine of the Rat](image1)

**Fig. 1. Absorption of PQ from Small Intestine of the Rat**

Rat (9 weeks old) small intestine was recirculated with an aqueous mixture of PQ (5 mg) and the test compound (BDS — ▲ —, TDS — ■ —, or PVP — ○ —) (50 mg) and PQ (5 mg) alone (○ — ) in 100 ml physiological saline by intestinal perfusion for 3 h. Each point indicates the mean ± S.E. of 3 experiments. a — c) Significantly different from the PQ alone at p < 0.05, p < 0.01, and p < 0.001, respectively.

![Fig. 2. Excretion Rate of PQ in the Feces](image2)

**Fig. 2. Excretion Rate of PQ in the Feces**

Rats (5 weeks old) were orally treated simultaneously with PQ (—○—) at 50 mg/kg and one of the test compounds (BDS — ▲ —, TDS — ■ — and PVP — ○ —) at 500 mg/kg. Each point indicates the mean ± S.E. of 4 or 5 animals. a) Significantly different from the PQ alone at p < 0.05.

![Fig. 3. Excretion Rate of PQ in the Urine](image3)

**Fig. 3. Excretion Rate of PQ in the Urine**

Rats (5 weeks old) were orally treated simultaneously with PQ (—○—) at 50 mg/kg and one of the test compounds (BDS — ▲ —, TDS — ■ — and PVP — ○ —) at 500 mg/kg. Each point indicates the mean ± S.E. of 4 or 5 animals. a) Significantly different from the PQ alone at p < 0.05.

**Table 4. TBA Value in Rats on the 14th Day after PQ Oral Administration**

<table>
<thead>
<tr>
<th></th>
<th>Lung</th>
<th>Liver</th>
<th>Kidney</th>
</tr>
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<tbody>
<tr>
<td>PQ</td>
<td>123.7 ± 25.4(a)</td>
<td>288.9 ± 46.4(a)</td>
<td>312.2 ± 17.2</td>
</tr>
<tr>
<td>PQ + DS</td>
<td>84.0 ± 13.9(a)</td>
<td>227.1 ± 18.0</td>
<td>277.8 ± 8.2</td>
</tr>
<tr>
<td>PQ + GS</td>
<td>97.3 ± 13.5(a)</td>
<td>280.5 ± 23.8(a)</td>
<td>390.3 ± 90.5(a)</td>
</tr>
<tr>
<td>PQ + PVP</td>
<td>52.0 ± 6.2(a)</td>
<td>238.2 ± 18.6</td>
<td>345.5 ± 17.1(a)</td>
</tr>
<tr>
<td>PQ + BDS</td>
<td>28.4 ± 10.2(a)</td>
<td>188.1 ± 19.4(a)</td>
<td>272.8 ± 20.3</td>
</tr>
<tr>
<td>PQ + TDS</td>
<td>19.1 ± 3.2(a)</td>
<td>255.3 ± 24.8</td>
<td>290.9 ± 12.2</td>
</tr>
<tr>
<td>Normal</td>
<td>27.6 ± 7.2(a)</td>
<td>187.9 ± 17.6(a)</td>
<td>211.3 ± 20.2</td>
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</table>

The animals were orally treated simultaneously with PQ at 50 mg/kg and one of the test compounds at 500 mg/kg. a, b) Significantly different from the PQ only at p < 0.05 and p < 0.01, respectively. c, d) Significantly different from the normal at p < 0.05 and p < 0.01, respectively.
combination of PQ with a test compound.

BDS and TDS were less effective in suppressing PQ absorption from the rat small intestine than DS, GS or PVP. However, BDS and TDS were more effective in depressing synthesis of lipid peroxide than DS or GS. This indicates that both BDS and TDS have activity to reduce synthesis of lipid peroxide independent of the level of PQ.

DISCUSSION

Our previous studies on detoxification of PQ poisoning with carbohydrate sulfates in mice and rats revealed that carbohydrate not having a sulfate group such as glucose, sucrose or dextran failed to alleviate the poisoning. Introduction of sulfate groups into the molecule brought about potent activity to lessen PQ toxicity. The high molecular weight DS and the low molecular weight GS exhibit a very similar effect on the absorption and excretion of PQ in rats. This effect is dependent on the proportion of sulfate groups in the carbohydrate molecule rather than on the molecular weight.  

In the present study, high molecular polyvinyl sulfate (PVS) or sulfonate (PVS), and low molecular alkyl-disulphonate (PDS, BDS, TDS and EDS) were effective in alleviating acute toxicity of PQ in mice, as were DS, SS and GS.  

The survival rate for animals receiving PQ at 200 mg/kg alone was increasingly improved when the dose of antides was increased from 2 to 10 times the dose of PQ (400 to 2000 mg/kg), demonstrating the alleviation of PQ poisoning (Table 1). This activity is somewhat low with EDS, which was the smallest in molecular size among the test compounds; only 20% of animals receiving EDS at 400 mg/kg were alive 14 days after the treatment. At the same dose, PDS, BDS and TDS achieved survival rates of 40–50% with increase in the number of carbon atoms. The rate was as high as 90% for animals receiving high molecular weight PVP or PVS with PQ, indicating that the molecular size affects the activity. When the dose was increased to 8 to 10 times the dose of PQ (200 mg/kg), all test compounds except EDS achieved a 100% survival rate. In contrast, MS, OS, having only one sulfate group, failed to improve survival of mice even when dosed orally simultaneously with PQ in a dose of 1 to 2 times larger than the PQ dose. ISA with one sulfonate group and one hydroxyl group was also ineffective.

The efficacy was attenuated as the dosing interval after PQ was prolonged (Table 2). As shown by our previous gel-filtration study with DS and GS, PQ is associated with the interaction between its pyridinium cation and the sulfate anion of DS or GS. This association, providing PQ incorporated in molecules having sulfate or sulfonate groups, hindered the absorption of PQ. This effect was greater with PVP and PVS which have greater molecular weight than it was with PDS, BDS, TDS or EDS. This difference in efficacy arising from difference in molecular size was clearly shown in studies on the compounds’ effects on gastrointestinal absorption during in situ perfusion. When a segment of the intestine was perfused in situ with a solution of PQ containing either BDS or TDS, the suppression of absorption of PQ was less than that produced with PVP (Fig. 1). When these test compounds were mixed with PQ and orally dosed, they improved LD50 in mice consistent with results of other experiments; namely, increase in the ratio of test compound to PQ increased the LD50 value of PQ (Table 3). MS and OS, both of which have only one sulfate group in the molecule, were not effective, although the pyridinium cation of PQ was able to associate with their sulfate anion, possibly because the association made them more lipophilic due to the absence of another anion group in the alkylchain. This increased lipophilicity may have facilitated absorption of the complex of PQ. It is likely that ISA suppressed absorption only slightly because the complex of ISA and PQ is weakly hydrophilic due to no hydroxyl group being involved in the molecular association. It is estimated that modification of solubility, as well as the increased molecular size due to the association plays an important role in the detoxification mechanism.

The lipid peroxide concentrations in organs rose in rats receiving PQ (Table 4). This rise in lungs was suppressed by concomitant administration of a test compound (BDS, TDS or PVP). Those (DS, GS or PVP) having potent inhibitory activity against intestinal absorption of PQ were less effective in suppressing the formation of lipid peroxide except for PVP. The difference in suppression of lipid peroxide formation may be related to the difference in absorption of test compounds; BDS and TDS, small in molecular size, may be absorbed along with PQ or separately and inhibit peroxidation of lipid in organs, while carbohydrate sulfates and the high molecular weight alkylsulfate PVP, which are little absorbed if at all, had difficulty blocking absorption of PQ completely and allowed some absorbed PQ molecules to exert the action to form lipid peroxide in lungs. Therefore, the suppression and suppressing tendency of lipid peroxide in lungs based on PVP and DS or GS seems to be dependent on the inhibition of PQ-absorption from the intestine. In liver, BDS significantly decreased the TBA value caused by PQ to a normal level, and other test compounds (DS, PVS and TDS) except for GS also tended to decrease the value. In kidneys, the lipid peroxide concentration did not indicate significant difference between normal and PQ alone-treated rats. This efficiency was the most evident in lungs abundant in oxygen because active oxygen generated by the action of the PQ radical contributes to the formation of lipid peroxide. This suggests that BDS and TDS have a potent effect on the PQ radical or active oxygen generated by the radical. Consequently, the suppression of the formation of lipid peroxide based on BDS and TDS may be attributed to their abilities as scavenger for active oxygen or PQ radical. If the treatment with these test compounds is delayed, some PQ molecules are absorbed; this means that fewer animals will be saved even if PQ absorption is inhibited by the treatment. Of mice receiving BDS or TDS 30 min after PQ, however, as many as 50% were alive (Table 2). This rate was 60% in mice receiving TDS 60 min after PQ. The effects of these treatments on the PQ radical or active oxygen, and on the association with PQ and the low molecular sulfonate (BDS and TDS), in body fluid and tissue, may account for their
higher than expected survival rates. BDS and TDS were nevertheless more effective in depressing synthesis of lipid peroxide in lungs than either DS or GS; the LD₅₀ value of PQ treated with BDS or TDS increased only about 3 times that of PQ alone. This fact is consistent with the view²⁷−³⁰ that the mode of early fatality from PQ poisoning cannot be explained only by lung toxicity.

The present study revealed that high molecular polyvinylsulfate (PVP) or sulfonate (PVS), and low molecular alkylsulfonates (PDS, BDS, TDS and EDS) can alleviate the toxicity of PQ. Also, their activity as antidote and the mode of the action varied depending on molecular size. In brief, this work indicates that high and low molecular size alkylsulfate or sulfonate salts having more than one sulfate or sulfonate group in an alkyl chain unit may be able to alleviate PQ poisoning, as can carbohydrate sulfate.

The main mechanism for the detoxification must be suppression of PQ absorption from the intestine. A low molecular alkylsulfonate was also proved to be effective in suppressing the formation of lipid peroxide in lungs. A study on the radical scavenger of alkylsulfonates will be reported in the next paper.

REFERENCES