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Original article

Renal effects of continuous infusion of recombinant interleukin-2 in children

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Abstract. Recombinant interleukin-2 (rIL-2) is a new promising treatment for cancer, but is associated with severe renal toxicity. This study is the first to analyse the renal effects of rIL-2 in children. Twenty-one cycles of continuous rIL-2 infusion were studied in 15 patients; mean age was 6.9 years and average weight 18.9 kg. Interstitial fluid retention and oliguria (baseline, 1.7 ml/kg per hour; nadir, 0.5 mg/kg per hour) were associated with hypotension (baseline, 101/56 mm Hg; nadir, 85/43 mm Hg) and decreased intravascular volume (plasma renin activity increased $\times 10$). Weight gain (+7.9%) was observed in 13 cycles whereas weight loss (–6.3%) was shown in 8 cycles because of digestive and cutaneous losses, mainly in the youngest patients. This prerenal azotaemia was characterized by a decrease in creatinine clearance (from 101 to 36 ml/min per 1.73 m^2) and a low fractional excretion of sodium (FE_{Na}) (from 0.70% to 0.09%). Hypotension and hypovolaemia needed vascular filling ($n = 12$), dopamine ($n = 7$) and interruption of rIL-2 ($n = 2$). Most abnormalities occurred as early as day 2 of therapy and were always reversible after a short period with sodium leakage (diuresis = 2.2 ml/kg per hour, FE_{Na} = 2.01%). Hypophosphataemia was associated with low urinary excretion of phosphorus, suggesting an increased uptake of inorganic phosphorus by rapidly proliferating lymphoid cells.

Key words: Recombinant interleukin-2 – Acute renal failure – Prerenal azotaemia – Capillary leak syndrome

Introduction

Immunotherapy with recombinant interleukin-2 (rIL-2) was first used in adults by Rosenberg et al. [1, 2], and has been shown to induce regression of advanced cancer; the dose of rIL-2 was found to be significantly associated with tumour response [3]. Major limitations are dose-dependent side effects, mainly hypotension and azotaemia [4–7] but also including: chills, fever, erythema pruritus, diarrhoea, vomiting, weakness, headache, anaemia, and thrombopenia. The renal effects were characterized in adults [8, 9]. rIL-2 regularly produces a high-output, low-resistance state, similar to septic shock; the capillary leak syndrome results in decreased intravascular volume with hypotension and poor renal perfusion, responsible for prerenal azotaemia. Our paediatric oncology group initiated immunotherapy with rIL-2 in children with advanced neuroblastoma [6]. The aim of this prospective study was to characterize the metabolic and renal effects of this treatment in children.

Patients and methods

Fifteen children (4 girls, 11 boys; mean age 6.9 years, range 3.5–17.5 years; mean weight 18.9 kg, range 9.3–36.5 kg) received 21 cycles of rIL-2; 6 of the 15 had a second cycle of rIL-2 4 weeks after the end of the first cycle. Thirteen patients had advanced neuroblastoma (3 underwent nephrectomy), 1 osteosarcoma and 1 lymphoma. From October 1987 to December 1988, 2 phase II protocols were used. In the first patients received rIL-2 and autologous lymphokine-activated killer (LAK) cells (11 cycles); in the second they received the same schedule without LAK cells (10 cycles). Informed consent was obtained from parents for therapy and investigations, and the two protocols were accepted by the Comité d'Ethique de l'Université Claude Bernard (Lyon).

rIL-2 was supplied by Biogen (Basel, Switzerland) for 2 patients and by EuroCetus (Amsterdam, The Netherlands) for the others; it was given as a continuous infusion of 3×10^6 Cetus units/m^2 per day over 5 days as previously reported [6]. Only the first 5 days of therapy, followed by 48 h of rest, were common to all children and were studied for each patient.

The children were admitted to the paediatric intensive care unit and monitored for heart and respiratory rate, central body temperature, mean 24-h arterial blood pressure (BP), central venous pressure, diuresis, weight, and chest X-rays. Additional treatment included piperacillin, vitamin C, magnesium and zinc by the intravenous route. Biochemical plasma monitoring included electrolytes, calcium, phosphorus, arterial blood gases, blood urea nitrogen, serum creatinine (SCr), proteins and albumin (twice daily); plasma renin activity (PRA) every 4 days. Consecutive 24-h urine collections were taken for electrolytes, calcium,

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Table 1. Main clinical and biological effects of recombinant interleukin-2 (rIL-2) in 21 courses of therapy

Data[a]	baseline[b]	rIL-2 therapy[c]	*P*	recovery[d]
Systolic BP (mm Hg)	101 ±2	85 ± 1	<0.001	104 ± 5
Diastolic BP (mm Hg)	56 ±2	43 ± 2	<0.001	58 ± 5
Weight gain ($n = 13$) (%)	–	7.9 ± 1.1	–	+2.1 ± 1.5
Weight loss ($n = 8$) (%)	–	6.3 ± 1.5	–	–0.2 ± 1.4
Urine output (ml/kg per hour)	1.7 ±0.2	0.5 ± 0.1	<0.001	2.2 ± 0.3
SCr (μmol/l)	55 ±4	133 ±22	<0.001	61 ± 8
Cr clearance (ml/min per 1.73 m^2)	101 ±9	36 ± 6	<0.001	121 ±15
PRA (basal = B)	B	×10.0 ± 1.5	–	×2.5 ± 1.1
Plasma sodium (mmol/l)	139 ±1	130 ± 1	<0.001	138 ± 1
Plasma potassium (mmol/l)	4.0 ±0.1	3.0 ± 0.1	<0.001	3.9 ± 0.2
FE_{Na} (%)	0.70 ±0.08	0.09 ± 0.02	<0.001	2.01 ± 0.39
Serum phosphorus (mmol/l)	1.42 ±0.06	0.72 ± 0.06	<0.001	1.15 ± 0.09
Urinary P/Cr	4.40 ±0.62	0.91 ± 0.21	<0.001	ND
Serum calcium (mmol/l)	2.36 ±0.03	2.06 ± 0.03	<0.001	2.33 ± 0.06
Urinary Ca/Cr	0.21 ±0.06	0.04 ± 0.01	<0.001	ND
Proteinaemia (g/l)	70 ±1	58 ± 2	<0.001	75 ± 3

P, compared with baseline value
BP, Blood pressure; SCr, serum creatinine; PRA, plasma renin activity; FE_{Na}, fractional sodium excretion; ND, not determined

[a] Mean ± SEM
[b] Day 0
[c] Nadir/peak
[d] After discontinuation of therapy, 3–22 days

phosphorus, creatinine, enzymuria (alanine-aminopeptidase, gamma-glutamyl transpeptidase, *N*-acetyl glycosaminidase), cytopathological examination (phase contrast microscopy, tubular score 0–5) and estimation of proteinuria; urinary protein electrophoresis (polyacrylamide gel), aminoacid chromatograms and glycosuria were examined every 4 days. Fractional urinary excretion of sodium was calculated as

$$FE_{Na} = \frac{\text{Urine Na}}{\text{Plasma Na}} \times \frac{\text{Plasma Cr}}{\text{Urine Cr}} \times 100$$

Fever was treated with paracetamol. In order to prevent fluid overload, fluid intake was limited to 20–25 ml/kg per day adapted for body temperature, diuresis and digestive losses. When hypotension (>2 SD decrease for age) or hypovolaemia (negative central venous pressure) occurred, vascular filling was achieved with 20% albumin (1 g/kg over 15–30 min) and haemodynamics were maintained with dopamine (5–50 μg/kg per min); if severe hypotension (a drop >40 mm Hg systolic BP or a requirement for high fluid therapy) or renal failure (SCr >400 μmol/l) occurred, rIL-2 infusion was reduced or stopped until side effects resolved.

Clinical and laboratory data from the 21 courses of therapy in 15 children are shown in Tables 1 and 2 as baseline, nadir or peak during rIL-2 therapy, and recovery values. All values are reported as the mean ± SEM; Student's *t*-test was used to evaluate the statistical significance of differences (Fisher and Yates statistical tables).

Results

Clinical data are shown in Table 1. The peak or nadir of parameters occurred in all patients as early as day 2 after starting rIL-2 treatment and returned to baseline 3–22 days after discontinuation of therapy. Systolic and diastolic BP decreased significantly, followed by a complete and quick recovery. Fever of more than 39°C was present in all patients. Fluid retention was responsible for weight gain in 13 cycles, whereas weight loss occurred in 8 of the 11 cycles where important diarrhoea and/or vomiting were noted. Most children experienced peripheral oedema but no life-threatening complications were observed in relation to fluid overload. Urine volume decreased significantly during infusion but this was followed by polyuria. In parallel, a 50% decrease in Cr clearance followed by a high filtration rate was observed. At the same time, PRA was greatly increased (×10).

Renal toxicity is shown in Table 1 and Fig. 1; SCr increased in all patients and always returned to normal values. Concomitantly, FE_{Na} decreased and was followed by urinary sodium loss, as shown by high FE_{Na}, before returning to original values. Morphological tubular

changes were shown by increased cytopathological scores between day 1 and day 7 (Table 2). Other signs of renal toxicity are shown in Table 2 and included: increased enzymuria; absence of glycosuria; mild global hyperaminoaciduria in half of the patients. Proteinuria was present in most children and never exceeded 1 g/day; electrophoresis showed that it was mainly of mixed glomerular and tubular type; proteinuria then returned to normal levels in all patients (Table 2).

Table 1 shows that serum phosphorus decreased by 50% between day 3 and day 7, whereas the urinary phosphorus/Cr ratio dramatically decreased. A mild decrease in serum calcium and protein was noted. Disturbances in electrolytes consisted mainly in a decrease in sodium and potassium (Table 1). No significant change was noted in plasma pH, base excess, $P\,CO_2$ or alkaline reserve.

Discussion

In adults, the renal effects of rIL-2 are mainly azotaemia, oliguria, fluid retention and intense tubular avidity for filtered sodium [8]. Prerenal azotaemia is suggested in our patients by a decrease in glomerular filtration rate, a lowered urinary excretion of sodium and a decreased intravascular volume, as suggested by the high PRA. Most clinical and biological expressions of the syndrome are similar in adults and children [8, 9]. The mean arterial BP decreases by 25% and 20% respectively, urine output decreases by 75% and 71%, FE_{Na} falls from 0.78% to 0.04% and from 0.70% to 0.09%; the mean nadir SCr is 2.6 and 2.4 the baseline values. These abnormalities occur between day 2 and day 7 and may be related to a vascular

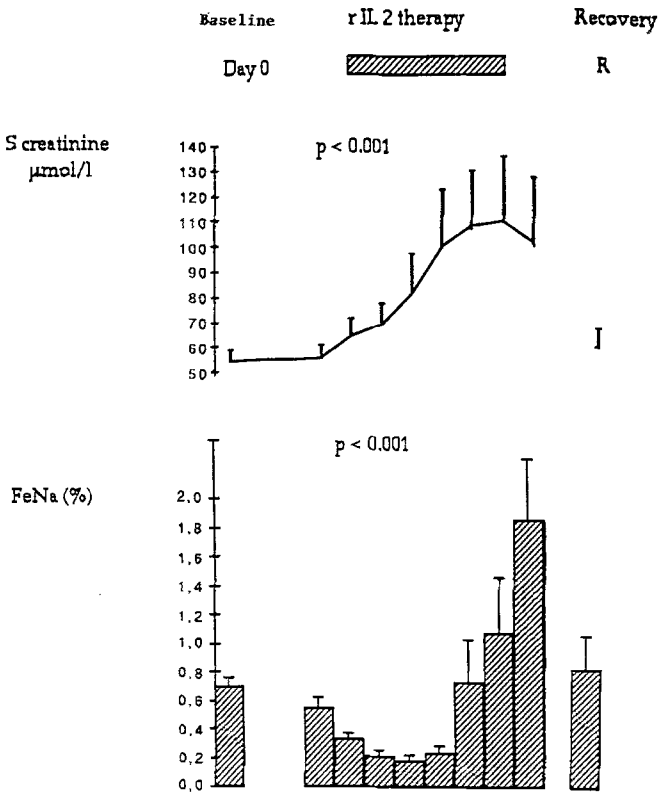

Fig. 1. Mean ± SEM daily serum creatinine (*SCr*) and fractional excretion of sodium (FE_{Na}) through 21 courses of recombinant interleukin-2 (*rIL-2*) therapy in 15 children. Baseline (day 0), daily monitoring, and recovery (3–22 days after discontinuation of therapy); *P* compared with baseline values

Table 2. Main urinary disorders in 21 courses of rIL-2 therapy

Data[a]	baseline[b]	rIL-2 therapy[c]	*P*	recovery[d]
Cytopathological tubular score (0–5)	0	1.8 ±0.3	–	ND
AAP (mmol/mmol Cr)	5.3 ±1.7	18.5 ±2.2	<0.001	8.1 ±4.3
GGT (mmol/mmol Cr)	5.9 ±0.8	10.6 ±0.8	<0.001	6.3 ±0.7
NAG (mmol/mmol Cr)	2.6 ±0.8	9.6 ±2.0	<0.001	3.1 ±0.7
Glycosuria	0	0	–	0
Aminoacid chromatograms				
normal (%)	62	14	–	ND
abnormal (%)	38	86	–	ND
Proteinuria				
24-h dosage (g)	0.02±0.01	0.36±0.08	<0.001	0.10±0.05
Electrophoresis (%)				
normal	65	6	–	ND
tubular	15	18	–	ND
glomerular	5	0	–	ND
mixed	15	76	–	ND

P, Compared with baseline value
AAP, Alanine-aminopeptidase; GGT, gamma-glutamyl transpeptidase; NAG, N-acetyl glycosaminidase

[a] Mean ± SEM
[b] Day 0
[c] Nadir/peak
[d] After discontinuation of therapy, 3–22 days

leak syndrome. However, in our population, children either gained (n = 13) or lost (n = 8) weight despite constant oliguria and hypotension; this could be explained by digestive and cutaneous losses, mainly in the youngest patients, and by an improvement in the management of haemodynamic conditions since our preliminary study [10]. As in adults, this renal hypoperfusion syndrome is always reversible when rIL-2 is stopped [2, 9]; in our study, the recovery was obtained 3–22 days after discontinuation of rIL-2.

These data, together with the cytopathological tubular damage and enzymuria, suggest that renal impairment may be due to haemodynamically mediated acute tubular necrosis, without alteration in proximal functions, as there is neither glycosuria nor phosphaturia. Tubular dysfunction is predominant, but there may be glomerular alterations such as shown by mixed-type proteinuria; IL-2 production has been suggested as a possible mechanism for proteinuria in the nephrotic syndrome [11], and nephrotic syndrome associated with rIL-2 therapy has been reported [12].

The features of shock which result from rIL-2 infusion may be related to the depression of left ventricular function that precludes the necessary rise in cardiac output required to compensate for the reduction in systemic vascular resistance [12, 13]. Such haemodynamic disturbances seem to be mediated by other cytokines that activate endothelial cells leading to the blood vessels becoming leaky to macromolecules [7, 13–15]. These disorders, such as the frequent "flu-like" syndrome, may be attenuated by prior treatment with cyclo-oxygenase-inhibitors [7, 14]. The risk of renal impairment from increased renal vascular resistance associated with prostaglandin synthesis inhibition [16–18] deterred us from using it in our patients during their initial course of rIL-2; fever and the "flu-like" syndrome were controlled with paracetamol.

Hypophosphataemia associated with a decrease in urinary phosphorus is well known in adults, and has been explained by endogenous redistribution of inorganic phosphorus, such as an increased uptake by rapidly proliferating lymphoid cells [8, 9]. The same picture is found in children but associated causes for hypophosphataemia can be identified in some patients such as malnutrition or digestive losses; we found no evidence for an acid-base disorder, sepsis or the Fanconi syndrome. Although phosphataemia decreased, a symptom-free lowering in the plasma calcium level was noted, mainly related to the decrease in protein level because of increased capillary permeability and fluid replacement [9]. The same mechanism may be involved for sodium and potassium since the low excretion of electrolytes, calcium and phosphorus probably resulted from avid tubular reabsorption under conditions of decreased renal plasma flow. However, no significant decrease in sodium or potassium has been noted in adults [8, 9].

Several schedules have been used in adults for rIL-2 therapy and our choice of continuous infusion was based on a better tolerance than bolus injections [7, 19]. The aim of our critical care management was to maintain haemodynamic status rather than diuresis since volume expansion and diuretics were previously shown to be ineffective [9]. Our regimen was based on adapted fluid restriction, vascular filling with 20% albumin and vasopressors [2]. Only 2 courses of therapy required discontinuation of rIL-2. Except for these 2 cases, vascular filling and dopamine infusion were discontinued on the same day as rIL-2. It is emphasized that glucocorticoids can reduce fluid retention and decrease rIL-2 morbidity, but they are detrimental to the antitumour effect of LAK cells [20] and were excluded from our protocols.

In adults, renal toxicity is considered to be more severe in patients with pretherapy SCr values above 140 µmol/l and in those with a single kidney [7–9]. In our study, no patient had significant renal dysfunction before therapy; of the 3 children who underwent nephrectomy, 2 experienced standard disturbances and the other developed more severe renal failure; the 4 other more affected children experienced either severe concomitant digestive losses or pretherapy reversible nephrotoxic episodes.

In summary, rIL-2 therapy induces a reversible vascular leak syndrome with prerenal azotaemia followed by acute tubular necrosis. These findings in paediatric patients are comparable to studies in adults; however there are differences concerning the less important weight gain related to digestive and cutaneous losses. Most of our data show that the clinical and biological tolerance of 21 cycles of continuous rIL-2 therapy in children aged 3.2–17.5 years is reasonably good.

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Literature abstracts

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Carnitine status of pediatric patients on continuous ambulatory peritoneal dialysis

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Plasma carnitine and the effect of oral carnitine supplementation on serum triglycerides was studied in 12 pediatric patients receiving continuous ambulatory peritoneal dialysis (CAPD). Baseline evalution of all patients included plasma carnitine and serum triglyceride values. Following randomization into two groups, only group 2 patients received oral *L*-carnitine supplementation, 100 mg/kg/day, for 2 months. The initial laboratory evaluation was repeated at the conclusion of the study. Plasma carnitine values were also determined from a control population. Mean baseline plasma carnitine concentrations of group 1 (39.8 ± 8.0 nmol/ml) and group 2 (45.2 ± 10.3 nmol/ml) patients were not significantly different from each other or from the control population. Serum triglyceride values were elevated in both groups (group 1 – 206.5 ± 100.0 mg/dl; group 2 – 279.3 ± 74.5 mg/dl). After 2 months, the mean plasma carnitine concentration of group 2 patients increased to 147.7 ± 84.1 nmol/ml, significantly greater than the value of group 1, 32.8 ± 8.0 nmol/ml ($p < 0.004$). However, no significant change in the serum triglyceride level was noted in either group. We conclude that the plasma carnitine status of pediatric patients receiving CAPD is normal and that oral carnitine supplementation does not lead to the resolution of hypertriglyceridemia.