Abnormalities in Cadmium Fluoride Kinetics in Serum, Bile, and Urine after Single Intravenous Administration of Toxic Doses to Rats

Tomotaro Dote, Kazuya Adachi, Emi Yamadori, Masafumi Imanishi, Hiroshi Tsuji, Eri Tanida and Koichi Kono

Department of Hygiene and Public Health, Osaka Medical College, Japan

Abstract: Abnormalities in Cadmium Fluoride Kinetics in Serum, Bile, and Urine after Single Intravenous Administration of Toxic Doses to Rats: Tomotaro Dote, et al. Department of Hygiene and Public Health, Osaka Medical College—Cadmium fluoride (CdF₂, CdF for short) is the most lethal and hepatotoxic of all Cd-containing compounds. The toxic effects of CdF appear to depend on its detoxification and elimination. This study was designed to determine the early dynamics of the absorption, systemic distribution, and metabolism of CdF. The kinetics of cadmium and fluoride were investigated in the blood, bile, and urine of rats as a model of accidental occupational exposure to CdF. The serum concentration-time profiles measured after intravenous CdF (1.34, 2.67 or 4.01 mg/ per kg body weight) administration were analyzed by compartmental modeling using the WinNonlin program. Bile and urine were collected for 300 min after the administration. The kinetic profiles indicate that the clearance of Cd was diminished in the 2.67 and 4.01 mg/kg groups, leading to a persistently high serum Cd level. The mean total biliary excretions of Cd in the 2.67 and 4.01 mg/kg groups were significantly higher than that in the 1.34 mg/kg group. The abnormal kinetics of Cd was attributable to severe hepatic injury that diminished the capacity for Cd accumulation. The elimination of serum F was delayed in the 4.01 mg/kg group. The mean urinary F excretion amount was not significantly higher in the 4.01 mg/kg group than in the 2.67 mg/kg group. The abnormal kinetics of F was attributable to nephrotoxicity that diminished its elimination from the kidney.

(J Occup Health 2008; 50: 339–347)

Key words: Cadmium fluoride, Acute exposure, Toxicokinetics, Blood, Bile, Urine

Cadmium fluoride (CdF₂, CdF) is a white crystalline compound that is highly heat resistant (melting point: 1,100°C). It is used as an insulator of super high-speed, mass telecommunications equipment. Because CdF particles are released into the air during the manufacturing process, there is a considerable risk that industrial workers will inhale them. With a solubility of 4.3 g/100 ml in water (25°C), CdF dissolves readily in blood; thus, there is the possibility that acute exposure can cause harmful systemic effects. It is therefore necessary from the viewpoint of occupational health management to investigate the harmful effects of CdF. In our previous study, we determined the lethal dose of CdF after intravenous administration to rats¹. The dose-response study used three doses of 1.34, 2.67 and 4.01(LD₈₈) mg/ per kg body weight CdF. We reported that the AST and ALT activities measured at 300 min in the 2.67 and 4.01 mg/kg groups were significantly higher than those of rats in the control group¹. The results showed that CdF is the most lethal¹ and hepatotoxic of all Cd-containing compounds, such as cadmium chloride and cadmium nitrate (Cd(NO₃)₂, CdN for short)². We also concluded a dose of 4.01 mg/kg causes renal dysfunction, and acute renal failure was induced at doses higher than 2.67 mg/kg¹. The effects of CdF seemed to arise not only from CdF toxicity but also from the absorption, systemic distribution, and metabolism of CdF. CdF toxicity also depends on the detoxification and elimination of CdF. CdF is ionized into cadmium (Cd) and fluoride (F). The liver is the major organ involved in the metabolism and detoxification of Cd⁵. The biliary excretion of Cd is an important excretory pathway and it is related to fecal and urinary excretion⁴. On the other hand, the kidney is also one of the organs damaged by Cd exposure. F clearance is mainly dependent on renal function⁵,⁶. Therefore, renal injury directly decreases urinary F excretion⁷. Renal and hepatic dysfunctions are directly related to disorders in
CdF metabolism. This study was designed to investigate the early dynamics of Cd and F in the blood, bile, and urine in rats as a model of accidental occupational exposure to CdF. The aims of this study were to determine how widely the kinetics and metabolism of CdF vary with dose and to investigate the relationships between the kinetics and the harmful effects on the liver and kidneys following acute exposure to CdF.

Materials and Methods

Animals and diet

Ten week-old SPF male Sprague-Dawley rats, weighing 300–350 g, were obtained from Japan SLC. They had free access to rat chow (Funabashi Farm MM-3; Funabashi City, Chiba, Japan) and tap water, and they were housed in a separate room at constant temperature (22.0 ± 1.0°C) under a 12-h light/dark cycle. All aspects of this study were conducted under the guidelines recommended by the Osaka Medical College Ethical Association for Accreditation of Laboratory Animal Care.

Chemicals

CdF solution (0.2 g/l) was prepared by dissolving CdF (99% purity, Wako Pure Chemical Industries, Ltd., Osaka, Japan) in 0.9% saline.

Experimental design

1) Exposure

Twenty rats were assigned to four exposure groups (n=5 for each group). All the rats were anesthetized with sodium pentobarbital. Then, CdF and saline (1 ml) were injected through the tail vein using a syringe pump (model PHD 200P; Harvard Apparatus, Inc., Holliston, MA, USA) for 5 min. The serum CdF level is rapidly increased by inhalation compared to dermal exposure, because the particles and the mist of CdF penetrate alveolar-capillary vessel walls remarkably well and are directly absorbed into the blood. Therefore, intravenous injection models the rapid absorption of CdF into the blood, such as occurs in acute inhalation exposure. This study is also a clinical model of acute lethal toxicity. Workers treat the powder and solution of CdF in the manufacturing process and the scraping of CdF products. CdF fly apart in the air as particles and AUC0–∞ decreases of the peripheral compartment was tied off with a silk ligature near the duodenal wall, and the proximal portion was catheterized (24-G indwelling needle; Terumo Corp.). Bile was collected at 30-min intervals for 300 min after the CdF administration.

2) Repeated blood sampling

Under sodium pentobarbital anesthesia, the carotid artery was catheterized (24-G indwelling needle; Terumo Corp., Tokyo, Japan) to obtain blood samples (0.4 ml) from each individual animal 0, 5, 10, 30, 60, 120, and 300 min after the CdF administration.

3) Kinetic analysis

The serum concentration-time profiles of Cd and F measured after intravenous CdF administration were analyzed by compartmental modeling using a nonlinear, least squares regression program (WinNonlin; Pharsight Corp., Cary, NC). The WinNonlin program calculates model predictions using standard equations. The best fits of the Cd and F data were obtained using a two-compartment and a one-compartment model, respectively, with a 1/(Y) iterative weighting scheme, where Y is the serum concentration predicted using the model. The two-compartment parameter estimated from the regression analysis included the half-life of Cd in the α phase (T1/2α), the half-life of Cd in the β phase (T1/2β), the apparent volume of distribution at the steady state (Vss), the rate constant for Cd transfer from the central to the peripheral compartment (Kc1), the rate constant for Cd return from the peripheral to the central compartment (K1c), the elimination rate constant from the central compartment (K10), and the mean residence time (MRT). The apparent volume of the peripheral compartment (Vp) was calculated as Vp = V1 · K12/K12, where V1 is the volume of the central compartment. The one-compartment parameter estimates from the regression analysis included the Vss, K10, and MRT. A noncompartmental modeling method was applied to determine the area under the curve values (AUC0–300 and AUC0–∞).

4) Repeated bile sampling

The bile duct was cannulated as follows. The abdomen was opened by midline incision, and the bile duct was isolated by following the portal vein up to the median hepatic lobe. The distal portion of the bile duct was tied off with a silk ligature near the duodenal wall, and the proximal portion was catheterized (24-G indwelling needle; Terumo Corp.). Bile was collected at 30-min intervals for 300 min after the CdF administration. Volume, specific gravity, and Cd and F concentrations were determined. The experiments were started at 9:00 a.m. to exclude the
effects of circadian rhythm on bile formation\textsuperscript{9}).

5) Urine sampling
Twenty rats were assigned to one of four groups (n=5 for each group). All the rats were anesthetized with sodium pentobarbital. CdF (1.34, 2.67 or 4.01 mg/kg) or saline was injected as described above. After the administration, saline was administered for 2 h (3 ml/h) to ensure an adequate urine volume. Urine was accumulated for 300 min after the administration and was obtained via an indwelling catheter (18-G indwelling needle; Terumo Corp.). Catheters were inserted at a 20° angle. Urinary volume, specific gravity, and urine Cd and F concentrations were determined.

6) Cd and F measurement
Cd concentrations in the serum, bile, and urine were analyzed by atomic absorption spectrometry (AAS 180–80; Hitachi, Ltd., Tokyo, Japan). The F concentration was determined by the F selective electrode method (Orion Model 720 AQ). The total Cd and F excretion amounts were calculated taking into consideration the differences in bile and urine volumes.

Statistical analysis
Data are expressed as mean ± SD. Statistical analyses were performed using SPSS (SPSS Inc., Chicago, IL, USA). \( p<0.05 \) was considered statistically significant. Overall differences among the groups were evaluated by one-way ANOVA. When the results obtained by one-way ANOVA were found to be significant, the differences between individual groups were evaluated by Fisher’s protected least significant difference (LSD) test.

Results
The changes in serum Cd concentration are shown in Fig. 1. The mean serum Cd concentrations in the 1.34, 2.67, and 4.01 mg/kg groups were 4,600, 5,600 and 6,500 µg/l at 5 min, 1,348, 2,029 and 2,510 µg/l at 30 min, and 130, 170 and 370 µg/l at 300 min, respectively. The mean serum Cd concentrations of all the groups differed significantly from that of the control group at 300 min. Although the mean serum Cd concentrations of the 2.67 mg/kg group did not differ significantly from those of the 1.34 mg/kg group at 60, 120 and 300 min, they significantly differed at 30 min. The best fits of the Cd data were obtained using a two-compartment model. The kinetic parameters of Cd are shown in Table 1. The means of \( T_{1/2} \) of the 2.67 and 4.01 mg/kg groups increased compared with those of the 1.34 mg/kg group. The means of \( K_12 \) and \( K_21 \) of the 2.67 mg/kg group were lower than those of the 1.34 mg/kg group. The mean of \( K_{10} \) of the 4.01 mg/kg group was lower than that of the 1.34 mg/kg group. The changes in serum

Fig. 1. Serum concentrations of cadmium (Cd) at 5, 10, 30, 60, 120, and 300 (min) after a single intravenous injection of CdF (1.34, 2.67, or 4.01 mg/kg) or saline. Mean ± SD; n=5. The serum concentration axis is logarithmic. *\( p<0.05 \) 1.34 mg/kg group vs. 4.01 mg/kg group, †\( p<0.05 \) 1.34 mg/kg group vs. 2.67 mg/kg group by ANOVA Fisher’s protected LSD.
F concentrations are shown in Fig. 2. The mean serum F concentrations in the 1.34, 2.67, and 4.01 mg/kg groups were 480, 720 and 1,120 µg/l at 5 min, and 26, 44 and 136 µg/l at 300 min, respectively. Those of the 1.34 and 2.67 mg/kg groups did not differ significantly from that of the control group at 300 min. The best fits of the F data were obtained using a one-compartment model. The kinetic parameters of F are shown in Table 2. The means of Vss did not differ significantly among the three dosage groups. The mean of K10 of the 4.01 mg/kg group was lower than that of the 2.67 mg/kg group. The mean of MRT of the 4.01 mg/kg group was higher than that of the 2.67 mg/kg group.

The means of AUC0→300 and AUC0→∞ of the 4.01 mg/kg group were significantly higher than those of the 1.34 and 2.67 mg/kg groups. The mean volumes of bile at

<table>
<thead>
<tr>
<th>Parameter</th>
<th>1.34</th>
<th>2.67</th>
<th>4.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1/2α (min)</td>
<td>8.9 ± 2.0</td>
<td>15.2 ± 5.4*</td>
<td>14.5 ± 4.6</td>
</tr>
<tr>
<td>T1/2β (min)</td>
<td>105 ± 9</td>
<td>240 ± 151</td>
<td>236 ± 156</td>
</tr>
<tr>
<td>Vss (ml/kg)</td>
<td>224 ± 19</td>
<td>557 ± 399</td>
<td>668 ± 303*</td>
</tr>
<tr>
<td>K12 (10−2/min)</td>
<td>4.0 ± 1.4</td>
<td>2.0 ± 0.3*</td>
<td>2.6 ± 1.3</td>
</tr>
<tr>
<td>K13 (10−2/min)</td>
<td>1.8 ± 0.4</td>
<td>0.9 ± 0.4*</td>
<td>1.4 ± 0.8</td>
</tr>
<tr>
<td>K10 (10−2/min)</td>
<td>3.0 ± 0.5</td>
<td>2.4 ± 1.0</td>
<td>1.7 ± 0.9*</td>
</tr>
<tr>
<td>MRT (min)</td>
<td>107 ± 10</td>
<td>233 ± 179</td>
<td>260 ± 185</td>
</tr>
<tr>
<td>V1 (ml/kg)</td>
<td>72 ± 17</td>
<td>145 ± 45</td>
<td>215 ± 105*</td>
</tr>
<tr>
<td>V2 (ml/kg)</td>
<td>152 ± 5</td>
<td>412 ± 365</td>
<td>453 ± 288</td>
</tr>
<tr>
<td>AUC0→300 (min · µg/ml)</td>
<td>195 ± 21</td>
<td>240 ± 21*</td>
<td>347 ± 25*</td>
</tr>
<tr>
<td>AUC0→∞ (min · µg/ml)</td>
<td>214 ± 24</td>
<td>271 ± 37</td>
<td>444 ± 89*</td>
</tr>
</tbody>
</table>

Mean ± SD; n=5; *p<0.05 vs. 1.34 mg/kg group by ANOVA Fisher’s protected LSD. A two-compartment model was used with 1/(Ŷ)² weighting, where Ŷ is the serum cadmium concentration predicted using the model. AUC was calculated using a noncompartmental modeling method.

Fig. 2. Serum concentrations of ionized fluoride (F) at 5, 10, 30, 60, 120, and 300 (min) after a single intravenous injections of CdF₂ (1.34, 2.67, or 4.01 mg/kg) or saline. Mean ± SD; n=5. The serum concentration axis is logarithmic. *p<0.05 vs. 1.34 mg/kg group †p<0.05 vs. 2.67 mg/kg group by ANOVA Fisher’s protected LSD.
each interval were 0.59 ml in the control group and 0.39 ml in the CdF treated groups. During the 300 min after the CdF administration, the mean bile volume decreased significantly compared with that of the control group (Table 3). The changes in biliary Cd secretions are shown in Fig. 3. Biliary Cd secretion occurred mainly after early exposure, and the amount excreted decreased gradually after 120 min. The means of the secretion amounts determined until 120 min and 300 min were, respectively, 11 and 15 µg for the 1.34 mg/kg group, 74 and 120 µg for the 2.67 mg/kg group, and 92 and 142 µg for the 4.01 mg/kg group. The means of the total biliary Cd secretion amounts were significantly higher in the 2.67 and 4.01 mg/kg groups than in the 1.34 mg/kg group. The changes in biliary F secretions are shown in Fig. 4. The means of the excretion amounts determined until 60 min and 300 min were, respectively, 0.17 and 0.31 µg for the 1.34 mg/kg group, 0.62 and 1.00 µg for the 2.67 mg/kg group, and 0.86 and 1.41 µg for the 4.01 mg/kg group. Approximately 55–60% of the total F was secreted by 60 min in all the three groups. The urine volume and urinary Cd and F excretions are shown in Table 3. The mean urine volumes were significantly lower in all the three CdF administration groups than in the control group. The mean urinary Cd excretion amount was significantly higher in the 4.01 mg/kg group than in the other treated groups. The mean urinary F excretion amount was not significantly higher in the 4.01 mg/kg group than in the 2.67 mg/kg group. The emission rates (%) of Cd and F are shown in Table 4. The mean ratio of excretion rates were 4.4, 18.1 and 14.2 %. The means of the biliary Cd emission rates were significantly higher in the 2.67 and 4.01 mg/kg groups than in the 1.34 mg/kg group. On the other hand, the mean ratios of non-biliary rates were 95.6, 81.9 and 85.8 % for the 1.34, 2.67 and 4.01 mg/kg groups, respectively. The ratio of the doses was 1:2:3. Therefore, the ratio of non-biliary Cd was 1:1.7: 2.7. The means of the urinary Cd emission rates were apparently lower than those of the biliary Cd and they did not differ among the three groups. The means of biliary F emission rates were apparently lower than those of urinary F and they did not differ among the three groups. The means of the urinary F emission rates were significantly lower in the 4.01 mg/kg group than in the 1.34 and 2.67 mg/kg groups.

**Discussion**

High concentrations of serum Cd persisted during the early stage of exposure. Thus, Cd was gradually eliminated from the serum and distributed widely to the other areas, particularly in the 4.01 mg/kg group. T Vss, MRT, and AUC0→300 increased and K10, K21, and K12 decreased in the 2.67 and 4.01 mg/kg groups to a greater

---

**Table 2.** Kinetic parameters calculated from serum ionized fluoride concentrations 5, 10, 30, 60, 120, and 300 min after a single intravenous injection of CdF (1.34, 2.67 or 4.01 mg/kg)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Dose (mg/kg)</th>
<th>1.34</th>
<th>2.67</th>
<th>4.01</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vss (ml/kg)</td>
<td>1.225 ± 590</td>
<td>1.510 ± 498</td>
<td>1.469 ± 243</td>
<td></td>
</tr>
<tr>
<td>K10 (10–2/min)</td>
<td>1.0 ± 0.2</td>
<td>1.0 ± 0.2</td>
<td>0.8 ± 0.1†</td>
<td></td>
</tr>
<tr>
<td>MRT (min)</td>
<td>108 ± 24</td>
<td>99 ± 17</td>
<td>130 ± 21†</td>
<td></td>
</tr>
<tr>
<td>AUC0→300 (min · µg/ml)</td>
<td>54 ± 26</td>
<td>61 ± 23</td>
<td>104 ± 27‡†</td>
<td></td>
</tr>
<tr>
<td>AUC0→∞ (min · µg/ml)</td>
<td>57 ± 25</td>
<td>66 ± 25</td>
<td>131 ± 44‡†</td>
<td></td>
</tr>
</tbody>
</table>

Mean ± SD; n=5; †p<0.05 vs. 1.34 mg/kg group ‡p<0.05 vs. 2.67 mg/kg group by ANOVA Fisher’s protected LSD. A one-compartment model was used with 1/(Y)² weighting, where Y is the serum cadmium concentration predicted using the model. AUC was calculated using a non-compartment modeling method.

**Table 3.** Bile volume, urine volume and excretions of cadmium (Cd) and ionized fluoride (F) 5 h after a single intravenous injection of saline or CdF (1.34, 2.67, 4.01 mg/kg)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Saline</th>
<th>1.34 mg/kg</th>
<th>2.67 mg/kg</th>
<th>4.01 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bile volume (ml)</td>
<td>5.9 ± 1.1</td>
<td>3.8 ± 1.0 *</td>
<td>4.2 ± 0.9 *</td>
<td>3.7 ± 0.7 *</td>
</tr>
<tr>
<td>Urine volume (ml)</td>
<td>3.45 ± 0.4</td>
<td>1.85 ± 0.3 *</td>
<td>1.62 ± 0.5 *</td>
<td>1.23 ± 0.5 *</td>
</tr>
<tr>
<td>Cd in urine (µg)</td>
<td>0.003 ± 0.001</td>
<td>0.137 ± 0.072</td>
<td>0.131 ± 0.051</td>
<td>0.225 ± 0.14‡†</td>
</tr>
<tr>
<td>F in urine (µg)</td>
<td>2.5 ± 0.7</td>
<td>30.41 ± 4.2</td>
<td>50.8 ± 31.5</td>
<td>41.7 ± 7.7</td>
</tr>
</tbody>
</table>

Mean ± SD; n=5, One-way ANOVA, Fisher’s protected LSD; *p<0.05 vs. saline group; †p<0.05 vs. CdF (2.67 mg/kg group).
Fig. 3. Change in biliary cadmium secretion after a single intravenous injection of CdF (1.34, 2.67, or 4.01 mg/kg) or saline. Mean ± SD; n=5 *p<0.05 vs. 1.34 mg/kg group †p<0.05 vs. 2.67 mg/kg group by ANOVA Fisher’s protected LSD.

Fig. 4. Change in biliary ionized fluoride secretion after a single intravenous injection of CdF (1.34, 2.67, or 4.01 mg/kg) or saline. Mean ± SD; n=5 *p<0.05 vs. 1.34 mg/kg group †p<0.05 vs. 2.67 mg/kg group by ANOVA Fisher’s protected LSD.
degree than in the 1.34 group. These kinetic profiles indicate that the clearance of Cd was diminished in the 2.67 and 4.01 mg/kg groups, leading to a persistently high serum Cd level. There were no significant changes in serum Cd concentrations between the doses of 1.34 mg/kg and 2.67 mg/kg at 60, 120, and 300 min. However, the mean serum Cd concentrations in the 1.34 and 2.67 mg/kg groups were 1.348 and 2.029 µg/ml at 30 min, and were significantly higher in the 2.67 mg/kg group than in the 1.34 mg/kg group. Kinetic parameters would have been strongly affected by high concentrations of Cd at 30 min rather than by low concentrations at 60, 120, and 300 min. These results suggest that the 2.67 and 4.01 mg/kg groups were less able to metabolize serum Cd than the 1.34 mg/kg group. Severe hepatocellular injury was also induced at the dose of 4.01 mg/kg, as AST and ALT activities were greater than 1,500 IU/l in rats injected with this dose 1. Therefore, the elimination of serum Cd was delayed by hepatic dysfunction.

Serum F concentrations attenuated unexponentially in all the groups. They recovered to the control level in the 1.34, and 2.67 mg/kg groups. The means of Vss did not differ significantly among the three dosage groups, indicating that serum F was almost eliminated 300 min after CdF administration. However, Kow decreased and MRT and AUC increased in the 4.01 mg/kg group. We previously reported that BUN was significantly higher in the 4.01 mg/kg group than in the control group 1. Therefore, the elimination of serum F was delayed by renal dysfunction in the 4.01 mg/kg group. The mean bile volumes of all the CdF-treated groups were significantly less than that of the control. It was reported that during the 300 min after CdN administration, bile flowed constantly, at a mean rate of 1.5 ml/h and there were no significant differences among the mean bile emission rates of the CdN 2.1, 4.2 or 6.3 mg/kg groups in which the Cd concentrations were 1.0, 2.0, and 3.0 mg/kg, respectively 10). In a previous study, we concluded that CdF causes severe hepatocellular injury, compared to other Cd compounds, such as CdCl2 or CdN, on the basis of the biochemical findings. We suggest that in the present study the bile volume was decreased due to the severe hepatotoxicity of CdF, because it was reported that a high concentration of Cd caused a rapid decrease in bile flow within 40 min in isolated perfused livers of rats 11). The hepatotoxicity of CdF is stronger than that of CdN at the same Cd concentration. Therefore, the severe hepato-dysfunction caused by CdF might be due to cholestasis.

Although biliary secretion of Cd slowly increased in the 1.34 mg/kg group, it apparently increased in the 2.67 and 4.01 mg/kg groups as shown by their time courses. The mean total biliary excretions of Cd in the 2.67 and 4.01 mg/kg groups were more than eight-fold that in the 1.34 mg/kg group. The mean of the biliary Cd emission rates were significantly higher in the 2.67 and 4.01 mg/kg groups than in the 1.34 mg/kg group.

The biliary excretion of Cd is regulated by the Cd-binding capacity of liver proteins 12). It has been proposed that Cd induces the synthesis of metallothionein(MT), which is then stored in the liver as a non-toxic Cd-MT complex 13). It has also been suggested that Cd is detoxified by MT isoform 1, one of four isoforms 14, 15). Therefore, if the liver were exposed to Cd beyond its accumulation capacity, the excess Cd would thus be available for biliary excretion. The relationship between time and excretion indicates that the Cd was eliminated through bile in the 2.67 and 4.01 mg/kg groups. However, most Cd might have been retained in liver, because the ratio of non-biliary Cd was 1:1.7: 2:7. Furthermore, it was also reported that Cd is involved in oxidative stress and the collapse of mitochondrial membrane potential 16). In a previous report, it was shown that the activities of mitochondrial AST were markedly high after i.v. administration of CdF at 4.01 mg/kg 17). Therefore, severe hepatic injury might also diminish the liver’s capacity for Cd accumulation and detoxification.

The means of biliary F emission rates were apparently lower than those of the urinary F. Biliary F was dose-dependently excreted. It was reported that F has little hepatotoxicity 7). It was also reported that the elimination of F is mainly dependent on the kidney 17). Therefore, the relationship between time and excretion indicates that F is directly eliminated through bile regardless of hepatic

<table>
<thead>
<tr>
<th></th>
<th>1.34 mg/kg</th>
<th>2.67 mg/kg</th>
<th>4.01 mg/kg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cd</td>
<td>4.4 ± 1.9</td>
<td>18.1 ± 4.3*</td>
<td>14.2 ± 1.7*</td>
</tr>
<tr>
<td>Urine</td>
<td>0.04 ± 0.02</td>
<td>0.02 ± 0.004</td>
<td>0.02 ± 0.01</td>
</tr>
<tr>
<td>F</td>
<td>0.28 ± 0.13</td>
<td>0.45 ± 0.08</td>
<td>0.42 ± 0.04</td>
</tr>
<tr>
<td>Urine</td>
<td>27.4 ± 3.8</td>
<td>22.9 ± 14.2</td>
<td>12.5 ± 2.3*</td>
</tr>
</tbody>
</table>

Mean ± SD; n=5, One-way ANOVA, Fisher’s protected LSD; *p<0.05 vs. CdF (1.34 mg/kg group).
Conclusions

The mean urinary volumes of all the CdF-treated groups were significantly less than that of the control. In our previous study, we reported that urine volume apparently decreased in CdF-treated groups. Additionally, it has been reported that urine volume decreases and BUN and serum creatinine increases 5 h after the intravenous administration of CdN (3 Cd mg/kg)\(^1\). It has also been reported that BUN and serum creatinine considerably increase after the intravenous administration of CdCl\(_2\) (CdL) (2.1 Cd mg/kg)\(^2\). The hypouria seen in all the CdF-treated groups might indicate a more severe renal dysfunction is caused by CdF than by CdN or CdL. The mean urinary Cd excretion amount was significantly higher in the 4.01 mg/kg group than in the other treated groups. The means of urinary Cd emission rates were lower than those of biliary Cd, suggesting that Cd was distributed primarily in the liver. Therefore, Cd is either stored in the liver as a Cd-MT complex or transported via the blood to the kidneys, where it may accumulate in the lysosomes of the proximal tubules\(^5\). In a previous study, we observed proximal tubular damage after acute exposure to CdF at 4.01 mg/kg. Cd may be removed from injured proximal tubular cells or directly eliminated without accumulation in damaged lysosomes. The mean urinary F excretion amount was not significantly higher in the 4.01 mg/kg group than in the 2.67 mg/kg group. The means of urinary F emission rates were significantly lower in the 4.01 mg/kg group than in the 1.34 and 2.67 mg/kg groups. Our previous study showed that BUN was significantly higher after i.v. administration of CdF at 4.01 mg/kg than in the control group, and that serum creatinine slightly increased and creatinine clearance slightly decreased as well\(^5\). It has also been confirmed that F metabolism is strongly associated with the glomerular filtration rate\(^6\). Therefore, the disorder of F excretion would be attributable to the glomerular dysfunction in the 4.01 mg/kg group. Although the kidney is also a target of F toxicity, we previously reported that the dosage of F in CdF (≤4.01 mg/kg) had little toxic effect on renal function\(^5\). It is also well known that Cd induces renal injury\(^7\), which is mainly caused by the nephrotoxicity of the Cd contained in CdF.

**Conclusions**

The serum kinetics of Cd are considerably disturbed and the biliary excretion of Cd increases after acute CdF exposure beyond the accumulation capacity of the liver. Furthermore, the abnormalities in Cd kinetics are accelerated by extensive hepatic dysfunction. F clearance from serum was relatively delayed in the high-dose group. F metabolism is mainly dependent on renal function. Therefore, urinary F excretion is disturbed and F is retained in the extravascular space owing to CdF nephrotoxicity.

**References**


