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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*-dichlorodiamine platinum(II) (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 night be due to effects on the glomerular tuft.

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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 *cis*ßplatinum 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])

Day	1	2	3	4	5	9	16
cis-Platinum 20 mg/m² IV	×	×	×	×	×		
Bleomycin 15 mg/m² IV		×				×	×
Vinblastine 6 mg/m² IV	×	×					

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-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-DTPA divided by the area under the plasma timeactivity curve extrapolated from t=0 to t=∞ [2].

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

External assessment of mean transit time of ^{99m}TC-DTPA in the organism during hydration and mannitol load (t½ 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 (t½ ext) of the final slope of this curve [9] *(Appendix).*

Assessment of extracellular volume during hydration and mannitol load [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_t-DTPA) and were compared to the increases following the injection at steady state (Q_o-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 [FEVD(t)]. Accordingly, the changes in the extracellular volume were considered proportional to FEVD(ti)/FEVD(to), where FEVD(ti) 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 FEVD(to) from the injection of ^{99m}TC-DTPA at steady state. The ECV corrected for these changes [ECV_{corr}(ti)] was then calculated as $ECV_{corr}(ti) = ECV_{DTPA} \times [FEVD(ti)/FEVD(to)]$.

Glomerular filtration rate during hydration and mannitol load. The glomerular filtration rate during hydration and mannitol load (GFR_{unst}) was calculated as $GFR_{unst} = ECV_{corr}(ti)/t½_{ext} \times$ *(Appendix).*

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

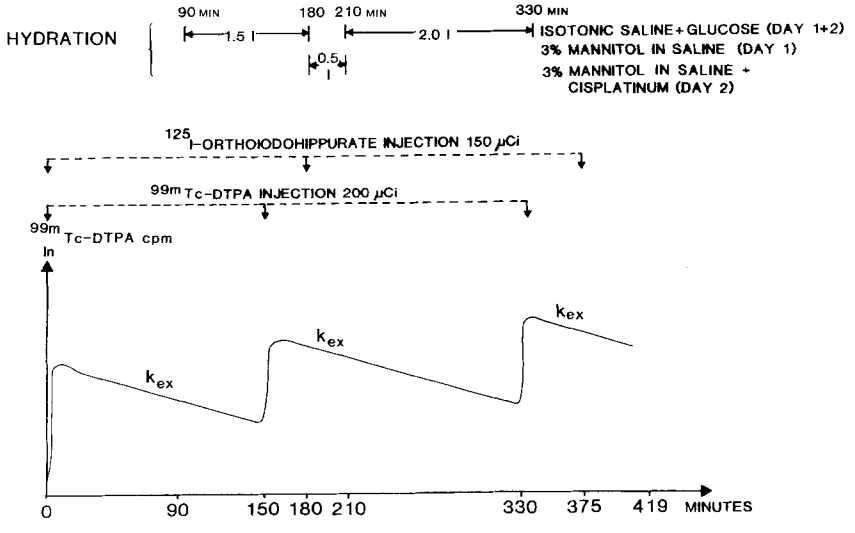

Fig. 1. General procedure for administration of hydration ^{125}I-orthoiodohippurate and ^{99m}Tc-DTPA on day 1 and day 2. On both days the patients were monitored for 420 min with external detection

Table 2. Functional status at the control state of 25 patients with cancer of the testis whose kidney function was followed for 1 year after initiation of treatment with the Einhorn regimen [5]

	Age (years)	Height (m)	Weight (kg)	Se-creatinine μmol/l	^{51}Cr-EDTA clearance ml/min/1·73 m^2
Mean	27.7	177.0	70.4	88.5	117.1
SEM	1.46	1.47	2.91	3.35	4.03
Range	16–47	162–189	52–120	68–132	76–149

General procedure in the study of acute nephrotoxicity of cis-platinum

The examinations were performed on 3 consecutive days. On day 0, ^{99m}Tc-DTPA clearance and $ECV_{DTPA}(t)$ were determined.

On day 1 and 2, hydration was started at t=90 min (Fig. 1) and given as 4 l of isotonic fluids and 0.5 l 3% mannitol in saline in a slightly modified regimen of Frich et al [6]. On day 2, 20 mg/m^2 of *cis*ßlatinum was added to the mannitol, which was given over 180 min < t < 210 min. This constituted the only difference between day 1 and day 2. (The administration of bleomycin and vinblastine at day 2 was postponed until after termination of the kidney examination.)

^{99m}Tc-DTPA 220 μCi was injected at t=0, 150, and 300 min, and the subsequent changes in the externally measured time-activity curve were used to calculate ECV_{corr} (t) and $t^1/_{2ext}$ (Fig. 1). The injections of ^{99m}Tc-DTPA defined the beginning of the prehydration, the mid-hydration and the post-hydration periods.

To calculate AUC(t44), injections of ^{125}I-orthoiodohippurate were given at t=0, 180, and 375 min.

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

Se-creatinine (μmol/l) and ^{51}Cr-EDTA clearance (ml/min) were determined before and at 2, 4, 6, and 12 months after the start of treatment. The ^{51}Cr-EDTA clearance was determined by a one-plasma-sample method [8].

Results

The age, height, and weight together with the se-creatinine and ^{51}Cr-EDTA clearances of the 25 patients before treatment are shown in Table 2.

Table 3 shows the results of the examinations performed on day 0 in the 9 patients who were examined for acute nephrotoxicity of *cis*-platinum. The ^{51}Cr-EDTA clearance in these 9 did not differ significantly from the that recorded in the other 16. The results of the determination of GFR, like those for clearance of ^{51}Cr-EDTA and of ^{99m}Tc-DTPA, were almost identical.

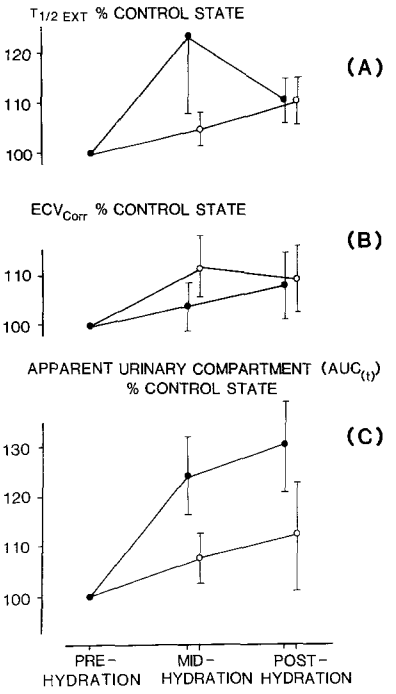

Fig. 2. The effect of placebo (●) (day 1) and cis-platinum (o) (day 2) on $t^1/_{2ext}$ (A), ECV_{corr} (t) (B) and AUC(t44) (C). The results are given as the percent (+/− SD) of the values obtained on day 0

Table 3 also includes the results of the pre-hydration values of $t^1/_{2ext}$ and AUC(t44) of day 1 and day 2. There was no significant difference between the baseline results for the 2 days.

In Fig. 2 $t^1/_{2ext}$, $ECV_{corr}(t)$ and AUC(t44) during the mid- and post-hydration periods are presented as percentages of the prehydration values.

On day 1 there was a significant ($P < 0.05$) increase in $t^1/_{2ext}$ during the mid- and post-hydration periods (paired *t*-test). On day 2 the increase was only significant for the posthydration period. There was no significant difference between the results for day 1 and day 2 in either the mid- or the posthydration period. The $ECV_{corr}(t)$ increased insignificantly (Fig. 2b) on days 1 and 2, and there was no increase of GFR_{unst} during the hydration and mannitol load on either of the 2 days.

The most pronounced changes were seen with regard to AUC(t44) (Fig. 2c) which increased on day 1 by 24% (±8%) and by 31% (±8%) during the mid- and the post-hydration periods, respectively ($P < 0.01$). The correspon-

Table 3. Functional status of the nine patients who underwent examination for acute nephrotoxicity of cis-platinum

	Age (years)	Height (m)	Weight (kg)	Se-creatinine μmol/l	^{51}Cr-EDTA clearance ml/min/1.73 m^2	^{99m}Tc-DTPA clearance ml/min/1.73 m^2	ECV (^{99m}Tc-DTPA) (l)	$t^1/_{2ext}$ Day 1 (min)	$t^1/_{2ext}$ Day 2 (min)	Apparent urinary compartment Day 1 (l)	Apparent urinary compartment Day 2 (l)
Mean	23.6	178.0	72.6	89.3	114.8	115.7	16.58	111.6	116.7	82.4	89.4
SEM	1.57	1.41	2.5	6.7	8.1	4.99	0.55	6.59	5.78	11.69	30.6
Range	16–30	173–185	60–85	70–132	76–140	96–142	14.95–20.16	86–136	95–135	39.2–123.5	38.9–132.2

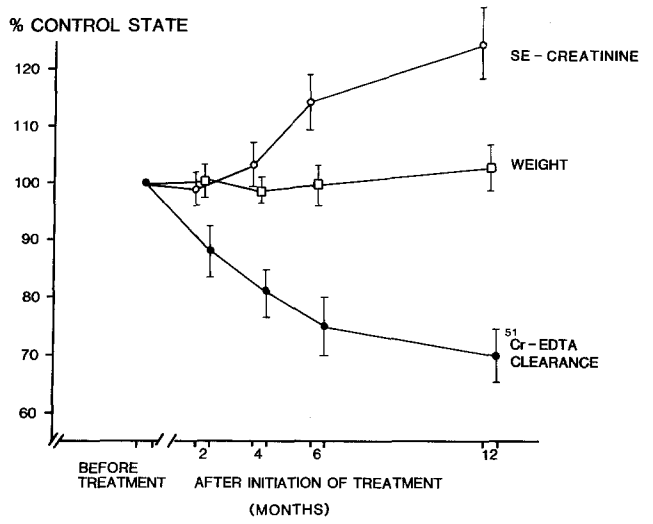

Fig. 3. Results of se-creatinine, ^{51}Cr-EDTA clearance, and the weight of the 25 patients during the 1-year follow-up after the onset of treatment with the Einhorn regimen [5]. *Bars* indicate SEM

ding increases on day 2, of 8% (±5%) and 11% (±10%) were not significant. The difference between the results for the 2 days was significant ($P < 0.01$). There was no systematic difference between the increase in hippurate clearance on day 1 in the two patients who had already received *cis*-platinum and the seven patients previously untreated with *cis*-platinum.

Results of the 1-year followup of the 25 patients are shown in Fig. 3. ^{51}Cr-EDTA clearance was 12% (+4%) ($P < 0.05$) lower than the initial values as early as 2 months after the onset of treatment. Both 4 months and 12 months after termination of the treatment, the decrease was 18% (±4%) ($P < 0.01$) and 29% (±4%) ($P < 0.01$), respectively. Thus, the function of the kidneys continued to decrease ($P < 0.05$) after the treatment had been stopped.

During the year of observation, the ^{51}Cr-EDTA clearance of the 9 patients who were examined for acute nephrotoxic effect of *cis*-platinum did not differ significantly from that of the other 16 patients. In 8 of the 9 patients, the ^{51}Cr-EDTA clearance had decreased 2 months after the onset of treatment. In 7 of the 9 patients AUC(t44) was smaller on day 2 than on day 1 during the post-hydration period. However, the individual difference between day 2 and day 1 was not significantly correlated ($P > 0.05$) to the degree of reduction of ^{51}Cr-EDTA clearance observed 2 months or 1 year after initiation of treatment.

A significant increase in se-creatinine was not seen until 6 months after initiation of treatment ($P < 0.05$). The body weight remained unchanged throughout the year of observation.

Discussion

Our results indicate that there is a demonstrable, acute nephrotoxic effect of *cis*-platinum in man. This effect was identified as a significant difference between the ^{125}I-orthoiodohippurate clearance on the day of placebo and the day of *cis*-platinum treatment. Under normal circumstances a constant fraction of approximately 90% of ^{125}I-orthoiodohippurate is extracted from the plasma during a single passage through the kidneys. This is why the clearance of ^{125}I-orthoiodohippurate is considered to be proportional to the ERPF. Changes in ^{125}I-orthohippurate could theoretically be due to a reduction of ERPF, or a reduction of the tubular extraction of ^{125}I-orthohippurate.

During the post-hydration period on days 1 and 2 we observed no change of the GFR_{unst}. This is in agreement with Meijer et al. [15], who observed no proteinuria at the end of induction chemotherapy and concluded, therefore, that the glomerular permeability remained constant during treatment.

Is this conclusion likely, however, if the difference between ^{125}I-orthoiodohippurate clearance on days 1 and 2 is caused by a change in ERPF?

If the colloid osmotic pressure of plasma is constant, the GFR is proportional to the difference between the filtration pressure and the pressure in the capsules of Bowman. A decrease of ERPF caused by a constriction of the afferent arteriole of the nephron would tend to lower the filtration pressure. In this case, a simultaneous lowering of the intratubular pressure would also have to be postulated, since the GFR remained constant. Such a lowering of the intratubular pressure should be possible if the function of the proximal tubular cells is not impaired by the *cis*-platinum, so that they may increase the proximal tubular reabsorption rate.

A relative decrease in ERPF can also result from an increase in the resistance of the efferent arteriole or in the capillaries. In fact, an increase in the resistance of the capillaries could be mediated via an uptake of platinum out of peritubular capillaries into the interstitium, which appears to be the case since platinum is accumulated in the kidney [12]. In this case the filtration rate would tend to increase during the hydration load, but would have to be paralleld by an increase in the pressure in the proximal tubules and Bowman's capsules if the GFR should remain constant. Owing to the low resistance across the glomerular membrane an increase in the filtration pressure could, of course, be transmitted to the tubules and cause an immediate increase in the intratubular pressure. This explanation, on the other hand, cannot simultaneously explain the decrease in GFR observed after 2 months of treatment. The change in renal haemodynamics may therefore be only epiphenomenon not causally related to the long-term nephrotoxicity. Yet, if the proximal tubular reabsorption were also affected in the acute case and caused the intratubular pressure to increase, the increased intratubular pressure might after a while succeed the increased filtration pressure. The result could be a decrease in GFR similar to the results we obtained 2 months after the initiation of treatment.

If *cis*-platinum reduced the proximal tubular extraction of ^{125}I-orthoiodohippurate, the clearance of this tracer would decrease. Tubular toxicity has been claimed by several authors [7, 12, 17] and is seen with increasing doses of DDP. Although Meijer et al. were not able to demonstrate any tubular proteinuria measured as beta-2-microglobulinuria in 1983 [15], others have reported proteinuria [20]. Furthermore, many patients show signs of hypomagnesemia during treatment with *cis*-platinum [19], which indicates that the tubules constitute a major target of toxicity of *cis*-platinum on the nephron in man.

If, as discussed above, the intratubular pressure is increased as a consequence of an acute tubular action of *cis*-

platinum, this may be overridden by the increased filtration pressure induced by the hydration load. Consequently, the GFR should not be expected to decrease until later, when the organism is in steady state and the filtration pressure has normalized. In our opinion, this is the best explanation of the results, and we therefore favour tubular toxicity as the most likely cause of both acute reduction of AUC(t44) and the chronic reduction of GFR.

An important aspect of our study is the continued decrease of GFR after the termination of the treatment. Since *cis*-platinum accumulates in the kidney [10] it may continue to exert its cytotoxic effect. Another possibility is that an increase of the intratubular pressure may itself damage the tubular cells and create a vicious circle. Further studies in animal models should elucidate whether the extraction of hippurate is acutely affected during treatment with *cis*-platinum and whether the intratubular pressure, if increased, continues to rise.

In conclusion, by monitoring the function of the kidneys during *cis*-platinum treatment and hydration and mannitol diuresis, we found an acute reduction of the clearance of ^{125}I-orthoiodohippurate from the organism. However, should a similar acute reduction be observed with some of the new *cis*-platinum analogues this may not imply that the chronic nephrotoxicity will be the same as that of DDP. Renal function continued to decrease during the 1-year followup, and careful monitoring of the patients for more than 1 year is therefore called for. This may also be the case with some of the new *cis*-platinum congeners. Whether acute nephrotoxicity is demonstrated or not, the need for longitudinal long-term studies of kidney function during testing of the new *cis*-platinum congeners is necessary.

Appendix

The glomerular filtration rate (GFR) can be calculated as

$$GFR = \frac{V_D}{\bar{t}}, \quad (1)$$

where V_D is the distribution space of the tracer and $\bar{t}$ is the mean transit time of the tracer in the organism [11]. The V_D of ^{99m}Tc-DTPA defines the size of ECV. Therefore, ^{99m}Tc-DTPA clearance can be thought of as the fraction of ECV that is cleared per unit of time. If ^{99m}Tc-DTPA were completely and immediately distributed in ECV following a bolus injection, the initial concentration of ^{99m}Tc-DTPA in ECV would be $C_o = Q_o/ECV$, where Q_o is the amount of tracer injected. In this case, the disappearance of ^{99m}Tc-DTPA from ECV could be described by $C(t) = C_o e^{-t/t} = C_o e^{-kt}$, where k is the time constant. We could write

$$^{99m}\text{Tc-DTPA clearance} = \frac{ECV \cdot Q_o}{\bar{t}\, Q_o} = \frac{Q_o}{C_o \bar{t}}. \quad (2)$$

$$\text{As} \int_0^\infty C_o\, e^{-t/\bar{t}} dt = C_o \bar{t},$$

^{99m}Tc-DTPA clearance is Q_o divided by the area below the ECV time-activity curve extrapolated to infinity.

However, ^{99m}Tc-DTPA is not immediately and completely distributed in the ECV. Yet, if a bolus injection of ^{99m}Tc-DTPA is given IV, the typical time-activity curve registered by means of small CdTe detectors (Fig. 4) will behave very much like the idealized case. Normally, the time until maximum radioactivity is reached will be about

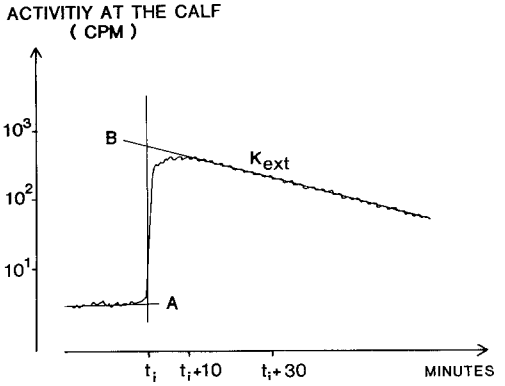

Fig. 4. The fast exchangeable volume of distribution of ^{99m}Tc-DTPA [FEVD(t)] was calculated as the amount of injected ^{99m}Tc-DTPA divided by the increase of externally recorded radioactivity ($\Delta_{(ti)}$cpm). $\Delta_{(ti)}$cpm equals B-A, where B is the intercept of the final slope (k_{ext}) on the ordinate at the time of injection at $t = t_i$ and A is the background at $t = t_i$

12 min [1], and shortly thereafter a final slope (k_{ext}) can be defined. We therefore considered the externally derived time-activity curves to be sufficiently representative of an arbitrary ECV time-activity curve and extrapolated k_{ext} to the time of injection to define a $C_o$ext as

$$C_o\text{ext} = \frac{Q_o}{FEVD\ (t)}, \quad (3)$$

where FEVD(t) can be conceived of as a a 'fast exchangeable volume of distribution' of the tracer. $C_o$ext is read directly as the rise of activity following an injection of ^{99m}Tc-DTPA (Fig. 4).

Because of interindividual variation, the geometry of the field of view of the detectors is unpredictable. FEVD(t) is therefore an individual, arbitrary estimate of ECV and can only be used to monitor intraindividual changes in ECV calculated as indicated in *Methods*.

Because of the short time until the maximum activity is registered, $1/k_{ext}$ can be considered almost identical with t. Since we have $1/k_{ext} \times 1n2 = t1n2 = t1/2ext$, changes in t will be directly proportional to changes of t½ext. Therefore, during hycration and mannitol load, t was estimated as shortly as possible after each injection of ^{99m}Tc-DTPA as

$$\bar{t} \approx t1/2ext. \quad (4)$$

The t½ext and the FEVD(t) were used to calculate an arbitrary GFR (GFR_{unst}) as shown in *Methods* by defining an ECV corrected for the acute change [$ECV_{corr}(t)$] and insertion into eg. [1].

^{125}I-Orthoiodohippurate clearance was calculated as the apparent volume of distribution (AVD(t44)) of Tauxe et al. [9]:

$$AVD\ (t44) = \frac{Q_o - {}^{125}\text{I-orthoiodohippurate}}{C^{125}\text{I-H}\ (t44)}, \quad (5)$$

where C^{125}I-H(t44) is the plasma activity of ^{125}I-orthoiodohippurate at t = 44 min after the injection. According to the concept of an apparent volume of distribution, the tracer is distributed in three compartments, $V_1 + V_2 + V_3(t)$ (Fig. 5). $V_1 + V_2$ constitute the conventional distribution space of the tracer (ECV). If the amount of tracer which at t = ti has left the organism is thought of as contained in a volume [$V_3(t)$] with the same concentration as in V_1 and V_2, this imaginary volume can be conceived of as an apparent

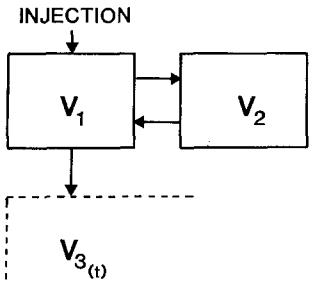

Fig. 5. $V_1+V_2+V_{3(t44)}$ is the apparent volume of distribution (AVD(t44) at $t=t_i+44$ min after the bolus injection of ^{125}I-orthoiodohippurate. According to the model. V_1+V_2 equals ECV. $V_3(t44)$ is the apparent urinary compartment [AUC(t44)]. See text for details

urinary compartment. In steady state, V_1+V_2 are constants, and AVD(t44) will be closely correlated to ^{125}I-orthoiodohippurate clearance. However, since $ECV_{corr}(t)$ might differ during the hydration and mannitol load, we used the AUC(t44) as the index of the ^{125}I-orthoiodohippurate clearance and performed the calculation as

$$AUC\,(t44) = AVD\,(t44) - ECV_{corr}\,(t). \quad (6)$$

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