Influence of Chronic Lithium Treatment on Urinary Amount of Furosemide in Rats

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ABSTRACT—The present study was undertaken to examine whether the urinary amount of furosemide is influenced by chronic lithium treatment. LiCl at 2 mEq/kg/day in 1 ml vehicle (5% glucose solution) or 1 ml of vehicle alone was injected intraperitoneally for 8 days into Wistar rats. On day 8, 30 mg/kg of furosemide in 3% body weight of 1% NaCl was given orally, and urine was collected for 6 hr after dosage. The urinary amount of furosemide in the Li-treated rats was significantly lower than that in the control animals [Li group (n = 12): 514 ± 75 (mean ± S.E.) vs. control group (n = 12): 916 ± 85 μg/kg/6 hr, P < 0.01]. This finding indicates that pharmacokinetic alterations of furosemide might occur during chronic treatment with lithium.

Since serum lithium concentrations can be increased by a concurrent use of diuretic agents such as thiazides and bumetanide (1, 2), these diuretics should not be given to patients stabilized on lithium unless serum lithium concentrations can be closely monitored and appropriate dosage adjustments made. On the other hand, furosemide, a loop diuretic agent, does not significantly change serum lithium concentrations (2) and therefore, might be used in the treatment of hypertension and other related diseases in patients on lithium therapy.

Furosemide is readily absorbed from the gastrointestinal tract and its bioavailability is about 60% (3). Furosemide is extensively bound to plasma proteins (98.8%), but the agent is rapidly secreted by the organic anion transport system of the renal proximal tubule (3, 4).

Lithium is reported to influence the pharmacokinetics of other agents. For example, lithium disturbs the absorption of chlorpromazine from the gastrointestinal tract and diminishes its bioavailability (5, 6). Lithium also inhibits the organic anion transport system of the renal proximal tubule and decreases the urinary excretion of p-aminohippurate (7, 8). Based on these findings, it is assumed that the pharmacokinetic profiles of furosemide might be altered by lithium.

The present study was the first step to address this issue. Furosemide was given orally to groups of rats with or without chronic lithium treatment. The urinary amount of furosemide in rats with lithium was compared to that in animals without lithium.

MATERIALS AND METHODS

Male Wistar rats (Charles River Laboratory, Kanagawa, Japan) (10–11 weeks old, 300–350 g) were maintained for more than 2 weeks under conditions of light from 7 a.m. to 7 p.m. and dark from 7 p.m. to 7 a.m. with free access to food and water.
The first experiment was performed to determine the optimal nontoxic lithium dosage for the subsequent study. Rats were randomly divided into three groups. One milliliter of 5% glucose vehicle was injected intraperitoneally (i.p.) to the first group of rats (n = 6) once daily for 7 days (day 1 to day 7), and these served as the control animals. Lithium chloride (LiCl) (Sigma, St. Louis, MO, U.S.A.) in 1 ml vehicle was given i.p. to two groups of rats at increasing dosages of 2.0 (n = 6) and 3.0 (n = 6) mEq/kg/day once daily for 7 days (day 1 to day 7). Body weight was measured every day. Since the previous study demonstrated massive polyuria 4 days after the initiation of lithium therapy in rats (9), water intake and urine volume for 24 hr were determined on day 3 to day 7 in the present study. Blood samples for plasma renin activity (PRA) and plasma lithium were obtained 24 hr after the final dosage of lithium on day 8.

Since body weight did not decrease and PRA did not increase by the 2.0 mEq/kg/day dosage of LiCl, this dosage was judged to be nontoxic and was used for the subsequent experiment.

Second experiment: The rats were divided into two groups of twelve each. One milliliter of 5% glucose vehicle or LiCl. 2.0 mEq/kg/day in 1 ml vehicle, was injected i.p. once daily for 8 days (day 1 to day 8). Three percent body weight (b.w.) of 1% NaCl solution (on day 7) and 30 mg/kg of furosemide (Sigma, St. Louis, MO, U.S.A.) in 3% b.w. of 1% NaCl solution (on day 8) were given orally to each group of rats, and urine was collected for 6 hr after dosage. Blood samples for PRA and plasma lithium were obtained 24 hr after the final dosage of lithium (on day 9).

Urinary sodium concentration and plasma lithium concentration were determined by a flame photometer (775-A, Hitachi, Tokyo, Japan). Urinary chloride concentration was determined by an autoanalyzer (736, Hitachi, Tokyo, Japan). Urinary concentration of furosemide was measured by high performance liquid chromatography (10). PRA was measured by a RIA method (11).

The results are expressed as means ± S.E. Data are analyzed by analysis of variance and Student’s t-test as appropriate.

RESULTS

First experiment

Body weight gradually increased in the vehicle- and Li, 2 mEq/kg/day-treated groups of rats (Table 1). This parameter of the two groups did not significantly differ at any observation point. On the contrary, body weight began to decrease on day 4 and remarkably decreased on day 7 in the animals treated with Li at 3 mEq/kg/day. As expected, water intake and urine volume increased significantly following each dosage of Li therapy. PRA measured on day 8 was remarkably elevated in the group treated with Li at 3 mEq/kg/day (Table 2). Plasma lithium concentrations increased in a dose-dependent manner.

Second experiment

When 3% b.w. of 1% NaCl solution was given as a furosemide control on day 7, urine volume and urinary excretions of sodium and chloride were significantly greater in the Li-treated rats than in the control rats (Fig. 1). These parameters significantly increased following furosemide in the control, but not in the Li-treated animals. No significant difference was observed in urinary excretion of volume, sodium or chloride between the two groups on day 8. Urinary amount of furosemide in the Li-treated rats was significantly smaller compared to that in the control rats. There were no significant differences between the two groups in body weight (g) [control group 333 ± 7 (day 1), 347 ± 8 (day 7) and 347 ± 10 (day 8); Li-treated group 337 ± 9 (day 1), 350 ± 9 (day 7) and 349 ± 8 (day 8)] or PRA (ng/ml/hr, day 9) (control group: 4.1 ± 0.6, Li-treated group 3.9 ± 0.4). The value of plasma lithium concentration was 0.60 ± 0.10 mEq/l.
Table 1. Body weight, water intake and urine volume during lithium (Li) treatment in Wistar rats

| Parameter      | Group     | 1      | 2      | 3      | 4      | 5      | 6      | 7      |
|----------------|-----------|--------|--------|--------|--------|--------|--------|--------|
| Body weight    | control   | 332±1  | 334±10 | 337±11 | 339±9  | 343±10 | 345±13 | 348±12 |
| (g)            | Li 2 mEq  | 337±8  | 339±9  | 340±8  | 344±8  | 347±8  | 349±7  | 350±9  |
|                | Li 3 mEq  | 339±4  | 340±6  | 342±4  | 341±6  | 332±6  | 334±8  | 305±7* |
| Water intake   | control   | ND     | ND     | ND     | ND     | ND     | ND     | ND     |
| (ml/100 g/day) | Li 2 mEq  | 10.7±1.0 | 9.2±0.4 | 8.4±0.4 | 9.7±0.8 | 10.2±0.5 |
|                | Li 3 mEq  | 11.4±1.8 | 10.9±1.6 | 20.5±3.4* | 29.4±5.9** | 42.8±7.3** |
|                |           | 10.5±0.3 | 13.7±3.5 | 30.9±7.0** | 48.4±9.9* | 63.9±9.6** |
| Urine volume   | control   | ND     | ND     | ND     | ND     | ND     | ND     | ND     |
| (ml/100 g/day) | Li 2 mEq  | 5.2±0.5 | 4.2±0.3 | 5.1±0.4 | 5.2±0.3 | 5.6±0.7 |
|                | Li 3 mEq  | 7.6±1.4 | 7.6±1.2 | 16.2±2.4** | 25.1±5.7** | 33.9±6.4** |
|                |           | 5.5±0.2 | 9.6±2.3* | 25.4±6.0** | 37.6±8.0** | 55.8±7.3** |

Mean ± S.F., *P < 0.05, **P < 0.01, compared to the control. ND = not determined. LiCl was injected intraperitoneally to rats once daily for 7 days. control = vehicle (n = 6), Li 2 mEq = Li at the dose of 2 mEq/kg/day (n = 6). Li 3 mEq = Li at the dose of 3 mEq/kg/day (n = 6).

Table 2. Plasma renin activity (PRA) and plasma lithium (Li) concentration on day 8

| Parameter      | Group     | Li 2 mEq | Li 3 mEq |
|----------------|-----------|----------|----------|
| PRA (ng/ml/hr) | control   | 3.4±0.9  | 3.7±0.5  | 10.7±3.6** |
| Plasma Li (mEq/l) | ND     | 0.72±0.08 | 1.36±0.23 |

Mean ± S.F., **P < 0.01, compared to the control. ND = not determined. Blood samples were obtained 24 hr after the final dosage of Li.

DISCUSSION

Lithium is a potent agent with a relatively narrow therapeutic dosage range. For this reason, it is important to avoid lithium toxicity since metabolic changes secondary to the weight loss and other sequelae may interfere with the parameters under observation. In the present study, body weight did not decrease by administration of LiCl (2 mEq/kg/day for 7 days). This finding is compatible with the observation of Das et al. (12) who used a similar dosage of LiCl in rats. We have found that the body weight of rats is decreased by treatment with 3 mEq/kg/day of LiCl. These data suggest that the 2 mEq/kg/day of LiCl is not a toxic dose. Kierkegaard-Hansen (13) reported that PRA does not change in lithium-fed rats who had no signs of intoxication (mean serum Li = 0.44 mEq/l), while PRA increased remarkably in rats with intoxication (mean serum Li = 1.29 mEq/l). The high PRA during intoxication might be induced by sodium depletion (14, 15). The PRA of rats treated with Li at 2 mEq/kg/day did not change significantly in both experiments, and their trough concentrations of plasma lithium (0.72±0.08 mEq/l in the first experiment and 0.60±0.10 mEq/l in the second experiment) were lower than those that had been documented in rats with intoxication (mean 1.29 mEq/l) (13). The PRA increased in rats that were treated with 3 mEq/kg/day of LiCl and had a trough plasma lithium of 1.36±0.23 mEq/l. These data provide additional evidence that lithium intoxication was not induced by the 2 mEq/kg/day dosage of LiCl.

In the group of rats treated with Li at 3 mEq/kg/day, body weight began to decrease on day 4, which might be a result of the toxic
Fig. 1. Urine volume and urinary excretions of sodium, chloride and furosemide in rats with (Li-treated group, n = 12) or without (control group, n = 12) lithium treatment. Mean ± S.E. Three percent body weight (b.w.) of 1% NaCl solution (on day 7) or 30 mg/kg of furosemide in 3% b.w. of NaCl solution (on day 8) was given orally to each group of rats, and urine was collected for 6 hr after dosage.
The present study demonstrated that the urinary amount of furosemide following oral administration of the agent is influenced by chronic treatment with lithium. This observation suggests that the pharmacokinetic alterations of furosemide might occur during the repeated dosage of lithium.

The decreased amount of urinary furosemide in rats treated with lithium might be accounted for by one or more of the following possible mechanisms: 1) Absorption of furosemide from the gastrointestinal tract is reduced and therefore, its bioavailability is diminished. This phenomenon has already been reported for chlorpromazine (5, 6). 2) Protein-bound furosemide is increased, and consequently, its renal clearance is decreased (18, 19). To our knowledge, however, no data are available concerning an influence of lithium on protein binding of other agents. 3) Tubular secretion of furosemide is disturbed. Szczepanska-Konkel et al. (7) and Sugihara et al. (8) reported the inhibitory effects of lithium on p-aminohippurate secretion in rats. Since furosemide as well as p-aminohippurate are secreted by the organic anion transport system of the renal proximal tubule, the tubular secretion of furosemide might also be inhibited by lithium. The present study is unable to rule out any of these possibilities, and further studies including an intravascular injection trial are needed to evaluate them.

Diuresis following NaCl solution that is caused by a multifactorial mechanism involving renal and hormonal factors (20–22) was greater in the Li-treated rats than in the control animals. Lithium per se induces a diuresis by several mechanisms (23, 24): 1) inhibition of the hydro-osmotic response of ADH in the collecting duct. 2) increased output of tubular fluid from the proximal tubules. 3) lowering of the cortico-medullary osmotic gradient and 4) impaired response of aldosterone to endogenous stimuli. These mechanisms might contribute to the enhanced diuresis observed in the Li-treated rats.

Although a diuresis and natriuresis following NaCl solution in the control rats were small compared to those in the Li-treated animals, urine volume and urinary sodium excretion significantly increased after furosemide in the control, but not in the Li-treated rats. Consequently, there was no significant difference among the two groups in these parameters after furosemide. The urinary amount of furosemide was relatively small in the Li-treated rats. Since the diuretic effects of furosemide depend, at least in part, on its urinary amount (3, 25), the effects of furosemide are considered to be reduced in these rats. Massive diuresis after NaCl solution only might mask such a reduced diuretic effect of furosemide in rats treated with lithium. Another study using animals without administration of NaCl solution is needed to examine this hypothesis.

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