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Short communication

Potentiation of *cis*-diamminedichloroplatinum nephrotoxicity by amikacin in rats*

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Summary. The nephrotoxic interaction between *cis*-diamminedichloroplatinum (CDDP) and amikacin (AMI) was studied in rats. Following a single dose of CDDP (5 mg/kg i.v.), AMI (60 mg/kg s.c.) was given for 14 days. When given alone CDDP caused a 40% fall in the glomerular filtration rate (GFR), whereas AMI alone had no effect on GFR. This nonnephrotoxic course of AMI potentiated the CDDP-induced fall in GFR. Only a limited recovery of renal function was observed during a 15-week follow-up period.

Introduction

As many chemotherapeutic drugs are myelosuppressive, anticancer treatment may be complicated by serious infections requiring specific antibiotic treatment. Aminoglycosides are the drugs of choice for many gram-negative bacterial infections. Since both the chemotherapeutic drug *cis*-diamminedichloroplatinum (CDDP) and aminoglycosides are nephrotoxic, a potentiation of the nephrotoxicity is possible when these drugs are used in combination.

Clinically, the incidence of nephrotoxicity has been reported to be greater in patients receiving CDDP in combination with aminoglycosides than in patients receiving CDDP alone. The degree of renal impairment has usually been mild and not clinically significant [7]. However, acute renal insufficiency has been reported following the combined use of CDDP with gentamicin-cephalotin [6].

Experimental studies in rats have shown a potentiation of the CDDP-induced nephrotoxicity by tobramycin [1, 9]. The present study deals with acute and chronic changes in renal function in rats, caused by the interaction between a single dose of CDDP immediately followed by amikacin (AMI) for 14 days. AMI was chosen as the aminoglycoside to be studied, as we have previously shown that it is less nephrotoxic than gentamicin [10].

Materials and methods

Adult male Wistar rats of an outbred strain were used (Zentral Institut für Versuchstierzucht, Hannover, FRG). Food and tap water were available ad libitum.

Renal function determination. The glomerular filtration rate (GFR) and effective renal plasma flow (ERPF) were determined by a plasma clearance technique, as previously described in detail elsewhere [11]. In pentobarbital-anesthetized rats (60 mg/kg i.p.), a dose of 0.25 MBq Cr-51 EDTA and 0.04 MBq I-125 Iodohippurate (Amersham International, Amersham, England) was injected i.v. A single, timed blood sample of about 0.5 ml was obtained from the orbita 60 min after the i.v. injection, allowing for repeated use in the same animal.

Experimental design. At the start of the experiment, the animals were divided into four groups, each consisting of 8–10 animals. The rats were about 12 weeks old. The mean body wt of the various groups then ranged from 300 to 325 g (Table 1).

CDDP (kindly provided by Bristol-Myers BV, Weesp, The Netherlands) was given in a single i.v. injection at a dose of 5 mg/kg body wt. (CDDP-5). AMI (kindly provided by Bristol-Myers BV, Weesp, The Netherlands) was given s.c., daily for 2 weeks, at a dose of 60 mg/kg (AMI-60). Controls received saline i.v. and/or s.c. When the drugs were given in combination, the AMI was started on the day of the CDDP injection. Renal function was measured at weeks 2, 6, and 15 after the first drug injection.

Statistics. Statistical differences between the means of the various parameters were assessed by one-way analysis of variance. In case of statistically significant differences, i.e., an F value indicating $P < 0.05$, the Newman-Keuls test was applied to detect which pair(s) of means were different. The analyses were carried out with commercially available software (SPSS/PC+; SPSS Inc, Chicago, Ill) on a personal computer.

Results

Data on the longitudinal changes in BW, GFR, and ERPF following the various treatments are presented in Table 1.

A single CDDP injection of 5 mg/kg was fatal for three out of nine rats. In the remaining six animals, CDDP-5 caused a significant, 40% fall in GFR, measured 2 weeks after the injection. Only a slight recovery of the GFR was observed during the follow-up. The ERPF fell as well, but compared with that of controls, the difference was not statistically significant.

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Table 1. Longitudinal changes in body wt (g), GFR and ERPF (ml/min per 100 g body wt) of the various groups of rats treated

	C	CDDP-5	AMI-60	CDDP-5/AMI-60
Week 0	(8)	(9)	(8)	(10)
Body wt	311 ± 19	300 ± 18	325 ± 30	315 ± 30
Week 2	(8)	(6)	(8)	(6)
Body wt	343 ± 26	304 ± 26*	349 ± 32	302 ± 43*
GFR	0.740 ± 0.087	0.427 ± 0.149*	0.794 ± 0.066	0.208 ± 0.193**
ERPF	1.774 ± 0.164	1.331 ± 0.358	1.747 ± 0.209	0.703 ± 0.627**
Week 6	(8)	(6)	(8)	(5)
Body wt	390 ± 35	347 ± 37	413 ± 46	335 ± 76
GFR	0.676 ± 0.046	0.453 ± 0.140*	0.682 ± 0.060	0.249 ± 0.238**
ERPF	1.461 ± 0.076	1.278 ± 0.277	1.359 ± 0.217	0.679 ± 0.657**
Week 15	(8)	(6)	(8)	(3)
Body wt	460 ± 41	423 ± 32	490 ± 45	424 ± 97
GFR	0.638 ± 0.064	0.429 ± 0.116*	0.616 ± 0.050	0.217 ± 0.191**
ERPF	1.288 ± 0.137	1.191 ± 0.201	1.205 ± 0.161	0.595 ± 0.301**

All data are mean ± SD
* $P < 0.05$ vs controls (C); ** $P < 0.05$ vs C, AMI-60, and CDDP-5
Statistically significant differences between CDDP-5 and AMI-60 are not presented

The GFR and ERPF of rats treated with AMI at a dose of 60 mg/kg for 14 days did not differ significantly from those of controls.

The combined treatment of CDDP-5 and AMI-60 was fatal for four out of ten adult rats. The GFR and ERPF of the remaining six rats, measured at week 2, were significantly lower than those of controls as well as those of rats treated with either AMI-60 or CDDP-5 alone. During the follow-up, another three rats that received the combined treatment died with signs of renal failure. Neither the GFR nor the ERPF showed much further recovery, and both levels remained significantly below those of the other three groups.

Discussion

The present experiments were carried out to study the effect of the nonnephrotoxic course of an aminoglycoside given immediately after a single nephrotoxic dose of CDDP. The results indicate that the aminoglycoside, AMI, potentiates the renal impairment induced by CDDP.

Although both CDDP and aminoglycosides are nephrotoxic, the mode of action and time course of the renal changes are different. Even a single dose of CDDP has been reported to induce nephrotoxic changes [2, 3, 8]. Functional changes reach their peak 3–7 days after a single injection. A partial recovery of the renal function occurs predominantly in the following 1–2 weeks, but some permanent impairment remains.

With aminoglycosides, dose-dependent functional changes develop only after prolonged treatment. In rats, the main decrease in GFR has been found during the second week [4, 5, 10]. Subsequently, the GFR may increase again despite the continuation of the aminoglycoside treatment, and the kidney becomes temporarily insensitive to aminoglycosides [4, 5].

The interaction between CDDP and AMI may be viewed from two perspectives: it may be regarded either as a potentiation by AMI of the CDDP nephrotoxicity or as an increased sensitivity to AMI in the kidney predamaged by CDDP. In our opinion, the permanence of the impairment to the GFR caused by this combined treatment is an important feature. The changes in GFR induced by this treatment display almost the same characteristics as the changes in GFR induced by treatment with CDDP alone. Consequently, we surmise that the changes induced by the combined treatment can best be explained as an aminoglycoside-induced potentiation of CDDP nephrotoxicity. Our present findings are in agreement with previous reports that a nonnephrotoxic dose of tobramycin [1, 9], given shortly after CDDP treatment, potentiated the CDDP-induced nephrotoxicity. This indicates that such a potentiation may be common for all aminoglycosides.

In conclusion, the inoculation of a nonnephrotoxic course of AMI immediately following a single dose of CDDP causes a potentiation of the impairment to renal function caused by CDDP alone.

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