Decreased Diuretic Response to Furosemide in Rats with Acute Hepatic Failure

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Furosemide diuresis is occasionally reduced in cirrhotic patients with ascites. To define this phenomenon, the amounts of water, electrolytes, and furosemide excreted in urine were measured in control and CCl₄-induced acute hepatic failure (AHF) rats. The diuretic action of furosemide (10 mg/kg, i.v.) was reduced in AHF rats, accompanied by increased plasma aldosterone concentration and accelerated urinary K⁺ excretion rate. Furosemide transiently increased the urinary inulin excretion rate (UV_{IN}) in both control and AHF rats. Then the UV_{IN} quickly returned to the baseline value in control rats, but rapidly dropped below the baseline in AHF rats. To clarify the contribution of aldosterone in these phenomena, AHF rats were adrenalectomized (ADX) and treated with or without exogenous aldosterone. The UV_{IN} in ADX rats given no infusion or a low-dose aldosterone infusion was similar in pattern to that of the control group, but the UV_{IN} in the ADX rats given a high-dose aldosterone infusion showed a pattern similar to that of the AHF rats not adrenalectomized. These findings indicate that an increase in plasma aldosterone concentration is an important factor responsible for the decreased diuretic action of furosemide, along with the reduced glomerular filtration rate.

Keywords — furosemide; acute hepatic failure rat; decreased diuretic response; glomerular filtration rate; aldosterone

Introduction

The use of diuretics to inhibit sodium retention is the most usual form of treating ascites. Furosemide, a potent loop diuretic that induces the rapid onset of marked diuresis, is often used to treat patients with cirrhosis or chronic liver disease with ascites, but its efficacy is often decreased in such patients.¹⁻⁵⁾ Some factors, such as delivery of diuretics in urine,^{1,2)} proximal Na⁺ reabsorption,³⁾ plasma aldosterone concentration,⁴⁾ prostaglandins,⁶⁾ and renal hemodynamics,⁷⁾ have been suggested to be responsible for the reduced action, but the decisive factor has not been determined.

The increased response to urinary excretion of furosemide has been reported in rats with acute renal failure,⁸⁾ and it is suggested that this is due to decreased concentrating ability at distal parts along the nephron.

The diuretic action of furosemide in rats with carbon tetrachloride-induced acute hepatic failure (AHF) was investigated particularly. The increased plasma aldosterone concentration and reduced glomerular filtration rate (GFR) were

indicated as causes of the decreased diuretic action of furosemide.

Materials and Methods

Materials — Furosemide was kindly supplied by Hoechst Japan Ltd., (Kawagoe, Japan) for the standard of high performance liquid chromatographic analysis. The furosemide injection (Lasix[®], Hoechst Japan Ltd.) was used for the animal experiments. *d*-Aldosterone was purchased from Sigma Chemical Co. (St. Louis, MO, U.S.A.). Inulin (pyrogen-free) was obtained from Nutritional Biochemicals (Cleveland, OH, U.S.A.). Other chemicals were of reagent grade.

Diuretic Response Study — The study was performed as described previously.^{8,9)} Briefly, male Wistar rats each weighing 240—280 g were anesthetized with an intraperitoneal injection of urethane (1 g/kg). The urinary bladder and right jugular vein were cannulated to collect urine and to infuse and/or inject solutions, respectively. A 5% (w/v) glucose solution containing 8 mg/ml of inulin was infused (2.3 ml/h)

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throughout the experiment. For the adrenalectomy (ADX) experiments, the adrenal glands of the animals were removed just after the start of the infusion. After two consecutive 30-min urine samplings during the baseline period, 10 mg/kg (10 mg/ml, 1 ml/kg) of furosemide was administered by rapid intravenous injection.

The urine samples were collected periodically for 2.5 h, and the volume was determined from the weight. Blood was sampled *via* abdominal aorta at the end of the experiment, and a serum sample was separated. *d*-Aldosterone was dissolved in the infusate and was infused at a rate of 8.5 or 25 ng/min (0.22 or 0.65 μ g/ml, 2.3 ml/h).¹⁰ The GFR was measured by the inulin clearance using the serum concentration and the urinary excretion rate of inulin for the final urine sample.

Animal Treatment — Animals received an oral administration of 50% CCl₄ in corn oil (2 ml/kg) to induce the AHF. Control rats were given the same volume of corn oil. Animals were fasted for 24 h after the administration. Experiments were started 48 h after the dosing with CCl₄. The conditions of these animals were monitored by the biochemical analysis of serum samples. Serum glutamate oxalaoacetate transaminase (GOT) and glutamate pyruvate transaminase (GPT) activities increased about 10-fold in AHF rats compared with control rats ($p < 0.001$), but the serum concentrations of urea

nitrogen and creatinine increased slightly. The serum albumin concentration was 4.2 ± 0.2 mg/dl in control rats ($N = 5$) and 4.5 ± 0.2 mg/dl in AHF rats ($N = 5$).

Analytical Methods — Furosemide concentrations in serum and urine were determined by high performance liquid chromatography with the detection at 280 nm (Trirotor III with a Uvidec-100-III UV spectrophotometer, JASCO, Tokyo, Japan).⁸ Concentrations of Na⁺, K⁺, and Cl⁻ were measured using an ion meter (F-8AT, Horiba Ltd., Kyoto, Japan) with ion-specific electrodes (Na⁺-, K⁺-, or Cl⁻-specific electrodes for Sera-100, Horiba Ltd., Kyoto, Japan). The aldosterone concentration in plasma was estimated by radioimmunoassay (ALDOCTK-125 aldosterone radioimmunoassay kit, Commissariat a L'energie Atomique, Italy). Inulin was assayed by a colorimetric method.¹¹ Biochemical analysis of serum was performed using an automatic assay system, Clinalyzer (JCA-SIM6R, Nihon Denshi Co. Ltd., Tokyo, Japan). Data were expressed by the mean $\pm$ S.E., and statistical evaluations were performed using the analysis of variance with the *t*-test.

Fig. 1. Cumulative Urinary Recovery of Furosemide in Control and Acute Hepatic Failure (AHF) Rats

Recovery was calculated as the percent of the dose injected. Open and closed circles denote data from control and AHF rats, respectively. Points and vertical bars represent the mean $\pm$ S.E. for 5 animals.

Fig. 2. Urinary Excretion-Response Curve and Total Efficiency (Inset) of Furosemide in Control and Acute Hepatic Failure (AHF) Rats

Open and closed symbols represent data from control and AHF rats, respectively. Columns and vertical bars denote the mean $\pm$ S.E. for 5 animals.

a) significantly different from control rats ($p < 0.001$).

Results

Urinary Excretion-Response Curve for Furosemide

The urinary excretion and the diuretic action of furosemide were compared in control and AHF rats. As shown in Fig. 1, the cumulative amounts of furosemide recovered in urine were slightly smaller in AHF rats than control rats, but these were not significantly different at any time.

The curve formed by the plots of the urinary ($\text{Na}^+ + \text{K}^+$) excretion rate ($\text{UV}_{\text{Na}+\text{K}}$) against the furosemide excretion rate (UV_{FM}), for the AHF rats were shifted to the right compared

with the control rats (Fig. 2). The total efficiency, which was calculated from the ratio of total urinary excretion of ($\text{Na}^+ + \text{K}^+$) to that of furosemide and corrected for the difference in the urinary recovery of furosemide, was also decreased in AHF rats (inset in Fig. 2). The cumulative diuretic response also decreased in AHF rats compared with the control rats.

Urinary Excretion of Electrolytes and Water after Furosemide Injection

The relationship between urine flow rate (UFR) and $\text{UV}_{\text{Na}+\text{K}}$ were the same in both control and AHF rats (Fig. 3-A). Plots of the urinary Cl^- excretion rate (UV_{Cl}) against the $\text{UV}_{\text{Na}+\text{K}}$ were also essentially the same in both control

Fig. 3. Relationships among Urinary Excretion Rates of Water, Na^+ , K^+ , and Cl^- in Control and Acute Hepatic Failure (AHF) Rats

Open and closed circles represent the data from control and AHF rats, respectively. The straight and dotted lines denote linear regression lines for control and AHF rats, respectively.

Fig. 4. Urinary Excretion Rate of Inulin after a Furosemide Injection in Control and Acute Hepatic Failure (AHF) Rats

Data are shown as percentages of the value of baseline period. Open and closed circles denote data from control and AHF rats, respectively. Points and vertical bars represent the mean $\pm$ S.E. for 5 animals.

a) significantly different from control rats ($p < 0.05$).

and AHF rats (Fig. 3-B). However, the slope of the line fitted to the urinary K^+ excretion rate (UV_K) against the Na^+ excretion rate (UV_{Na}) was steeper for the AHF rats than for the control rats (Fig. 3-C).

Since the urinary K^+ excretion is regulated by corticosterone,¹²⁻¹⁵⁾ the plasma concentration of aldosterone was measured. The plasma aldosterone concentration was significantly higher in AHF rats (1.78 ± 0.15 ng/ml, $N = 4$) than in control rats (0.71 ± 0.07 ng/ml, $N = 5$) ($p < 0.01$).

Effects of Acute Hepatic Failure on the Glomerular Function after Furosemide Injection

The time course of the urinary excretion of

Fig. 5. Effects of Aldosterone on the Urinary Excretion Rate of Inulin after a Furosemide Injection in Acute Hepatic Failure (AHF) Rats with Adrenalectomy (ADX)

Data are shown as percentages of the value of baseline periods. Symbols represent AHF-ADX rats without aldosterone infusion (Δ), AHF-ADX rats with 8.5 ng/min aldosterone infusion ($\circ$), and AHF-ADX rats with 25 ng/min aldosterone infusion ($\bullet$). Points and vertical bars represent the mean $\pm$ S.E. for 4 or 5 animals.

a) significantly different from other groups ($p < 0.01$).

inulin (UV_{IN}) was monitored in both control and AHF rats (Fig. 4). Since the UV_{IN} during the baseline periods in AHF rats (3.2 ± 1.0 mg/min) was about 60% compared with that in control rats (5.2 ± 1.3 mg/min), the data were expressed as the percentage values of baseline periods of each animal to correct the inter-individual variations of the GFR. Immediately after the intravenous injection of furosemide, the UV_{IN} was increased similarly in the two groups. Then the UV_{IN} quickly returned to the baseline value in control rats, but rapidly dropped below the baseline in AHF rats. Since the inulin infusion rate was the same in both groups, the inulin concentration in plasma was

TABLE I. Effect of Aldosterone on Furosemide Action in Acute Hepatic Failure Rats with Adrenalectomy

	Baseline UV_{IN} ^{a)} (μ g/min)	Final GFR ^{b)} (ml/min)	Furosemide recovery (% of dose)	Total efficiency ^{c)} (μ eq/ μ g)
No-Aldo ^{d)}	280 ± 40	1.16 ± 0.18	60.2 ± 3.3	0.56 ± 0.09
Low-Aldo ^{e)}	336 ± 20	1.39 ± 0.06	62.6 ± 4.4	0.62 ± 0.09
High-Aldo ^{f)}	355 ± 71	0.66 ± 0.21 ^{g)}	42.7 ± 6.5 ^{g)}	0.46 ± 0.09

Data are expressed by the mean $\pm$ S.E. for 4 or 5 animals. a) urinary excretion rate of inulin before the furosemide injection; b) glomerular filtration rate; c) [total efficiency] = [total urinary excretion of ($Na^+ + K^+$)]/[total urinary excretion of furosemide]; d) no-aldosterone infusion group; e) low-dose aldosterone infusion group; f) high-dose aldosterone infusion group; g) significantly different from other groups ($p < 0.01$).

significantly higher in AHF rats ($20.6 \pm 2.6 \mu\text{g/ml}$) than in control rats ($8.6 \pm 1.0 \mu\text{g/ml}$) ($p < 0.005$). Therefore, the calculated GFR for the final urine sample in AHF rats ($0.034 \pm 0.008 \text{ ml/min}$) was less than 10% of that in control rats ($0.424 \pm 0.094 \text{ ml/min}$) ($p < 0.001$).

Effects of Aldosterone on Furosemide Action in the Rat

To determine the effect of aldosterone concentration on the diuretic action of furosemide, the AHF rats with ADX were given infusions of various doses of aldosterone. The pattern of UV_{IN} in AHF rats with ADX not given aldosterone infusion or given a low-dose aldosterone infusion (Fig. 5) was similar to that in control rats (see Fig. 4), but the UV_{IN} in those ADX rats given a high-dose aldosterone infusion (Fig. 5) showed a pattern similar with that of the AHF rats not adrenalectomized (see Fig. 4). In these conditions, the GFR was decreased about 50% in the high-dose aldosterone infusion group compared with the other groups, whereas the GFR in the low-dose aldosterone infusion group was similar to that of the no-aldosterone infusion group (Table I).

The cumulative urinary recovery of furosemide was also significantly lowered in the high-dose aldosterone infusion group than in the low-dose aldosterone infusion group and no-aldosterone group (Table I). Cumulative diuretic response was also decreased in the high-dose aldosterone group. Total efficiency, which corrected the difference of urinary furosemide excretion, was smaller in the high-dose aldosterone group than in the other groups (Table I), but the difference was not significant.

Discussion

Furosemide, a loop diuretic, possesses potent diuretic activity exhibited by inhibition of $\text{Na}^+/\text{K}^+/\text{2Cl}^-$ reabsorption at the ascending limb of Henle's loop.¹⁶⁻¹⁸⁾ The urinary excretion of furosemide is recognized as the determinant of its pharmacological action.^{9,19,20)} This drug has been widely used to manage edematous states accompanying various diseases. However, a decreased response to loop diuretics has often

been reported in cirrhotic or chronic liver disease patients with ascites.¹⁻⁵⁾ As shown in Fig. 2, a decreased response also occurred in the CCl_4 -treated rats. Therefore, the factors responsible for this reduced action of furosemide were investigated in detail.

The relationship between UFR and $\text{UV}_{\text{Na}+\text{K}}$ in the AHF rats was similar to that in the control rats, but the pattern of the plots of UV_{K} against UV_{Na} differed (Fig. 3). The high UV_{K} in AHF rats may be explained by the high aldosterone concentration in the plasma, because aldosterone is the major factor regulating Na^+ reabsorption and K^+ excretion *via* Na^+-K^+ exchange at distal parts of the nephron.¹²⁻¹⁵⁾ Increased Na^+ reabsorption and K^+ excretion reduce natriuresis and diuresis.¹²⁻¹⁵⁾ Antinatriuretic and antidiuretic actions have been observed in rats with glycerol-induced acute renal failure infused with aldosterone.⁸⁾ If this is also the case for CCl_4 -treated rats, the diuretic action of furosemide may be reduced in AHF rats due to a high plasma aldosterone concentration. This is a possible explanation for the decreased action of the loop diuretics in cirrhotic patients with ascites whose aldosterone concentration in plasma is often reported to be higher than that of normal subjects.²¹⁾ A similar suggestion was made for piretanide by analysis of the relationship between the aldosterone concentration and the response.⁴⁾

On the other hand, the GFR has sometimes been reported to be decreased by furosemide administration in patients with chronic hepatic failure or cirrhosis with ascites.^{7,22-24)} Although the reduction of the effective plasma volume or changes in renal hemodynamics has been suggested as the factor responsible for this phenomenon, the precise mechanism is not clear. In the present study, the GFR decreased after furosemide injection in AHF rats (Fig. 4), which had a higher aldosterone concentration in plasma than normal rats. Therefore, to investigate the contribution of aldosterone in this GFR reduction, AHF rats were adrenalectomized and given various doses of exogenous aldosterone. As shown in Fig. 5 and Table I, the UV_{IN} and GFR were not reduced after furosemide injection in AHF rats with ADX given no aldoste-

rone infusion or a low-dose aldosterone infusion. However, the UV_{IN} and GFR were reduced after the furosemide injection in these ADX rats given the high-dose aldosterone infusion. This low-dose of aldosterone has been reported to produce the physiological level of aldosterone in the plasma of ADX rats.¹⁰⁾ Therefore, in the case of no infusion or low-dose aldosterone infusion, the aldosterone concentration in plasma may be lower than or similar to the normal physiological level. In this case, the GFR was not influenced by furosemide. On the other hand, the GFR decreased after the furosemide injection into ADX rats with the high-dose aldosterone infusion. This high-dose was about 2.5 times higher than the low-dose and was selected on the basis of the difference of plasma aldosterone concentration in AHF rats (1.78 ng/ml) and control rats (0.71 ng/ml). Therefore, it is found that the high aldosterone concentration in plasma and AHF are necessary for the GFR reduction after furosemide administration. If the GFR is reduced, the delivery of water and electrolytes to the action site of furosemide will be decreased. Thus, the furosemide action will be diminished. This is also the possible explanation for the reduced action of the loop diuretics in cirrhotic patients with ascites.

The furosemide recovery also decreased about 30% in the AHF and ADX rat groups with high-dose aldosterone infusion compared with the groups with no-aldosterone and low-dose aldosterone infusion (Table I). The tendency of the urinary recovery of furosemide to be reduced was also observed in AHF rats compared with control rats (Fig. 1). This reduction of furosemide recovery is thought to be one of the factors in the decreased diuretic action of this drug. Since the urinary excretion of furosemide mainly depends on the renal tubular secretion,^{25,26)} the reduction of the furosemide recovery in urine may be caused by the low plasma albumin concentration accompanying the hepatic failure, the renal dysfunction, and the diminution of the renal blood flow. Inoue *et al.*²⁷⁾ has reported that the urinary excretion of furosemide was reduced with the low albumin concentration in plasma. However, this is not the case, because no change was observed in the

albumin concentration between control and AHF rats. The renal dysfunction was not obvious in these rats. The diminution of renal blood flow was supported by the reduction of GFR in this condition. The reductions of GFR and urinary excretion of furosemide coincide with the report by Daskalopoulos *et al.*⁷⁾ who observed the reduction of inulin and *p*-aminohippurate clearances after furosemide administration in chronic hepatic disease patients with ascites. Consequently, the present findings of reduced GFR may be explained by the relation to the tubuloglomerular feedback mechanism,²⁸⁻³⁰⁾ although there is no direct evidence for the relation of the aldosterone and GFR.

On the other hand, we observed a shift of the furosemide excretion-response curve to the right and a significantly reduced total efficiency in AHF rats compared with control rats (Fig. 2). We also found a slightly decreased total efficiency (about 20% reduction) in AHF and ADX rats with the high-dose aldosterone compared with the no-aldosterone and low-dose aldosterone infusion (Table I). These observations suggest the contribution of the other factors rather than the furosemide recovery to the decreased diuretic action of this drug, since the difference of furosemide recovery in these experiments was already corrected for the diuretic action. For example, the increased concentrating ability along the nephron induced by the high aldosterone concentration in plasma or the decreased delivery of water and electrolytes caused by the reduced GFR, would decrease the diuretic action of furosemide.

From the above results the contribution of plasma aldosterone in reducing the GFR and diuretic response after furosemide injection is indicated. However, since the other factors can not be excluded by the *in vivo* experiment, *in vitro* experiments, such as the isolated perfused kidney approach, are necessary for further understanding.

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