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Comparative nephrotoxicity of carboplatin and cisplatin in combination with tobramycin

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Summary. The nephrotoxic potentials of cisplatin and carboplatin, alone and in combination with the aminoglycoside antibiotic tobramycin, were compared in male rats. Sixty (60) male Sprague-Dawley rats were divided into six groups of ten rats each and received the following treatments: Group I, saline; group II, cisplatin (5 mg/kg); group III, cisplatin (5 mg/kg) + tobramycin (50 mg/kg); group IV, carboplatin alone (50 mg/kg); group V, carboplatin (50 mg/kg) + tobramycin (50 mg/kg); and group VI, tobramycin alone (50 mg/kg). Carboplatin and cisplatin were each administered as a single i.v. injection on day 1. Tobramycin was administered i.–m. once daily on days 1–5. All rats were euthanatized on day 6. Smaller body weight gains occurred in groups II–V than in saline controls. Serum urea nitrogen (BUN) levels recorded on day 6 were elevated in group III. BUN values of all other groups were normal. Histopathologic examination of kidneys revealed acute tubular injury in rats treated with cisplatin, whether alone or in combination with tobramycin, and in carboplatin/tobramycin-treated rats. Carboplatin and tobramycin, when administered separately, were not nephrotoxic. The combination of cisplatin and tobramycin proved to be the most nephrotoxic treatment.

Introduction

Cisplatin (*cis*-diamminedichloroplatinum II; CDDP) is a widely used and highly effective antitumor agent against several types of neoplasms, including testicular, ovarian, and lung tumors and carcinomas of the head and neck [3, 4, 10, 16, 26, 27, 34, 36]. One of the major dose-limiting side-effects of this valuable drug is nephrotoxicity [1, 2, 9, 11, 19–21, 23, 28, 30, 32, 33]. Therefore, a search for platinum-containing analogues with the same or increased efficacy against cancer, but with less nephrotoxicity and other side-effects than cisplatin, has been in progress for some time.

Carboplatin (*cis*-diammine-1,1-cyclobutane dicarboxylate platinum II; CBDCA; JM-8) is a new platinum-containing analogue which promises good anticancer activity and decreased nephrotoxicity [5–8, 13–15, 22, 24, 25, 29, 31, 35].

Infections are a frequent cause of morbidity in the compromised cancer patient and often necessitate antibiotic therapy. The use of certain broad-spectrum antibiotics, which are potentially nephrotoxic in themselves, may add to the renal toxicity of the anticancer agent. Tobramycin (TOB), an aminoglycoside antibiotic, has been shown to have an additive nephrotoxic effect upon cisplatin nephrotoxicity in rats [18].

In an attempt to evaluate the potential nephrotoxic liability of combined antitumor and antibiotic therapy, we have investigated and compared the nephrotoxicity of cisplatin and carboplatin, alone and in combination with TOB.

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Materials and methods

Sixty (60) male 7-week-old Sprague-Dawley rats (Crl: CD(SD) BR] weighing 150–170 g were obtained from Charles River Breeding Laboratories, Inc., Wilmington, Mass. They were conditioned for 5 days prior to use in the study. Study rats were housed individually in wire-bottom stainless steel cages. Food (Purina Rodent Chow ≠5001, Ralston Purina, St. Louis, Mo) and water were provided ad libitum, except as necessary prior to obtaining blood samples for urea nitrogen (BUN) determinations.

Sixty (60) male rats with BUN values within the normal range established in our laboratory were each randomly assigned to one of six treatment groups consisting of ten rats each. The treatment groups with their respective test compounds and dosages are outlined in Table 1. Single doses of cisplatin (Platinol, Bristol Laboratories, Syracuse, NY) or carboplatin (Bristol Laboratories, Syracuse, NY) were administered i.v. on day 1 and TOB (Dista Products Company, Indianapolis, Ind) was injected i.m. on days 1–5. Rats in the negative control group received

Table 1. Study design

Group no.	Test Compound	Dose level (mg/kg)	Concentration (mg/ml)	Dose volume (ml/100 g) i.v./i.m.
I	Saline	–	0	0.25/0.125
II	Cisplatin	5.0	2.0	0.25/–
III	Cisplatin/TOB	5.0/50	2.0/40	0.25/0.125
IV	Carboplatin	50	25	0.2/–
V	Carboplatin/TOB	50/50	25/40	0.2/0.125
VI	TOB	50	40	–/0.125

an i.v. injection of saline (Travenol Laboratories, Inc., Deerfield, Ill) on study day 1, and a single i.m. injection of saline on each of study days 1–5.

The cisplatin dose of 5.0 mg/kg had been previously determined in our laboratory to produce a suitable level of histopathologically evident nephrotoxicity in male Sprague-Dawley rats. This dose was comparable to the LD_{10} (IV injection, 14-day observation) of 6.8 mg/kg reported for cisplatin in Fischer 344 male rats [33].

The dose of 50 mg/kg was used for carboplatin as it was the maximum tolerated (nonlethal) single dose determined in our laboratory. This dose is approximately equal to the LD_{10} of 52 mg/kg in F344 male rats.

The TOB dose of 50 mg/kg was 10% of the LD_{50} in rats [18] and was considered to be a non-nephrotoxic dose.

Body weights were recorded twice, once on day 1 and once on day 5, and percentage gains for each group were determined and compared. Serum urea nitrogen (BUN) was determined for all rats 2 days before treatement and at the termination of the study on study day 6 (Centrifichem System 600, Baker Instruments, Allentown, Pa). Blood samples were collected from the tail vein prior to the study and by cardiac puncture at the termination of the study.

On study day 6, all rats were euthanatized with an i.p. injection of sodium pentobarbital. Kidneys were collected and examined grossly. A longitudinal section of the left kidney and a cross section of the right kidney from each rat were preserved in 10% neutral buffered formalin for histopathological evaluation. Kidney tissue was embedded in paraffin, sectioned at approximately 3–6 μm, and stained with hematoxylin and eosin.

Microscopic renal lesions were scored using a slightly modified, previously described scheme for comparison of aminoglycoside nephrotoxicities, which was deemed suitable for platinum-containing agents as well [17]. Lesions encountered in the renal cortex and the outer stripe of the medulla included tubular vacuolar or granular degeneration, peritubular mononuclear cell infiltration, tubular necrosis, tubular dilatation, tubular basophilia, and peritubular (interstitial) fibrosis. The severity of each of these lesions in both kidneys of each rat was scored as follows: 0, absence of lesion; 1, lesion present in fewer than 10% of the nephrons; 2, lesion present in 10%–50% of the nephrons; 3, lesion present in 51%–90% of the nephrons; and 4, lesion present in more than 90% of the nephrons. The lesion scores were summed to produce a single nephrotoxicity score for each rat, with a possible range of 0–24.

Statistical significance of differences in BUN values, body weight data, and nephrotoxicity scores between groups was evaluated using a one-way analysis-of-variance model. The Dunnett multiple comparison procedure (two-tailed at $\alpha = 0.05$) was used to compare mean parameter values of each test group with negative control, and mean values of cisplatin /TOB and carboplatin/TOB with TOB. Independent multiple t-statistics ($\alpha = 0.05$) were used to compare mean parameter values of cisplatin with carboplatin and cisplatin/TOB, carboplatin with carboplatin/TOB, and cisplatin/TOB with carboplatin/TOB.

Results

All rats exhibited body weight gains during the course of the study (Table 2). Control rats exhibited a 15% body weight gain during the study. Smaller body weight gains than in controls were observed in groups receiving cisplatin or carboplatin, alone or in combination with TOB. The smallest body weight gain occurred in group III (cisplatin/TOB), where a 3% gain was observed. TOB-treated rats (group VI) showed body weight gains comparable to those in controls.

Table 2. Body weight gains

Group no.	Treatment	Body weights (g)		
		Day 1	Day 5	% Change
I	Saline (control)	223 ± 4[a]	256 ± 4	15 ± 1
II	Cisplatin	219 ± 3	237 ± 4*	8 ± 1*
III	Cisplatin/TOB	219 ± 3	227 ± 5*	3 ± 1*
IV	Carboplatin	220 ± 4	243 ± 5	10 ± 1*
V	Carboplatin/TOB	220 ± 3	237 ± 3*	8 ± 1*
VI	TOB	219 ± 4	252 ± 5	15 ± 1

[a] Mean ± standard error
* Significantly different from control at $\alpha = 0.05$

Table 3. Pre- and post-treatment mean BUNs

Group no.	Test compound(s)	Pretreatment BUN (mg/dl)	Post-treatment BUN (mg/dl)
I	Saline (control)	16	14 ± 0.6[a]
II	Cisplatin	15	16 ± 1.3
III	Cisplatin/TOB	15	37 ± 5.7*
IV	Carboplatin	18	14 ± 0.5
V	Carboplatin/TOB	14	13 ± 0.4
VI	TOB	15	13 ± 0.6

[a] Mean ± standard error
* Significantly different from control, group II, and group V values at $\alpha = 0.05$

The results of the BUN determinations are presented in Table 3. The mean BUN level of group III rats was elevated on day 6 to above the pretreatment mean and above the mean BUN values of the negative control rats (group I). Mean BUN values of the other treatment groups were all within the normal range and not elevated significantly above control means.

At necropsy, pallor (a grayish-white zone) at the corticomedullary junction was observed in ten rats in group II and nine rats in group III. The severity of this change appeared to be slightly greater in group III rats. Pallor of the cortex was observed in seven rats in each of groups III and V and in ten rats in group VI. The severity of this change was equal in groups III and V, and only slightly more marked in group VI. No gross changes were observed in kidneys of rats in group IV.

The mean nephrotoxicity scores for each treatment group are presented in Fig. 1, and the means for each of six renal lesions are listed by treatment group in Table 4. The negative control rats exhibited a number of renal cortical lesions that closely resembled some of the drug-related nephrotoxic lesions observed in this study. These lesions included multifocal tubular degeneration, pertibular mononuclear cell infiltration, tubular dilatation, and pertibular fibrosis. The morphologic character and extent of these lesions in the saline-treated rats were similar to those occasionally observed in control rats for other studies pre-

Table 4. Mean histopathologic nephrotoxicity scores in rats

Group no. ($n = 10$)	Test compound(s)	Mean score for each renal lesion[a]						Total mean nephrotoxicity score
		Deg	MCI	Nec	Dil	Bas	Fib	
I	Saline	0.8	1.2	0	0.2	0	0.2	2.4 ± 0.5[b]
II	Cisplatin	1.7	0.8	2.1	0	1.3	0	5.9 ± 0.6*
III	Cisplatin/TOB	2.7	0.4	2.5	0	1.0	0.2	6.8 ± 0.5*
IV	Carboplatin	0.8	0.9	0.1	0.1	0	0.2	2.1 ± 0.6[c]
V	Carboplatin/TOB	1.4	1.1	0.2	0.6	0	0.7	4.0 ± 0.6[d]
VI	TOB	0.8	0.8	0	0.2	0	0.4	2.2 ± 0.4

[a] Deg, tubular degeneration; MCI, peritubular mononuclear cell infiltration; Nec, tubular necrosis; Dil, tubular dilatation; Bas, tubular basophilia; Fib, peritubular fibrosis
[b] Mean ± standard error
[c] Significantly different from group II score
[d] Significantly different from group III and group IV scores
* Significantly different from control at $\alpha = 0.05$

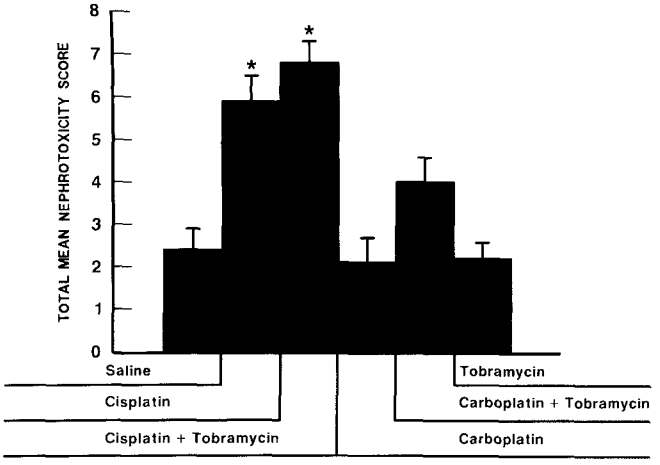

Fig. 1. Total mean nephrotoxicity scores of rats treated with saline, cisplatin (5 mg/kg), cisplatin + tobramycin (5 + 50 mg/kg), carboplatin (50 mg/kg), carboplatin + tobramycin (50 mg/kg) and tobramycin (50 mg/kg). Mean scores of ten rats are displayed with standard errors. Total scores represent a composite of six lesion scores listed in Table 4

viously conducted in our laboratory. The renal cortical lesions observed in the control rats of this study provided baseline data against which similar lesions in drug-treated rats were compared.

Rats treated with TOB 50 mg/kg alone (group VI) exhibited slight tubular degeneration, peritubular mononuclear cell infiltration, tubular dilatation, and tubular fibrosis. These lesions were qualitatively and quantitatively similar to those in the negative control rats. Therefore, this dose of TOB was considered non-nephrotoxic. The most prominent renal lesion present in rats in groups II (cisplatin) and III (cisplatin/TOB) was tubular necrosis in the outer stripe of the medulla (Figs. 2 and 3). Tubular necrosis was observed in nine rats in each of groups II and III. The severity of tubular necrosis in group III (TOB and cisplatin) was slightly greater than that in group II. Tubular vacuolar or granular degeneration, peritubular mononuclear cell infiltration, and tubular basophilia also occurred frequently in groups II and III. The mean severity scores for these three lesions were comparable, except in the case of tubular degeneration, which appeared to be more exten-

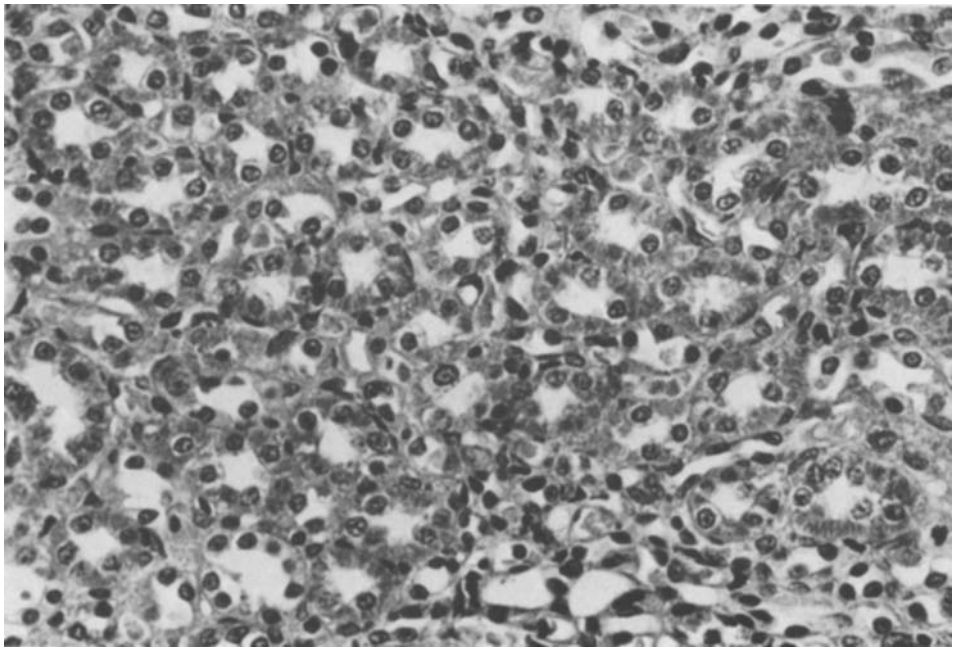

Fig. 2. Normal outer stripe of the renal medulla of a control rat

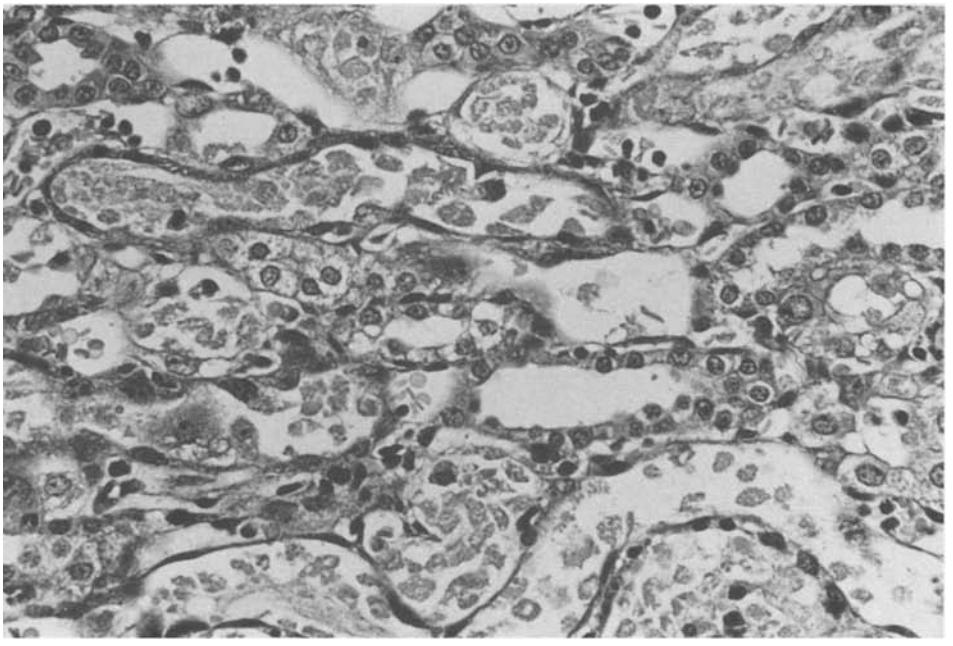

Fig. 3. Acute tubular necrosis in the outer stripe of the medulla in rat treated with cisplatin 5.0 mg/kg. This lesion was qualitatively and quantitatively similar to that seen in rats treated with cisplatin 5.0 mg/kg and tobramycin 50 mg/kg

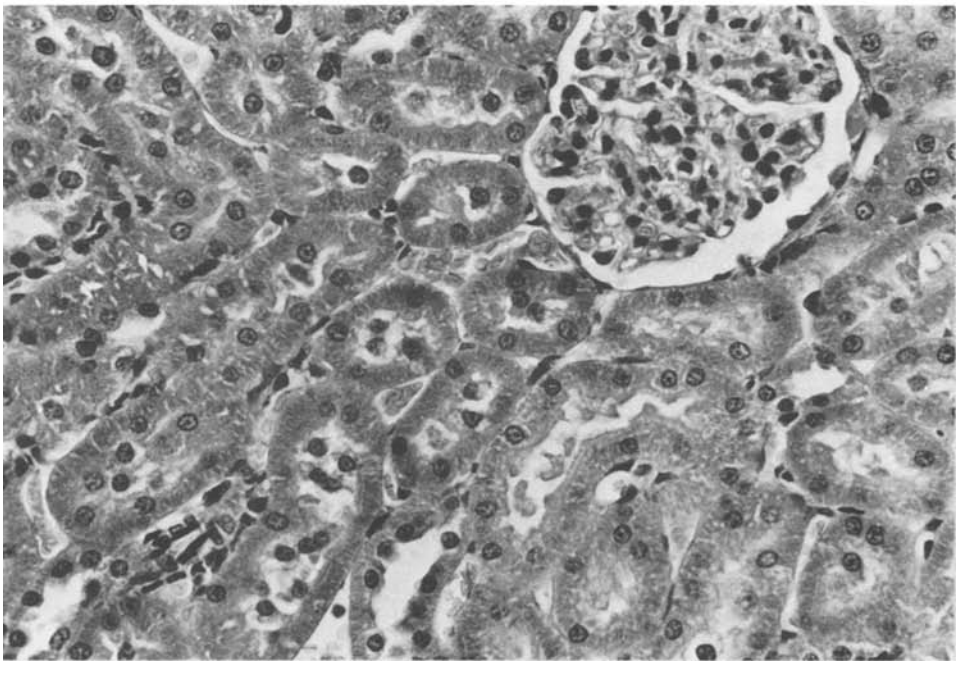

Fig. 4. Normal renal cortex in a control rat

sive in the outer region of the renal cortices of group III than of group II rats (Figs. 4 and 5).

The mean total nephrotoxicity score of carboplatin-treated rats (group IV) was also similar to that of the negative control group. Qualitatively, the lesions were nearly identical to those of the controls. The mean total nephrotoxicity score of rats treated with both carboplatin and TOB was greater than that of rats treated with either carboplatin or TOB alone. The difference was due to an increased incidence and severity of tubular degeneration, necrosis, dilatation, and peritubular fibrosis. Peritubular fibrosis in four of six affected rats was multifocal and distributed prominently along the corticomedullary junction (Fig. 6). This particular distribution of peritubular fibrosis was distinctly different from the foci of spontaneous peritubular fibrosis exhibited by control rats, which tended to be scattered randomly in the outer cortex. The fibroplasia exhibited by group V (carboplatin /TOB) rats was characterized by proliferations of fibroblasts and an absence of mature collagen bundles. The peritubular fibrosis in these rats was considered to be immature, produced during the time frame of the study, and therefore treatment-related. The peritubular fibrosis in group V was attributed primarily to a carboplatin drug effect, because its distribution along the corticomedullary junction resembled the distribution of cisplatin lesions in group II. Tubular degeneration in the renal cortex was also more prominent in group V (carboplatin/TOB) rats than in rats treated with either

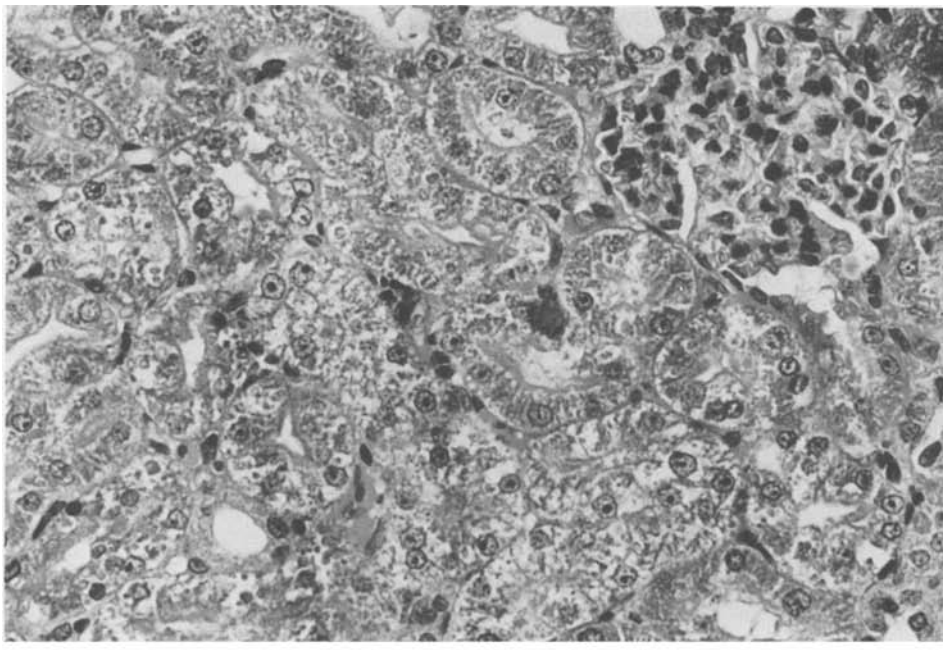

Fig. 5. Acute vacuolar (granular) tubular degeneration in outer cortex of rat treated with cisplatin and tobramycin. This lesion was not observed in rats treated with cisplatin, carboplatin, or tobramycin alone

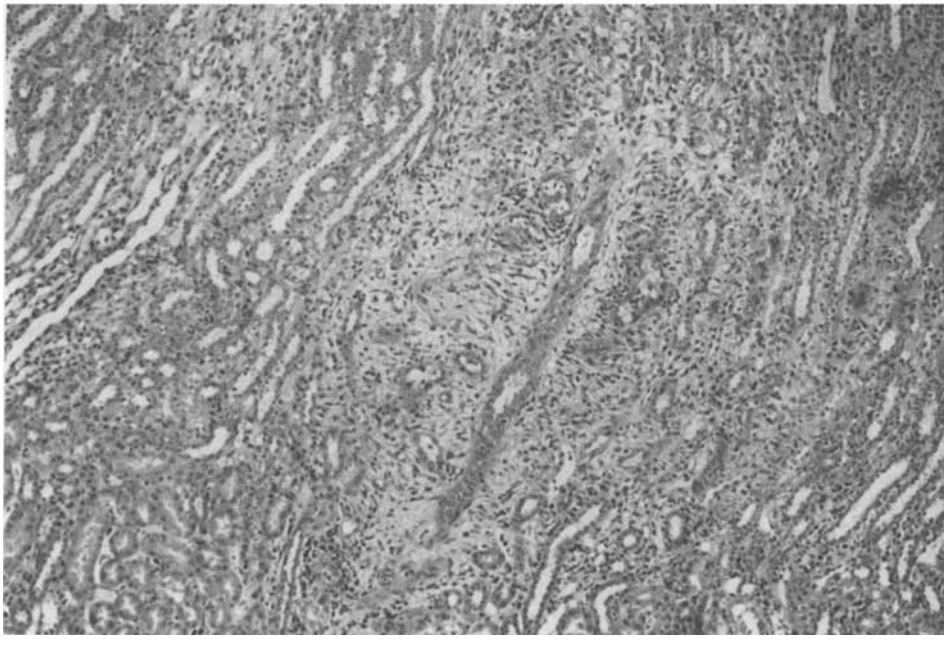

Fig. 6. Peritubular fibrosis at the corticomedullary junction in the most severely affected rat treated with a combination of carboplatin 50 mg/kg and tobramycin 50 mg/kg. Comparable lesions were not apparent in rats of other treatment groups.

carboplatin or TOB alone (Fig. 7). Tubular degeneration in the renal cortex was attributed primarily to TOB, as this lesion was also seen in rats treated with a combination of cisplatin and TOB.

Discussion

In this study, cisplatin alone produced tubular necrosis along the outer stripe of the medulla, which is the principal lesion of acute cisplatin nephrotoxicity [33]. Carboplatin, however, did not produce any significant nephrotoxicity when administered alone at ten times the cisplatin dose.

The coadministration of cisplatin and TOB in the present study produced acute tubular necrosis typical of cisplatin toxicity, plus acute tubular degeneration of the inner and outer cortex. These findings are in general agreement with those of Kawamura et al. [18], who reported that the combination of cisplatin and tobramycin produced acute tubular necrosis in the inner and outer cortex to a greater extent than did cisplatin alone. Our studies further demonstrated that TOB 50 mg/kg, when administered along with carboplatin, precipitated nephrotoxicity, although neither carboplatin 50 mg/kg nor TOB 50 mg/kg was nephrotoxic when administered alone.

The addition of TOB to either cisplatin or carboplatin treatment appeared to have an additive effect upon the nephrotoxicity of these anticancer agents. In the case of the cisplatin/TOB combination, the higher nephrotoxicity of the combination appeared to have been contributed pri-

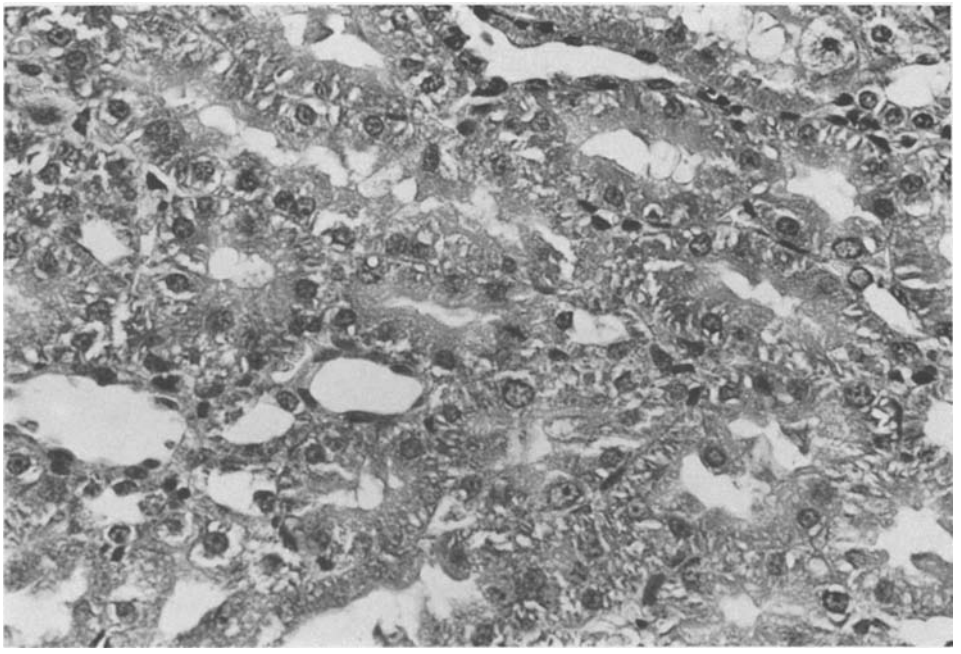

Fig. 7. Acute vacuolar tubular degeneration in the outer cortex of a rat treated with a combination of carboplatin and tobramycin

marily by the TOB component of the combination, as cortical tubular degeneration was the renal lesion most increased. Diffuse cortical tubular degeneration was not observed with either cisplatin or carboplatin alone, but was observed in both combinations with TOB. In the case of the carboplatin/TOB combination, multifocal peritubular fibrosis along the corticomedullary junction and cortical tubular degeneration were features of the combination's nephrotoxicity, but were not observed in rats treated with either carboplatin or TOB alone. Unlike the diffuse cortical tubular degeneration, pertitubular fibrosis was attributed to an effect of carboplatin, because distribution of the lesion along the corticomedullary junction resembled the distribution of lesions produced by the analogue cisplatin.

The conclusion of our study was that the coadministration of TOB 50 mg/kg daily for 5 days in conjunction with a single 5.0 mg/kg dose of cisplatin was more nephrotoxic than the same dose of TOB in combination with carboplatin 50 mg/kg.

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References

1. Bitran JD, Desser RK, Billings AA, Kozloff MF, Shapiro CM (1982) Acute nephrotoxicity following *cis*-dichloro-diamine-platinum. Cancer 49: 1784
2. Blackley JD, Hill JB (1983) Renal and electrolyte disturbances associated with *cis*-platin. Ann Intern Med 95: 628
3. Bruckner JW, Cohen CJ, Wallach RC, Kabakow B, Deppe G, Greenspan EM, Gusberg SB, Holland JF (1978) Treatment of advanced ovarian cancer with cis-dichlorodiammine-platinum (II): Poor-risk patients with intensive prior therapy. Cancer Treat Rep 62: 555
4. Burchenal JH (1978) A clinical overview of dichlorodiammino platinum. Biochimie 60: 915
5. Calvert AH, Harland SJ, Harrap KR, Wiltshaw E, Smith IE (1984) JM8 development and clinical projects. Dev Oncol 17: 240
6. Calvert AM, Harland SJ, Newell DR, Siddik ZH, Jones AC, McElwain TJ, Raju S, Wiltshaw E, Smith IE, Baker JM, Peckham MJ, Harrap KR (1982) Early clinical studies with *cis*-diammine-1,1-cyclobutane decarboxylate platinum II. Cancer Chemother Pharmacol 9: 140
7. Curt GA, Grygiel JJ, Corden BJ, Ozols RF, Weiss RB, Tell DT, Myers CE, Collins JM (1983) A phase I and pharmacokinetic study of diammine-cyclobutane-dicarboxylatoplatinum (NSC 241240). Cancer Res 43: 4470
8. Daskal Y, Prestayko AW, Crooke ST (1980) Morphological manifestations of Cisplatin analogs in rats: an ultrastructural study. In: Prestayko AW, Crooke ST, Carter SK (eds) Cisplatin. Academic, New York, p 249
9. Dentino M, Luft FC, Yum MN, Williams SD, Einhorn LH (1978) Long-term effect of *cis*-diamminedichloride platinum (CDDP) on renal function and structure in man. Cancer 41: 1274
10. Einhorn LH, Williams SD (1979) The role of cisplatinum in solid-tumor therapy. N Engl J Med 300: 289
11. Goldstein RS, Noordewier B, Bond JT, Hook JB, Mayor GH (1981) *cis*-Dichlorodiamineplatinum nephrotoxicity: time course and dose response of renal function impairment. Toxicol Appl Pharmacol 60: 163
12. Gonzalez-Vitale JC, Hayes DM, Cvitkovic E, Sternberg SS (1978) Acute renal failure after *cis*-dichlorodiammineplatinum (II) and gentamicin-cephalothin therapies. Cancer Treat Rep 62: 693
13. Harland SJ, Smith IE, Smith N, Alison DI, Calvert AH (1984) Phase II study of *cis*-diammine-1,1-cyclobutane dicarboxylate platinum II (CBDCA, JM8) in carcinoma of bronchus. Dev Oncol 17: 353
14. Harrap KR (1983) Platinum analogues: criteria for selection. In: Muggia FM (ed) Cancer chemotherapy, vol 1. Nijhoff, Boston, p 171
15. Harrap KR, Jones M, Wilkinson CR, Clink HM, Sparrow S, Mitchley BCV, Clarke S, Veasey A (1980) Antitumor, toxic and biochemical properties of cisplatin and eight other platinum complexes. In: Prestayko AW, Crooke ST, Carter SK (eds) Cisplatin. Academic, New York, p 193

16. Highby DJ, Wallace HJ, Albert DJ, Holland JF (1974) Diamminochloroplatinum: a phase I study showing responses in testicular and other tumors. Cancer 33: 1219
17. Hottendorf GH, Gordon LL (1980) Comparative low-dose nephrotoxicities of gentamycin, tobramycin, and amikacin. Antimicrob Agents Chemother 18: 176
18. Kawamura J, Soeda A, Yoshida O (1981) Nephrotoxicity of *cis*-diamminedichloroplatinum (II) (*cis*-platinum) and the additive effect of antibiotics: Morphological and functional observation in rats. Toxicol Appl Pharmacol 38: 535
19. Kociba RJ, Sleight SD (1971) Acute toxicologic and pathologic effects of *cis*-diamminedichloroplatinum (NSC-119875) in the male rats. Cancer Chemother Rep 55: 1
20. Krakoff IH (1979) Nephrotoxicity of *cis*-dichlorodiammineplatinum (II). Cancer Treat Rep 63: 1523
21. Lehane D, Winston A, Gray R, Daskal Y (1979) The effect of diuretic pretreatment on clinical, morphological and ultrastructural Cisplatinum induced nephrotoxicity. Int J Radiat Oncol Biol Phys 5: 1393
22. Lelieveld P, Van der Vijgh WJF, Veldhuizen RW, Van Velzen D, Van Putten LM, Atassi G, Danguy A (1984) Preclinical studies on toxicity, antitumor activity and phrmacokinetics of cisplatin and three recently developed derivatives. Eur J Cancer Clin Oncol 8: 1087
23. Madias NE, Harrington JT (1978) Platinum nephrotoxicity. Am J Med 65: 307
24. Nicaise C, Rozencweig M, Crespeigne N, Lenaz L, Kenis Y (1983) Phase I study of carboplatin (CBDCA) at a 5-day i.v. schedule. Proceedings of the Second European Conference of Clinical Oncology, Amsterdam, November 1983, vol 1, 67
25. Peckham MJ, Horwich A, Hendry WF (1985) Advanced seminoma: treatment with *cis*-platinum-based combination chemotherapy or carboplatin (JM-8). Br J Cancer 52: 7
26. Rozencweig M, von Hoff DD, Slavik M, Muggia FM (1977) *cis*-diamminedichloroplatinum (II), a new anticancer drug. Ann Intern Med 86: 803
27. Rozencweig M, von Hoff DD, Abele R, Muggia FM (1980) *cis*-platin. In: Pinedo HM (ed) EORTC Cancer Chemotherapy Annual 2. Excerpta Medica, Amsterdam, pp 107–117
28. Schaeppi U, Heyman IA, Fleischman RW, Rosenkrantz H, Ilievski V, Phelan R, Cooney DA, Davis RD (1973) *cis*-Dichlorodiammineplatinum (II) (NSC-119875): Preclinical toxicologic evaluation of intravenous injection in dogs, monkeys and mice. Toxicol Appl Pharmacol 25: 230
29. Smith IE, Harland SJ, Robinson BA, Evans BD, Goodhart LC, Calvert AH, Yarnold J, Glees JP, Baker J, Ford HT (1985) Carboplatin: a very active new cisplatin analog in the treatment of small cell lung cancer. Cancer Treat Rep 69: 43
30. Stark JJ, Howell SB (1978) Nephrotoxicity of *cis*-platinum (II) dichlorodiammine. Clin Pharmacol Ther 23: 461
31. Van Echo DA, Egorin MJ, Whitacre MY, Olman EA, Aisnir J (1984) Phase I clinical and pharmacologic trial of carboplatin daily for 5 days. Cancer Treat Rep 68: 1003
32. Von Hoff DD, Schilsky R, Richart CM, Reddick RL, Rozencweig M, Young RC, Muggia FM (1979) Toxic effects of *cis*-dichlorodiammineplatinum (II) in man. Cancer Treat Rep 63: 1527
33. Ward JM, Fauvie KA (1976) The nephrotoxic effects of *cis*-diammine-dichloroplatinum (II) (NSC-119875) in male F344 rats. Toxicol Appl Pharmacol 38: 535
34. Williams CJ, Whitehouse JMA (1979) *cis*-platinum, a new anticancer agent. Br Med J 1: 1689
35. Wiltshaw E, Evans BD, Jones AC, Baker JW, Calvert AH (1983) JM-8, successor to cisplatin in advanced ovarian carcinoma? Lancet 1: 587
36. Zubrod CG (1980) The fifth Myron Karon memorial lecture. The cure of cancer by chemotherapy – reflections on how it happened. Med Pediatr Oncol 8: 107

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