Effect of Experimental Renal Failure and Hypotonic Hyponatremia on the Pharmacodynamics of Cefazolin-Induced Seizures in Rats

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Received November 7, 2002; Accepted February 11, 2003

Purpose. The purpose of this study was to investigate the effect of experimental renal failure and hypotonic hyponatremia on the pharmacodynamics of cefazolin (CEZ)-induced seizures.

Methods. Rats received an intravenous infusion of CEZ until the onset of seizures. Renal failure was produced by bilateral ureteral ligation (UL) or uranyl nitrate (UN) injection. Hypotonic hyponatremia was produced by intravenous infusion of 5% dextrose in water or intraperitoneal infusion of distilled water after arginine vasopressin injection.

Results. The serum and brain concentrations of CEZ at the onset of seizures increased with increasing infusion rate, but the CSF concentration of CEZ at the onset of seizures was not affected by the infusion rate. The concentration of CEZ in CSF at the onset of seizures was significantly lower in UL rats than control rats, whereas there was no difference between UN rats and their controls. Serum concentrations of Na^+ and serum tonicity were lower in UL rats than UN rats. Hypotonic hyponatremia had no apparent effect on the CSF concentration of CEZ. The CSF concentration of CEZ at the onset of seizures was significantly lower in UN rats with hypotonic hyponatremia than their controls.

Conclusions. Renal failure with severe hypotonic hyponatremia is associated with increased central nervous system sensitivity to CEZ-induced seizures.

KEY WORDS: cefazolin; renal failure; hyponatremia; seizures; pharmacodynamics.

INTRODUCTION

Cefazolin (CEZ), a first-generation parenteral cephalosporin, has been reported to cause convulsions in patients with renal failure (1,2). Because CEZ is mainly eliminated by renal excretion (3), renal failure would be associated with increased serum concentrations of CEZ. However, it is still unknown whether renal failure can alter the pharmacodynamics of CEZ-induced seizures. Recently, we reported that renal failure produced by ureter ligation (UL) was associated with increased central nervous system (CNS) sensitivity to cefoselis (a fourth-generation parenteral cephalosporin)-induced seizures (4).

Renal failure can cause changes not only in the pharmacokinetics but also in the pharmacodynamics of certain drugs. The effects of experimental renal failure on the pharmacodynamics of CNS stimulants, such as theophylline (5), pentylentetrazole (6), cimetidine (7), and cefoselis (4), were investigated previously. It was found that UL rats showed increased CNS sensitivity to these drugs. In contrast, rats with renal failure produced by uranyl nitrate (UN) injection did not show any significant changes in CNS sensitivity. In addition, renal failure produced by intramuscularly injected glycerol did not alter theophylline neurotoxicity (8). These results suggest that the effects of experimental renal failure on the pharmacodynamics of drug-induced seizures might be dependent on the disease model.

The purpose of this study is to develop an animal model to investigate the pharmacodynamics of CEZ-induced seizures and to examine the effect of experimental renal failure on the pharmacodynamics of CEZ-induced seizures using two models of impaired renal function (UL and UN rats). Furthermore, we investigated the mechanisms of the increased CNS sensitivity to CEZ-induced seizures by focusing on serum concentrations of electrolytes.

MATERIALS AND METHODS

Animals

Male Wistar rats (Sankyo Labo Service Co., Inc., Tokyo, Japan), their body weights listed in the tables, were used in this investigation. The animal experiments were performed in accordance with The Guidelines for Animal Experiments of Tokyo Medical and Dental University.

Chemicals

CEZ sodium (Cefamezin®) used for animal experiments was obtained from Fujisawa Pharmaceutical Co., Ltd. (Osaka, Japan), and was dissolved in distilled water (267mg/mL, as CEZ). Arginine vasopressin (Pitressin®) used for animal experiments was obtained from Sankyo Co., Ltd. (Tokyo, Japan). Cefpirome sulfate (Broact®) used as internal standard was obtained from Shionogi Co., Ltd. (Osaka, Japan). UN was obtained from TAAB Laboratories (Berkshire, UK). All other chemicals were purchased from commercial sources and used without further purification.

Effect of Infusion Rate on the Concentrations of CEZ in Serum, Brain, and Cerebrospinal Fluid (CSF) at Onset of Seizures

The rats had an indwelling cannula implanted in the left jugular vein under light ether anesthesia 1 day before the experiment and were fasted until the CEZ infusion began. CEZ was infused through the cannula at one of three different rates (3.2, 6.5, or 12.7 g/h). The infusion was stopped immediately on the onset of seizures (kangaroo posture and falling back). The rats were then lightly anesthetized with ether, and samples of CSF, blood, and brain were obtained, in that order. CSF was obtained by cisternal puncture. Blood was obtained from the abdominal aorta and centrifuged to obtain serum. The whole brain was removed and the right half of the cerebrum was used for drug assay.

Effect of Experimental Renal Failure on the Concentrations of CEZ in Serum, Brain, and CSF at Onset of Seizures

Renal failure was produced by UL (two tight ligatures around each ureter and the ureters cut between the ligatures)

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0724-8741/03/0600-0937/0 © 2003 Plenum Publishing Corporation

about 24 h before the experiment. Sham-operated animals served as controls. To produce experimental renal dysfunction, another group of rats received a subcutaneous injection of UN per 10 mg/kg body weight in physiologic saline solution (10 mg/mL) 5 days before the experiment. Control animals received an injection of normal saline only. The rats had an indwelling cannula implanted in the right jugular vein under light ether anesthesia during surgery for UL or 4 days after UN injection. Blood samples to determine the concentration of urea nitrogen in serum were drawn from the tail vein just before the infusion. CEZ was infused through the cannula at 3.2 g/h. Then the same procedure as used to determine the effect of the infusion rate on the concentrations of CEZ was conducted. The concentration of urea nitrogen in serum was measured using Urea Nitrogen B-Test Wako (Wako Pure Chemical Industries, Osaka, Japan).

Effect of Renal Failure on the Serum Concentrations of Electrolytes in Rats

UL rats, UN rats, and their controls were produced using the above-mentioned procedures. The left carotid artery was cannulated for blood sampling under light ether anesthesia during surgery for UL or 4 days after UN injection and the animals were fasted. One day after cannulation, the concentrations of electrolytes and glucose in serum were measured using an i-STAT Portable Clinical Analyzer (Fuso Pharmaceutical Industries, Ltd., Osaka, Japan). Serum tonicity (or effective osmolality) was obtained by the following formula (9):

$$\text{Tonicity (mOsm/kg } H_2O) = \text{serum sodium conc.(mEq/l)} \times 2 + \text{serum glucose conc. (mg/dl)}/18$$

Effect of Experimental Acute Hyponatremia on the Concentrations of CEZ in Serum, Brain, and CSF at Onset of Seizures

The rats had an indwelling cannula implanted in the left jugular vein under light ether anesthesia. Then arginine vasopressin was injected into the thigh muscles of the hind legs at a dose of 25 IU/kg. Fifteen minutes after the arginine vasopressin injection, 5% dextrose in water (D5W) was infused through the cannula at a rate of 1 mL/min to 15% of body weight. To produce experimental acute hyponatremia, another group of rats received an intraperitoneal infusion of distilled water equal to 10% of their body weight. Control rats received only arginine vasopressin intramuscularly. About 2.5 h after the end of D5W or distilled water infusion or about 3 h after cannulation (control rats), a blood sample was obtained from the cannula for determination of the concentrations of electrolytes. Immediately thereafter, CEZ was infused through the cannula at 3.2g/h in rats. Then the same procedure as used to determine the effect of the infusion rate on the concentrations of CEZ was performed.

Effect of Experimental Renal Dysfunction by UN Injections with Acute Hyponatremia on the Concentrations of CEZ in Serum, Brain, and CSF at Onset of Seizures

UN rats were produced using the above-mentioned procedures. Five days after UN injection, the rats had an indwelling cannula implanted in the left jugular vein under light ether anesthesia. Fifteen minutes after cannulation, D5W was infused through the cannula at a rate of 1 mL/min to 10% of body weight. Control rats received only saline injection subcutaneously 5 days before the experiment. About 2.5 h after the end of D5W infusion or about 3 h after cannulation (control rats), a blood sample was obtained from the cannula for determination of the concentrations of urea nitrogen in serum and electrolytes. Immediately thereafter, CEZ was infused through the cannula at 3.2g/h in rats. Then the same procedure as used to determine the effect of the infusion rate on the concentrations of CEZ was conducted.

Assay of CEZ Concentration

The CEZ concentration was determined by high-performance liquid chromatography (HPLC). For the determination of CEZ in serum, 50 μL of serum, 5 μl of 0.1 M sodium and potassium-phosphate buffer (pH 7.0) containing cefpirome sulfate at 100 mg/mL as an internal standard and 50 μL of acetonitrile were mixed and vortexed for 10 s, and then centrifuged at 13,000 g for 2 min. Sixty microliters of supernatant and 540 μL of 0.02 M sodium and potassium phosphate buffer (pH 2.5) were mixed and vortexed for 10 s and then 5 μL of the mixture was injected onto the HPLC column.

For the assay of 30 μL of CSF, the concentration of the internal standard was reduced to 1 mg/mL and the injection volume was 100 μL.

For the determination of CEZ in brain, the right hemisphere was weighed accurately and homogenized with saline (5-fold volume of the hemisphere weight). Two hundred microliters of the homogenate, 20 μL of 0.1 M sodium and potassium phosphate buffer (pH 7.0) containing cefpirome sulfate at 1 mg/mL as an internal standard, and 200 μL of acetonitrile were mixed and vortexed for 10 s. One hundred microliters of the final mixture was injected onto the HPLC column.

The HPLC apparatus was an LC-9A (Shimadzu Co., Kyoto, Japan) equipped with an SPD-6A spectrophotometer (Shimadzu Co.) set at 254 nm. The column was TSKgel ODS-$80T_M$ (5 μm, 4.6 mm I.D. × 15 cm, Tosoh Co. Ltd., Tokyo, Japan). The mobile phase was 12% v/v acetonitrile in 0.02 M sodium and potassium-phosphate buffer (pH 2.5) and the flow rate was 1.0 ml/min.

Data Analysis

All results were expressed as the mean ± SD. Differences in the sample means between two groups were evaluated using the F-test for equality of variances, followed by Student's *t* test or Welch's *t* test. Other experimental results were analyzed by the Tukey–Kramer test. Differences were considered significant at $p < 0.05$.

RESULTS

Effect of Infusion Rate on the Concentrations of CEZ in Serum, Brain, and CSF at Onset of Seizures

The results are shown in Table I. Intravenous infusion of CEZ at doses ranging from 3.2 to 12.7 g/hr/rat produced a determinable onset of seizures, which occurred at between 12.3 ± 0.6 and 45.7 ± 2.7 min, depending on the drug infusion rate. The concentrations of CEZ in serum and brain at the

Table I. Effect of Infusion Rate on the Concentrations of Cefazolin in Serum, Brain, and Cerebrospinal Fluid at Onset of Seizures

	Infusion rate (g/h/rat)		
	3.2	6.5	12.7
Number of animals	7	7	5
Body weight (g)	254 ± 4	255 ± 3	259 ± 8
Infusion time (min)	45.7 ± 2.7	24.8 ± 3.2[a]	12.3 ± 0.6[a]
Total dose (g/kg)	9.60 ± 0.62	10.5 ± 1.4	10.0 ± 0.6
Serum concentration (mg/mL)	14.9 ± 1.5	25.0 ± 6.0[a]	29.7 ± 3.3[a]
Brain concentration (μg/g)	165 ± 20	270 ± 78[a]	300 ± 16[a]
CSF concentration (μg/mL)	96 ± 22	128 ± 30	134 ± 36

[a] Significantly different from the result obtained at the lowest infusion rate ($p < 0.05$).

onset of seizures were significantly increased by increasing the rate of drug infusion. In contrast, the CEZ concentration in the CSF at the onset of seizures was independent of the infusion rate.

Effect of Experimental Renal Failure on the Concentrations of CEZ in Serum, Brain, and CSF at Onset of Seizures

The results are summarized in Table II. Both UL and UN rats showed elevated concentrations of serum urea nitrogen compared to respective controls. UL rats gained weight apparently because of fluid retention, whereas UN rats lost weight probably because of reduced food intake after UN injection.

Renal failure produced by UL and UN treatment was associated with a significant decrease in the amount of CEZ required to induce seizures. Serum, brain, and CSF concentrations of CEZ in UL rats were significantly lower than those in control rats. In contrast, there were no significant differences in CEZ concentrations in serum, brain, and CSF at the onset of seizures between UN rats and their controls.

Effect of Renal Failure on the Serum Concentrations of Electrolytes in Rats

The results are summarized in Table III. Renal failure produced by UL and UN treatment was associated with a significant decrease in the serum concentration of Na^+ and serum tonicity, and serum concentrations of K^+ and Ca^{2+} were significantly affected by the renal failure. In addition, the serum concentrations of Na^+ and serum tonicity were significantly lower in UL rats than UN rats.

Table III. Effect of Renal Failure on the Serum Concentrations of Electrolytes in Rats

	Control	UN rats	UL rats
Number of animals	16	5	9
Serum urea nitrogen (mg/dL)	18 ± 2	325 ± 78[a]	169 ± 33[a,b]
Na^+ conc. (mEq/L)	142 ± 1	132 ± 6[a]	119 ± 4[a,b]
K^+ conc. (mEql/L)	4.15 ± 0.55	6.68 ± 1.37[a]	7.38 ± 0.85[a]
Ca^{2+} conc. (mEql/L)	2.55 ± 0.13	1.84 ± 0.21[a]	2.07 ± 0.13[a,b]
Tonicity (mOsm/kg H_2O)	293 ± 3	271 ± 11[a]	256 ± 11[a,b]

[a] Significantly different from the corresponding control group ($p < 0.05$).
[b] Significantly different from the UN treatment group ($p < 0.05$).

Effect of Experimental Acute Hyponatremia on the Concentrations of CEZ in Serum, Brain, and CSF at Onset of Seizures

The results are summarized in Tables IV and V. The serum concentrations of Na^+ and serum tonicity were lower in hyponatremic rats than their controls. No significant differences in the other electrolyte (K^+ and Ca^{2+}) concentrations in serum were observed between hyponatremic rats and their controls.

There was no difference in total dose between hyponatremic rats given the D5W infusion and their controls. In contrast, total dose was significantly lower in hyponatremic rats produced by distilled water infusion than their controls. CEZ concentrations in serum, brain, and CSF at the onset of seizures were not affected by dextrose or distilled water infusion.

Effect of Experimental Renal Failure Caused by UN Injection with Acute Hyponatremia on the Concentrations of CEZ in Serum, Brain, and CSF at Onset of Seizures

The results are summarized in Table VI. Serum urea nitrogen concentrations were significantly higher in hyponatremic rats with renal failure (UN-HypoNa rats) than their controls. Serum concentrations of Na^+ and serum tonicity in

Table II. Effect of Experimental Renal Failure on the Concentrations of Cefazolin at Onset of Seizures in Rats

	UL study		UN study	
	Control	Renal failure	Control	Renal failure
Number of animals	8	7	7	7
Body weight (g)	271 ± 10	310 ± 17[a]	258 ± 9	226 ± 15[a]
Serum urea nitrogen (mg/dL)	16 ± 3	126 ± 12[a]	16 ± 2	318 ± 139[b]
Infusion time (min)	48.0 ± 5.8	10.2 ± 3.2[a]	49.7 ± 5.1	19.3 ± 10.1[a]
Total dose (g/kg)	9.17 ± 1.23	1.71 ± 0.57[a]	10.0 ± 1.0	4.6 ± 2.4[a]
Serum concentration (mg/mL)	14.3 ± 1.9	6.3 ± 2.2[a]	16.3 ± 3.2	15.6 ± 6.9
Brain concentration (μg/g)	152 ± 46	69 ± 28[b]	161 ± 41	228 ± 122
CSF concentration (μg/mL)	87.8 ± 24.7	47.1 ± 27.5[b]	94 ± 17	127 ± 78

[a] Significantly different from the corresponding control group ($p < 0.001$).
[b] Significantly different from the corresponding control group ($p < 0.01$).

Table IV. Effect of Experimental Hyponatremia Produced by D5W Infusion on Certain Physiologic Characteristics and on the Concentrations of Cefazolin at Onset of Seizures in Rats

	Control	Hyponatremia
Number of animals	7	7
Body weight (g)	250 ± 8	261 ± 9[a]
Na^+ conc. (mEq/L)	139 ± 1	120 ± 2[b]
K^+ conc. (mEq/L)	4.14 ± 0.31	4.60 ± 0.66
Ca^{2+} conc. (mEq/L)	2.60 ± 0.15	2.37 ± 0.28
Tonicity (mOsm/kg H_2O)	285 ± 2	266 ± 8[c]
Infusion time (min)	41.3 ± 5.2	42.0 ± 5.1
Total dose (g/kg)	8.66 ± 0.90	8.54 ± 0.97
Serum concentration (mg/mL)	15.1 ± 2.4	18.6 ± 3.7
Brain concentration (μg/g)	160 ± 39	189 ± 37
CSF concentration (μg/mL)	99 ± 40	106 ± 36

[a] Significantly different from the corresponding control group ($p < 0.05$).
[b] Significantly different from the corresponding control group ($p < 0.001$).
[c] Significantly different from the corresponding control group ($p < 0.01$).

UN-HypoNa rats were significantly decreased, and serum concentrations of K^+ and Ca^{2+} were significantly affected by the renal failure with hyponatremia. Total dose and CEZ concentrations in serum, brain, and CSF at the onset of seizures were significantly lower in UN-HypoNa rats than their controls.

DISCUSSION

The purpose of this investigation was to clarify the risk factors for CEZ-induced seizures. The experiments were designed to establish whether there occurs a change in the pharmacodynamics of CEZ, irrespective of possible changes in the pharmacokinetics of the drug. It was therefore particularly important to distinguish between possible pharmacokinetically based apparent changes in the concentration-effect relationship (such as changes in serum protein binding and/or distribution kinetics) and actual changes in the pharmacodynamics of CEZ. The best way to do this would be to determine the concentration of CEZ at the site of action at a specified pharmacologic endpoint.

Table V. Effect of Experimental Hyponatremia Produced by Distilled Water Infusion on Certain Physiologic Characteristics and on the Concentrations of Cefazolin at Onset of Seizures

	Control	Hyponatremia
Number of animals	9	6
Body weight (g)	246 ± 5	270 ± 3[a]
Na^+ conc. (mEq/L)	139 ± 1	119 ± 1[a]
K^+ conc. (mEq/L)	4.07 ± 0.22	4.25 ± 0.27
Ca^{2+} conc. (mEq/L)	2.66 ± 0.14	2.59 ± 0.07
Tonicity (mOsm/kg H_2O)	288 ± 3	249 ± 2[a]
Infusion time (min)	40.2 ± 4.4	29.7 ± 9.9[b]
Total dose (g/kg)	8.57 ± 0.99	5.79 ± 1.93[c]
Serum concentration (mg/mL)	16.4 ± 2.7	15.5 ± 5.7
Brain concentration (μg/g)	170 ± 43	167 ± 76
CSF concentration (μg/mL)	95 ± 35	124 ± 70

[a] Significantly different from the corresponding control group ($p < 0.001$).
[b] Significantly different from the corresponding control group ($p < 0.05$).
[c] Significantly different from the corresponding control group ($p < 0.01$).

Table VI. Effect of Experimental Renal Failure with Hyponatremia on Certain Physiologic Characteristics and on the Concentrations of Cefazolin at Onset of Seizures in Rats

	Control	UN-HypoNa rats*
Number of animals	8	6
Body weight (g)	247 ± 7	235 ± 17
Serum urea nitrogen (mg/dL)	14 ± 2	232 ± 65[a]
Na^+ conc. (mEq/L)	142 ± 1	115 ± 7[b]
K^+ conc. (mEq/L)	4.43 ± 0.66	6.75 ± 1.42[a]
Ca^{2+} conc. (mEq/L)	2.64 ± 0.11	2.40 ± 0.25[c]
Tonicity (mOsm/kg H_2O)	293 ± 1	248 ± 6[b]
Infusion time (min)	43.2 ± 9.0	8.0 ± 3.1[b]
Total dose (g/kg)	9.17 ± 1.81	1.83 ± 0.75[b]
Serum concentration (mg/mL)	14.4 ± 2.5	7.2 ± 3.9[a]
Brain concentration (μg/g)	155 ± 33	84 ± 40[c]
CSF concentration (μg/mL)	78.8 ± 19.2	36.2 ± 16.9[a]

* Hyponatremia was produced by D5W infusion to UN rats.
[a] Significantly different from the corresponding control group ($p < 0.01$).
[b] Significantly different from the corresponding control group ($p < 0.001$).
[c] Significantly different from the corresponding control group ($p < 0.05$).

Previous study showed an experimental strategy to determine the appropriate biologic fluid or tissue to reflect the drug concentration at the site of action (10). The present study was based on their strategy: CEZ was infused to rats at three different rates, and the drug concentrations in serum, brain, and CSF were determined.

The results of this study showed that CEZ concentrations in the serum and brain at the onset of seizures were significantly affected by the rate of drug infusion, whereas the CEZ concentration in the CSF at the pharmacologic endpoint was independent of the infusion rate (Table I). These results suggest that the drug concentration in the CSF is a more appropriate index of the drug concentration at the site of action. It might be reasonable because cephalosporins such as CEZ inhibit GABA receptor binding in CNS (11).

To examine the risk factors for CEZ-induced seizures, we first investigated the effect of experimental renal failure on the pharmacodynamics of CEZ-induced seizures in rats (Table II). In the present study, renal failure produced by UL or UN treatment was associated with a significant decrease in the amount of CEZ required to induce seizures. This result suggests that renal failure is one of the risk factors for CEZ-induced seizures. In addition, serum, brain, and CSF concentrations of CEZ at the onset of seizures were significantly lower in UL rats than control rats. In contrast, there were no differences in CEZ concentrations in serum, brain, and CSF at the onset of seizures between UN rats and their controls. These results suggest that UL causes an increase in sensitivity to CEZ-induced seizures, whereas no apparent change is induced in UN rats. Thus, the effect of experimental renal failure on the pharmacodynamics of CEZ-induced seizures is considered to be dependent on the disease model. The smaller amount of CEZ required to induce seizures in UN

rats would reflect the delayed elimination of CEZ associated with renal failure.

Previously, neurotoxicity of theophylline was examined in rats with acute renal failure (5,8). Renal failure produced by UL was associated with an increased CNS sensitivity to theophylline-induced seizures. UN or glycerol-induced renal failure did not affect the CNS sensitivity to theophylline-induced seizures. However, all three (UL, UN, and glycerol) models for producing renal failure apparently resulted in similar elevations in serum creatinine and urea nitrogen concentrations (5,8). Thus, it is impossible to determine whether the CNS sensitivity to CNS stimulants increases from only the information of these biochemical indices, while other indices may need to be used to assess the CNS sensitivity to CNS stimulants.

To find such indices, we examined the serum concentrations of electrolytes and serum tonicity in UL and UN rats (Table III). The results of this study showed that renal failure significantly decreased the serum concentration of Na^+ and serum tonicity. UL rats had severer hypotonic hyponatremia than UN rats.

There have been many reports of seizures caused by severe hyponatremia (12–17). Therefore, we investigated the effect of experimental acute hyponatremia on the pharmacodynamics of CEZ-induced seizures. In the present study, D5W infusion to 15% body weight plus an injection of vasopressin caused severe hyponatremia (Table IV). There were no differences in CEZ concentrations of the serum, brain, and CSF at the onset of seizures between the hyponatremic rats and their controls.

The manifestations of hypotonic hyponatremia are largely related to dysfunction of the central nervous system because hypotonic hyponatremia causes the entry of water into the brain (resulting in cerebral edema) (12,17). Measured osmolality gives no information about the tonicity of body fluids. The distinction between tonicity and osmolality is important for the clinical assessment of hydration (11). Tonicity, or effective osmolality, is a measure of the movement of water across a semipermeable membrane.

D5W infusion to normal rats caused severe hyponatremia, but the tonicity in these rats was not as low as that in UL rats. Previous study showed that acute fluid overload could increase the sensitivity of the central nervous system to the neurotoxic effect of theophylline (18). However, there was little difference in the CSF concentration between the D5W infusion plus vasopressin injection group (220 ± 29 mg/L) and the vasopressin injection only group (268 ± 44 mg/L). The hyponatremic rats produced by the D5W infusion may not have exhibited hypotonicity. In the next study, we examined the pharmacodynamics of CEZ-induced seizures using severe hypotonic hyponatremic rats produced by intraperitoneal infusion of distilled water (Table V). Water infusion to normal rats causes severe hyponatremia, and the tonicity in these rats is as low as in UL rats. Severe hypotonic hyponatremia produced by water infusion is associated with a significant decrease in the amount of CEZ required to induce seizures, but there are no differences in CEZ concentrations of the serum, brain, and CSF at the onset of seizures between severe hypotonic hyponatremic rats and their controls. These results suggest severe hypotonic hyponatremia produced by water infusion is associated with changes in the pharmacokinetics of CEZ, whereas no apparent change in the pharmacodynamics of CEZ-induced seizures is found in these rats.

We also investigated the effect of experimental renal failure induced by UN injection with acute hypotonic hyponatremia on CEZ neurotoxicity (Table VI). Serum, brain, and CSF concentrations of CEZ at the onset of seizures were significantly lower in UN-HypoNa rats than their controls. These results indicate that renal failure with severe hypotonic hyponatremia is associated with an increased CNS sensitivity to CEZ-induced seizures.

Changes in drug effects under renal impairment may be due to an increase in the concentrations of uremic toxins such as guanidino compounds (19,20). The present study showed that not only uremic toxins but also serum concentrations of electrolytes and serum tonicity could affect the CNS sensitivity.

In conclusion, renal failure is one of the risk factors for CEZ-induced seizures, and renal failure with severe hypotonic hyponatremia, such as in UL rats is associated with an increased CNS sensitivity to CEZ-induced seizures.

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