Acute and long-term nephrotoxicity of cis-platinum in man

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Summary. To detect whether the nephrotoxicity of cis-diaminodichloroplatinum (DDP) is acute and can be demonstrated at an early stage in man, a method for estimating the function of the kidneys during intensive hydration was devised. The method includes a calculation of the clearance of $^{125}$I-orthoiodohippurate and an estimation of the glomerular filtration rate (GFR) from fast changes of the extracellular volume (ECV) and the mean transit time of $^{99m}$Tc-DTPA in this volume.

We examined nine patients with testicular cancer on 2 consecutive days for acute nephrotoxicity while they were undergoing treatment with cis-platinum. Placebo was given on day 1, cis-platinum on day 2. On both days the patients were hydrated with 4 l saline, glucose, and mannitol (0.5 l) over a period of 4 h, which resulted in an increase of $^{125}$I-orthoiodohippurate clearance on both days ($P < 0.01$). The increase was, however, lower on the day of treatment with cis-platinum than on the day with placebo ($P < 0.05$). There were no acute changes in the GFR. This indicates that treatment with DDP inhibits the active transport of $^{125}$I-orthoiodohippurate in the tubules; that is to say there is an acute effect on the kidney function.

There were no acute changes in the GFR, but in the long-term followup study we found that the GFR had decreased significantly ($P < 0.05$) after 2 months of treatment. During the first year after the initiation of treatment the GFR changes were found to progress. A significant increase in se-creatinine was not observed until 6 months after the initiation of treatment ($P < 0.05$). The degree of chronic nephrotoxicity did not correlate in individual patients with the acute changes in kidney function.

Introduction

In 1979 Frich et al. [6] showed that hydration and mannitol diuresis reduced the nephrotoxicity of cis-dichlorodiammine platinum(H) (DDP). The nephrotoxicity of this antineoplastic drug is the dose-limiting factor in clinical practice [13]. The nephrotoxic effect has for some time been suspected to be predominantly tubular, as indicated by analysis of the osmolarity of the urine and papillary content of preurine in experimental animal studies [18]. However, in 1983 Meijer et al. [15] found clinical evidence that the nephrotoxicity might be due to effects on the glomerular tuft.

Animal studies have shown that some of the newly developed platin analogues are less nephrotoxic than DDP at equally antineoplastic dosages [3, 16]. Some of these analogues are now being tested in clinical trials. In such trials it would be of great value to have a reliable assessment of the possible effect on renal function early in the treatment.

The aim of the present investigation was to study whether acute nephrotoxicity would be demonstrable in man as an effect on the glomeruli or tubules, hopefully providing a sensitive approach for rapid comparison of analogue therapeutic agents with regard to nephrotoxicity.

It is not simple, however, to measure the function of the kidneys during the hydration that accompanies administration of DDP. The conventional techniques for determination of the glomerular filtration rate, i.e., the clearance of $^{99m}$Tc-DTPA, assume that the organism is in steady state [14]. The hydration and mannitol load invalidate this assumption. The same difficulty is present in determination of the effective renal plasma flow (ERPF) or the function of the tubules by the clearance of $^{125}$I-orthoiodohippurate.

We decided to approach the problem in two ways. The first was to adapt the methods for studying $^{99m}$Tc-DTPA and $^{125}$I-orthoiodohippurate clearance to the non-steady state of hydration and mannitol load. The other was to study the isolated influence of hydration and mannitol load on $^{99m}$Tc-DTPA and $^{125}$I-orthoiodohippurate clearance by effecting hydration and mannitol diuresis on the day before cisplatinum treatment.

To relate the results of the measurements of acute nephrotoxicity of cis-platinum to the chronic effect of the drug, we monitored the function of the kidneys for 1 year in 25 patients receiving treatment with cis-platinum, bleomycin, and vinblastine [5].

Patients

Twenty-five consecutive patients (range 16–47 years) with testicular cancer were included in the study. A subgroup of nine was formed for the study of acute nephrotoxicity of DDP. This part of the study was carried out during the first treatment course in seven of the patients, while the last two patients were examined after receiving accumulated doses of 280 mg and 420 mg cis-platinum.

The 25 patients constituted the study group for examinations of the chronic effect of DDP.
Table 1. Cytostatic treatment of testicular cancer (modified Einhorn regimen [5])

<table>
<thead>
<tr>
<th>Day</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>9</th>
<th>16</th>
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</thead>
<tbody>
<tr>
<td>cis-Platinum 20 mg/m² IV</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
<td>×</td>
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<tr>
<td>Bleomycin 15 mg/m² IV</td>
<td>×</td>
<td></td>
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</tr>
<tr>
<td>Vinblastine 6 mg/m² IV</td>
<td>×</td>
<td></td>
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</tbody>
</table>

Start of new treatment course on day 22

The antineoplastic treatment was given over a period of approximately 4 months in six courses of treatment with cis-platinum, bleomycin, and vinblastine. cis-Platinum was always given with hydration and mannitol load [6]. Details of the treatment are shown in Table 1.

Methods

Methods used in the study of acute nephrotoxicity of cis-platinum

Glomerular filtration rate at steady state (GFR) (ml/min). GFR was estimated as the clearance of \(^{99m}\)Tc-DTPA by means of a multiple plasma sample method [4]. A bolus of a known volume of 300 µCi \(^{99m}\)Tc-DTPA \((Q_o\text{-DTPA})\) was injected IV at \(t=0\). Plasma samples were withdrawn at \(t=0, 5, 10, 15, 20, 30, 40, 60, 90, 120, 150, 180, 200, 220, \) and 240 min.

The plasma time-activity curve was defined by performing a biexponential fit of the activity in the plasma samples according to a two-compartment model [2]. The clearance of \(^{99m}\)Tc-DTPA was calculated as \(Q_o\text{-DTPA} \div \text{area under the plasma time-activity curve extrapolated from } t=0 \text{ to } t=\infty \) [2].

Extracellular volume at steady state (ECV\text{DTPA}) (ml). ECV was also calculated from the time-activity curve, applying the concept of the distribution space of \(^{99m}\)Tc-DTPA (ECVDTPA) as composed of two compartments [11].

External assessment of mean transit time of \(^{99m}\)Tc-DTPA in the organism during hydration and mannitol load (\(t^{1/2}\) ext). A small CdTe detector (Memolog system) was pasted on the lateral surface of the calf 10–12 cm below the lateral meniscus of the knee [1]. Following a bolus injection of \(^{99m}\)Tc-DTPA, an externally derived time-activity curve was obtained mean transit time. The life of \(^{99m}\)Tc-DTPA in the organism was estimated from the half-time \((t^{1/2}\) ext) of the final slope of this curve [9] (Appendix).

Assessment of extracellular volume during hydration and mannitol load \(\text{ECV}_{corr}(t)\): Changes induced in the extracellular volume by hydration and mannitol load were monitored from the increase in activity following repeated injections of \(^{99m}\)Tc-DTPA \((Q_o\text{-DTPA})\) and were compared to the increases following the injection at steady state \((Q_s\text{-DTPA})\). The increase was measured by the CdTe detector and normalized with respect to the dose injected (Appendix). It was considered inversely proportional to a fast exchangeable volume of \(^{99m}\)Tc-DTPA \((\text{FEVD}(t))\). Accordingly, the changes in the extracellular volume were considered proportional to \(\text{FEVD}(t)/\text{FEVD}(to)\), where \(\text{FEVD}(t)\) was calculated from the increase in activity following the injection of a dose of \(^{99m}\)Tc-DTPA given during the hydration and mannitol load at \(t=ti\), and \(\text{FEVD}(to)\) from the injection of \(^{99m}\)Tc-DTPA at steady state. The ECV corrected for these changes \(\text{ECV}_{corr}(t)\) was then calculated as \(\text{ECV}_{corr}(t) = \text{ECV}_{DTPA} \times [\text{FEVD}(t)/\text{FEVD}(to)]\).

Glomerular filtration rate during hydration and mannitol load. The glomerular filtration rate during hydration and mannitol load \(\text{GFR}_{unt}\) was calculated as \(\text{GFR}_{unt} = \text{ECV}_{corr}(t)/t^{1/2}_{ext} \times \) (Appendix).

Estimation of clearance of \(^{125}\)I-orthiodihippurate during the hydration and mannitol load \(\text{AUC}(t44)\). The \(^{125}\)I-orthiodihippurate clearance was determined as an apparent urinary compartment \(\text{AUC}(t44)\) (Appendix) defined as \(\text{AUC}(t44) = \text{AVD}(t44) - \text{ECV}_{corr}(t)\), where \(\text{AVD}(t44)\) is the apparent volume of distribution of Tauxe [21]. \(\text{AVD}(t44)\) was calculated as \(\text{AVD}(t44) = Q_{o1} - \frac{\text{ECV}_{corr}(t)}{125}\text{I-H/C}_{125}\text{I-H}(t44)\), where \(Q_{o1} - \frac{125}\text{I-H}\) is the amount of \(^{125}\)I-orthiodihippurate injected as a bolus at \(t=ti\) and \(C_{125}\text{I-H}(t44)\) is the plasma-activity of the \(^{125}\)I-orthiodihippurate at \(t=ti + 44\) min. Blood samples were also drawn at \(t=(ti-10)\) and \((ti-1)\) min to correct for background.

![Fig. 1. General procedure for administration of hydration \(^{125}\)I-orthiodihippurate and \(^{99m}\)Tc-DTPA on day 1 and day 2. On both days the patients were monitored for 420 min with external detection.](image-url)