Cisplatin increases urinary sodium excretion in rats: gender-related differences

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Key words: *cisplatin; sodium urinary excretion; rats; gender-related differences.*

Summary. *Objective. There are well-documented reports of cisplatin-associated hyponatremia in the literature, but there are no data on gender-dependent differences. The aim of the present study was to define characteristics of 24-hour urinary sodium excretion in young adult Wistar rats of both genders and to evaluate the gender-related effect of cisplatin.*

Materials and methods. Twelve control Wistar rats (6 males and 6 females) and 12 cisplatin-treated Wistar rats (6 males and 6 females) after a single and repeated injection of cisplatin (once a day for 3 days) at a dose of 2.5 mg/kg body weight into the caudal vein were examined. The experiment was carried out by measuring 24-h urinary sodium, potassium, chloride, magnesium, creatinine excretion and pH in the urine of age-matched male and female rats.

Results. The 24-h urinary sodium excretion, sodium/chloride ratio, and diuresis showed no gender-related differences in control rats. After a single administration of 2.5 mg/kg cisplatin, 24-h urinary sodium excretion was not significantly higher in cisplatin-treated rats than in gender-matched controls. After repeated cisplatin administration, 24-h urinary sodium excretion was significantly higher in cisplatin-treated male rats as compared to matched controls ($P<0.05$). No such effect was found in cisplatin-treated female rats.

Conclusion. The study data show that cisplatin enhances urinary sodium excretion in male but not in female rats. The mechanism of such a gender-related effect is not yet clear. Further investigations are necessary to elucidate the mechanism of this pharmacological effect of cisplatin.

Introduction

Nephrotoxicity is an inherent adverse effect of certain anticancer drugs. The mechanisms of chemotherapy-induced renal dysfunction generally include vascular or structural damage of the kidneys. Cisplatin (CP) is one of the most widely used agents in cancer treatment. Cisplatin may produce renal salt wasting and thus may cause symptomatic orthostatic hypotension and hyponatremia (1). Cisplatin regimens can lead to a more or less pronounced hyponatremia in 4 to 10% of cases combined with hypomagnesemia (2). Preclinical studies show that low urine osmolarity could be a major determinant in the increase of CP-induced nephrotoxicity (3).

There is evidence indicating that certain drugs could be the reason for hyponatremia as an adverse effect, which depends on patient's gender (4). There are no data on gender-related CP adverse effects. The aim of the present study was to define characteristics of 24-hour urinary sodium (Na) excretion in young adult Wistar rats of both genders, its relationship with potassium (K), chloride (Cl) ions and magnesium (Mg) urinary excretion. Elucidation of gender-related adverse effects provides important additional information, which indicates the urgency of investigating the mechanisms of gender-related adverse effects. The pathophysiological mechanisms that result in hyponatremia, hypomagnesemia, hypokalemia must be highlighted in order to prevent their occurrence and consequences. Elucidation of gender-related effects of various drugs through preclinical investigation is an important field of pharmacology.

Materials and methods

Twelve control intact Wistar rats (6 males and 6 females) and 12 CP-treated Wistar rats (6 males and 6 females) after a single and repeated injection of CP at a dose of 2.5 mg/kg body weight (cisplatin Ebewe

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solution 50 mg/100 mL, Ebewe Pharma Ges.m.b.H., A-4866 Unterach, Austria) into the caudal vein (once a day for 3 days) were examined. This dose was chosen in accordance with the literature data on preclinical CP pharmacodynamics (5).

The experiment was carried out on age-matched male and female rats. The mean age of male and female control rats was 64±9 days and 62±8 days, respectively. The mean age of CP-treated male and female rats was 64±9 days and 62±8 days, respectively. The mean weight of male rats was 228±37 g in the control group and 221±44 g in the CP-treated group. The mean weight of female rats was 186±22 g in the control and 181±21 g in the CP-treated groups. The weight was significantly higher in male than in female rats in both the groups (P<0.05).

The animals were housed in standard colony cages with free access to tap water, the room temperature was 21±1˚C, and the rats were exposed to the natural light-dark cycle. All experiments were performed according to the institutional guidelines for animal care in order to avoid any unnecessary distress to the animals and to reduce the number of animals used. The animals were housed under described conditions and acclimated for at least 5 days before an experiment. The 24-h urine was collected holding a rat alone in a special cage (diuresis cage for rats 3700D000/3701D000, Tecniplast, Italy) for 24 h (from 9:00 AM till 9:00 AM of the next day) with free access to tap water, without food, under the same temperature and light conditions.

The 24-h urinary levels of K, Na, Cl ions were analyzed with an EML-105 electrolyte analyzer (Radiometer, Denmark). The 24-h urinary Mg level was analyzed using photometric colorimetric test with a factor for lipid brightening (liquicolor "Magnesium"). Urinary pH was measured with a pH/mV/ion meter (ION Meter pH 340/ION, Germany).

We calculated the 24-h excretion of K, Na, Cl, Mg, as well as 24-h urinary K, Na, Cl excretion per 100 g of body weight and Na/Cl ratio.

We applied STATISTICA for Windows software (StatSoft, USA, 1995) to carry out the analysis of our data. Data were expressed as means ± SD values from n animals. Using Student's test, comparisons between groups were made. A P value of <0.05 was considered significant.

Results

Diuresis and Na excretion after a single dose of cisplatin in rats (Table 1). The 24-h diuresis, 24-h urinary Na level, 24-h Na excretion, and Na/Cl ratio in control rats showed no statistically significant gender-related differences (P>0.05).

After a single administration of CP, no significant differences in 24-h diuresis in the control male (15.5±7.4 mL) and female rats (13.8±2.7 mL) versus CP-treated male (12.1±2.7 mL) and CP-female (12.5±2.5 mL) rats were determined (P>0.05). The 24-h Na excretion was higher in CP-treated male rats as compared to CP-treated female rats (0.7±0.2 mmol and 0.4±0.2 mmol, respectively; P=0.05) (Table 1).

The Na/Cl ratio was significantly higher only in CP-treated male rats as compared to gender-matched controls (0.8±0.1 mmol versus 0.49±0.1 mmol; P<0.05). The Na/Cl ratio in CP-treated male rats was higher than in CP-treated female rats (P=0.05).

Study results did not show any significant changes in urinary Na, K, Cl, or Mg, creatinine excretion in CP-treated female rats as compared to gender-matched control rats after a single administration of CP.

The 24-h urine pH showed no statistically significant difference between control females (6.74±0.2) and control males (6.94±0.4; P>0.05). There were no significant differences in 24-h urine pH comparing CP-treated males (7.09±0.5) and CP-treated females

Table 1. Diuresis and 24-h urinary K, Na, Cl, Mg excretion in male and female control and cisplatin-treated rats after a single administration of cisplatin

Group	n	24-h diuresis (mL)	24-h K excretion (mmol)	24-h Na excretion (mmol)	24-h Cl excretion (mmol)	24-h Mg excretion (mmol)	Na/Cl ratio
Control rats							
females	6	13.8±2.7	0.9±0.3	0.48±0.1	0.89±0.3	0.02±0.01	0.52±0.1
males	6	15.5±7.4	1.0±01	0.46±0.2	0.89±0.4	0.02±0.01	0.49±0.1
CP-treated rats							
females	6	12.5±2.5	0.8±0.3	0.4±0.2	0.76±0.2	0.024±0.01	0.54±0.1*
males	6	12.1±2.7	1.1±0.4	0.7±0.2*	0.83±0.2	0.024±0.01	0.8±0.1**

Data are presented as means ± standard deviation.
*P=0.05, as compared to female rats; **P<0.05, as compared to the control group.

(6.64±0.2) with controls and between the genders (P>0.05).

Diuresis and Na excretion after repeated doses of cisplatin in rats. After 3 days of repeated administration of CP, the 24-h diuresis in CP-treated males (10.9±3.0 mL) and CP-treated females (12.0±2.7 mL) showed no statistically significant differences versus controls and between the genders (P>0.05).

The 24-h Na excretion was significantly higher in CP-treated male rats (0.58±0.3 mmol) than in male control rats (0.3±0.1 mmol) (P<0.05). No influence of CP treatment on Na excretion was determined in CP-treated female rats (P>0.05). The Na/Cl ratio showed no statistically significant differences between CP-treated and control rat groups (P>0.05). The value of 24-h Na excretion per 100 g of body weight in CP-treated female rats was significantly higher than in control female rats (0.24±0.1 vs. 0.12±0.08 mmol; P<0.05), but 24-h Na excretion in CP-treated female rats was significantly lower that in CP-treated male rats (0.24±0.1 mmol vs. 0.44±0.08; P<0.05) (Table 2).

The results did not show any significant changes in 24-h urinary K, Cl, Mg, creatinine excretion in CP-treated female rats as compared to gender-matched control rats after 3 days of CP administration.

The 24-h urinary pH showed no statistically significant difference between control females and control males (7.02±0.3 vs. 6.98±0.3; P>0.05). The 24-h urinary pH in CP-treated males (7.18±0.6) and CP-treated females (7.09±0.5) showed no statistically significant differences versus controls and between the genders (P>0.05).

Discussion

Cisplatin is a major antineoplastic drug for the treatment of solid tumors, but it shows a dose-dependent renal toxicity. Unbound CP is freely filtered at the glomerulus and taken up into renal tubular cells mainly by a transport-mediated process. Cisplatin has multiple intracellular effects, causing direct cytotoxicity with reactive oxygen species, activating mitogen-activated protein kinases, and stimulating inflammation and fibrogenesis. These events cause tubular damage and tubular dysfunction with Na, K, and Mg wasting (6, 7). In addition to elevation of serum creatinine levels and uremia, electrolyte abnormalities are well-known adverse effects of cisplatin (8). The potential for development of clinically significant hyponatremia early in the course of CP therapy with any infusion routes in cancer patients is known (9). No studies on CP gender-related toxicity are available.

The present study shows the influence of CP on urinary Na excretion in Wistar rats. After a single administration of CP, the 24-h urinary Na excretion, 24-h urinary Na excretion per 100 g body weight, and Na/creatinine ratio did not differ in CP-treated rats of both sexes as compared to gender-matched controls. The study results revealed gender-related differences in Na excretion caused by repeated treatment with CP: the male rats treated once a day for 3 days with 2.5 mg/kg showed a significant increase in urinary Na excretion, but no significant increase was observed in the CP-treated female rats. In the CP-treated female rats, an increase in urine Na excretion was less pronounced and was statistically significant only when calculated per 100 g of body weight per 24 h. These data show that CP might exert a gender-related effect on urinary Na excretion in rats.

Diuresis is directly related to Na excretion (10), but there are no data on diuretic effects of CP. The pathogenesis of CP-induced renal failure is related to reduced renal blood flow due to a severe tubular damage and enhanced renovascular resistance. It is also known that alpha(1)-adrenoreceptors, the major subtype of alpha-adrenoreceptors in renal vasculature, play the pivotal role in regulating renal hemodynamics.

Table 2. Diuresis and 24-h urinary K, Na, Cl, Mg excretion in male and female control and cisplatin-treated rats after repeated doses of cisplatin

Group	n	24-h diuresis (mL)	24-h K excretion (mmol)	24-h Na excretion (mmol)	24-h Cl excretion (mmol)	24-h Mg excretion (mmol)	Na/Cl ratio
Control rats							
females	6	11.8±3.5	0.8±0.24	0.23±0.2	0.6±0.2	0.022±0.01	0.40±0.2
males	6	12.3±3.3	1.2±0.3	0.3±0.1	0.8±0.2	0.025±0.01	0.39±0.1
CP-treated rats							
females	6	12.0±2.7	0.7±0.3	0.42±0.2	0.74±0.4	0.019±0.01	0.54±0.1
males	6	10.9±3.0	0.93±0.3	0.58±0.3*	1.0±0.3	0.027±0.01	0.55±0.2

Data are presented as means ± standard deviation.
*P<0.05, as compared to the control group.

Furthermore, the augmented renal adrenergic responsiveness in the CP-induced renal failure in rats was possibly mediated by the alpha(1)-adrenoreceptors. Treatment of male rats with CP (5 mg/kg i/p) showed that alpha(1A)- and alpha(1D)-adrenoreceptors were the major subtypes in mediating adrenergically induced renal vasoconstriction (11). There are data on gender-dependent modulation of alpha(1)-adrenergic responses in rats. Alpha(1A)-adrenoreceptor expression is higher at all ages studied, in female rats more than in male ones. Prazosin binding by alpha(1)-adrenoreceptors is more pronounced in young adult female rats than in young adult male rats (12). Endothelial damage produces a selective increase in alpha(1)-adrenergic agonist reactivity in arteries of male rats. Net contractile responses to phenylephrine were significantly increased by arterial endothelium disruption in males but not females. This gender-dependent effect was stimulus specific (13).

Furthermore, the Na,K-ATPase $alpha_1$ subunit expression was decreased following a 24-h exposure to CP, and these results suggest that Na,K-ATPase-dependent active transport of CP does not occur in resistant cells, and furthermore, the Na,K-ATPase $alpha_1$ subunit plays an important role in the transport of cisplatin (14). Data from several studies indicated decreased function of the Na,K-ATPase pump in female heart, ileum, liver, brain tissues as compared to male ones (15). Moreover, it has been shown that female sex hormones (estrogen and progesterone) can inhibit Na,K-ATPase enzyme activity in many tissues, whereas the male sex hormone (testosterone) may stimulate enzyme activity (15, 16). These mechanisms could appear to be responsible for increased acute symptomatic hyponatremia and increased urinary Na excretion (17). Na,K-ATPase-dependent active transport of CP across the cell membrane, its intracellular accumulation could have a link to gender-related CP toxicity. Male gender increases sensitivity to renal injury in response to some factors (18).

Nephrotoxicity and Mg depletion are well-known side effects of CP treatment. The study on Mg-depleted female rats treated with CP (2.5 mg/kg once weekly for 3 weeks) revealed an almost complete disappearance of Na,K-ATPase (alpha-subunit), Na/H-exchanger, and Na,K,2Cl-cotransporter, suggesting a dramatic synergistic effect of CP and Mg depletion on renal function including the expression pattern of outer medullary Na transporters (5). Our data did not show CP-caused changes in 24-h urinary Mg or 24-h K excretion in rats of both genders treated with CP (2.5 mg/kg once a day for 3 days).

The observed gender-dependent differences in Na excretion in repeatedly CP-treated male rats could appear to be important in the light of gender-specific Na ion transport and homeostasis characteristics in rats. Female rats drank more of 3% NaCl solution than did males. Female rats consistently ingested about twice as much NaCl solution as did male rats regardless of the palatability of the solution or of body Na levels (19). On the other hand, Na appetite elicited by a prolonged Na deprivation is higher in male than in female rats (20). Exogenous testosterone lowered Na intake in adult rats of both sexes (21). Basal fractional excretion of Na was significantly lower in male as compared to female rats at a similar lower renal perfusion pressure (22). Female rats have a decreased renal hemodynamic function as compared to male (23, 24). The renal excretion of Na is, in part, controlled by gender differences in the renal density of the thiazide diuretic receptors. The density of the thiazide receptor was twofold higher in female than in male rats (25).

Increased Na excretion after administration of CP might be the reason for hyponatremia. One of the mechanisms of hyponatremia, the syndrome of inappropriate antidiuretic hormone secretion, has been associated with cisplatin (9). An increased sensitivity of Na transport systems in the renal tubules to the circulating vasopressin cannot be excluded. The experimental results in vivo provide evidence that tubular V1 vasopressin receptor activity results in increased urine flow in the euvolemic state in rats (26). The classical short-term effect (within minutes) of vasopressin results in increased Na, Cl, and water transport in kidney cells. More recently, long-term actions (several hours) of vasopressin have been evidenced on water and Na fluxes, due to transcriptional enhancement in the expression of Na/K/2Cl-cotransporter (27). The V1 receptor mediates the natriuretic effect of vasopressin in rats (28). Increased Na excretion in male rats could be related to activated hemodynamics as well, because the pressor response to vasopressin secretion is greater in males vs. females due to a reduced total peripheral resistance in female rats (29).

Conclusions

The present study data indicate that cisplatin toxicity can be more pronounced in male rats. Toxicity-related mechanisms could be responsible for an increased disposition to urinary Na excretion, symptomatic hyponatremia of cisplatin-treated male rats. Thus, further studies of the gender-dependent mechanisms of cisplatin effect on kidney tubular damage and tubular dysfunction causing Na wasting could be important.

Cisplatina didina žiurkių natrio išsiskyrimą su šlapimu. Su lytimi susiję skirtumai

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Raktažodžiai: cisplatina, natrio išsiskyrimas su šlapimu, žiurkės, su lytimi susiję skirtumai.

Santrauka. Literatūros duomenys rodo, kad gydymas cisplatina gali lemti hiponatremiją, tačiau su lytimi susiję skirtumai iki šiol netyrinėti. *Tyrimo tikslas.* Nustatyti cisplatinos poveikį abiejų lyčių jaunų Wistar žiurkių natrio išsiskyrimui su šlapimu.

Tyrimo medžiaga ir metodai. Ištyrėme vienodo amžiaus 12 kontrolinių Wistar žiurkių (6 patinus ir 6 pateles) ir 12 Wistar žiurkių (6 patinus ir 6 pateles) po vienkartinės ir pakartotinių (3 dienų) cisplatinos 2,5 mg/kg per parą dozių. Matavome žiurkių patinų ir patelių natrio, kalio, chloro, magnio, kreatinino išsiskyrimą paros šlapime ir šlapimo pH.

Rezultatai. Ištyrus natrio išsiskyrimą su paros šlapimu, Na/Cl santykį ir diurezę, nerasta su lytimi susijusių skirtumų kontrolinių žiurkių grupėse. Po vienkartinės 2,5 mg/kg cisplatinos dozės natrio išsiskyrimas cisplatina gydytų abiejų lyčių žiurkių grupėse statistiškai reikšmingai nesiskyrė nuo atitinkamos lyties kontrolinių žiurkių natrio kiekio paros šlapime. Skiriant cisplatiną pakartotinai (2,5 mg/kg per parą, 3 dienas į uodegos veną), natrio išsiskyrimas su šlapimu buvo statistiškai reikšmingai didesnis cisplatina gydytų žiurkių patinų grupėje, lyginant su kontrolinių žiurkių analogiškais duomenimis ($p<0,05$), o cisplatina gydytų patelių grupėje natrio išsiskyrimo su šlapimu pokyčių nenustatyta.

Išvada. Tyrimo duomenys rodo, kad cisplatina žiurkių patinėliams didina natrio išsiskyrimą su šlapimu, tačiau šio poveikio patelėms nenustatyta. Su lytimi susijusio cisplatinos poveikio mechanizmai nežinomi, todėl tikslinga atlikti tyrimus, tirti cisplatinos su lytimi susijusio natrio išsiskyrimo su šlapimu farmakologinio poveikio mechanizmus.

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