Renal haemodynamics, sodium and water reabsorption during continuous intravenous infusion of recombinant interleukin-2

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ABSTRACT

1. Renal haemodynamics, lithium and sodium clearance were measured in 14 patients treated with recombinant interleukin-2 for metastatic renal cell carcinoma.

2. Patients were studied before and after 72 h of continuous intravenous infusion of recombinant interleukin-2 (18 × 10^6 i.u.·24 h·m^2) and 48 h post therapy. Cardiac output was measured by impedance cardiography. Effective renal plasma flow and glomerular filtration rate were determined by the renal clearances of 131I-hippuran and 99mTc-diethylenetriaminepenta-acetic acid (DTPA) respectively. Renal clearance of lithium (C<sub>Li</sub>) was used as an index of proximal tubular outflow.

3. Treatment caused a transient decrease in mean arterial blood pressure and systemic vascular resistance, but cardiac output remained unchanged. Renal blood flow decreased and renal vascular resistance increased during and after treatment. Sodium clearance decreased from 1.10 (0.63/1.19) ml/min to 0.17 (0.18/0.32) ml/min (P = 0.003). Glomerular filtration rate remained unchanged, whereas the median C<sub>Li</sub> decreased from 26 (17/32) ml/min to 17 (10/21) ml/min (P = 0.008). Calculated absolute proximal reabsorption rate of water increased from 63 (40/69) ml/min to 71 (47/82) ml/min (P = 0.04). The urinary excretion rate of thromboxane B<sub>2</sub> and the ratio between excretion rates of thromboxane B<sub>2</sub> and 6-keto-prostaglandin-F<sub>1alpha</sub> increased by 98% (P = 0.022) and 175% (P = 0.022) respectively.

4. The study suggests a specific recombinant interleukin-2-induced renal vasoconstrictor effect. Changes in renal prostaglandin synthesis may contribute to the decrease in renal blood flow. The lithium clearance data suggest that an increased proximal tubular reabsorption rate may contribute to the decreased sodium clearance during recombinant interleukin-2 treatment.

INTRODUCTION

Interleukin-2 based immunotherapy has resulted in the attainment of durable responses in tumours refractory to conventional therapy [1–5]. The side effects are, however, considerable and the development of a capillary leak syndrome with leakage of proteinaceous fluid from the vascular space, hypotension and organ dysfunction limits the dose of recombinant interleukin-2 (rIL-2) that patients can tolerate [1–16]. An increase in plasma
creatinine frequently leads to dose reduction of rIL-2 [5]. Studies in patients receiving high-dose bolus rIL-2 suggested that changes in renal function were secondary to the haemodynamic changes [10–12,14], but also glomerular and other renal lesions have been proposed as concurrent factors [15,16]. The fractional excretion of sodium decreases during rIL-2 therapy [10–12,15,16]. Use of volume expanders to maintain central venous pressure and vasopressors to maintain systolic blood pressure above 90 mmHg did not prevent avid renal water and sodium reabsorption [6–12,14–16]. Plasma sodium concentration (PNa) was preserved, but this approach resulted in weight gains of 5–10% and oedema, suggesting an abnormal extracellular volume homoeostasis during rIL-2 therapy. Due to the many rIL-2 induced side-effects most patients received a variety of supplementary medication, e.g. non-steroidal anti-inflammatory drugs (NSAIDs), vasopressors, volume expanders, diuretics and anti-emetics, which all may have contributed to the observed renal side-effects. Renal function was evaluated by serial measurements of plasma creatinine [10–12,14], renal creatinine clearance [15] or inulin clearance [16]. It is, however, well recognized that changes in plasma creatinine level and endogenous creatinine clearance are poor predictors of day-to-day changes in renal function [17].

Continuous intravenous infusion of rIL-2 has been claimed to reduce toxicity compared with high-dose bolus therapy. However, only a few studies have examined the renal effects of continuous intravenous infusion of rIL-2. A case report demonstrated a marked decrease in effective renal plasma flow and creatinine clearance [13]. Two additional studies demonstrated a decrease in creatinine clearance, urinary output and sodium clearance and an increase in urinary N-acetyl-β-D-glucosaminidase activity [18,19].

In the present study, we evaluated the renal haemodynamic effects of high-dose rIL-2 administered by continuous intravenous infusion in patients receiving a minimum of supplementary medication. Renal haemodynamics were evaluated by the renal clearance of radiolabelled diethylenetriaminepenta-acetic acid (DTPA) and hippuran. To further characterize the renal effects of rIL-2 therapy, we evaluated renal tubular function by use of the lithium clearance method [20,21].

METHODS

Patients
Fourteen patients (seven male/seven female) treated with rIL-2 administered by continuous infusion for metastatic renal cell carcinoma were studied. Median age was 55.5 (range 27–67) years. None of the patients were unilaterally nephrectomized; median time from uninephrectomy to the start of treatment was 6 (1.5–60) months. The median glomerular filtration rate (GFR) was 68 (45–102) ml/min compared with 98 (93–121) ml/min in the other patients. Entry criteria comprised: ambulatory performance status [ECOG (Eastern Cooperative Oncology Group) 0–1; Karnofsky ≥ 80%]; plasma creatinine within the normal range; no history or current evidence of cardiovascular disease; no infections requiring antibiotic therapy; no treatment with corticosteroids; no brain metastases at CT-scan. The treatment protocol was approved by the local ethics committee and all patients gave informed consent before the initiation of treatment with rIL-2. Additional informed consent was obtained from each patient before renal monitoring.

Treatment with rIL-2
The rIL-2 (Proleukin: EuroCetus Corp., Amsterdam, The Netherlands) was administered intravenously at a dose of 18 × 10⁶ i.u. 24 h⁻¹ m⁻² by continuous infusion as previously described [5]. One induction cycle consisted of two infusion periods of 120 h and 108 h duration respectively, separated by a 6-day rest period. Severe toxicity, e.g. a decrease in systolic blood pressure of more than 40 mmHg, and/or an increase in plasma creatinine above 400 μmol/l, was counteracted by dose reductions. Vasopressors were not given, and intravenous fluid was not administered unless a weight loss was recorded. During the rIL-2 infusion periods the patients received the following supplementary medication: acetaminophen (750 mg) every 4 h to control fever, cimetidine (400 mg) every 12 h prophylactically against gastrointestinal bleeding, atropine/diphenoxylate for diarrhoea and antiemetics if needed. Diuretics were not given. In accordance with the protocol, NSAIDs were not allowed during the monitoring period to avoid interference with renal function. However, pain and hyperthermia necessitated administration of NSAIDs in two patients during the treatment. Results from these two patients are presented separately.

All measurements were performed in relation to the first 120 h infusion period.

Haemodynamic studies
Blood pressure by sphygmomanometry and heart rate were measured every 2 h during the infusion periods. During the renal clearance studies measurements were taken every hour. By use of impedance cardiography [22] cardiac output was measured continuously for a period of at least 5 min during the renal clearance studies.

Renal clearance studies
The patients were investigated on three occasions: before (day 0), during (day 4) and 2 days after (day 8) the first 120 h infusion period. Smoking and intake of caffeine-containing drinks or chocolate were not allowed the night before or during the investigation. After an overnight fast the patients arrived at the laboratory on each
study day at 08:30 h. Tap water (200–250 ml/h) was administered orally to facilitate urine collection. The patients were confined to bed except for standing when voiding every 60 min.

Effective renal plasma flow (ERPF) was measured by a constant infusion technique with urine collections using \(^{131}\text{I}\)-hippuran at a total dose of 2.33 MBq (0.11 mSv). GFR was measured after a bolus injection of 30 MBq (0.75 mSv) of \(^{99m}\text{Tc-DTPA}\) (CIS Bio International, France). After an equilibration period of at least 1 h, the renal clearances of \(^{131}\text{I}\)-hippuran (C\(_{\text{Hipp}}\)) and \(^{99m}\text{Tc-DTPA}\) were determined and averaged for two consecutive 1 h periods from the urinary excretion rates and plasma samples from the beginning, middle and end of each period. The volume of distribution of \(^{99m}\text{Tc-DTPA}\) was determined from the y intercept of the plasma disappearance curve and the injected dose. Haematocrit was measured at the beginning of the renal clearance studies on each study day.

Lithium clearance study

Urine flow rate (V), GFR, ERPF and the renal clearances of sodium and lithium were measured simultaneously. A test dose of lithium carbonate (600 mg, 16.2 mmol) was given orally at 22:00 h the evening before each investigation. Sodium (C\(_{\text{Na}}\)) and lithium (C\(_{\text{Li}}\)) clearances were determined and averaged for two consecutive 1 h periods from the urinary excretion rates and plasma samples from the beginning, middle and end of each period.

To evaluate the extent of distal lithium reabsorption during rIL-2 treatment, C\(_{\text{Li}}\) and GFR were measured before and after oral administration of 10 mg of amiloride in three of the patients on day 0 and day 4. In these patients, GFR was measured by a constant infusion technique with urine collection by use of \(^{99m}\text{Tc-DTPA}\) at a total dose of 26 MBq (0.65 mSv). One-hour renal clearances of \(^{99m}\text{Tc-DTPA}\), lithium and sodium were determined and averaged for two 1-h periods before and for two 1-h periods in the middle and end of each period.

To evaluate the effect of prophylactically administered acetaminophen on urinary prostaglandin excretion, 6-keto-PGF\(_{1\alpha}\) and thromboxane B\(_2\) were measured in eight healthy volunteers before and 1 h after oral administration of 750 mg of acetaminophen. Tap water (200–250 ml/h) was administered orally to facilitate urine collection.

**Analytical methods**

Activities of \(^{131}\text{I}\)-hippuran and \(^{99m}\text{Tc-DTPA}\) in plasma and urine were determined in a well counter. P\(_{\text{cr}}\) and plasma sodium concentration were measured with a Technicon SMA®C instrument and urinary sodium concentration with a Technicon RA 1000 instrument (Tarrytown, N.Y., U.S.A.). Plasma and urinary lithium concentrations were measured by atomic absorption spectrophotometry (Perkin-Elmer model 403, Norwalk, CT, U.S.A.). 6-Keto-PGF\(_{1\alpha}\) and thromboxane B\(_2\) in urine were measured by radioimmunoassay (Amersham International plc, Amersham, U.K.). The intra-assay coefficient of variation was 3% for 6-keto-PGF\(_{1\alpha}\) and 5% for thromboxane B\(_2\) measurements.

**Calculations**

Mean arterial blood pressure (MAP) was calculated as the diastolic pressure plus one-third of the pulse pressure. Systemic vascular resistance was calculated as MAP divided by cardiac output.

GFR, ERPF, C\(_{\text{Li}}\) and C\(_{\text{Na}}\) were calculated using standard formulae. All clearance values were corrected to 1.73 m\(^2\) body surface area. Renal vascular resistance was calculated as MAP divided by the renal blood flow, calculated as ERPF/(1 – haematocrit). Filtration fraction was calculated as GFR/ERPF.

Calculation of the proximal reabsorption rate of water and sodium was based on the assumption that C\(_{\text{Li}}\) provides an accurate measurement of the rate of end-proximal delivery of sodium and water [20]:

\[
\text{APR} = \frac{\text{GFR} - C_{\text{Li}}}{C_{\text{Li}}} 
\]

Fractional excretion of lithium (FE\(_{\text{Li}}\)) was calculated as C\(_{\text{Li}}\)/GFR.

**Statistical analysis**

Wilcoxon’s paired signed rank test was used to compare pretreatment with on-treatment and post-treatment data. Two-sided tests were used, and a P value less than 0.05 was considered statistically significant. Data are presented as median values with lower and upper quartiles.

**RESULTS**

A total of 14 patients was studied. Two patients received N SAIDs and their results are presented separately. One patient treated with amiloride before the initiation of...
rIL-2 treatment was not included in the lithium clearance study. The three patients in the amiloride study were evaluated by GFR, C\textsubscript{Li}, and C\textsubscript{Na}. Thus, nine patients participated in the renal haemodynamic study (five female/four male). Seven of the patients were unilaterally nephrectomized. During therapy \textsuperscript{131}I-hippuran clearance was not determined in one patient due to technical problems. Complete post-therapy measurements were obtained in eight patients.

Eleven patients were included in the lithium clearance study (five female/six male). Post-therapy measurements were not performed in one patient because of technical problems. Eight of the patients were unilaterally nephrectomized.

One of the two patients (one female/one male) treated with NSAIDs was uninephrectomized.

All patients received 100% of the planned rIL-2 doses from the start of treatment to day 4. The median rIL-2 dose was 32 (29/35) \times 10^6 i.u./24 h. rIL-2 was diluted in 5% dextrose in water at a final concentration of 36000 i.u./ml. The median infused volume was 888 (792/984) ml/24 h. From the start of treatment to the renal studies on day 4, additional intravenous fluid was administered to three patients. Two patients each received 2 units of packed erythrocytes on day 2 of treatment. None of the two patients (one female/one male) treated with N SAIDS was uninephrectomized.

P\textsubscript{cr} increased in all patients from day 0 to day 4; the median increase was 24 (12/33)% (P = 0.0022). Two days after treatment (day 8), the increase was -3 (-21/+15)% (P = 0.67). Median values of GFR did not change significantly during or after rIL-2 treatment. GFR was in the range 40-114 ml/min before treatment. After 4 days of treatment and 2 days after treatment, GFR ranged from 26 to 128 ml/min and from 37 to 114 ml/min respectively. The median decreases were -3 (-15/+14)% (P = 1.0) and -14 (-39/+35)% (P = 0.58) respectively. Changes in P\textsubscript{cr} and GFR were negatively correlated during (r = -0.63, P = 0.037) and after treatment (r = -0.74, P = 0.014).

ERPF decreased in all patients during (day 4) and 2 days after treatment. The median decreases were 21 (11/29)% and 17 (6/44)% respectively (P = 0.012). Thus, filtration fraction increased during and after treatment. Haematocrit was unchanged during and after treatment. The median haematocrit values were 34.5, 33.25 and 32.5 on days 0, 4 and 8 respectively. Therefore, renal blood flow followed the same pattern of changes as ERPF during and after rIL-2 treatment. Renal vascular resistance increased in 7 out of 8 patients during treatment (P = 0.025), and in 6 out of 8 patients (P = 0.036) after treatment. The volume of distribution of \textsuperscript{99m}Tc-DTPA showed no statistically significant changes during or after rIL-2 treatment. The median distribution volumes were 11857 (9740/13439) ml, 11777 (9895/13161) ml and 11579 (10195/16126) ml before, during and after treatment respectively.

Urinary excretion rates of 6-keto-PGF\textsubscript{1α} and thromboxane B\textsubscript{2} showed an increase during treatment in 5 and 7 (out of 7) patients respectively. After 4 days of rIL-2 therapy, the median excretion rate of 6-keto-PGF\textsubscript{1α} increased from 39 (37/52) ng/h to 48 (45/89) ng/h (P = 0.15), and the median thromboxane B\textsubscript{2} excretion rate

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Table 1 Renal haemodynamic effects of IL-2 therapy

<table>
<thead>
<tr>
<th></th>
<th>Before treatment (day 0) (n = 9)</th>
<th>During treatment (day 4) (n = 9)</th>
<th>After treatment (day 8) (n = 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma creatinine (µmol/l)</td>
<td>98 (78/116)</td>
<td>115 (95/138)*</td>
<td>90 (75/138)</td>
</tr>
<tr>
<td>GFR (ml min\textsuperscript{-1} \times 1.73 m\textsuperscript{-2})</td>
<td>74 (55/99)</td>
<td>69 (57/90)</td>
<td>68 (47/92)</td>
</tr>
<tr>
<td>ERPF (ml min\textsuperscript{-1} \times 1.73 m\textsuperscript{-2})</td>
<td>308 (207/465)</td>
<td>257 (171/342)*</td>
<td>235 (182/332)*</td>
</tr>
<tr>
<td>RBF (ml min\textsuperscript{-1} \times 1.73 m\textsuperscript{-2})</td>
<td>456 (304/685)</td>
<td>389 (263/489)*</td>
<td>348 (274/474)*</td>
</tr>
<tr>
<td>Filtration fraction</td>
<td>0.23 (0.21/0.30)</td>
<td>0.31 (0.29/0.34)*</td>
<td>0.28 (0.22/0.32)*</td>
</tr>
<tr>
<td>Renal vascular resistance</td>
<td>0.22 (0.14/0.29)</td>
<td>0.28 (0.16/0.31)*</td>
<td>0.24 (0.20/0.30)*</td>
</tr>
<tr>
<td>Heart rate (beats/min)</td>
<td>88 (79/99)</td>
<td>98 (95/103)*</td>
<td>88 (80/96)</td>
</tr>
<tr>
<td>MAP (mmHg)</td>
<td>92 (83/103)</td>
<td>81 (78/86)*</td>
<td>87 (76/103)</td>
</tr>
<tr>
<td>Cardiac output (l/min)</td>
<td>5.4 (4.8/6.9)</td>
<td>5.6 (5.4/7.0)</td>
<td>5.8 (4.5/6.1)</td>
</tr>
<tr>
<td>Systemic vascular resistance</td>
<td>16.1 (11.9/22.1)</td>
<td>14.4 (11.1/16.5)*</td>
<td>18.2 (15.2/20.4)</td>
</tr>
</tbody>
</table>

Table 1 Renal haemodynamic effects of IL-2 therapy

Values are medians with lower/upper quartiles in brackets. Statistical significance: *P < 0.05 compared with day 0, Wilcoxon paired test.

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**Haemodynamic and renal haemodynamic study (Table 1)**

Mean arterial pressure and systemic vascular resistance decreased and heart rate increased in all patients during treatment, but returned to baseline values 2 days after treatment.
Renal effects of recombinant interleukin-2

Table 2  Lithium and sodium clearance, fractional excretion of lithium and sodium, and APR of water during rIL-2 therapy
Values are medians with lower/upper quartiles in brackets. Statistical significance: *P < 0.05 and **P < 0.01 compared with day 0, Wilcoxon signed rank test.

<table>
<thead>
<tr>
<th></th>
<th>Before treatment (day 0)</th>
<th>During treatment (day 4)</th>
<th>After treatment (day 0)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 11)</td>
<td>(n = 11)</td>
<td>(n = 11)</td>
</tr>
<tr>
<td>C(lit/min·1.73m⁻²)</td>
<td>26 (17/32)</td>
<td>17 (10/21)*</td>
<td>18 (15/21)</td>
</tr>
<tr>
<td>FE(lit)(%)</td>
<td>30 (28/35)</td>
<td>20 (15/26)**</td>
<td>28 (26/33)</td>
</tr>
<tr>
<td>CNa(lit/min·1.73m⁻²)</td>
<td>1.01 (0.63/1.19)</td>
<td>0.17 (0.13/0.32)**</td>
<td>0.67 (0.29/1.82)</td>
</tr>
<tr>
<td>FENa(%)</td>
<td>1.10 (0.93/1.79)</td>
<td>0.29 (0.18/0.36)**</td>
<td>0.80 (0.44/1.86)</td>
</tr>
<tr>
<td>APR(lit/min·1.73m⁻²)</td>
<td>63 (40/69)</td>
<td>71 (47/82)*</td>
<td>46 (28/65)</td>
</tr>
</tbody>
</table>

Table 3  Effects of amiloride on GFR, lithium and sodium clearance, and fractional excretion of sodium and lithium before and during rIL-2 therapy
Values are means of three patients.

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Amiloride</th>
<th>Baseline</th>
<th>Amiloride</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 3)</td>
<td>(n = 3)</td>
<td>(n = 3)</td>
<td>(n = 3)</td>
</tr>
<tr>
<td>GFR(lit/min·1.73m⁻²)</td>
<td>106</td>
<td>97</td>
<td>104</td>
<td>106</td>
</tr>
<tr>
<td>C(lit/min·1.73m⁻²)</td>
<td>33</td>
<td>31</td>
<td>22</td>
<td>24</td>
</tr>
<tr>
<td>CNa(lit/min·1.73m⁻²)</td>
<td>1.3</td>
<td>1.9</td>
<td>0.8</td>
<td>0.8</td>
</tr>
<tr>
<td>FE(%)</td>
<td>32</td>
<td>32</td>
<td>21</td>
<td>22</td>
</tr>
<tr>
<td>FENa(%)</td>
<td>1.2</td>
<td>3</td>
<td>0.3</td>
<td>0.8</td>
</tr>
</tbody>
</table>

from 126 (67/169) ng/h to 375 (318/633) ng/h (P = 0.022). The ratio between urinary excretion rates of thromboxane B₂ and 6-keto-PGF₁α therefore increased from 2.4 (1.6/3.5) to 6.6 (4.5/9.6) during treatment (P = 0.022).

The additional study in eight healthy volunteers showed that acetaminophen had no effect on the urinary excretion rates of thromboxane B₂ and 6-keto-PGF₁α. The urinary excretion rate of thromboxane B₂ was 56 (38/134) ng/h before and 63 (49/88) ng/h after administration of acetaminophen (P = 0.58). The values for 6-keto-PGF₁α were 28 (20/42) ng/h and 24 (21/37) ng/h (P = 0.89) respectively. The ratio between the urinary excretion of thromboxane B₂ and 6-keto-PGF₁α was 2.5 (1.5/3.1) before and 2.3 (1.7/3.0) after administration of acetaminophen (P = 0.89).

Sodium and water excretion (Table 2)
CNa and FENa decreased in all patients during treatment (P = 0.003). Changes were reversible and not statistically significant 2 days post therapy (P = 0.87). PNa decreased from 139 (135/142) mmol/l on day 0 to 134 (131/135) mmol/l on day 4 (P = 0.003). Post treatment the median PNA was 136 (134/139) mmol/l. The median V was 6.5 (5.5/9.1) ml, 4.5 (3.1/6.1) ml and 4.1 (2.2/7.1) ml on days 0, 4 and 8 respectively. Body weight increased by 0.6 (0.1/0.9) kg on day 4 (P = 0.04), and 0.7 (0.0/1.8) kg on day 8 (P = 0.12).

Amiloride study (Table 3)
Amloride had no effect on the lithium clearance before or during rIL-2 treatment. After 4 days of rIL-2 treatment, FENa had decreased by 38.3%, 47.4% and 12.6% respectively. After administration of amiloride, the decrease in FENa was 36.5%, 41.3% and 12.2% respectively. Amloride increased CNa and FENa as expected.

Results from NSAID-treated patients (Table 4)
MAP in the two patients decreased from 98 to 80 mmHg and 88 to 67 mmHg after 4 days of rIL-2 treatment. Two days post therapy the values were 88 mmHg and

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Table 4 Renal haemodynamics, lithium and sodium clearance, and derived parameters in two patients treated with NSAIDs

<table>
<thead>
<tr>
<th></th>
<th>Before treatment (day 0)</th>
<th>During treatment (day 4)</th>
<th>After treatment (day 8)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Patient 1</td>
<td>Patient 2</td>
<td>Patient 1</td>
</tr>
<tr>
<td>ERPF (ml·min⁻¹·1.73 m⁻²)</td>
<td>287</td>
<td>209</td>
<td>183</td>
</tr>
<tr>
<td>GFR (ml·min⁻¹·1.73 m⁻²)</td>
<td>98</td>
<td>68</td>
<td>53</td>
</tr>
<tr>
<td>Cₐ (ml·min⁻¹·1.73 m⁻²)</td>
<td>22</td>
<td>22</td>
<td>8</td>
</tr>
<tr>
<td>FEₐ (%)</td>
<td>0.51</td>
<td>0.97</td>
<td>0.14</td>
</tr>
<tr>
<td>Cₛ (ml·min⁻¹·1.73 m⁻²)</td>
<td>0.52</td>
<td>1.44</td>
<td>0.27</td>
</tr>
<tr>
<td>FES (%)</td>
<td>76</td>
<td>46</td>
<td>45</td>
</tr>
<tr>
<td>APR (ml·min⁻¹·1.73 m⁻²)</td>
<td>76</td>
<td>46</td>
<td>45</td>
</tr>
</tbody>
</table>

76 mmHg, respectively. ERPF, GFR, Cₐ, and FEₐ decreased during rIL-2 treatment. APR decreased in both patients compared with a decrease in only 2 of the 11 patients who did not receive NSAIDs. Cₚ decreased from 0.51 to 0.01 ml/min, and from 0.97 to 0.09 ml/min from day 0 to day 4. FES, decreased from 0.52 to 0.03% and 1.44 to 0.18% in the same period.

DISCUSSION

Renal and central haemodynamic parameters are presented for 14 patients with metastatic renal cell carcinoma treated with a high-dose continuous intravenous infusion of rIL-2; only two patients received NSAIDs, and none received vasopressor agents. Nine of the patients were uninephrectomized and the other five patients had a tumour in one of the kidneys. Thus, the majority of our patients had reduced renal function at the start of treatment, which might have influenced the observed changes in renal values because of the reduced functional reserve. The renal clearance of DTPA after a bolus injection correlates well with the renal clearance of inulin in patients with normal and impaired renal function [25,26]. The rIL-2-induced vascular leak may increase the volume of distribution of DTPA, and the plasma to interstitial fluid clearance of DTPA during rIL-2 treatment are not available. A significant correlation was demonstrated between individual changes in GFR and Pᵣ, but the changes in GFR were small and the median values were not significantly different from baseline. Cimetidine, which was used prophylactically in the present study, is known to inhibit the tubular secretion of creatinine and may cause a transient increase in plasma creatinine [26], but the median Pᵣ level returned towards baseline within 2 days of cessation of rIL-2 therapy, when most patients were still receiving cimetidine. The increase in Pᵣ might therefore be caused by an increased outflow of creatinine from muscle tissue, but an inhibitory effect of rIL-2 treatment on the tubular secretion of creatinine cannot be excluded either.

ERPF and renal blood flow decreased significantly during and after therapy. The renal clearance of hippurin may, however, have underestimated ERPF if rIL-2 therapy decreased the tubular extraction of hippurin. Furthermore, since the extraction fraction of hippurin is often reduced in patients with impaired renal function the present results should be interpreted with caution. The modest decrease in MAP cannot explain the decrease in renal blood flow, because MAPs remained within the normal renal autoregulatory range [27]. Furthermore, the renal blood flow and renal vascular resistance were still affected 2 days after treatment, when MAP had returned to control values.

A decrease in sodium excretion and weight gain are common findings during high-dose rIL-2 therapy [11,12,14,16]. Total body water was not estimated, but causes of weight gain other than fluid accumulation were unlikely. The intake of fluids and food was almost normal during the first days of treatment. Sodium loss because of treatment-induced hyperthermia and diarrhea may only explain the decrease in Pₛ, in a few patients, suggesting that in most patients water was reabsorbed in excess of sodium.

The proximal tubular reabsorption rate of water was...
evaluated by use of the lithium clearance method. Although none of the assumptions on which the lithium clearance method is based seem to be entirely correct, the errors are relatively small and tend to cancel out [29], and there is general agreement that the method is the best available for estimating tubular function in humans. The most recent editorial review concludes that C_Li provides a reasonable estimate of end-proximal fluid delivery. FE_Li, in most situations may therefore be appreciated as "a useful semiquantitative, directional marker of the fractional delivery of sodium and fluid from the proximal tubules" [30]. Furthermore, because of the statistical variance of the estimate of GFR and C_Li, the small increase in APR should be interpreted with caution and should be considered merely as a tendency to an increase.

Distal reabsorption of lithium has been demonstrated in sodium-depleted animals [20,32]. Amiloride inhibits distal lithium reabsorption in sodium-depleted animals [20,32]. Bruun et al. [33] and Boer et al. [34] showed no significant changes in FE_Li after amiloride administration in normal humans subjected to a low sodium diet, which resulted in fractional sodium excretions comparable to those found in the present study. Neither did amiloride affect FE_Li in the present study. Supporting the validity of the lithium clearance concept during rIL-2 therapy, use of moderate water diuresis to facilitate urine collection, as in the present study, has been shown not to influence the C_Li [20,35].

In accordance with the interpretation of our results, Webb et al. [12] and Kozeny et al. [14] reported a decrease in fractional phosphate excretion from 19.8 to 1.4% and 7 to 0.7%, respectively, during rIL-2 therapy. Normally 80-90% of the filtered phosphate is reabsorbed in the proximal tubules and phosphate excretion has been used as a marker of proximal tubular outflow.

Heys et al. [18] have reported the effect of rIL-2 and 5-fluorouracil on renal lithium clearance. A significant decrease in GFR (creatinine clearance) and C_Li was demonstrated after 48 h of rIL-2 treatment. The APR was not given, but when calculated from the reported mean values (Table 2) it decreased from 64 to 39 ml/min after 48 h and returned to baseline on day 7. The proximal fractional reabsorption rate (1- C_Li/ GFR) showed no significant changes after 48 h of rIL-2 treatment, but seemed to increase slightly in the post-therapy period. In contrast to the findings of Heys et al. [18], the changes in C_Li and FE_Li were not significant 2 days post therapy in the present study. The reason for this discrepancy is not directly apparent, since 5-fluorouracil by itself had no effect on renal function [18].

The pathogenesis of the renal effects of rIL-2 remains unclear. Prerenal as well as intrinsic renal lesions have been proposed [11,12,15,18,19]. The kidneys are susceptible to vascular leak [36]. Renal oedema, however, would be expected to also decrease GFR because of increased hydrostatic pressure in Bowman's capsule. The specific renal vasoconstriction may have multiple causes. An unchanged cardiac output with a decrease in systemic vascular resistance and renal vasoconstriction have also been demonstrated during the initial phase of endotoxic shock in experimental animals [37]. However, the hypodynamic period was followed within 12 h by a hyperdynamic phase, characterized by an increase in cardiac output, a further decrease in systemic vascular resistance and a sustained low MAP, whereas renal blood flow was restored [37]. Tumour necrosis factor, endothelin-1, nitric oxide and kinins are some of the mediators of the renal response to sepsis [38,39], and activation of these factors may have contributed to the response elicited by rIL-2. Hypotension leads to activation of several neurohumoral systems capable of influencing renal function. Among these are the renin-angiotensin system and efferent renal sympathetic nerves, but activation of these systems normally causes an increased production of intrarenal vasodilator prostaglandins and kinins to attenuate the effect on renal haemodynamics [40,41]. Plasma renin activity increases during rIL-2 treatment [12,13]. Increased renal angiotensin II production may increase renal vascular resistance but cannot explain the observed increase in APR, because the angiotensin II effect on APR is concentration dependent and biphasic with a maximum close to the physiological plasma concentration [42]. Increased efferent renal sympathetic nerve activity may increase renal reabsorption of sodium and water throughout the nephron at stimulation levels not influencing renal blood flow and renal vascular resistance [43]. Studies have suggested that increased efferent renal sympathetic nerve activity may contribute to the sodium and water retention in patients with cirrhosis and congestive heart failure [44,45], and a role for increased efferent renal sympathetic nerve activity in rIL-2-induced sodium retention is possible.

Vasodilator prostaglandins modulate renal blood flow, are natriuretic and promote free water excretion [46]. However, prostaglandins increase natriuresis per se. Increased urinary thromboxane B_2 and 6-keto-PGF_1α has previously been reported after intraperitoneal administration of rIL-2 to patients with ovarian cancer. This study used low-dose rIL-2 and the ratio between thromboxane B_2 and 6-keto-PGF_1α was unchanged [48]. Renal or central haemodynamic side-effects were not reported. Increased urinary thromboxane B_2 excretion, weight gain, and a decrease in GFR and sodium excretion has been demonstrated in chronically rIL-2-treated rats [49]. A administration of low-dose indomethacin normal-
ized GFR and the urinary excretion rate of sodium and thromboxane B₂, and decreased body weight. High-dose indomethacin was associated with a further decrease in GFR and urinary sodium and prostaglandin E₂ excretion [49]. In the present study, the urinary excretion rates of 6-keto-PGF₁α were unchanged, whereas the urinary excretion rate of thromboxane B₂ and the ratio between thromboxane B₂ and 6-keto-PGF₁α increased. The present findings may therefore suggest that changes in renal prostaglandin synthesis contributed to the decreased renal blood flow. The observed increase in urinary thromboxane B₂ excretion during rIL-2 therapy may originate from rIL-2-activated polymorphonuclear neutrophils which adhere to vascular endothelium and release thromboxane B₂ and other vasotoxins as free-oxygen radicals and neutral proteases [50]. Activated polymorphonuclear neutrophils have been suggested to mediate the capillary leak syndrome in the lung [50].

The use of NSAIDs during rIL-2 therapy remains controversial. The pattern of changes in renal blood flow and renal vascular resistance in the two patients treated with NSAIDs was similar to that in the other patients. Although changes were more pronounced than for the entire group, similar fluctuations were observed in other patients that did not receive NSAIDs. Two previous studies showed acute renal failure with a decrease in GFR and preserved ERPF during high-dose rIL-2 therapy [15,16]. These studies were performed after 24 and 72 h of rIL-2 therapy respectively, and with the use of vasopressors [15] and volume expanders [15,16]. NSAIDs were given in the majority of patients, but based on the preserved ERPF, Shalmi et al. [15] questioned whether NSAIDs aggravate rIL-2-induced renal failure. The effects of NSAIDs on renal circulation depend on the activation state of renal vasoconstrictor mechanisms [40,41] and may therefore depend on concomitant therapy and treatment duration. Selective thromboxane inhibitors have not been tested in clinical rIL-2 trials. The decrease in AFR in two patients who received NSAIDs should not necessarily be interpreted as an effect of NSAIDs on the proximal tubular reabsorption. A similar effect was demonstrated in 2 of 11 patients who did not receive NSAIDs.

Taken together, continuous intravenous infusion of rIL-2 caused a transient decrease in MAP but did not affect cardiac output. However, rIL-2 induced a sustained decrease in renal blood flow that even persisted into the post-therapy period when blood pressure was normalized. These results suggest a specific rIL-2-induced renal vasoconstrictory effect. The concurrent changes in the urinary excretion of thromboxane B₂ and 6-keto-PGF₁α may suggest that changes in renal prostaglandin synthesis contributed to the decrease in renal blood flow. The lithium clearance data suggest that an increased proximal tubular reabsorption rate may contribute to the decreased sodium clearance during rIL-2 treatment.

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REFERENCES


20 Thomsen, K. (1990) Lithium clearance as a measure of sodium and water delivery from the proximal tubules. Kidney Int. 37 (Suppl. 28), S10–S16


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