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Strong Acute Toxicity, Severe Hepatic Damage, Renal Injury and Abnormal Serum Electrolytes after Intravenous Administration of Cadmium Fluoride in Rats

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Abstract: Strong Acute Toxicity, Severe Hepatic Damage, Renal Injury and Abnormal Serum Electrolytes after Intravenous Administration of Cadmium Fluoride in Rats: Kazuya ADACHI, *et al.* Department of Hygiene and Public Health, Osaka Medical College—Cadmium fluoride (CdF) is commonly used as an insulator for ulta high speed mass telecommunications equipment, and there is a considerable risk that industrial workers will inhale CdF particles. Despite the possibility that acute exposure can cause harmful systemic effects, there are no studies to date that address the health consequences of acute CdF exposure. This study therefore aimed to determine the acute lethal dose of CdF and its effects on various target organs, including the liver and kidney. We also determined the effect of CdF on serum electrolytes and acid-base balance. The effective lethal dose was determined and dose-response study was conducted after intravenous administration of CdF in rats. The 24 h LD_{50} of CdF was determined to be 3.29 mg/kg. The dose-response study used doses of 1.34, 2.67, 4.01 mg/kg CdF. Saline or sodium fluoride solution were used for controles. Severe hepatocellular injury was induced at doses greater than 2.67 mg/kg, as demonstrated by AST and ALT activities greater than 1,500 IU/*l* in rats injected with a dose of 4.01 mg/kg. Acute renal failure was induced at doses greater than 2.67 mg/kg. Decreased serum Ca, increased serum K and metabolic acidosis were induced at a dose of 4.01 mg/kg. Decreased serum Ca was caused by exposure to ionized F. CdF has the strongest lethal and hepatic toxicity among all Cd containing compounds.
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Key words: Cadmium fluoride, Hepatic injury, Hyperkalemia, Hypocalcaemia, Metabolic acidosis, Kidney dysfunction

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Cadmium (Cd) is a soft, ductile, silver-white, electropositive metal. Cd commonly exists in the +2 valence state, and can exist in compounds that have diverse physical and chemical properties[1]. Cd compounds have many applications in the electronics industry. For example, cadmium chloride ($CdCl_2$) and cadmium nitrate (Cd $(NO_3)_2$, CdN), which both dissolve easily in water, are commonly used in the production of rechargeable batteries, specifically in the production of Ni-Cd batteries[2]. Cadmium oxide (CdO), which does not dissolve easily in water, conducts electricity well and is highly resistant to heat. It is therefore commonly used as an electric contact material in the manufacture of electronic circuits. Cadmium fluoride (CdF_2, CdF) is a white crystalline material that is highly heat resistant (Melting point: 1,100°C), and it is used in a solid state as an insulator in ultra high speed, mass telecommunications equipment.

Since 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 m*l* in water (25°C), CdF dissolves readily in blood, and there is thus the possibility that acute exposure could cause harmful systemic effects. It is believed that specific toxicities are caused by combination effects of dissociated Cd, ionized F and CdF.

Research on Cd toxicity has most often focused on $CdCl_2$ and CdO. There are reports indicating that $CdCl_2$ can cause acute hepato- and nephro-toxicity and that CdO can cause acute lung disorders[3, 4]. Research on fluoride (F) toxicity has most often used on NaF, and previous reports indicate that ionized F causes acute renal tubular injury[5]. To date, however, there are no studies that have addressed the harmful effects of acute exposure to Cd, in the form of CdF. This study therefore aimed to determine the acute lethal dose of CdF and the dose-response effects on various target organs, including the liver and kidney. Given that abnormal serum electrolyte and metabolic

acidosis are commonly caused by ionized F exposure, and that metabolic acidosis develops with severe hepatic injury, this study also determined the effect of CdF on serum electrolytes and the acid-base balance.

Materials and Methods

Ten-week-old SPF male Sprague-Dawley rats, weighing 300–350 g, were obtained from Japan SLC. The animals 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.

CdF solutions (0.2 g/*l*) were prepared by dissolving CdF (99% pure, Wako Pure Chemical Industries, Ltd., Osaka, Japan) in 0.9% saline. Sodium fluoride (NaF) solutions (0.1 g/*l*) were prepared by dissolving NaF (99% pure, Wako Pure Chemical Industries, Ltd., Osaka, Japan) in 0.9% saline.

Lethal dose study

Thirty-five (35) rats were assigned to one of seven exposure groups (n = 5 animals per group). All rats were anesthetized with sodium pentobarbital. Seven doses of CdF (2.2, 2.4, 2.8, 3.2, 3.3, 4.0, 5.4 mg/kg) were injected through the tail vein by syringe pump (model PHD 200P; Harvard Apparatus, Inc., MA, USA) for five minutes. A probit dose-mortality curve was created based on mortality at 24 h (Curtis, 2001), and the lethal dose of CdF was determined with the use of SPSS software (Chicago, IL).

Dose-response study with blood samples

The maximum dose was set at 4.01 mg/kg (LD_{88}). Doses of 1.34, 2.67 and 4.01 mg/kg were selected for the dose-response study. The ratios of these doses were 1:2:3. The Cd concentrations were 1.0, 2.0 and 3.0 mg/kg, respectively. Saline or NaF solution was used as control. NaF was used to investigate the effect of F. The dose of NaF was equal to that of F in 4.01 mg/kg CdF. Thirty rats (30) were assigned to one of five exposure groups (6 animals per group). All rats were anesthetized with sodium pentobarbital. Rats were injected with CdF (1.34, 2.67 or 4.01 mg/kg), saline or NaF. Blood samples were obtained from the right carotid artery 5 h after injection. The following serum enzyme activities were measured according to standard protocols: aspartate aminotransferase (AST, ultraviolet method), alanine aminotransferase (ALT, ultraviolet method), mitochondrial asparate aminotransferase (m-AST, malate dehydrogenase enzyme-ultraviolet method), lactate dehydrogenase (LDH, ultraviolet method), LDH isozyme (agarose gel electrophoresis cataphoresis method), and glucose (glucose oxidase method). Liver function was determined from the levels of these serum enzyme activities and glucose (glucose oxidase method). Renal function was determined from the levels of blood urea nitrogen (BUN, urease-glutamic dehydrogenase method) and creatinine (Cr, Jaffe method). The following serum electrolyte levels were determined according to standard protocols: sodium (Na ion-selective electrode method), potassium (K ion-selective electrode method), chloride (Cl ion-selective electrode method), total Ca (OCPC method), P (molybdic acid UV method) and Mg (xylidyl blue colorimetry). The following acid base parameters were also measured: pH, PCO_2, PO_2, HCO_3^-, base excess (BE) and O_2 saturation (O_2 SAT) (288 Blood Gas System; Bayer, Osaka, Japan). Alveoloarterial oxygen difference (A-aDO_2) and anion gap values were calculated.

Dose-response study using urine samples

Twenty-five (25) rats were assigned to one of five groups (n = 5 animals per group). All rats were anesthetized with sodium pentobarbital. CdF (1.34, 2.67 or 4.01 mg/kg), saline or NaF was injected as described above. After injection, saline was administered for 2 h (3 m*l*/h) to ensure adequate urine volume. The urine that accumulated during the 5 hour period after injection was collected from indwelling catheters (18-G indwelling needle; Terumo Corp., Tokyo, Japan). Catheters were inserted at a 20° angle. The following urinary variables were measured: volume, relative density, K, Na, sodium clearance (C_{Na}: urine Na/serum Na × 100), creatinine clearance (Ccr), N-acetyl-β-D-glucosaminidase (NAG; Shionogi Co. Ltd., Osaka, Japan), NAG/Cr (the value of NAG was corrected by Cr because it was apparently affected by urine volume), glucose and ionized F (F ion electrode method). Total activities and weights were calculated, taking into consideration the variations in urine volume.

Pathological observation

Liver and kidney tissues were sampled. They were fixed with formalin solution for 24 h, then stained with hematoxylin and eosin.

Statistical analysis

Data are expressed as means ± SD. Statistical analyses were performed with SPSS software. $p<0.05$ was considered statistically significant. Overall differences between groups were determined by one-way ANOVA. If the one-way ANOVA was significant, then differences between individual groups were estimated by Fisher's protected least significant difference (LSD) test.

Results

All rats in the 2.2 mg/kg group survived for at least 24 h after injection, whereas all the rats in the 5.4 mg/kg group died within 24 h of injection. According to the dose- mortality curve, the LD_{50} and LD_{90} for CdF were

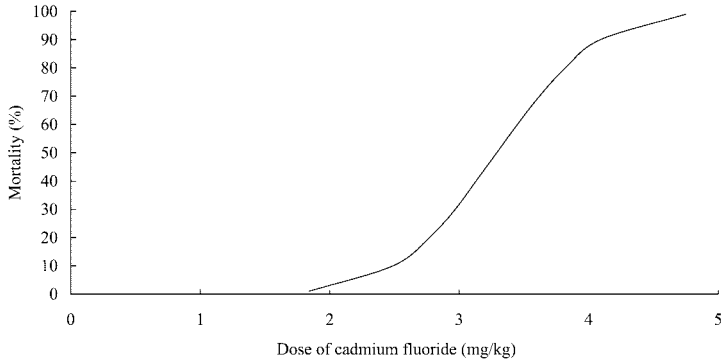

Fig. 1. The dose-mortality curve at 24 h after administration of CdF_2. The curve was based on probit regression analysis.

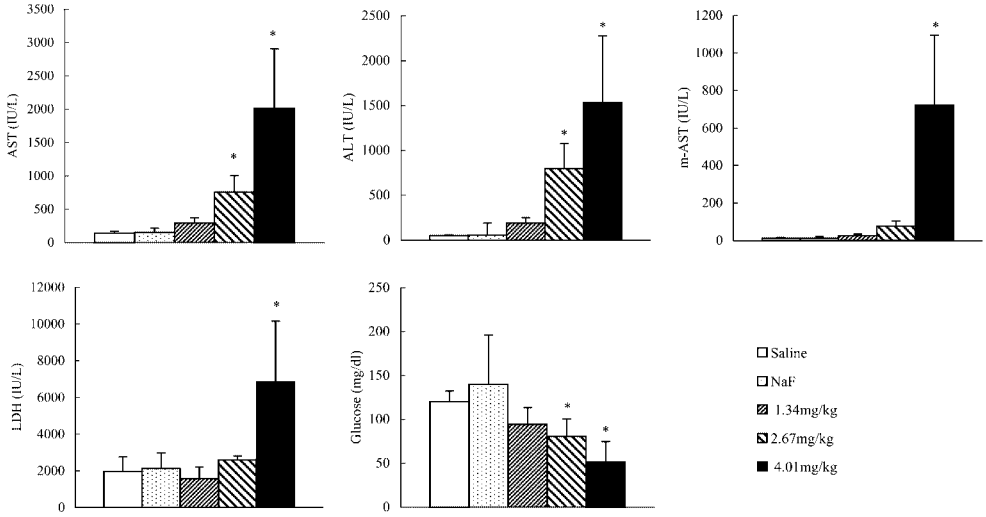

Fig. 2. The values of serum hepatic enzyme activities and glucose at 5 h after a single intravenous injection of saline, NaF (2.23 mg/kg) or CdF_2 (1.34, 2.67, 4.01 mg/kg). Mean ± SD; n=6, One-way ANOVA, Fisher's protected LSD; *p<0.05 vs. saline.

determined to be 3.29 and 4.09 mg/kg, respectively (Fig. 1).

In the CdF treated groups, AST and ALT activities increased in a dose-dependent manner. The AST and ALT activities measured from rats in the 2.67 and 4.01 mg/kg group were significantly higher than from rats in the saline group. Mean values of AST and ALT were more than 1,500 IU/L in the 4.01 mg/kg group. m-AST and LDH did not increase in the 1.34 and 2.67 mg/kg groups, but m-AST and LDH activities in the 4.01 mg/kg group were remarkably higher than those in the other groups. In the CdF treated groups, serum glucose significantly decreased, in a dose-dependent manner, to 50% of the glucose level measured in the saline group. There were no significant differences observed between the saline and the NaF treated group (Fig. 2). LDH_5 isozyme increased in the 4.01 mg/kg group (data not shown).

In the CdF treated groups, BUN increased in a dose-dependent manner. Additionally the BUN levels measured in the 4.01 mg/kg group were significantly higher than the BUN levels measured in the saline group. Serum Cr showed an increasing trend in the 4.01 mg/kg group (Table 1).

In the CdF treated groups, serum K increased in a dose-dependent manner, and serum K in the 4.01 mg/kg group was significantly higher than in the saline group. Serum Ca significantly decreased in the 2.67 and 4.01 mg/kg groups, as compared with the saline group. Serum P significantly increased in the 4.01 mg/kg group, as compared with the saline group. The anion gap slightly increased in the 4.01 mg/kg group (Table 2). There were no considerable changes in Mg in any of the groups (data

Table 1. Serum BUN and Cr at 5 h after a single intravenous injection of saline or CdF2 (1.34, 2.67, 4.01 mg/kg)

		CdF_2 (mg/kg)		
	Saline	1.34	2.67	4.01
BUN (mg/d*l*)	15.9 ± 6.6	17.2 ± 2.6	21.7 ± 1.6	26.8 ± 6.2*
Cr (mg/d*l*)	0.49 ± 0.04	0.42 ± 0.04	0.42 ± 0.04	0.55 ± 0.09

Mean ± SD; n=6; ANOVA; Fisher's protected LSD; *p<0.05 vs. saline.

Table 2. Serum electrolytes at 5 h after a single intravenous injection of saline or CdF_2 (1.34, 2.67, 4.01 mg/kg)

		CdF_2 (mg/kg)		
	Saline	1.34	2.67	4.01
Na (mEq/*l*)	144.8 ± 1.7	144.0 ± 2.1	144.3 ± 0.8	144.8 ± 1.7*
K (mEq/*l*)	4.38 ± 0.44	4.52 ± 0.48	4.62 ± 0.34	5.74 ± 0.68*
Ca (mg/d*l*)	11.9 ± 0.35	11.7 ± 0.08	11.3 ± 0.41*	11.4 ± 0.15*
P (mg/d*l*)	8.4 ± 1.2	9.4 ± 0.5	9.1 ± 0.3	10.0 ± 1.4*
Anion gap (mEq/*l*)	13.5 ± 2.2	13.0 ± 1.8	13.6 ± 1.4	15.1 ± 1.9

Mean ± SD; n=6; ANOVA; Fisher's protected LSD;*p<0.05 vs. saline.

Table 3. Blood gas values at 5 h after a single intravenous injection of saline or CdF_2 (1.34, 2.67, 4.01 mg/kg)

		CdF_2 (mg/kg)		
	Saline	1.34	2.67	4.01
pH	7.38 ± 0.04	7.41 ± 0.04	7.41 ± 0.06	7.37 ± 0.07
PCO_2 (mmHg)	47.6 ± 10.1	43.9 ± 4.2	35.3 ± 5.6*	35.7 ± 11.3*
PO_2 (mmHg)	106.6 ± 29	107 ± 15	126 ± 21	143 ± 53*
HCO_3^- (mmol/*l*)	25.4 ± 1.8	27.4 ± 2.0	21.9 ± 1.1*	20.1 ± 3.5*
BE (mmol/*l*)	0.42 ± 0.78	0.56 ± 1.05	1.98 ± 1.37	4.23 ± 2.05*

Mean ± SD; n=6; ANOVA; Fisher's protected LSD; *p<0.05 vs. saline.

not shown).

There were no significant differences in pH between any group. PCO_2 and HCO_3^- significantly decreased in the 2.67 and 4.01 mg/kg groups compared with the saline group. PO_2 significantly increased in the 4.01 mg/kg group compared with the saline group. BE significantly decreased in the 4.01 mg/kg group compared with the saline group (Table 3). There were also no significant differences observed between the saline group and the NaF treated group (data not shown).

Urine volume decreased in a dose-dependent manner in the CdF treated groups, as compared with the saline group. Urine volume in the 4.01 mg/kg group was approximately three times less than that of the saline group. The urinary F did not increase in a dose-dependent manner in the CdF treated groups. There were no significant differences in urinary F between the CdF

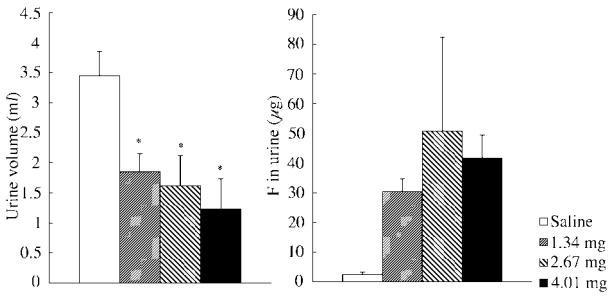

Fig. 3. The urine volume and excretion of F for 5 h after a single intravenous injection of saline, or CdF_2 (1.34, 2.67, 4.01 mg/kg). Mean ± SD; n=5, One-way ANOVA, Fisher's protected LSD; *p<0.05 vs. saline.

Table 4. Urinary excretion values at 5 h after a single intravenous injection of saline or CdF_2 (1.34, 2.67, 4.01 mg/kg)

		CdF_2 (mg/kg)		
	Saline	1.34	2.67	4.01
K (mEq)	0.43 ± 0.1	0.36 ± 0.1	0.22 ± 0.1*	0.19 ± 0.1*
Na (mEq)	0.66 ± 0.1	0.23 ± 0.06*	0.16 ± 0.1*	0.04 ± 0.03*
C_{Na} (m*l*/min)	4.58 ± 0.8	1.61 ± 0.4*	1.12 ± 0.7*	0.26 ± 0.2*
Ccr (m*l*/min)	0.72 ± 0.15	0.81 ± 0.09	0.73 ± 0.21	0.56 ± 0.12
NAG/Cr (U/g)	51.2 ± 9.7	62.6 ± 15	69.2 ± 26	71.2 ± 24*
Glucose (mg)	0.37 ± 0.4	0.37 ± 0.1	1.75 ± 2.5	2.40 ± 2.7

Mean ± SD; n=5; ANOVA; Fisher's protected LSD; *p<0.05 vs. saline.

Table 5. Serum BUN, Cr and electrolytes at 5 h after a single intravenous injection of saline, NaF (2.23 mg/kg) or CdF_2 (4.01 mg/kg)

	Saline	NaF	CdF_2
BUN (mg/d*l*)	15.9 ± 6.6	17.0 ± 2.5	26.8 ± 6.2*
Cr (mg/d*l*)	0.49 ± 0.04	0.53 ± 0.18	0.55 ± 0.09
K (mEq/*l*)	4.38 ± 0.44	4.73 ± 0.22	5.74 ± 0.68*
Ca (mg/d*l*)	11.9 ± 0.35	11.3 ± 0.21*	11.4 ± 0.15*
P (mg/d*l*)	8.4 ± 1.2	10.6 ± 0.8*	10.0 ± 1.4*

Mean ± SD; n=6; ANOVA; Fisher's protected LSD; *p<0.05 vs. saline.

treated groups (Fig. 3).

Excretion of K was significantly lower in the 2.67 and 4.01 mg/kg groups compared with the saline group. Excretion of K in the 4.01 mg/kg group was approximately half of that of the saline group. Na excretion in the CdF treated groups was significantly lower than in the saline group. C_{Na} in the CdF treated groups were significantly lower than in the saline group. Ccr slightly decreased in the 4.01 mg/kg group, and NAG/Cr and urine glucose increased in the 2.67 and 4.01 mg/kg groups compared with the saline group (Table 4). There were no significant differences observed between the saline and the NaF treated group (data not shown).

Table 5 shows serum values of the saline group, the NaF treated group and the CdF treated group. BUN significantly increased in the CdF treated group and showed an increasing trend in the NaF group, when compared with the saline group. Cr slightly increased in the CdF treated group when compared with the saline group. Serum K significantly increased in the 4.01 mg/kg group. Serum K in the NaF treated group slightly increased as compared with the saline group. Serum Ca significantly decreased in the NaF treated group and the 4.01 mg/kg group. Serum P significantly increased in the NaF treated group and the 4.01 mg/kg group.

Fig. 4 shows the urine volume and excretion of F of the saline group, the NaF treated group and the CdF treated group. Urine volume in the CdF treated group significantly decreased compared with the saline group. There were no significant differences in urine volume between the saline group and the NaF treated group. The urinary F in the CdF treated group was significantly decreased compared with the NaF treated group.

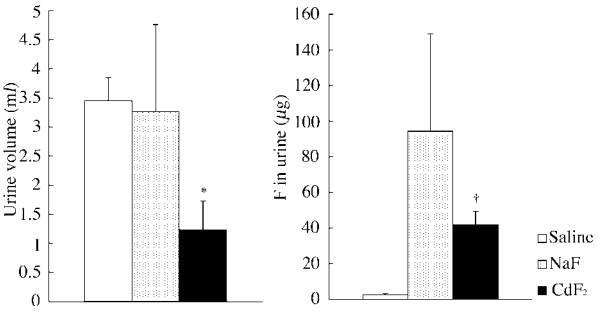

Fig. 4. The urine volume and excretion of F for 5 h after a single intravenous injection of saline, NaF (2.23 mg/kg) or CdF_2 (4.01 mg/kg). Mean ± SD; n=5, One-way ANOVA, Fisher's protected LSD; *p<0.05 vs. saline; †p<0.05 vs. NaF treated group.

The urinary F in the CdF treated group was less than

half of that of the NaF treated group.

The pathological findings were as follows. Lipid droplets in hepatocytes that indicate hepatotoxic manifestations increased in the 2.67 and 4.01 mg/kg CdF groups, and the CdF treated groups caused the increases in hyaline droplets and degeneration of the proximal tubular epithelium compared with the saline group. There were no remarkable differences in glomeruli between any group.

Discussion

The 24 h $LD_{50\ i.v.}$ (rat) of CdO, $CdCl_2$ and CdN have been reported to be 25 mg/kg[6], 5.5 mg/kg and 5.5 mg/kg[7], respectively. The $LD_{50\ i.v.}$ 3.29 mg/kg that we calculated for CdF suggests that CdF may have the strongest toxicity among all Cd compounds.

$CdCl_2$ -induced hepatotoxicity occurs rapidly as evidenced by increased serum aminotransferase activities as early as 1 hr after exposure and increases remarkably until 6 h[11]. The present findings indicated that AST and ALT activities were more than 700 IU/*l* in the CdF 2.67 mg/kg group (2.0 Cd mg/kg) and more than 1,500 IU/*l* in the CdF 4.01 mg/kg group (3.0 Cd mg/kg) at 5 h after CdF injection. Previous studies have reported that the activities of these enzymes are about 300 IU/L at 10 h after injection of $CdCl_2$ (1.9 Cd mg/kg)[8] and about 700 IU/*l* at 5 h after injection of CdN (3.0 Cd mg/kg)[7]. The m-AST and LDH activities in the 4.01 CdF mg/kg group were about 700 IU/*l* and 7,000 IU/*l*, respectively. Similar to the above data on AST and ALT, it has previously been reported that the m-AST and LDH activities were half of those observed after CdF injection at 5 h after intravenous injection of CdN (3.0 Cd mg/kg)[7]. m-AST is an indicator of mitochondrial injury and is an important factor in the clinical assessment of severe liver injury[9]. The large increase in m-AST activity in the 4.01 mg/kg group suggests that severe liver injury occurred in these animals. One possible mechanism of Cd toxicity involves the binding of Cd^{2+} to sulfhydryl groups on critical proteins. This binding contributes to oxidative stress and the collapse of mitochondrial membrane potential[10]. This may explain the remarkable increase in m-AST activity in the 4.01 mg/kg group.

Five hours after injection of CdF, the serum glucose level in the 4.01 mg/kg group (3.0 mg Cd/kg) fell to half the value observed in the saline group. In previous reports, there were no apparent decreases in serum glucose levels at 5 h after intravenous injection of CdN (3.0 Cd mg/kg)[7] and only mild decreases in serum glucose 10 h after administration of $CdCl_2$ (3.0 mg Cd/kg)[8]. The hypoglycemia observed in the 4.01 mg/kg group was probably a result of impaired gluconeogenesis, which would indicate massive hepatic injury. Severe hepatocellular injury was also pathologically confirmed by the increase of lipid droplets. Thus, we conclude that CdF caused severe hepatic injury, as compared with other Cd compounds such as $CdCl_2$ or CdN.

The atomic structure of Cd compounds are known to strongly determine their harmfulness. F is the most electronegative element, and the electrons that combine F and Cd in CdF tend to gravitate towards F. We hypothesize that the specific form may be connected with the strong hepatotoxicity of CdF.

It has been proposed that Cd induces the synthesis of metallothionein (MT), which is then stored in the liver as a Cd-MT complex[18]. Another report suggests that the Cd-MT complex exists within the liver and is non toxic[19]. It is possible that hepatocellular injury resulting from CdF exposure is further promoted by decreased production of Cd-MT complexes. It is also likely that undetoxified CdF increases and enhances hepatocellular injury.

Apparent decreased urine volume indicate acute renal failure in the CdF treated groups. Acute renal failure associated with CdF is unlikely to result from the effects of F. This hypothesis was confirmed by the finding that the urine volumes and the excretion of F, K and Na were all decreased in the CdF treated groups but did not change in the NaF treated group.

BUN was significantly higher in the 4.01 mg/kg group than in the saline group. Serum Cr slightly increased and Ccr slightly decreased in the 4.01 mg/kg group as well. Since LDH isozyme values in this group indicate no apparent hemolysis, we conclude that 4.01 mg/kg CdF caused slight glomerular dysfunction. There were no remarkable pathological differences in glomeruli betweem any group.

It has been reported that urine volume decreased and BUN and Cr increased at 5 h after intravenous injection of CdN (3.0 mg/kg Cd)[7]. It has also been reported that BUN and Cr considerably increased after intravenous injection of $CdCl_2$ (2.1 mg/kg Cd)[11].

The increase in NAG/Ccr and urine glucose in the 2.67 mg/kg and the 4.01 mg/kg groups intimate acute proximal tubule injury. These results accorded with the pathological findings. There were no remarkable changes in NAG/Cr in the NaF group. This finding indicates the renal tubular toxicity was caused by CdF rather than by ionized F. Cd affects primarily the proximal tubular epithelium, resulting in increased Cd levels in the urine, β_2-microglobulinuria, aminoaciduria, glucosuria and decreased renal tubular reabsorption of phosphate[14]. NAG/Cr, β_2-microglobulin and urine glucose increased at 5 h after intravenous injection of CdN (3 mg/kg Cd)[7]. Yet NAG did not increase after 6 h of 2.86 mg/kg F exposure[13]. Accordingly, we surmise that there is little renal tubular injury caused by F, given that the effective dose of F in the 2.23 mg/kg NaF treated group was approximately 1 mg/kg in this study.

In the CdF treated groups, serum K increased in a dose-dependent manner, and serum K in the 4.01 mg/kg group was significantly higher than in the saline group. Serum

K level greater than 5.5 mEq/*l* is indicative of hyperkalemia in humans[15]. According to this standard, the level of K in the 4.01 mg/kg CdF treated group indicated hyperkalemia. Increased K in the NaF treated group indicates that the increased serum K resulted mainly from exposure to the ionized F contained in NaF. *In vitro* studies have shown that K efflux from erythrocytes results when erythrocytes make contact with F[13]. Additional studies in dogs have shown that hyperkalemia results when NaF is administered intravenously[16]. Increased K in the CdF treated groups indicates a combination effect of acute proximal tubule injury and exposure to ionized F contained in NaF and CdF. In this study, hyperkalemia was further exacerbated by the complication of acute renal failure.

Serum Ca was significantly decreased in the 2.67 and 4.01 mg/kg groups, as compared with the saline group. Decreased serum Ca was also observed in the NaF treated group. This decrease of serum Ca indicates that Ca and F combined to form CaF_2. Decreased serum Ca in response to F exposure can be explained by the formation of insoluble CaF_2, which consumes Ca and decreases Ca concentration in the blood[12]. These findings thus suggest that the observed decreased in serum Ca in the NaF and CdF treated groups results from exposure to ionized F. Increased P in the NaF and CdF treated groups results directly from the decreased Ca.

The decrease in BE, HCO_3^- and the decreased anion gap in the 4.01 mg/kg group are indicative of metabolic acidosis. Metabolic acidosis leads to compensatory hyperventilation, decreased PCO_2 and increased PO_2. Changes in A-aDO_2 and O_2SAT indicate no primary respiratory disorder, meaning blood pH was kept within the reference range. Metabolic acidosis may have been caused by severe hepatic injury and renal tubular injury.

Conclusions

CdF is the most lethal and has the highest hepatic toxicity among all Cd containing compounds, and its specific molecular structure is strongly connected with its harmful effects. Abnormal changes in serum electrolytes resulting from CdF exposure mainly caused by the effect of ionized F. Also, severe liver damage complicated by metabolic acidosis, and the various toxicities associated with CdF enhanced by diminished liver function. CdF damages the liver severely, and increases in the undetoxified form of CdF further damage the liver and kidney.

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