Relationship between Cisplatin or Nedaplatin-Induced Nephrotoxicity and Renal Accumulation

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Nedaplatin is known to exhibit antitumor activity similar to that of cisplatin. However, concerning side effects, nedaplatin causes renal toxicity less frequently than cisplatin. In this study, we compared the incidence of renal toxicity between cisplatin and nedaplatin by investigating the difference in kidney tissue accumulation. Kidney tissue accumulation of cisplatin administered at 3.75 mg/kg was similar to that of nedaplatin administered at 24 mg/kg. At these doses, the plasma creatinine level and urinary excretion of glucose and N-acetyl-β-D-glucosaminidase (NAG) similarly increased. There was a correlation between kidney accumulation of cisplatin and nedaplatin and the increases in plasma creatinine level and urinary excretion of NAG. Therefore, our results suggest that nedaplatin less frequently causes renal toxicity in comparison to cisplatin due to lower kidney accumulation.

Key words cisplatin; nedaplatin; platinum accumulation; nephrotoxicity

MATERIALS AND METHODS

Animal Experiments We used male Sprague–Dawley (SD) rats (Japan SLC, Inc.) weighing 180 to 230 g. These rats were acclimated under the following conditions: lighting cycle, 12 h; room temperature, 24°C; and humidity, 55%. Water and food were given ad libitum. The experiment was conducted in accordance with the Osaka University of Pharmaceutical Sciences Animal Experiment Guidelines.

The rats were divided into 5 groups, a group treated with physiological saline (n=10), a group treated with 3.75 mg/kg of cisplatin (n=5), a group treated with 7.5 mg/kg of cisplatin (n=10), a group treated with 7.5 mg/kg of nedaplatin (n=5), and a group treated with 24 mg/kg of nedaplatin (n=6). These drugs or saline were administered intravenously to each rat. Urine was collected in metabolic cages for 18 h starting from 48 h after administration of cisplatin and nedaplatin. After urine volume was measured, urine specimens were centrifuged to measure urinary excretion of glucose and N-acetyl-β-D-glucosaminidase (NAG) and the creatinine level. Seventy-two hours after drug administration, blood was collected, and the kidney was removed under anesthesia with sodium pentobarbital (50 mg/kg, i.p.). Blood samples were centrifuged to measure the plasma creatinine level. In addition, creatinine clearance was calculated from the plasma creatinine level and urinary excretion of creatinine. For the measurement of glucose, we used a “Glucose B-test Wako” kit (Wako Pure Chemical Industry Co., Ltd.). For the measurement of creatinine, we used a “Creatinine Test Wako” kit (Wako Pure Chemical Industry Co., Ltd.). For the measurement of NAG, we used a “NAG Test Shionogi” kit (Shionogi Pharmaceutical Co., Ltd.). Cisplatin was purchased from Sigma Inc., and nedaplatin was supplied by Shionogi Pharmaceutical Co., Ltd.

Platinum Content Kidney tissue accumulation of cisplatin and nedaplatin was investigated by atomic absorption analysis, regarding the platinum content of the renal cortex as the drug level. The renal cortex (100 mg) was placed in a dryer at 100°C overnight, and incinerated in 1 ml of 61% nitric acid. The nitric acid was diluted and the platinum level

cis-Diamminedichloroplatinum(II) (cisplatin) is a potent antitumor agent, and a high response rate has been achieved in patients with lung cancer, testicular tumor, ovarian cancer, bladder cancer, prostate cancer, or head and neck cancer.1-2) In the structure of cisplatin, chloride is shifted, comprising a hydrate and inhibiting DNA synthesis via binding to DNA and cross-linking.3) However, cisplatin causes side effects, such as renal toxicity, gastrointestinal disorders, and auditory disorders.4) In particular, renal toxicity is serious, and is considered a dose-limiting factor in the clinical use of cisplatin.5-7)

Cisplatin is mainly excreted from the kidney, and the kidney tissue content of this agent is higher than the concentrations in other organs.8,9) As cisplatin is retained in the kidney tissue for a long duration, it may readily cause nephrotoxicity. It has also been reported that cisplatin-related nephrotoxicity develops in a dose-dependent manner in animals and humans.10,11)

As cisplatin-related renal toxicity is a dose-limiting factor, anticancer platinum compounds that do not induce renal toxicity, and replace cisplatin, have been developed.12) Among these platinum compounds, cis-diammine(glycolato) platinum (nedaplatin) has antitumor activity equivalent to that of cisplatin; however, renal toxicity is relieved.13-17) In an in vitro experimental system using renal cortical slices, nedaplatin did not cause renal cell disorders although the concentration was 10 times higher than that of cisplatin.18) However, it is unclear why renal toxicity is less marked despite similar antitumor activity. Recently, Cui et al. have demonstrated that a correlation is detected between content of platinum in the renal cortex and nephrotoxicity induced by nedaplatin.19) However, there is no report of the relationship accumulation of cisplatin and nedaplatin in the kidney to their nephrotoxicity.

In this study, we compared the grade of renal toxicity between cisplatin and nedaplatin with respect to kidney accumulation, as there is a correlation between the doses of many anticancer platinum preparations and renal toxicity.

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was measured using a frameless atomic absorption spectrophotometer (SolaarA-880, Jarrell-Ash). Concerning the platinum content, an assay line was prepared from platinum standard solution (Wako Pure Chemical Industry Co., Ltd.), and the platinum level was determined, and corrected as values per wet renal cortex weight (g).

**Histological Examination** For histological investigation, the kidney was fixed in 10% neutral buffered formalin solution, and paraffin blocks were prepared. Using a microscope, sections were prepared, and hematoxylin and eosin (H&E) staining was performed.

**Data Analysis** All values are expressed as the mean±S.E. Statistical analysis was performed by one-way analysis of variance followed Dunnett’s test. Pearson’s correlation coefficient test was used. A p value less than 0.05 was considered significant.

**RESULTS**

In our preliminary studies, we obtained the results that both drugs prominently accumulated 24 h after their injections in the kidney and then such accumulation levels persisted still after 96 h (data not shown). Creatinine levels in blood plasma as an index of nephrotoxicity increased significantly 72 h after the administration of cisplatin or nedaplatin. Therefore, on the basis of such preliminary data, we investigated the relationship between accumulation in the kidney and nephrotoxicity induced by cisplatin or nedaplatin 72 h after the injections. The kidney tissue level of each platinum preparation was shown in Fig. 1. After administration at the same dose (7.5 mg/kg), kidney accumulation of cisplatin was 2.6 times higher than that of nedaplatin. Kidney accumulation of cisplatin administered at 3.75 mg/kg was similar to that of nedaplatin administered at 24 mg/kg. Thus, kidney accumulation of cisplatin was higher than that of nedaplatin. Subsequently, we investigated the influence of these preparations on kidney function under similar conditions.

The rate of increase in the plasma creatinine level after administration of cisplatin at 3.75 mg/kg was similar to that after administration of nedaplatin at 24 mg/kg; there was a correlation between the drug distribution and the grade of nephrotoxicity (Fig. 2A). The correlation between the changes in the plasma creatinine level and the platinum content of the renal cortex is shown in Fig. 2B (r=0.934, p<0.0001). Furthermore, 7.5 mg/kg of cisplatin markedly increased the plasma creatinine level; however, 7.5 mg/kg of nedaplatin did not influence the plasma creatinine level. As demonstrated for the plasma creatinine level, 7.5 mg/kg of nedaplatin did not influence creatinine clearance, and 24 mg/kg of nedaplatin significantly decreased creatinine clearance. The rate of decrease was similar to that after administration of cisplatin at 7.5 mg/kg (Fig. 3).

Cisplatin is known to mainly affect the proximal tubule. Therefore, we investigated the influence of cisplatin and nedaplatin on urinary excretion of NAG (Fig. 4A) and glucose (Fig. 5), which is mainly used as a parameter of disorders of the proximal tubule. Administration of cisplatin at 7.5 mg/kg significantly increased urinary excretion of NAG and glucose (Figs. 4A, 5). The rate of increase in urinary excretion of NAG was similar between cisplatin at 3.75 mg/kg and nedaplatin at 24 mg/kg. However, there was no signifi-
cant influence on urinary excretion of glucose at any doses in comparison to the control group. There was a correlation between the changes in urinary excretion of NAG and the platinum content of the kidney tissue ($r=0.680$, $p<0.0001$) (Fig. 4B).

Figure 6 shows histological changes in the renal cortex after administration of cisplatin and nedaplatin. Cisplatin at 3.75 mg/kg did not influence the histology; however, this agent at 7.5 mg/kg caused necrosis of the kidney tubule, affecting the morphology of the kidney tubule. Nedaplatin at 24 mg/kg did not induce any morphological changes in the cortex.

DISCUSSION

In this study, we investigated whether a lower incidence of nephrotoxicity related to nedaplatin, in comparison to that related to cisplatin, is associated with a difference in kidney distribution. With respect to nedaplatin-related reduction of creatinine clearance and increases in the plasma creatinine level, urinary excretion of NAG and glucose, glomerular disorders and disorders of the kidney tubule were milder than those related to cisplatin. In addition, when comparing kidney accumulation of the two agents at the same dose, kidney accumulation of nedaplatin was approximately 40% of that of cisplatin, suggesting that a dose of nedaplatin about 6 times higher than that of cisplatin is required to cause the same grade of nephrotoxicity. There was a positive correlation between renal toxicity and the platinum content of the kidney tissue; the results of this study suggest that kidney tissue accumulation of platinum drugs to some degree leads to kidney dysfunction. It has reported that the concentration of nedaplatin must be about 3 times higher than that of cisplatin to obtain similar antitumor effects between nedaplatin and cisplatin using human stomach adenocarcinoma cell line.20) Our results showed that a dose of nedaplatin about 6 times higher than that of cisplatin was required to induce the same grade of renal toxicity; therefore, experimentally, renal toxicity may not occur at the dose for achieving antitumor effects similar to those of cisplatin. These findings suggest that nedaplatin exhibits potent antitumor effects at a dose at which renal toxicity does not occur, and that nedaplatin is safer than cisplatin in patients with kidney dysfunction. However, according to a study, in these patients, the serum level of nedaplatin remained high for a long duration, and side effects, including renal toxicity, should be considered.21)

The grade of nephrotoxicity related to nedaplatin and cisplatin was dose dependent, and was similar at the doses at which kidney accumulation was similar. A study has reported that cisplatin-related nephrotoxicity is dose-dependent10,11; our results supported this finding. Cisplatin transfers to the
kidney immediately after administration, and is retained for a longer duration than in other organs. The relationship between nephrotoxicity and kidney accumulation has been indicated. In an in vitro experimental system using renal cortical slices, a study examined the relationship between renal cell disorders related to platinum complexes, including cisplatin, and slices accumulation of the platinum complex. According to the study, there was a correlation between renal toxicity related to a liposome of cisplatin, and slices accumulation of platinum and cellular disorders related to platinum complexes, including cisplatin at the same dose, maximum kidney accumulation was similar between the two agents. However, in a steady state, kidney accumulation of cisplatin was higher, which may lead to renal toxicity. As nedaplatin disappears in plasma immediately after administration, the rate of kidney excretion may be higher than that of cisplatin, contributing to a low kidney accumulation of nedaplatin. As another possibility, the renal cell level of nedaplatin may be lower than that of cisplatin, since it is speculated that cisplatin is ingested by the tubular epithelial cells via a transport system on the basolateral membrane of the kidney tubule. However, we can not conclude which hypothesis should be adopted based on the results of this study. Our results suggest that kidney accumulation of platinum drugs is an important factor influencing the grade of nephrotoxicity. However, this agent has been shown to enhance renal toxicity in the presence of dehydration, and sufficient fluid replacement is important.

In conclusion, these results showed that kidney accumulation of nedaplatin was lower than that of cisplatin, leading to a much lower incidence of renal toxicity related to nedaplatin.

REFERENCES