ACTION OF CISPLATIN AND CYCLOPLATAM ON THE RAT KIDNEY

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Cisplatin is a very effective therapeutic substance for chemotherapy of malignant tumors, but its use is limited by its high nephrotoxicity [5]. Consequently, ways are being sought to prevent disturbances of renal activity and attempts have been made to synthesize a new platinum preparation with equally high antitumor activity but with lower toxicity for the kidneys. One such new substance is cycloplatam [amine(cyclopentylamine)-S-(-)-malatoplatinum (II)] [3], which has marked ability to affect tumor growth but does not cause the blood level of creatinine in mice to rise [4].

The aim of this investigation was to compare the action of cisplatin and cycloplatam on the kidney after their administration to rats.

EXPERIMENTAL METHOD

Experiments were carried out on 32 female Wistar albino rats weighing 250-300 g. Cisplatin was injected intraperitoneally in a dose of 5 mg/kg body weight, cycloplatam in doses of 10 and 25 mg/kg body weight. Each group consisted of eight animals. On the 5th day after injection, water was introduced into the stomach through a tube in a volume of 5 ml/100 g body weight, after which the urine was collected for 2 h. After the end of the experiment blood was taken from the rats under ether anesthesia and the kidney removed. The urea concentration was determined in the blood serum and urine by the reaction with diacetylmonoxime, and creatinine was determined by Jaffe's reaction. The renal cortex was dried in an incubator at 105°C and incinerated with concentrated HNO_3, after which the Na^+ and K^+ concentrations were determined in it and also in the blood serum and urine, on a Zeiss III flame photometer in an air–propane flame, and calcium and magnesium were determined on an atom-absorption spectrophotometer ("Hitachi," Japan). The platinum content in the kidney tissue was determined by neutron activation analysis [1].

EXPERIMENTAL RESULTS

The urea and creatinine concentrations in the blood serum were increased almost ninefold 5 days after injection of cisplatin and glomerular filtration (creatinine clearance) was reduced by 7.7 times, diuresis was reduced (Table 1), marked changes were found in the kidney tissues — their weight was increased by 44%, the water content in the renal cortex was increased, and its Na^+ content increased but its K^+ content reduced (Table 2). The changes listed above agree fully with the characteristic manifestations of the nephrotoxic action of cisplatin [2, 6].

After injection of cycloplatam in doses twice and 5 times higher than that of cisplatin (10 and 25 mg/kg body weight), all the rats were still alive on the 5th day, no change was observed in the mass of the kidney or its water content, and there was no sign of uremia or disturbances of the ionic composition of the blood serum and kidney tissue (Tables 1 and 2).

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TABLE 1. Concentration (in mM) of Urea (Ur), Creatinine (Cr), and Electrolytes in Blood Serum of Rats and Creatinine Clearance (C_{Cr}), in ml/h/100 g Body Weight, after Injection of Cisplatin and of Cycloplatam (M ± m)

Experimental conditions	Ur	Cr	Na	K	Mg	Ca	C_{Cr}
Control	5,81±0,20	0.075±0.004	150±2,5	4,9±0,34	0,91±0,06	2,45±0,01	14,6±1,09
Cisplatin, 5 mg/kg	56.3±9,8*	0,66±0.12*	135±3,2**	5.5±0,39	1,21±0,14	2,42±0,13	1,90±0,97*
Cycloplatam, mg/kg:							
10	5,66±0,45	0,095±0.003*	149±2,3	4,8±0,13	0,86±0,13	2,20±0,06	12,1±0,96
25	4.33±0,17***	0,092±0.005*	153±1,2	4,8±0,26	0,76±0,07	2,25±0,06	12,6±1,33

Legend. *p < 0.001, **p < 0.01, ***p < 0.05 compared with control.

TABLE 2. Diuresis (V, in ml/100 g body weight), Mass (M) of Both Kidneys (in mg/100 g body weight), and Content of Water (in g/g dry substance), Electrolytes (in μmoles/g wet weight of kidney substance), and Platinum (Pt, in μg/g dry weight of kidney substance) in Kidney Tissues of Rats after Injection of Cisplatin and Cycloplatam (M ± m)

Experimental conditions	V	M	H_2O	Na	K	Mg	Ca	Pt
Control	11.38±0,13	627±18,0	3.28±0,04	66,6±1,4	73,6±1,8	8,2±0,39	1,6±0,07	2,55±0,15
Cisplatin, 5 mg/kg	0,61±0.23*	905±35,2*	4.22±0,09*	70,4±2,2**	65.2±1,6**	7,3±0,22**	1,65±0,25	59,1±3,05*
Cycloplatam, mg/kg:								
10	1,67±0.16	633±32,5	3,48±0,07	64,7±2,5	69,7±1,0	7,35±0,10**	1,46±0,04	45,6±1,72*
25	1,48±0.23	620±33,4	3,35±0,06	68,4±1,5	75,1±1,3	8,2±0,13	1,51±0,10	104,9±2,95*

Legend. *p < 0.001, **p < 0.05 compared with control.

The results of determination of the platinum content in the kidney tissue are most interesting. After injection of cisplatin the platinum concentration in the kidney reached 50.6 ± 1.63 μg/g dry substance (Table 2). This was apparently comparable with data on the development of nephrotoxicity, with swelling of the kidney and disturbance of its electrolyte composition. In the experiments with cycloplatam, however, when injected in a dose of 25 mg/kg, the kidney accumulated twice as much platinum as in the experiments with cisplatin, but nephrotoxicity did not develop. Consequently, not only the quantity of platinum accumulating in the kidney, but also the compounds with which it combines in the cells, determine damage to the nephron. Support for this possibility is given by the data obtained by the writers previously on prevention of the nephrotoxic action of cisplatin by administration of certain organic acids and bases which normally may be secreted by cells of the proximal segment of the nephron. In this case less urea and creatinine accumulates in the blood, the kidney does not swell, although the quantity of platinum in the kidney is just as great as after injection of cisplatin, with its severe nephrotoxic action [2]. These results can probably be explained on the grounds that the administered organic acids or bases in the proximal segment of the nephron temporarily screen certain molecular elements in the kidney, as a result of which the cisplatin interacts predominantly with other components. The difference between cycloplatam and cisplatin may be a difference in their ability to bind with components of the proximal tubular cells, interaction with which determines renal damage and is inhibited by additional administration of secreted organic substances. This difference is evidently linked with the presence of a bulky cyclopentyl substituent group in the amino part of the cycloplatam molecule, creating steric hindrances for interaction with certain substrates.

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