Cisplatin is a widely used and highly effective antitumor agent. However, its nephrotoxicity is one of its major side effects (Weiner & Jacobs 1983; Jones et al. 1985). Carboplatin is a new platinum-containing analogue, with good antitumor activity and decreased nephrotoxicity (Lellouch et al. 1984; Calvert et al. 1982; Curt et al. 1983; Boyen et al. 1985; Smith & Brock 1988). Cisplatin-induced acute renal failure has been extensively studied (Weiner & Jacobs 1983; Daleke-Yates & McVay 1985; Jones et al. 1985; Siddhi et al. 1986; 1987). Pathological alterations following cisplatin are localized to the S2 segment of the proximal tubule (Weiner & Jacobs 1983; Jones et al. 1985) and the first change in S2 are nuclear segregation and ribosome dispersion (Jones et al. 1985). These findings suggest that the effect of cisplatin on renal cell nuclear function is related to tubular cell injury. In the present study, the differences in pharmacokinetics between cisplatin and carboplatin and their effect on the renal cells were examined in order to investigate the mechanism of cisplatin-induced nephrotoxicity.

Materials and Methods

Cisplatin (Nippon Kayaku, Tokyo, Japan) was freshly dissolved in saline and carboplatin (Bristol Myers Japan, Tokyo, Japan) in 5% glucose prior to use.

Animals: Male Sprague-Dawley rats weighing 200 to 300 g were housed with free access to water and rat chow throughout the experiment.

Platinum concentrations: The experimental animals received either cisplatin at a single dose of 8.5 mg/kg or carboplatin 80 mg/kg intravenously under light anesthesia. Each dose was an equitoxic dose and approximate to LD50. These doses were determined by flameless atomic absorption spectrophotometry (HI- TACHO, 180-70, Tokyo, Japan). Protein in the homogenate was determined by the method of Burton (1956) and serum creatinine levels in the rats treated with cisplatin were significantly higher than in those treated with 100 mg/kg of carboplatin. Cisplatin markedly suppressed the renal nuclear DNA synthesis both in vivo and in vitro when compared with carboplatin. It is concluded that the differences in nephrotoxicity between cisplatin and carboplatin are related to their different inhibitory effects on nuclear DNA synthesis in the renal cells.
p1crate method (Heinegard or 25 μg of cisplatin or carboplatin at 37°C for 1 hr. and then rewarmed 2 ml saline). The rats were killed at 1, 3, 5 or 7 days after treatment from untreated rats.

Triphosphate) carboplatin injection decayed biphasically with a rapid initial period but only up to 24 hr after carboplatin injection. After cisplatin injection accounted for 12.1% min. for cisplatin and 9.2% min. and 4 hr after carboplatin injection. The values are given as mean ± S.D. Statistical analysis was performed to determine if the differences between cisplatin and carboplatin were significant (P < 0.05 or < 0.01). The results are shown in fig. 4.

Discussion

First of all a preliminary experiment was performed to choose the doses to be used. Five rats were injected intravenously with either cisplatin or carboplatin at a single dose of the LD₅₀, respectively. Renal dysfunction and weight loss were observed in all cisplatin treated rats and alimentary tract bleeding was observed in all carboplatin treated rats at 7 days after the injection. One of the cisplatin treated rats died at 7 days, but no death were observed in carboplatin treated rats during 7 days. Based on these results, LD₅₀ was chosen in the pharmacokinetic study to avoid the influence of renal dysfunction and gastrointestinal bleeding after drug injection. LD₅₀ was chosen in the toxic study to distinguish the differences in toxicity.

It is well-known that cisplatin produces acute tubular necrosis in the S₃ segment of the proximal tubule (Weiner & Jacobs 1983; Jones et al. 1985). On the other hand, carboplatin produces little or no kidney damage (Efelevlev et al. 1980).

Toegler et al. (1989) reported that human plasma concentrations of total platinum following cisplatin injection decreased biphasically with a rapid initial period and a prolonged second phase (fig. 1). The initial and second half-life were 38 min. and 12.1 hr for cisplatin, 39 min. and 9.2 hr for carboplatin. Plasma in the whole plasma was detectable for up to 3 days after cisplatin injection but only up to 24 hr after carboplatin injection. Approximately 30% and 90% of total platinum were ultrafilterable for the first 30 min. following cisplatin and carboplatin injection, respectively. The proportion of ultrafilterable platinum in total platinum after carboplatin injection decreased slowly and accounted for 53% at 8 hr. Ultrafilterable platinum was detectable for only up to 2 hr after carboplatin, but 8 hr after carboplatin injection.

Renal tissue concentration of platinum after cisplatin injection were stable up to day 5 (fig. 2). The concentrations following carboplatin injection decreased during the postperiod. Plasma concentrations of total platinum following cisplatin injection decreased biphasically. This may be due to the failure to detect a phase, because the platinum levels for very early phases were not determined. The t₁/₂ of 38 min. for cisplatin was somewhat longer and the t₁/₂ of 12.1 hr for carboplatin and 9.2 hr for carboplatin, were shorter than in previous reports (Laznickova et al. 1980; Säidik et al. 1987). In our study, plasma concentrations of total platinum after cisplatin and carboplatin injection decreased biphasically. This may be due to the failure to detect a phase, because the platinum levels for very early phases were not determined. The t₁/₂ of 38 min. for cisplatin was somewhat longer and the t₁/₂ of 12.1 hr for cisplatin and 9.2 hr for carboplatin, were shorter than in previous reports (Laznickova et al. 1980; Säidik et al. 1987). The results may be due to the small number of the plots of the plasma levels.

Cisplatin is known to be rapidly bound to plasma proteins. The unbound platinum in total plasma platinum after cisplatin injection accumulated for 25% at 45 min. and 8% at one hour after the injection in rats (Säidik et al. 1987). Carboplatin is considered to be slowly bound to plasma proteins (Harrison et al. 1981; van Falho et al. 1984; Laznickova et al. 1986; Säidik et al. 1987). In our study, the proportion of ultrafilterable platinum in total plasma platinum after carboplatin injection was greater than that.
cisplatin was nuclear DNA. However, little information concerning the in vivo effect of cisplatin on DNA function is available (Roberts et al., 1980; Hanuslakova & Ujihara 1987). Based on previous studies and our pharmacokinetic findings, we examined the effect of each drug on the synthesis of nuclear DNA in renal cells. Cisplatin suppressed the synthesis of nuclear DNA in vivo at 12 and 24 hr after the injection, but DNA synthesis was accelerated at 72 hr after the injection. DNA synthesis by nuclei isolated from untreated rats was markedly suppressed after incubation with 10 or 25 μM of cisplatin in vitro. These results indicate that cisplatin affects renal cell nuclear function. The acceleration of synthesis at 72 hr might be caused by renal tubular regeneration, because regenerative cells which had cleared nuclei and autophagic vacuoles were observed at 72 hr after the injection (data not shown). Cisplatin did not suppress the synthesis of nuclear DNA in vitro, however, suppressed it in vivo, but to a smaller extent than cisplatin. These findings support previous results showing that high-dose cisplatin can produce severe nephrotoxicity (Curt et al., 1983). Siddik et al. (1987) reported that cisplatin and carboplatin might be related to the nephrotoxicities of the two compounds. In our study, renal tissue platinum levels after cisplatin injection were significantly higher than after carboplatin injection. This is consistent with the results of nuclear DNA synthesis in renal cells. In conclusion, DNA is the target responsible for the cytotoxic action of platinum compounds (Zelding & Kohn 1980; Roberts et al., 1986; Hanuslakova & Ujihara 1987). There may be a similar nuclear component to the mechanism of S, tubular cell injury. The difference in nephrotoxicity between cisplatin and carboplatin was probably due to the difference in the inhibitory effect on nuclear DNA synthesis. The effect of cisplatin on renal cells plays an important role in its nephrotoxicity.