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Persistent Sterile Leukocyturia Is Associated With Impaired Renal Function in Human Immunodeficiency Virus Type 1–Infected Children Treated With Indinavir

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ABSTRACT. *Background.* Prolonged administration of indinavir is associated with the occurrence of a variety of renal complications in adults. These well-documented side effects have restricted the use of this potent protease inhibitor in children.

Design. A prospective study to monitor indinavir-related nephrotoxicity in a cohort of 30 human immunodeficiency virus type 1–infected children treated with indinavir.

Methods. Urinary pH, albumin, creatinine, the presence of erythrocytes, leukocytes, bacteria and crystals, and culture were analyzed every 3 months for 96 weeks. Serum creatinine levels were routinely determined at the same time points. Steady-state pharmacokinetics of indinavir were done at week 4 after the initiation of indinavir.

Results. The cumulative incidence of persistent sterile leukocyturia (≥ 75 cells/μL in at least 2 consecutive visits) after 96 weeks was 53%. Persistent sterile leukocyturia was frequently associated with a mild increase in the urine albumin/creatinine ratio and by microscopic hematuria. The cumulative incidence of serum creatinine levels >50% above normal was 33% after 96 weeks. Children with persistent sterile leukocyturia more frequently had serum creatinine levels of 50% above normal than those children without persistent sterile leukocyturia. In children younger than 5.6 years, persistent sterile leukocyturia was significantly more frequent than in older children. A higher cumulative incidence of persistent leukocyturia was found in children with an area under the curve >19 mg/L*h or a peak serum level of indinavir >12 mg/L. In 4 children, indinavir was discontinued because of nephrotoxicity. Subsequently, the serum creatinine levels decreased, the urine albumin/creatinine ratios returned to zero, and the leukocyturia disappeared within 3 months.

Conclusions. Children treated with indinavir have a high cumulative incidence of persistent sterile leukocyturia. Children with persistent sterile leukocyturia more frequently had an increase in serum creatinine levels of >50% above normal. Younger children have an additional risk for renal complications. The impairment of the renal function in these children occurred in the absence of clinical symptoms of nephrolithiasis. Indinavir-associated nephrotoxicity must be monitored closely, especially in children with risk factors such as persistent sterile leukocyturia, age <5.6 years, an area under the curve of indinavir >19 mg/L*h, and a C_{max} >12 mg/L. *Pediatrics* 2002;110(2). URL: http://www.pediatrics.org/cgi/content/full/110/2/e19; *human immunodeficiency virus, children, indinavir, nephrotoxicity.*

ABBREVIATIONS. HIV, human immunodeficiency virus; AUC, area under plasma-concentration curve; IQR, interquartile range.

Indinavir is a potent human immunodeficiency virus (HIV)-protease inhibitor that has been used successfully in adults in combination with nucleoside reverse transcriptase inhibitors to suppress infections by HIV-1. Discontinuation of the antiretroviral therapy rapidly results in virologic rebound, decreased immune function, and the redevelopment of acquired immune deficiency syndrome-defining illness. Thus, antiretroviral drugs such as indinavir need to be continued for many years. This necessitates a careful surveillance for long-term toxicity of the medication.

The experience with the administration of indinavir to HIV-1–infected children has been limited because of the absence of a pediatric formulation and the well-documented side-effects of the drug on the upper and lower urinary tract in adults. Indinavir is metabolized by the liver, but ~20% of a single oral dose is excreted unchanged in the urine.[1] pH-dependent crystallization of indinavir in renal tubuli may cause renal symptoms such as kidney stones, flank pain (even without evident stone formation), interstitial nephritis, elevation of the serum creatinine, dysuria, and asymptomatic urine abnormalities such as hematuria, leukocyturia, and crystalluria. Indinavir crystals may illicit an inflammatory response in the tubules, leading to sterile leukocyturia and renal insufficiency.[2–7] To minimize renal side effects of indinavir, an increased fluid intake is advised.[8]

The incidence of indinavir-associated nephrolithiasis in adults varies from 4% to 43%.[2,9] Renal complications (including nephrolithiasis) from indinavir

are found in 0% to 80%[10–15] and nephrolithiasis in 0% to 20%[10,12–15] of children who have been treated with this drug.

Renal and urologic symptoms of indinavir crystals have been correlated with the serum levels of indinavir.[16] In children, sufficiently high area under the plasma-concentration curves (AUCs) for indinavir are required to achieve trough levels[13,17] associated with an optimal virologic response.[18–20] The risk of nephrotoxicity in children might therefore be higher than in adults.

In contrast to symptomatic nephrolithiasis, other renal complications such as leukocyturia, microscopic hematuria, and crystalluria usually do not lead to a decision to discontinue indinavir, although an association between recurrent severe leukocyturia and renal damage by indinavir-induced crystalluria has been reported in adults.[6,21]

Currently, it is unknown whether and when these asymptomatic signs of renal damage lead to renal complications and long-term renal damage. This prospective study was performed to monitor renal and urinary complications in a cohort of 30 HIV-1–infected children treated with indinavir. We hypothesized that indinavir-related nephrotoxicity might occur more frequently in children than in adults because of the higher risk for cellular damage to the still developing renal system.

METHODS

In 1997, a prospective, open, uncontrolled, multicenter study was initiated to evaluate the clinical, immunologic, and virologic response to combination therapy consisting of indinavir, zidovudine, and lamivudine in HIV-1–infected children.[15] Children >3 months old and 1 of the following 2 items: a decreased CD4$^+$ T-cell count (<1 year: <1750/mm^3, 1 to 2 years: <1000/mm^3, 3 to 6 years: <750/mm^3, >6 years: <500/mm^3) or a HIV-1 RNA load >5000 copies/mL were included. The follow-up period was 96 weeks after the initiation of indinavir. Two years after the initiation of this multicenter study, a separate study was started in 1 of the participating centers to analyze additional urinalysis parameters with a follow-up period of 96 weeks.

The Ethics Committee of the University Hospital Rotterdam approved the study. Patients and their caretakers provided written informed consent.

Laboratory Parameters

The routinely analyzed laboratory parameters of the children included dipstick analysis (Rapignost total screen L, Behring Diagnostics Inc, Westwood, MA) for urinary pH (at urine pH values below 5 solubility of indinavir increases[22]), erythrocytes, leukocytes, and bacteria at baseline (before the use of indinavir) and every 3 months thereafter. Routine biochemistry tests included serum creatinine. Steady-state pharmacokinetics of indinavir (400 mg/m^2 every 8 hours) were determined at week 4 after the initiation of indinavir. This procedure was repeated when a dosage adjustment of indinavir was necessary to normalize the area under AUC concentration to adult values (20 mg/L*h; range: 10–30 mg/L*h).[17]

Demographic parameters, indinavir start date and stop date, indinavir dosing regimens, urinary tract symptoms, concomitant treatment, HIV-1 RNA, and CD4$^+$ T-cell counts were recorded on structured data collection forms. Nephrolithiasis-related symptoms included renal colic, flank pain, the passing of a stone, and gross hematuria.

Additional laboratory tests were performed in children included in 1 center, from March 1999 onwards. Urinary pH was measured by means of calibrated electrode technique. Urine albumin and creatinine were measured to calculate the albumin to creatinine ratio as an indicator of renal damage. Urine light microscopy for presence of indinavir crystals under a polarized filter was performed and urine cultures were performed in patients with a positive dipstick test or microscopy for bacteria.

Sterile leukocyturia is considered to be caused by damage of renal tubuli. Therefore, we considered this the principal endpoint this study. Leukocyturia was defined by the presence of a dipstick test with >75 cells/μL. Persistent sterile leukocyturia was present when leukocyturia with negative urine cultures was found at at least 2 consecutive visits, after the start of indinavir. In children with >150 leukocytes/μL at at least 2 visits and a negative urine culture a renal ultrasound was performed.

Analysis

Cumulative incidences of persistent leukocyturia and serum creatinine >50% above age- and sex-specific normal values[23] were calculated with Kaplan-Meier analysis. The influences of pharmacokinetic factors were determined with the log rank test. The relation between the occurrence of persistent leukocyturia and an increased creatinine and between persistent leukocyturia and nephrolithiasis-related symptoms were analyzed using the Fisher exact test. To describe urine abnormalities associated with leukocyturia, we performed a cross-sectional analysis 12 weeks after the start of the measurement of the additional urinalysis.

RESULTS

Thirty HIV-1–infected children were enrolled between April 1997 and April 2000. Fifteen children were available for additional analyses between March 1999 and March 2001. The other 15 children were not available for additional analyses for various reasons: enrollment in a center different from that where the additional analyses were performed (n = 8), discontinuation of indinavir (n = 6; 5 children because of virologic failure and 1 because of nephrotoxicity), and age >18 years (n = 1). Baseline characteristics of the children are presented in Table 1.

A good clinical, immunologic, and virologic response was observed in all children who were treated with indinavir. Most of the children needed 600 mg/m^2 of indinavir every 8 hours to obtain an AUC of indinavir between 10 and 30 mg/L*h. The median interquartile range (IQR) AUC was 19 (14–28) mg/L*h with a median (IQR) peak level of 9 (6–12) mg/L. Baseline and follow-up serum creatinine and urinalysis data were available from 30 children in whom indinavir was initiated.

Cumulative Incidence of Persistent Sterile Leukocyturia (≥2 Times ≥75 Cells/μL)

Eleven (37%) of 30 children developed persistent sterile leukocyturia (2 times or more ≥75 leukocytes/μL). The cumulative incidence after 96 weeks was 53% with a mean time to leukocyturia of 74 weeks (95% confidence interval: 61–87 weeks) of combination therapy containing indinavir (Fig 1A).

The influence of age and sex on the cumulative incidence of persistent sterile leukocyturia was determined. Children were divided into 2 groups: younger and older than the median age of 5.6 years. Figure 1B shows that children younger than 5.6 years had a significantly higher cumulative incidence of persistent sterile leukocyturia than children older than 5.6 years (P = .05). Sex did not influence the incidence of leukocyturia.

TABLE 1. Patient Characteristics

Characteristic		
Age (y)	Median (range)	5.6 (2.4–9.9)
Male	N (%)	15 (50)
Body mass index (kg/m²)	Median (IQR)	16 (14–17)
HIV-1 RNA (copies/mL)	Median (IQR)	127 500 (18 400–661 000)
CD4 cells (cells/μL)	Median (IQR)	610 (230–880)
Indinavir regimen		
400 mg/m² tid	N (%)	8 (27)
500 mg/m² tid	N (%)	11 (37)
600 mg/m² tid	N (%)	7 (23)
≥700 mg/m² tid	N (%)	4 (13)
500/100 mg/m² bid*	N (%)	
Serum creatinine (μmol/L)	Median (IQR)	24 (19–38)
Urine		
Leukocytes >75 cells/μL	N (%)	0 (0)
Erythrocytes >60 cells/μL	N (%)	0 (0)

* Indinavir/ritonavir.

Cumulative Incidence of a Change of Serum Creatinine >50% Above Age- and Sex-Specific Normal Values

Six (20%) of 30 children had a change of serum creatinine >50% above age- and sex-specific normal values. The cumulative incidence after 96 weeks was 33% with a mean time to creatinine increase of 90 weeks (95% confidence interval: 82–98 weeks) of combination therapy containing indinavir (Fig 1C).

Relation Between Persistent Sterile Leukocyturia and an Increase of Serum Creatinine

One (5%) of the 19 children without persistent sterile leukocyturia had a change in serum creatinine >50% above age- and sex-specific normal values, whereas 5 (45%) of 11 children with persistent sterile leukocyturia had a change in serum creatinine >50% above age- and sex-specific normal values ($P = .02$). The median (IQR) time to a creatinine increase among patients with leukocyturia was 24 (0–48) weeks.

Relation Between Persistent Sterile Leukocyturia and Pharmacokinetic Parameters

Children with an AUC_{0-8} of indinavir higher than the median AUC of 19 mg/L*h had a significantly higher cumulative incidence of persistent sterile leukocyturia compared with those with an AUC ≤19 mg/L*h ($P = .05$). After 96 weeks 8 (67%) of the 12 children with an AUC >19 mg/L*h had persistent sterile leukocyturia, in contrast with 2 (13%) of 16 of the children with an AUC <19 mg/L*h. The cumulative incidences were 79% and 19%, respectively, after 96 weeks (Fig 1D). Having a maximum concentration (C_{max}) of indinavir of 12 (mg/L) was significantly ($P = .02$) associated with the presence of persistent sterile leukocyturia. (Fig 1F). Five (24%) of the 21 children with a C_{max} <12 mg/L had persistent sterile leukocyturia, whereas in 5 (71%) of 7 children with a C_{max} ≥12 mg/L, this abnormality was observed. No relation was found between C_{min} and the presence of persistent sterile leukocyturia, between age and AUC of indinavir, and between age and C_{max}.

Relation Between Persistent Sterile Leukocyturia and Nephrolithiasis-Related Symptoms

Four (19%) of the 21 children without persistent sterile leukocyturia presented with urologic symptoms, whereas 7 (78%) of 9 children with persistent sterile leukocyturia had symptoms during the follow-up time ($P = .003$).

Hematuria

Persistent hematuria (≥2 × ≥60 cells/μL) was not detected in any child.

In addition to the standard analyses performed in the 30 children, urine creatinine, urine albumin, quantitative pH measurements, and crystalluria were analyzed in 15 children. At the time of the start of the additional analyses, these children were using indinavir for a median of 75 weeks (IQR: 8–77 weeks).

A cross-sectional analysis at week 12 after the start of the initiation of additional analysis showed that in these children (median time on indinavir [IQR]: 87 [20–89] weeks) 33% of the patients had a change of serum creatinine >50% above age- and sex-specific normal values. In 4 of these 5 patients, an albumin/creatinine ratio >3.5 g/mmol was observed. In 2 of these patients, indinavir was discontinued because of nephrolithiasis on renal ultrasound.

Forty-three percent of the patients had leukocyturia, 21% had microscopic hematuria, 54% had crystalluria, and 29% had an albumin/creatinine ratio ≥3.5 g/mmol. Urine cultures were all negative for bacteria.

In Fig 2, urine abnormalities associated with leukocyturia at week 12 are presented. An increase of serum creatinine levels of >50% above age- and sex-specific normal values, an albumin/creatinine ratio ≥3.5 g/mmol, and hematuria were observed more frequently in children with leukocyturia. The median (IQR) albumin/creatinine ratio of children with and without persistent leukocyturia was 0.7 (0.6–2.5) and 2.8 (1.2–10.6), respectively. In contrast, indinavir crystalluria was not detected more frequently in children with leukocyturia. The presence of symptoms, urinary pH >5, and the presence of crystalluria were not associated with persistent sterile leukocyturia.
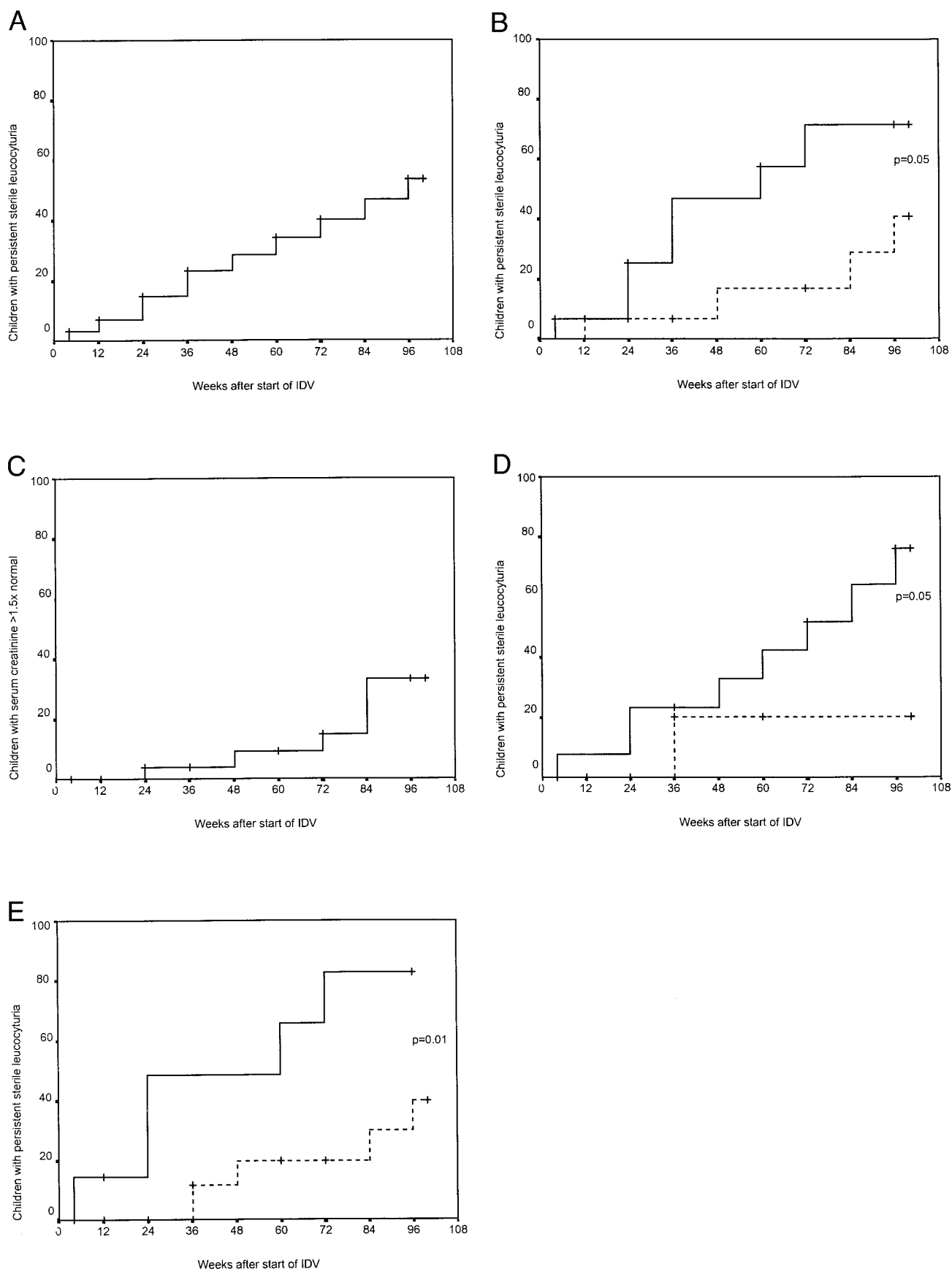
Fig 1. A, Cumulative incidence of persistent sterile leukocyturia. B, Cumulative incidence of persistent sterile leukocyturia in children <5.6 years (dotted line) and in children >5.6 years. C, Cumulative incidence of children with creatinine increase ≥50% above age- and sex-specific normal values. D, Cumulative incidence of persistent sterile leukocyturia in children with AUC of indinavir ≤19 (dotted line) or >19 mg/L*h. E, Cumulative incidence of persistent sterile leukocyturia in children with C_{max} ≤12 (dotted line) or >12 mg/L.
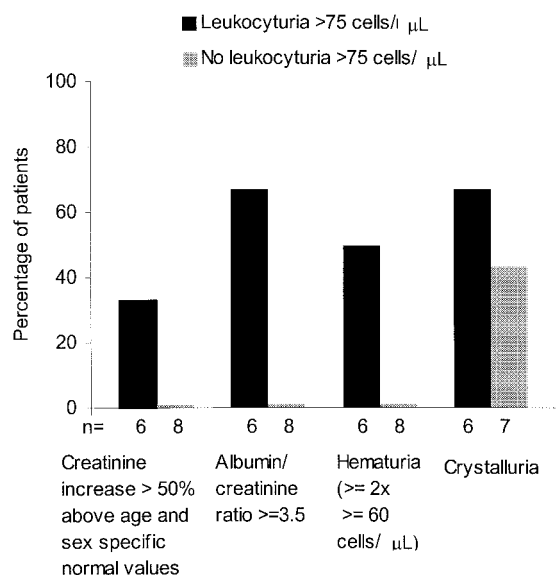
Fig 2. Urinary abnormalities associated with leukocyturia (cross-sectional week 12) in 15 children included in cohort B.

Symptoms of Nephrotoxicity After Discontinuation of Indinavir Because of Nephrotoxicity

In 4 of 15 children, indinavir was discontinued because of nephrotoxic symptoms ($n = 2$) or nephrolithiasis on renal ultrasound ($n = 2$). In these children, serum creatinine (μmol/L) levels decreased from a median (IQR) of 54 (49–75) at the last observation during the use of indinavir to 39 (28–42) 12 weeks after discontinuation of indinavir ($P = .07$). The albumin/creatinine ratio decreased from 16 (9–44) to 0.7 (0.4–2.1) g/mmol ($P = .07$). Leukocyturia disappeared within 3 months after the discontinuation of indinavir. Figure 3 shows the serum creatinine levels and the albumin/creatinine ratios of the 4 children that discontinued indinavir because of nephrotoxicity. Urine albumin/creatinine ratio increases preceded serum creatinine increases and may therefore may be an early marker of renal impairment.

In 3 other children that discontinued indinavir for other reasons (virologic failure, $n = 2$, and because of the poor taste of indinavir, $n = 1$) serum creatinine levels did not decrease, whereas the albumin/creatinine ratio showed a decrease from 3.94 (0.51–11.2) to 0 g/mmol ($P = .10$).

DISCUSSION

We here present the first study to our knowledge to monitor nephrotoxicity in HIV-1–infected children with a prolonged treatment with indinavir. We hypothesized that indinavir-related nephrotoxicity might occur more frequently in children than in adults because of the higher risk for cellular damage to the still developing renal system.

In our study, a cumulative incidence of persistent sterile leukocyturia ($\geq 2 \times \geq 75$ cells/μL) of 53% was observed after 96 weeks. This persistent sterile leukocyturia was frequently accompanied by a mild increase of the urine albumin/creatinine ratio and microscopic hematuria. The cumulative incidence of an increase in serum creatinine levels >50% above normal was 35% after 96 weeks. Children with persistent sterile leukocyturia more frequently had an increase of serum creatinine levels of >50% above normal ($P = .02$). This suggests that persistent sterile leukocyturia is an early indication for the development of renal damage.

Recently, Gagnon et al[21] found a significant reduction in the renal function of 3 adults with recurrent severe leukocyturia. Our data confirm the observations in adults of Gagnon et al, that reduction of renal function is associated with recurrent severe leukocyturia, but not with isolated hematuria or crystalluria. Renal damage resulting in leukocyturia and an increased creatinine may be a result of irritation of the
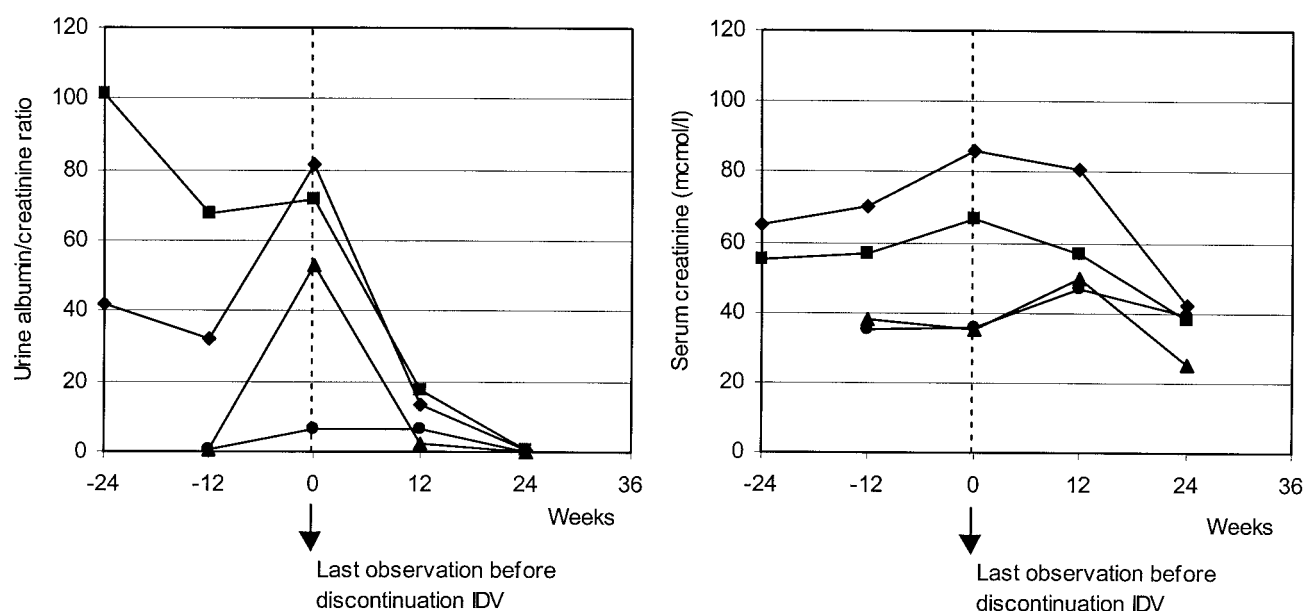

Fig 3. Urine albumin/creatinine ratio (g/mmol) and creatinine levels (μmol/L) during the use of indinavir and after discontinuation of indinavir in 4 children.

tubular epithelium. This is supported by the pathologic finding of tubulointerstitial nephritis in patients on therapy with indinavir.[4,24,25]

The prevalence of persistent leukocyturia in adults screened on the same nephrotoxicity monitoring program was 22% (J. P. Dieleman, personal communication, September 10, 2001), which is substantially lower than we observed in children. One might hypothesize that indinavir crystals more easily congest in the small tubuli of young children which may lead to a higher incidence of nephrolithiasis. The more frequent presence of persistent sterile leukocyturia in younger children confirms this observation. However, nephrolithiasis was only diagnosed by renal ultrasound in two asymptomatic children with persistent sterile leukocyturia.[26] Renal ultrasounds of the other children with persistent leukocyturia showed no nephrolithiasis. Because it is well documented that the occurrence of indinavir nephrolithiasis increases with a poor hydration status and high environmental temperatures,[27] the Dutch climate with relatively moderate temperatures may contribute to a lower incidence of nephrolithiasis in our patients. Persistent leukocyturia might have been prevented by an increased fluid intake. Because it is more difficult to achieve a large fluid intake in young children, a relatively small fluid intake in younger children may be the cause of the more frequent occurrence of persistent sterile leukocyturia in children younger than 5.6 years (cumulative incidence after 96 weeks: 78%).

We did not observe an association between indinavir crystalluria and leukocyturia. Because indinavir crystals can develop in the urine canister,[28] it is possible that crystalluria reflects the time lapse between urine collection and urinalysis.

We observed a higher cumulative incidence of persistent leukocyturia in children with an AUC_{0-8} of indinavir of >19 (mg/L*h) and in children with a peak level of indinavir higher than 12 (mg/L). This is in accordance with previous publications on the relation between levels of indinavir and urologic complications in adults. An AUC of indinavir <20 (mg/L*h) is associated with virologic failure.[17] This observation complicates the treatment of HIV-1–infected children with indinavir: to achieve optimal virologic suppression, an AUC higher than 20 (mg/L*h) is required, but to avoid persistent leukocyturia, an AUC <19 (mg/L*h) is needed.

These observations suggest that indinavir may be less useful in the treatment of HIV-1–infected children. However, indinavir is a very potent protease inhibitor which in combination with nucleoside analogues gives an excellent long-term clinical, virologic and immunologic response in adults and in children.[15,29,30] We therefore propose to monitor nephrotoxicity very closely in children treated with indinavir and change therapy only in the case of overt signs of renal impairment. In this respect, it is reassuring that the signs of renal impairment are reversible after discontinuation of indinavir. Serum creatinine levels decreased in the 4 children with signs of nephrotoxicity who discontinued indinavir. The urine albumin/creatinine ratio returned to zero in all patients. It still remains unclear whether renal impairment is reversible in all stages of damage or that a chronic renal insufficiency will develop above a critical level of cellular damage.

CONCLUSION

Prolonged therapy with indinavir is associated with a high risk for persistent sterile leukocyturia in children especially in those younger than 5.6 years. The presence of sterile leukocyturia is associated with a significant increase in serum creatinine levels. A high AUC (>19 mg/L*h) and high peak levels (>12 mg/L) of indinavir are associated with the occurrence of leukocyturia. Therapeutic drug monitoring of indinavir serum levels is therefore essential to estimate the risk of nephrotoxicity. Children with risk factors for the development of nephrotoxicity, such as an age <5.6 years, AUC of indinavir >19 mg/L*h, and C_{max} >12 mg/L, should be monitored routinely by means of urinalysis and analysis of serum creatinine levels.

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