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# Cisplatin nephrotoxicity in children after continuous 72-h and 3×1-h infusions

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**Abstract** Little is known about the association between the rate of cisplatin administration and the severity of cisplatin-induced renal damage in children. The purpose of this study was to compare severity and reversibility of renal damage in children after continuous and repetitive bolus administration of cisplatin and to correlate these data with pharmacokinetic parameters. Study subjects included six children (ten courses) receiving cisplatin as 1-h bolus infusions on three consecutive days (3×40 mg/m$^2$) and four children (eight courses) receiving 72-h continuous infusions (120 mg/m$^2$). In all courses, signs of glomerular and tubular damage were seen, as evidenced by elevated urinary excretion of $\alpha_1$-microglobulin, albumin and *N*-acetyl-β-D-glucosaminidase and decreased glomerular filtration rate (GFR). Comparing the two infusion regimens, the 1-h bolus administration of cisplatin was followed by significantly higher peak free platinum concentrations in plasma and urine ($P<0.001$), resulting in lower nadirs of the GFR ($P<0.005$). Correlations were found between both peak free platinum concentrations in plasma and urine and maxima of urinary albumin and *N*-acetyl-β-D-glucosaminidase excretion. Within 12 months after completion of cisplatin therapy, children in the 1-h bolus group had recovered only partially from subclinical nephrotoxicity, with five out of six showing pathological proteinuria. The results provide clear evidence that long-term ciplatin infusions are less nephrotoxic than repetitive bolus infusions.

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## Introduction

Cisplatin is an important anticancer drug in the chemotherapy of a variety of solid tumours in children, in particular osteosarcoma, neuroblastoma [1], germ cell tumours [2], and brain tumours [3]. The use of cisplatin, however, is associated with moderate to severe organotoxic side effects such as gastrointestinal toxicity, myelosuppression, ototoxicity, and nephrotoxicity. Pharmacokinetic studies in adults indicate that peak total [4–6] and peak free plasma platinum concentrations [7] correlate with cisplatin-induced renal toxicity. Therefore, extensive hydration and mannitol treatment have been established as standard support treatment during cisplatin administration and the usefulness of continuous cisplatin infusions has been debated. Nevertheless, acute nephrotoxicity and chronic renal damage still occur in adults [8–10] as well as in children [11, 12] after administration of therapeutic doses of cisplatin. Furthermore, the incidence of cisplatin-induced renal dysfunction may be underestimated because serum creatinine concentration is frequently the only parameter used to monitor kidney function during chemotherapy, even though the inadequacy of this parameter has been shown by several groups [10, 12, 13]. Due to the increasing number of children cured of their tumours, the long-term effects of cisplatin nephrotoxicity are becoming more and more important. In contrast to the frequent use of cisplatin in paediatric patients, only a few studies have been performed dealing with the pharmacokinetics of cisplatin in children [14–18], and little is known about the relationship between the pharmacokinetics of cisplatin and platinum-associated nephrotoxicity in children.

Therefore, the aims of the present study were, first, to compare cisplatin-induced nephrotoxicity in children receiving equal doses of cisplatin per course given either as continuous infusions over 72 h or as repetitive 1-h bo-

lus infusions on three consecutive days, second, to evaluate whether nephrotoxicity parameters were correlated with the pharmacokinetics of the two different delivery rates, and, third, to identify determinants in cisplatin-induced renal dysfunction.

## Materials and methods

### Patients and treatment

The analyses were performed in ten children receiving cisplatin chemotherapy for the treatment of osteosarcoma or medulloblastoma at the Department of Paediatrics of the University of Göttingen, Germany. All children and their parents gave informed consent prior to entering the study in accordance with the requirements of the University Ethics Committee. Cisplatin (120 mg/m$^2$ per course) was administered either as 72-h continuous intravenous infusions (40 mg/m$^2$/day, osteosarcoma patients, eight courses) or as intermittent 1-h bolus infusions on three consecutive days (40 mg/m$^2$/day, medulloblastoma patients, ten courses) according to the respective treatment protocols of the German Society of Paediatric Oncology and Haematology (GPOH; COSS-86c and HIT-91). Mean age was 9.7 years and varied from 6 to 18 years in the continuous infusion group and from 5 to 14 years in the repetitive bolus group. Concomitant chemotherapy and patient characteristics are shown in Table 1. Ifosfamide was given as continuous 24-h infusions (two courses of 3×3 g/m$^2$ in the repetitive bolus group and four courses of 2×3 g/m$^2$ in the continuous infusion group). There is no indication from the literature that the different types of tumours are associated with renal outcome. All patients had normal renal functional parameters (see below) before starting chemotherapy. Cisplatin (Platinex$^{TM}$) was administered in physiologic saline using a photoprotected infusion system. For hydration, a continuous infusion of glucose 5% and normal saline (1/1, per volume, 3 l/m$^2$/day) was given to all patients starting 12 h before and continuing until 48 h after the end of cisplatin infusion. KCl (2 mmol/kg), Ca gluconate 10% (2 ml/kg), Mg 20% (1 ml/kg), and glycerophosphate (0.4–0.8 ml/kg) were added to the daily basal solution. Furthermore, mannitol 15% (40 ml/m$^2$) was administered as an intravenous bolus infusion 1 h before starting cisplatin infusion and in the case of decreased diuresis (below $^2/_3$ of total fluid intake) during the courses.

### Blood and urine specimens

Blood samples were obtained from all patients before starting cisplatin therapy. During the courses, no exact time schedule for blood drawings could be maintained for patient care reasons. In the 3×1-h infusion group, blood samples were drawn after completion of the first cisplatin bolus administration and 5–7 times within the following 24 h. In the continuous infusion group, several blood samples were drawn during the 72-h cisplatin administration and one at 24 h after termination of the cisplatin infusion. Blood samples were collected in heparinized tubes. Immediately after centrifugation for 3 min at 14,000 rpm, 500 µl plasma was added to 50 µl 70% perchloric acid. After centrifugation for 5 min, the supernatant was withdrawn and the deproteinated samples and plasma samples were frozen at –20°C until platinum analysis was performed. The reliability of the deproteinating procedure using perchloric acid was evaluated by comparing platinum concentrations after acid precipitation with those obtained after ultrafiltration by an Amicon ultrafiltration system (MW 10,000 cut-off, Amicon, Danvers, MA). The mean platinum concentrations measured using perchloric acid precipitation amounted to 90% of the values after ultrafiltration and coefficients of variation were less than 6%. In order to detect peak urine cisplatin concentrations, urine specimens were collected as frequently as possible within the first 6 h after starting cisplatin infusion. Aliquots of 10 ml were frozen at –20°C for platinum analysis and the remaining urine was pooled for calculation of creatinine clearances and determination of nephrotoxicity markers.

### Platinum analyses

Platinum concentrations of the deproteinated plasma, whole plasma and urine were analysed by flameless atomic absorption spectroscopy at 2650°C and at a wavelength of 265.9 nm using a GBC 904 AA spectrometer (Maassen, Ravensburg, Germany). Dilution of urine and deproteinated plasma samples was performed with water when necessary. Whole plasma was diluted with perchloric acid (1:1 v/v) before analysis. A standard curve from 0.03 to 1 µg/ml was evaluated for each assay. After analysis of ten urine or four plasma specimens, a recalibration was performed. The lower detection limit was 30 ng/ml. Intra- and interassay coefficients of variation were less than 5% for urine and diluted plasma and less than 10% for undiluted plasma.

### Pharmacokinetic analysis

Pharmacokinetic parameters were determined for non-protein-bound (free) platinum by a two-compartment model using the Topfit computer model [19]. The following parameters for free platinum were calculated: Initial half-life ($T_{1/2}\alpha$), terminal half-life ($T_{1/2}\beta$), maximal concentration in plasma ($C_{max}$), area under the plasma concentration-time curve from time zero to infinity (AUC), volume of distribution in steady state ($V_{SS}$), total clearance ($Cl_t$), renal clearance ($Cl_r$) and the cumulative amount excreted in urine from time zero to infinity ($A_e$).

**Table 1** Characteristics of patients and infusion schedules for cisplatin treatment (*BSA* body surface area, *F* female, *M* male.) Osteosarcoma patients received a continuous infusion over 72 h, medulloblastoma patients received three 1-h infusions at three consecutive days within 72 h

| Diagnosis | Patient | Sex | Age (years) | BSA (m$^2$) | Cycles studied (*n*) | Dose per day (mg/m$^2$) | Dose per cycle (mg/m$^2$) | Infusion time (h) | Other medication |
|---|---|---|---|---|---|---|---|---|---|
| Osteosarcoma | 1 | F | 14 | 1.63 | 3 | 40 | 120 | 72 | Methotrexate |
| | 2 | F | 6 | 0.85 | 2 | 40 | 120 | 72 | ifosfamide |
| | 3 | F | 18 | 1.8 | 1 | 40 | 120 | 72 | etoposide |
| | 4 | F | 9 | 1.0 | 2 | 40 | 120 | 72 | Adriamycin |
| Medulloblastoma | 5 | F | 10 | 1.2 | 2 | 40 | 3×40 | 3×1 | Methotrexate |
| | 6 | M | 8 | 1.03 | 1 | 40 | 3×40 | 3×1 | ifosfamide |
| | 7 | F | 14 | 1.56 | 2 | 40 | 3×40 | 3×1 | etoposide |
| | 8 | M | 7 | 0.78 | 2 | 40 | 3×40 | 3×1 | cytarabine |
| | 9 | M | 5 | 0.81 | 2 | 40 | 3×40 | 3×1 | |
| | 10 | M | 6 | 0.88 | 1 | 40 | 3×40 | 3×1 | |

### Nephrotoxicity

Standard serum parameters (sodium, potassium, calcium, magnesium, phosphate, creatinine, blood urea nitrogen) were measured using routine specimens drawn before starting the respective cisplatin courses and daily under cisplatin treatment. Analyses were performed using a Beckman autoanalyser (Synchron CX5D, Beckman, Munich, Germany). Urinary nephrotoxicity markers were also determined the day before cisplatin infusion and during cisplatin courses using 24-h urine specimens. Urine was collected throughout the 72-h period of cisplatin administration and at least for the following 48 h of post-treatment hydration therapy. During the interval between cisplatin courses and after completion of chemotherapy, either 24-h or spontaneous urine specimens (second morning urine) were used. Proteinuria was analysed qualitatively by denaturing sodium dodecylsulfate-polyacrylamide gel electrophoresis (SDS-PAGE). Quantitative determination of total urinary protein excretion ($tProt_U$) and urinary marker proteins for glomerular function (immunoglobulin G, IgG; transferrin, TRF; urinary albumin, $Alb_U$) and tubular function ($\alpha_1$-microglobulin, $\alpha_1$-M; retinol-binding protein, RBP) were analysed using a Behring BNA nephelometer (840 nm, Behring, Marburg, Germany). The activity of the tubular enzyme *N*-acetyl-β-D-glucosaminidase (NAG) was quantified using an enzymatic assay as described by the manufacturer's protocol (Roche, Grenzach-Wyhlen, Germany). Tamm-Horsfall protein (THP) was analysed by SYNELISA (synchron enzyme-linked immunosorbent assay, Elias, Freiburg, Germany). The following values were considered as pathological: IgG >10 mg/l, TRF >10 mg/l, $Alb_U$ >20 mg/dl (≥20 mg/g $Crea_U$), $tProt_U$ 150 mg/l, $\alpha_1$-M >10 mg/l (≥15 mg/g $Crea_U$), RBP >1 mg/l, and THP <9 mg/24 h. The total amount of daily excreted IgG and TRF as well as the concentration ratios to creatinine could not be calculated since the concentration levels before starting cisplatin courses were under the detection limit. The glomerular filtration rate (GFR) was estimated using the creatinine clearance ($Cl_{cr}$ [(ml/min)/1.73 m$^2$]) calculated using the standard formula: $Cl_{cr} = (Crea_U \cdot Vol_U \cdot 1.73\ m^2)/(Crea_S \cdot time_C \cdot BSA)$, where $Crea_U$ and $Crea_S$ are the concentrations of creatinine in urine and serum (mg/dl), $Vol_U$ is the volume of urine excreted (ml), $time_C$ is the collection time (min) and BSA is the body surface area (m$^2$). Measurements were performed using 24-h urine specimens. Values below 87 ml/min were considered to be abnormal [20].

### Statistics

Results are given as means ± SD. To compare individual nephrotoxicity markers before and during cisplatin administration, the Student's *t*-test for paired data was used. Only one course per patient (with the best regression between the values measured and the calculated optimized parameters in the computer model) was taken into consideration for the statistical analyses of the pharmacokinetic parameters. To compare nephrotoxicity and pharmacokinetic parameters between the treatment groups, Student's *t*-test for unpaired data was used. Relationships between pharmacokinetic parameters and nephrotoxicity markers were tested by calculating Pearson's correlation coefficient. Due to the small number of study subjects, it was not possible to carry out multivariate analyses.

## Results

All children had normal serum parameters and normal excretion of urinary marker proteins before the first administration of cisplatin. In two patients, a low initial GFR was measured (78 ml/min and 84 ml/min) without obvious cause (probably due to incorrect collecting periods), but normal values were obtained before the start of the second course.

During cisplatin treatment, signs of cisplatin-induced glomerular and tubular injury were registered in all courses for both infusion groups. The pattern of cisplatin-induced proteinuria indicated that different parts of the tubular system were affected. A significant increase in urinary excretion of total protein, $\alpha_1$-M and NAG was seen under both infusion regimens, whereas albumin excretion increased significantly only in the 3×1-h infusion group compared to the preinfusion levels (Fig. 1). Apart from reduced tubular protein reabsorption, the amount of Tamm-Horsfall protein excreted daily dropped to less than 15% of the starting levels

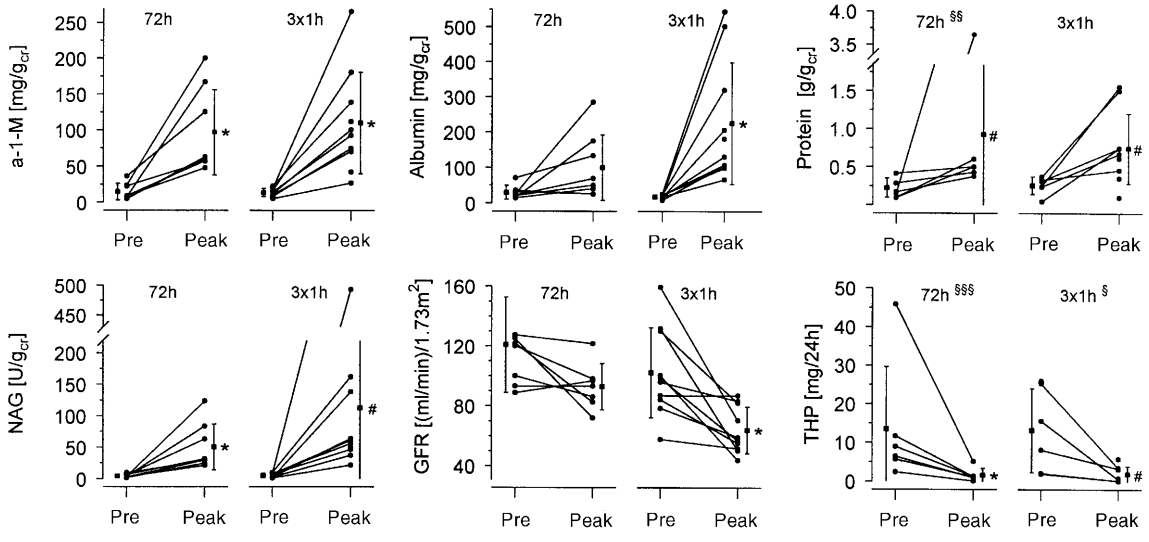


**Fig. 1** Changes in urinary markers for cisplatin-induced nephrotoxicity during treatment courses (*a-1-M* $\alpha_1$-microglobulin, *NAG N*-acetyl-β-D-glucosaminidase, *GFR* glomerular filtration rate estimated using creatinine clearance, calculated from 24-h urine collections, *THP* Tamm-Horsfall protein, *pre* values at start of course, *peak* maximum values during cisplatin course, *lines* connect values from the same individual, $n$=10 in the 3×1-h infusion group, $n$=8 in the 72-h infusion group, $^{\S}n$=9, $^{\S\S}n$=7, $^{\S\S\S}n$=6, mean values are shown ± SD besides individual results, *$P$<0.01, $^{\#}P$<0.05)

**Table 2** Changes in glomerular markers during cisplatin treatment. Values are means ± SD [*GFR* glomerular filtration rate estimated using creatinine clearance (calculated from 24-h urine collections), $Alb_U$ urinary albumin, *IgG* immunoglobulin G, *TRF* transferrin]. Since concentrations at start of courses were under the detection limit, no IgG/creatinine and TFR/creatinine ratios can be given

| | | GFR [(ml/min)/m²] | $Alb_U$ (mg/$g_{crea}$) | IgG (mg/l) | TRF (mg/l) |
|---|---|---|---|---|---|
| Level at start of course | 72-h infusion | 121 ±32 | 29.9 ±19.6 | <3.8 | <2.4. |
| | 3×1-h infusion | 102* ±30 | 18.4* ±5.0 | <3.8§ | <2.4§ |
| Maximum or minimum during course | 72-h infusion | 93# ±16 | 100 ±92.0 | 6.5 ±3.1 | 3.0† ±0.5 |
| | 3×1-h infusion | 63*# ±16 | 226* ±172 | 9.4§ ±4.5 | 5.0§† ±1.5 |

*P*<0.01, *start course vs during course, #minimum during course 72-h vs 3×1-h infusion, *P*<0.05, §start course vs during course and †maximum during course 72-h vs 3×1-h infusion

**Table 3** Prevalence of pathological findings in urinary nephrotoxicity parameters before, during and after treatment with cisplatin [*GFR* glomerular filtration rate estimated using creatinine clearance (calculated from 24-h urine collections), $Alb_U$ urinary albumin, $\alpha_1$-*M* $\alpha_1$-microglobulin, *IgG* immunoglobulin G]. Values given are numbers of pathological findings/numbers of patients or courses investigated

| Parameter | Before treatment | | During courses | | 1–3 months after | | 6–12 months after | |
|---|---|---|---|---|---|---|---|---|
| | 3×1-h, *n*=6 patients | 72-h, *n*=4 patients | 3×1-h, *n*=10 courses | 72-h, *n*=8 courses | 3×1-h, *n*=6 patients | 72-h, *n*=4 patients | 3×1-h, *n*=6 patients | 72-h, *n*=3 patients |
| GFR <87 (ml/min)/1.73 m² | 2/6 | 0/4 | 10/10 | 3/8 | 0/4[a] | 0/4 | 2/5[a] | 0/3 |
| Electrophoresis (pathological pattern) | 0/6 | 0/4 | 10/10 | 3/8 | 3/6 | 1/4 | 5/6 | 0/3 |
| $Alb_U$>20 mg/g crea. | 1/6 | 0/4 | 10/10 | 8/8 | 2/6 | 1/4 | 2/6 | 0/3 |
| $\alpha_1$-M >15 mg/g crea. | 1/6 | 0/4 | 10/10 | 8/8 | 4/6 | 1/4 | 2/6 | 0/3 |
| IgG >10 mg/l | 0/6 | 0/4 | 2/10 | 1/8 | 0/6 | 0/4 | 1/6 | 0/3 |

[a] GFR was not available in all patients

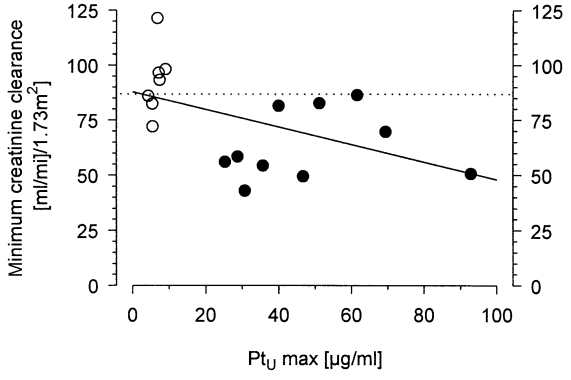


**Fig. 2** Relationship between peak platinum concentration in urine and minimum creatinine clearance (*open circles* 72-h infusion, *closed circles* 3×1-h infusion, *dotted line* threshold level of normal range, 87 ml/min, *solid line* regression curve, *r*=–0.50, *P*<0.05)

(*P*<0.05). Thus, the thick ascending limb of loop of Henle and early distal convoluted tubule were also damaged by cisplatin treatment. No significant differences were found when comparing the maximum loss of urinary total protein and the peak excretion of the different marker proteins between the two infusion groups. In contrast to this, the decrease in GFR registered after cisplatin administration depended on the infusion rate, with lower nadirs in the repetitive bolus group (*P*<0.01, Table 2). All minimum GFR values in the 3×1-h infusion group were within the pathological range below 87 (ml/min)/m² (Figs. 1, 2). The continuous cisplatin infusion resulted in a less marked decrease in GFR, with the majority of nadir values remaining within the normal range. The cisplatin-associated glomerular dysfunction was confirmed by an increase in urinary exretion of albumin and urinary IgG and TRF concentrations. All preinfusion levels of IgG and TRF were under the detection limit. Again, the repetitive 1-h infusion resulted in a significant loss of albumin, IgG and TRF (Table 2), whereas the increase in urinary excretion of glomerular marker proteins during continuous 72-h infusions was not statistically significant. Table 3 summarizes the time courses of several nephrotoxicity markers. Patients receiving continuous cisplatin infusions recovered from their functional impairments after completion of cisplatin chemotherapy. In the 1-h infusion group, however, microproteinuria and reduced creatinine clearance persisted in several patients. The most sensitive parameters for detection of cisplatin-associated renal functional disturbances were the qualitative assessment of proteinuria by SDS-PAGE as well as the urine concentration ratios

**Table 4** Pharmacokinetic parameters for free platinum obtained by fitting results of plasma and urine analyses to a two-compartment model ($T_{1/2}\alpha$ initial half-life, $T_{1/2}ß$ terminal half-life, $C_{max}$ peak plasma platinum concentration, *AUC* area under the plasma concentration-time curve from time zero to infinity, $A_e$ cumulative amount of platinum excreted in urine from time zero to infinity, $V_{SS}$ volume of distribution, $Cl_r$ renal clearance, $Cl_t$ total clearance)

| | $T_{1/2}\alpha$ (h) | $T_{1/2}\beta$ (h) | $C_{max}$ (ng/ml) | AUC $h \cdot \frac{(\mu g/ml)}{(100\mu g/ml^2)}$ | $A_e$ (% of dose) | $V_{SS}$ ($l/m^2$) | $Cl_t$ $\frac{(ml/min)}{m^2}$ | $Cl_r$ $\frac{(ml/min)}{m^2}$ |
|---|---|---|---|---|---|---|---|---|
| 72-h infusion ($n$=4) | 0.27 | 23.5 | 136 | 14.9 | 44.6 | 120 | 135 | 58 |
| SD | 0.27 | 14.6 | 68 | 4.6 | 7.4 | 96 | 76 | 37 |
| SEM | 0.13 | 7.3 | 34 | 2.3 | 3.7 | 48 | 38 | 19 |
| 3×1-h infusion ($n$=6) | 0.40 | 29.5 | 2530 | 12.4 | 38.3 | 147 | 141 | 55 |
| SD | 0.07 | 19.8 | 1071 | 5.5 | 2.0 | 111 | 47 | 20 |
| SEM | 0.03 | 8.1 | 437 | 2.1 | 0.8 | 45 | 19 | 8 |

For significance testing, only one course per patient was used (see text)

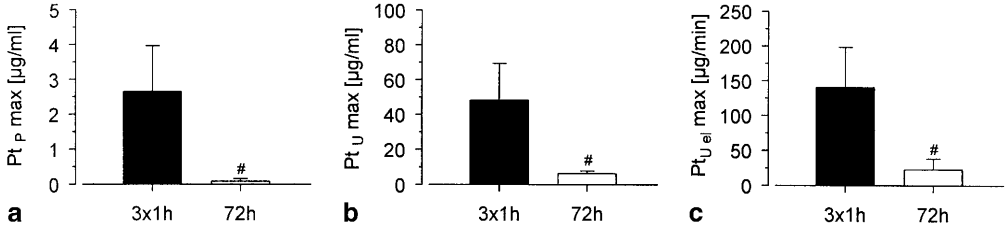


**Fig. 3** Peak free platinum concentrations in plasma ($Pt_P$) and urine ($Pt_U$) and maximal urinary excretion rate of free platinum ($Pt_{U\,el}$) after 3×1-h and 72-h infusion of cisplatin ($^{\#}P$<0.001)

of albumin to creatinine and of $\alpha_1$-M to creatinine (Table 3). In contrast to this, serum creatinine levels remained unchanged in all children throughout the whole study. The serum concentrations of sodium, potassium and calcium also remained within the normal range, whereas hypomagnesaemia and, less frequently, hypophosphataemia were observed in several patients. Due to a non-standardized substitution of calcium, magnesium and phosphate for prophylactic and therapeutic purposes, no quantitative evaluation of urinary loss of magnesium or phosphate was performed.

The higher nephrotoxicity of cisplatin observed following the 1-h infusion was partially reflected by the differences in cisplatin pharmacokinetics after high and low delivery rates. The pharmacokinetic parameters obtained for the repetitive 1-h bolus administration and the continuous 72-h cisplatin infusion are given in Table 4. In the repetitive bolus group, peak plasma concentrations of non-protein-bound platinum exceeded peak plasma levels of the long-term infusion about 19-fold ($P$<0.001). The higher platinum concentrations in plasma after the 1-h infusion were followed by higher peak concentrations of filterable platinum in urine and higher maximal urinary excretion rates (Fig. 3, $P$<0.001). Furthermore, urinary excretion of albumin and NAG depended on the maxima of free platinum concentrations in plasma ($P$<0.05, data not shown) and urine (Fig. 4). Therefore, besides the decrease in GFR (Fig. 1), the loss of albumin and NAG were also related to the administration rate of cisplatin. It is likely that the maximal urinary platinum levels were still underestimated in the bolus infusion group because the time intervals for urine collection ranged from 30 to 60 min and shortening of

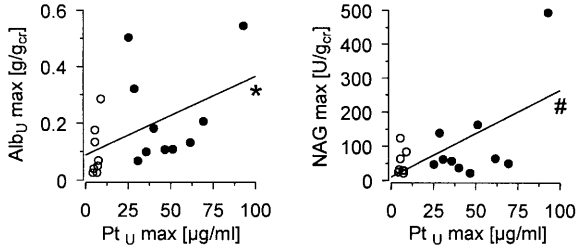


**Fig. 4** Correlation between peak platinum concentration in urine and proteinuria ($Alb_U$ *max* maximum urinary albumin excretion, *NAG max* maximum urinary excretion of *N*-acetyl-β-D-glucosaminidase, *open circles* 72-h infusion, *closed circles* 3×1-h infusion). Correlation coefficients were 0.61 (NAG, $^{\#}P$<0.01) and 0.48 ($Alb_U$, $^{*}P$<0.05)

the intervals could not be expected. There was a tendency towards higher amounts of available free platinum (AUC) after continuous cisplatin administration and also to higher cumulative renal elimination compared to values found after repetitive 1-h infusions. Due to the small number of patients, differences did not reach statistical significance (Table 4). The volume of distribution as well as the total and renal platinum clearances were not related to the cisplatin infusion rate, but there was great interindividual variability (Table 4). The total clearance values exceeded those for renal clearance 2.3- to 2.6-fold, providing evidence that considerable amounts of platinum were eliminated by pathways other than renal excretion.

## Discussion

Despite the prophylactic use of hyperhydration and forced diuresis, considerable reductions in GFR as well as proximal nephron toxicity resulting in hypomagnesaemia have been described as frequent in children receiving cisplatin [10, 11, 21, 22]. The results of this study provide further evidence of the high frequency of cisplatin-induced glomerular and tubular nephrotoxicity in children. Both the proximal but also the distal tubular system including the thin ascending limb of loop of Henle were damaged by cisplatin. All of our patients had microproteinuria and a decrease in GFR during cisplatin treatment, but the extent and reversibility of these changes depended on the infusion regimen.

Since the exposure time of cisplatin to cultured lymphoma cells was shown to be an important factor for cytotoxicity of the drug [23], several clinical trials have been performed in order to evaluate response rates and toxicity of continuous cisplatin infusions. From these studies in adults it was concluded that renal toxicity of cisplatin is reduced by prolonged infusions while antitumour effectivity was preserved [24–27]. In children, however, only a few attempts have been made to clarify this issue. Skinner and co-workers [28] concluded from nephrotoxicity studies in children that cisplatin administration rate appears to be a major risk factor for the development of toxicity and that dosing rates higher than 40 mg/m$^2$/day should be avoided. In the present work, daily doses of 40 mg/m$^2$ given as 1-h boluses or continuous infusions have been compared and a considerably higher renal dysfunction was documented with the 1-h bolus infusion regimen. Despite the small number of patients investigated, the present results suggest prolonged infusions of cisplatin should be preferred in clinical practice to reduce the risk of nephrotoxicity.

It is not clear, however, whether continuous cisplatin administration to children results in equal antitumour activity. Given that the area under the concentration-time curve (AUC) of free platinum is the most important factor for the cytotoxic effects of cisplatin, the effectivity of daily continuous cisplatin infusions may be equal or superior to short administration times. In the literature, higher [29, 30] or equivalent [31] AUC levels have been reported for long-term cisplatin infusions when compared with bolus delivery. In our patients, there was a tendency towards higher AUCs in the continuous infusion group (Table 4), which stands in very good agreement with the results of a recent comparative pharmacokinetic study by Ikeda et al. [32]. In adults receiving 100 mg/m$^2$ cisplatin, the highest AUC was achieved using a continuous infusion regimen. Even if no consistent data are available about the role of high peak plasma platinum concentrations in children, there is, on the other hand, no evidence from numerous cooperative studies that high peak platinum concentrations are necessary for tumour response to cisplatin chemotherapy.

In our study, the maxima of free platinum concentrations in plasma and urine were extremely different after bolus and long-term cisplatin infusions, whereas only marginal differences were found when comparing half-lifes, distribution volume, total clearance and renal clearance of free platinum. The apparent influence of high $C_{max}$ values of free platinum on the development of cisplatin-associated nephrotoxicity in the present study is consistent with results obtained from studies in adults [7, 33 34]. Nagai et al. [7] described relationships between $C_{max}$ of free cisplatin in plasma and peak serum creatinine and maximum BUN levels as well as minimum GFR after 80 mg/m$^2$ cisplatin over 2 and 4 h. In our paediatric patients, maximum urinary loss of albumin and NAG and minimum GFR were correlated with peak free platinum in both plasma and urine. Serum creatinine and BUN, however, showed no significant changes throughout the chemotherapeutic regimen used in the present study. Thus, serum creatinine has been shown once more to be an unsuitable parameter for monitoring cisplatin-induced nephrotoxicity. Although this has already been emphasized by several groups [10, 12, 22], serum creatinine and blood urea nitrogen very frequently remain the standard parameters for detecting renal dysfunction in children undergoing chemotherapy. This may be due to the subclinical nature of the toxicity in most children. On the other hand, the clear evidence of tubular damage provided by urinary loss of low-molecular-weight proteins and of tubular enzymes as well as the reductions in GFR indicate that the nephrotoxic potential of cisplatin chemotherapy is often underestimated. Even if functional impairments were partially reversible within the first 12 months of follow-up, the possibility that chronic renal failure may spontaneously develop [35] or that other nephrotoxic factors may cause further deterioration of renal function after completion of chemotherapy [36] cannot be excluded. Long-term investigations of renal function in a larger cohort of long-term survivors are necessary to clarify this point. Another aspect which is difficult to estimate is the contribution of other nephrotoxic drugs such as ifosfamide or methotrexate in the development of renal dysfunction. In particular, ifosfamide has been described as the cause of severe tubular toxicity in young children [37]. In our study, ifosfamide was given as continuous infusion to the children of both of the groups and the cumulative dose of ifosfamide in the continuous cisplatin group (24 g/m$^2$) slightly exceeded the dose of the bolus group (18 g/m$^2$). Recently, total ifosfamide dose was described to be the most relevant risk factor for the development of ifosfamide nephrotoxicity [38]. Compared to these data, the cumulative doses of ifosfamide given to our patients were rather small. Moreover, the nephrotoxicity parameters obtained during administration of ifosfamide in our patients revealed no evidence of relevant additional ifosfamide-induced deterioration of renal function. Even if an additional nephrotoxic effect of ifosfamide cannot be excluded definitely in both groups, this does not invalidate the results.

Urinary excretion of albumin and $\alpha_1$-M have been identified as the most suitable parameters for detection of cisplatin-induced nephrotoxicity, but polyacrylamide

gel electrophoresis was also a very sensitive tool for monitoring proteinuria, showing that five of six children in the 1-h bolus group suffered from microproteinuria 6–12 months after completion of cisplatin therapy. Contrary to objections raised by several authors against the use of creatinine clearance for estimating GFR [12, 22], creatinine clearances obtained in our patients were reliable, and to us this simple method remains the standard method for estimating glomerular function during hospitalization. Using the parameters mentioned above, all children had pathological findings during the cisplatin courses, and in the bolus infusion group functional alterations persisted for at least 12 months after cessation of cisplatin in the majority of patients.

In conclusion, subclinical glomerular and tubular toxicity occurred after cisplatin was given either as consecutive 1-h boluses or as a continuous infusion. There was an association between nephrotoxicity parameters and peak concentrations of free platinum in plasma and urine. Only partial reversibility of cisplatin-induced nephrotoxicity was seen particularly after bolus infusions. This study provides evidence that continuous infusion schedules seem to be superior to intermittent bolus administrations due to the lower associated toxicity and probably preserved antitumour effectivity, and that the high cisplatin delivery rates still applied to cancer patients in several paediatric treatment protocols should be carefully reconsidered.

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## LITERATURE ABSTRACTS

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### Acute renal failure with neurological involvement in adults associated with measles virus isolation

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**Background** Three people with clinical manifestations of acute renal failure with neurological involvement of unknown cause were admitted to a hospital in Mumbai, India. We describe clinical presentations and investigations of the cause.
**Methods** We analysed case reports and laboratory findings for the patients (age 37–43 years, two men, one woman) that were provided by the clinicians in charge. Serum and cerebrospinal fluid were tested for viral cause by IgM ELISA to Japanese encephalitis, West Nile fever, dengue, and measles. Samples were inoculated in vero-cell culture for virus isolation. The virus isolates were confirmed with indirect immunofluoresence with antimeasles immune sera and mouse monoclonal antibodies to measles HA and F proteins and with neutralisation tests using antimeasles immune sera.
**Results** Clinical features were fever, vomiting, oliguria or anuria, bilateral facial weakness, impaired hearing, blindness, proximal and distal areflexic limb paralysis, and respiratory paralysis. No patient had a macropapular rash. Blood urea nitrogen (4.64–27.8 mmol/L) and creatinine (601.1–1105.0 micromol/L) were high, and cerebrospinal fluid contained high concentrations of proteins and pleocytosis. Kidney biopsy samples in two patients showed severe interstitial nephritis. IgM antibodies to measles were found in blood and cerebrospinal fluid. Vero-cell cultures from serum and cerebrospinal fluid of one patient and cerebrospinal fluid of two patients, showed cytopathic effects characteristic of measles.
**Conclusions** Unusual manifestations of acute renal failure with neurological involvement associated with measles virus in adults presenting without rash was confirmed. Our findings may affect the development of measles-elimination programmes.

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### Racial disparities in access to simultaneous pancreas-kidney transplantation in the United States

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The purpose of our study is to assess the extent of racial differences in the access to simultaneous pancreas-kidney (SPK) transplantation and evaluate the potential influence of socioeconomic factors on access to transplantation. We performed a retrospective analysis of the US Renal Data System and United Network for Organ Sharing data on all patients with end-stage renal disease (ESRD) due to diabetes mellitus from 1988 to 1996 ($n$=562, 814), including all dialysis, wait list, and transplant patients. Racial differences in incidence, prevalence, insurance coverage, employment status, and transplantation rates were calculated. Caucasians had the highest prevalence of ESRD caused by type 1 diabetes (73%), followed by blacks (22%), Hispanics (3%), Native Americans (2%), and others (<1%). Both blacks and Native Americans increased their annual incidence of ESRD caused by insulin-dependent diabetes mellitus by 10% compared with only a 3.5% increase in Caucasians, whereas incidence rates increased annually by almost 8% for both blacks and Native Americans compared with a 3% increase for Caucasians. However, Caucasians received 92% of all SPK transplants, whereas all other racial groups combined received a disproportionate minority of the remaining transplants. Lack of private insurance and unemployment status were associated with annual changes in both incidence of ESRD caused by type 1 diabetes and SPK transplant rates. In conclusion, we observed striking racial disparities for access to SPK transplantation in the United States today, which may be related to employment status, access to private insurance, and subsequent health care. Our preliminary data support current efforts to encourage Medicare and Medicaid coverage for all patients requiring SPK transplantation regardless of racial or financial status.