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Short Communication

The Effects of Dimercaptosuccinic Acid and Other Chelating Agents on the Retention of Platinum in the Rat Kidney After Treatment with Cisplatin

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Summary. *The ability of three chelating agents, dimercaptopropanesulphonate (DMPS), dimercaptosuccinic acid (DMSA), and diethylenetriaminepentaacetic acid (DTPA), to reduce the retention of platinum in the kidneys was tested in male Sprague-Dawley rats treated 24 h previously with Cisplatin. DMPS and DMSA, when given as four daily doses of 1 mMol/kg, increased the urinary excretion from 10.1% ± 1.2% to 13.6% ± 1.3% and 13.5% ± 2.6%, respectively, but only DMSA caused a small but significant reduction in the kidney platinum content. DTPA was totally ineffective. It is concluded that none of these agents is likely to be useful for the reduction of Cisplatin-induced renal toxicity in the clinical situation.*

Introduction

Renal toxicity is an important potential complication following tumour chemotherapy with Cisplatin (*cis*-dichlorodiammino-platinum [II]), and a number of methods for reducing the renal toxicity have been investigated [4]. On the assumption that a reduction in the renal burden of platinum will reduce the nephrotoxicity, several complexing agents, including penicillamine [2], *S*-2-(3-aminopropylamino)ethylphosphothioic acid [5], and diethyldithiocarbamate [1], have been tested for their ability to reduce the nephrotoxicity of Cisplatin; the last two agents did reduce renal toxicity without any apparent effect on the anti-tumour activity, but no data on the reduction in the renal platinum content were given. In the present study three other chelating agents known to be effective for the removal of mercury, another metal which, like platinum, binds principally to sulphydryl groups in the kidneys and other tissues, have been tested for their ability to reduce the kidney platinum content and to increase urinary excretion of the metal in rats treated with Cisplatin.

Materials and Methods

The animals used were male Sprague-Dawley rats weighing about 200 g at the start of each experiment.

Cisplatin, kindly donated by Bristol Myers and Co., Brussels, Belgium, was injected IV at either 4 or 6.5 mg per kg body weight. The chelating agents, dimercaptopropane sulphonate (DMPS; Dimaval, by courtesy of Heyl and Co., Berlin, FRG), dimercaptosuccinic acid (DMSA; E. Merck, Darmstadt, FRG), and diethylenetriaminepentaacetic acid (DTPA – CaNa salt; by courtesy of Geigy and Co., Basel, Switzerland) were injected IP at a standard dose of 1 mMol per kg body weight, starting 24 h after injection of Cisplatin.

All animals were killed 24 h after the last injection of the chelating agent.

The kidneys and urine samples were wet-ashed and assayed for platinum by flameless atomic absorption spectrophotometry using a Beckman Model 1272 Spectrometer and a Massmann cuvette.

Results

The effects of a single treatment, or of four consecutive daily treatments, with 1 mMol DMPS, DMSA, or DTPA/kg beginning 24 h after Cisplatin injection on the percentage retention of platinum in the two kidneys 24 h later are shown in Table 1. This table also shows the percentages of the injected platinum which were excreted in the urine during the 5 days following the start of treatment with four daily doses of the various chelating agents.

The platinum concentrations, measured 48 h after injection of 1,300 μg or 5 days after 800 μg Cisplatin without chelating agent, were 10.13 ± 3.33 μg/g and 5.45 ± 0.84 μg/g fresh weight, respectively. Since the percentage retention and the percentage urinary excretion were similar for the two Cisplatin doses, the data from both series of experiments were combined for the compilation of Table 1.

Discussion

A single treatment with any of the chelating agents tested produced no significant change in the renal platinum content when this was measured 24 h after the treatment (Table 1). After four consecutive daily treatments only DMSA produced a statistically significant ($P < 0.05$) reduction, of about 20%, in the platinum content of the kidneys.

Both DMPS and DMSA, but not DTPA, caused significant enhancement ($P < 0.005$ and $P < 0.05$, respectively) of the urinary excretion following four consecutive daily treatments. However, the increased urinary excretion was low and amounted to only about 3% of the injected platinum.

In this study only a single dose level of chelating agent and a single time interval after Cisplatin have been studied. The chelate dose of 1 mMol per kg was chosen as the maximum likely to be applicable to man, having regard to the known toxicity of these chelating agents. The 24-h time interval between Cisplatin injection and the start of treatment was

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Table 1. The effects of chelating agents on the kidney content and urinary excretion of platinum in Sprague-Dawley rats after treatment with Cisplatin

Chelating agent	Kidney retention as % of injected dose		Urinary excretion as of % dose Days 1–5 after 4 daily treatments
	Single treatment	4 Daily treatments	
Control, untreated	2.56 ± 0.92 (9)	2.21 ± 0.30 (3)	10.1 ± 1.2 (4)
Dimercaptopropane sulphonate	3.06 ± 0.64 (6)	2.21 ± 0.26 (3)	13.6 ± 1.3* (4)
Dimercaptosuccinic acid	3.44 ± 0.62 (6)	1.76 ± 0.09* (4)	13.5 ± 2.6* (4)
Diethylenetriaminepentaacetic acid	3.11 ± 0.62 (6)	1.90 ± 0.31 (3)	10.0 ± 2.0 (4)

* Value significantly different from untreated controls $P < 0.05 > 0.001$
Figures in parentheses indicate the number of rats

selected to allow a reasonable time for the Cisplatin to exert its cytotoxic action before administering a strong chelating agent which might, through chelate formation, reduce the cytotoxic action.

The minimal effectiveness of these strong chelating agents is presumably due to their inability under in vivo conditions to release platinum from its complexes with methionine and other sulphur-containing moieties in the tissue proteins [3].

Assuming that an essential prerequisite for the reduction of the renal toxicity is the removal of platinum from its complexes with critical proteins in the kidney and its elimination from the body, none of the agents tested in this study produces more than a marginal effect, and it appears unlikely that any of them would be of any real value for the reduction of platinum nephrotoxicity in the clinical situation.

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