Incidence and risk factors for the development of indinavir-associated renal complications

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Objectives: To describe the incidence and risk factors for the development of indinavir-associated renal complications (IRC), and subsequent clinical outcome.

Patients and methods: This was a retrospective cohort study based on two large HIV centres in London. Eligible patients received indinavir for at least 1 week between 1 December 1995 and 28 February 1999. Development of IRC was ascertained by case-note review. Multivariate logistic regression and Cox Proportional Hazard’s model analysis were used to determine independent risk factors for the development of IRC.

Results: 781 patients were eligible. Median CD4 count and viral load at indinavir initiation were 117 × 10^6 cells/L and 47 332 copies/mL, respectively. Median indinavir exposure was 53 weeks (IQR: 20–83). Many patients received other potentially nephrotoxic drugs during indinavir treatment: co-trimoxazole (46%), aciclovir (33%) or both (20%). Overall IRC incidence was 7.3% (6.7 per 100 person-years indinavir exposure). Cases presented with loin pain (58%), renal colic (42%) or dysuria (19%). Identified precipitating events (26%) included fluid depletion or altered indinavir regimen. In the majority of cases indinavir therapy was continued and there was no progressive rise in creatinine levels. In the multivariate analysis, for indinavir treatment >74 weeks there was a reduced risk of developing IRC (OR = 0.23, 95% CI 0.09–0.57, P = 0.001). Concomitant aciclovir increased the IRC risk (OR = 1.99, 95% CI 1.14–3.51, P = 0.016). Factors not associated with outcome were age, gender, ethnicity, baseline CD4 count and viral load, concomitant co-trimoxazole, or use of specific antiretrovirals.

Conclusion: An overall IRC incidence of 7.3% was identified. Concomitant aciclovir doubled the risk of IRC and we therefore recommend careful monitoring when prescribing aciclovir with indinavir. A precipitating event was identified in 26% of IRC cases, many of which could have been avoided.

Introduction

The introduction of protease inhibitors (PIs) in 1995 represented a major advance in the management of HIV infection, and together with the non-nucleoside and nucleoside reverse transcriptase inhibitors they now form part of the standard of care for many HIV-infected patients. The efficacy of the four PIs currently licensed—saquinavir, ritonavir, indinavir and nelfinavir—has been demonstrated on immunological and virological outcomes, as well as in several clinical endpoint studies. The main limitations of these drugs are their complicated treatment schedules, and adverse effects that include hyperlipidaemia and lipo-dystrophy. Indinavir was the third PI to be licensed in the UK, and rapidly became one of the most widely used drugs in this class. Following oral administration, it is rapidly absorbed, and metabolized mainly by the liver; 20% is excreted unchanged in the urine, and solubility is known to be pH dependent. Its most important adverse event is indinavir renal syndrome (indinavir-associated renal complications, IRC), which has a spectrum of clinical presentations ranging from asymptomatic crystalluria, to
crystalluria associated with dysuria and flank pain, and severe renal colic.\textsuperscript{9,11} In most circumstances, renal stones are caused by crystallization of endogenous substances.\textsuperscript{12} However, indinavir renal stones result from precipitation and crystallization of the drug as indinavir monohydrate in the collecting tubule,\textsuperscript{9} similar to the mechanism of drug-associated crystalluria seen with adefovir and other sulfaphospho-containing drugs. In the majority of IRC cases, symptoms resolve with increased fluid intake and analgesia (although there is a risk of recurrence) and in the setting of high-grade ureteral obstruction due to nephrolithiasis, lithotripsy or intra-renal stenting may be indicated.\textsuperscript{9,11,13} There have been no reported cases of fulminant renal failure following nephrolithiasis, although there are two case reports of direct nephrotoxicity secondary to indinavir,\textsuperscript{14,15} and two other reports of renal atrophy with secondary hypertension.\textsuperscript{16,17}

The reported incidence of IRC based on data from approximately 2200 patients participating in clinical trials ranges from 2.6\% to 5\% in patients taking indinavir either alone or in combination, and up to 7\% when doses exceed the recommended 2.4 g/day.\textsuperscript{7} However, clinical experience indicates that the true incidence may be much higher, and IRC has been an important reason for hospital admission among patients receiving indinavir. Other information about IRC is based on case reports, case series and a few cross-sectional or retrospective studies,\textsuperscript{10,11,18,19} but these studies have lacked a standardized case definition, which may account for their differing rates of ascertainment of IRC. Definitions of IRC used have ranged from a variety of clinical symptoms (flank pain, haematuria, dysuria, renal colic), a raised creatinine level (>20\% above the normal maximum level)\textsuperscript{20} or the presence of indinavir crystals in the urine,\textsuperscript{9} which limits the comparability of findings from these studies. Only three small cohort studies (two retrospective\textsuperscript{20,21} and one prospective\textsuperscript{9}) have examined for risk factors for IRC. However, the number of cases of IRC in these studies was small ($n = 19, 17$ and 20, respectively), and they also used different outcome definitions.

Our objectives were to determine the incidence of IRC and to identify independent risk factors for its development in a large cohort of patients who had received indinavir. The identification of such risk factors would allow patients at high risk to be targeted and monitored more effectively, and so potentially reduce the likelihood of developing IRC.

**Materials and methods**

**Study population**

The study population was drawn from two large clinical HIV centres in London: King’s College Hospital in southeast London, and Chelsea and Westminster Hospital in west London, both of which have large and well-established patient databases. Eligible patients were HIV-1-infected individuals who had received indinavir for at least 1 week during the period 1 December 1995 to 28 February 1999.

**Data collection and case ascertainment**

Data were collected on each patient using both computerized databases and review of the medical records. Information abstracted from the computerized database included demographic data, clinical stage of HIV disease (using the 1987 CDC diagnostic criteria\textsuperscript{22}), CD4 cell count and viral load at initiation of indinavir, concomitant use of other antiretroviral drugs, and use of the following potentially nephrotoxic drugs: co-trimoxazole, aciclovir, ganciclovir, pentamidine and foscarnet.

Ascertainment of the development of IRC was by review of the medical records of all patients. Information collected included the clinical presentation, possible precipitating events, management and outcome. IRC was defined as the presence of loin pain, renal colic or dysuria, where infection had been excluded by a negative midstream urine culture. For those patients who had further investigations, results from urinary microscopy (for haematuria or crystalluria), radiological investigations (abdominal X-ray, intravenous urogram and renal ultrasound) and abnormal creatinine levels were also recorded. Prescription data were used to calculate the total duration of indinavir exposure. If patients failed to receive further indinavir prescriptions, 30 days were added to the date of the most recent prescription to give the estimated duration of therapy, as it was assumed that they had discontinued treatment. Patients were censored at the date of IRC diagnosis, date of discontinuation of indinavir (as patients were no longer at risk of developing IRC), date of last follow-up or at the censorship date of 31 March 1999, whichever was sooner.

**Statistical analyses**

Time to development of IRC was calculated using Kaplan–Meier methods, and potential risk factors for the development of IRC were examined using both logistic regression and Cox proportional hazards modelling. Risk factors investigated included demographic variables (age at initiation of indinavir, gender, HIV risk group, ethnicity), clinical stage of disease at initiation of indinavir, baseline CD4 cell count [analysed both as a continuous and categorical covariate (tertiles of ≤50, 51–200 and >200 × 10\(^6\) cells/L)], baseline viral load [analysed as a continuous and categorical covariate (quartiles of ≤500, 501–20 000, 20 001–150 000 and >150 000 copies/mL)], duration of indinavir therapy, concomitant antiretroviral therapy, and use of potentially nephrotoxic drugs. Interaction terms between the most frequently used potentially nephrotoxic drugs, co-trimoxazole and aciclovir, were examined for their impact on the development of IRC. Analyses were performed using the software packages SAS (version 6.12; SAS Institute, Inc., Cary, NC, USA) and Stata (version 6; StatCorp, College Station, TX, USA).
Indinavir-associated renal complications

Results

We identified 781 eligible patients from the two clinical sites [Chelsea & Westminster (n = 660) and King’s College Hospital (n = 121)] who had received indinavir at a dose of 800 mg tds as part of an antiretroviral combination for at least 1 week over a 3 year period between December 1995 and February 1999. The median duration of exposure to indinavir was 53 weeks (IQR: 20–83). The majority of patients were Caucasian (80%) and male (90%), with a median age of 36 years (IQR: 32–42) at initiation of indinavir. The largest risk group for HIV acquisition was men who have sex with men (79%); the majority of the remainder were heterosexual (13%) or injecting drug users (5%). At initiation of indinavir, 62% had a previous AIDS-defining illness, with a median CD4 count and viral load of $117 \times 10^9$ cells/L (IQR: 30–264) and 47332 copies/mL (IQR: 5353–182 398), respectively. Patient characteristics at the two hospital sites were similar except for ethnicity and stage of HIV disease—King’s College Hospital had a greater proportion of African patients (40% versus 5%, P < 0.001), reflecting the ethnic composition of the local HIV-infected population, whilst the Chelsea and Westminster Hospital had a greater proportion of patients with a prior history of an AIDS-defining illness (75% versus 40%, P < 0.001).

The most common nucleoside reverse transcriptase inhibitors (NRTI) prescribed with indinavir were lamivudine and stavudine (47%), zidovudine and lamivudine (22%), and stavudine and didanosine (14%). Of the potentially nephrotoxic drugs, 362 (46%) patients had received co-trimoxazole prophylaxis and 260 (33%) patients had received aciclovir (mainly at a prophylactic dose of 400 mg bd) with indinavir was also significantly associated with the likelihood of developing IRC. If patients tolerated indinavir for more than 74 weeks, there was a reduced risk of developing IRC (OR = 0.32, 95% CI 0.13–0.76, P = 0.01), when compared with patients who had <30 weeks of exposure. Concomitant use of aciclovir (mainly at a prophylactic dose of 400 mg bd) with indinavir was also significantly associated with IRC, with nearly a two-fold increased risk (OR = 1.76, 95% CI 1.02–3.03, P = 0.043). However, we found no significant association between the duration of aciclovir treatment or concomitant use of co-trimoxazole and IRC.

Table 2 shows the results of the multivariate logistic regression analysis. In this model, duration of indinavir exposure, at 77, 79, 86, 89, 98, 122 and 143 weeks. Thirty-three (58%) of the cases presented with loin pain, 24 (42%) with renal colic and 11 (19%) with dysuria in association with either loin pain or renal colic. Further investigations included urine dipstick, serum electrolytes, abdominal X-ray, intravenous urogram (IVU) and/or an ultrasound. However, not all 57 symptomatic patients had the same investigations performed. Of the 33 patients who presented with loin pain, 17/22 (77%) had haematuria, 5/20 (25%) had an abnormal abdominal X-ray, 5/18 (28%) had an abnormal IVU and 5/26 (19%) had an elevated creatinine (defined as $>120 \mu$mol/L). Of the 24 patients who presented with renal colic, 20/22 (91%) had haematuria, 4/16 (25%) had an abnormal abdominal X-ray, 8/17 (47%) had an abnormal IVU and 5/23 (22%) had a raised serum creatinine level.

Risk factors for the development of IRC

Table 1 compares the characteristics at initiation of indinavir in the 57 patients who developed IRC, and the remaining 724 without IRC. In the univariate analysis we found no statistically significant differences between the two groups in either demographic, baseline laboratory or clinical characteristics (Table 1). However, the duration of indinavir therapy was significantly associated with the likelihood of developing IRC. Of the 57 patients who developed IRC, and the remaining 724 without IRC. In the univariate analysis we found no statistically significant differences between the two groups in either demographic, baseline laboratory or clinical characteristics (Table 1). However, the duration of indinavir therapy was significantly associated with the likelihood of developing IRC. If patients tolerated indinavir for more than 74 weeks, there was a reduced risk of developing IRC (OR = 0.32, 95% CI 0.13–0.76, P = 0.01), when compared with patients who had <30 weeks of exposure. Concomitant use of aciclovir (mainly at a prophylactic dose of 400 mg bd) with indinavir was also significantly associated with IRC, with nearly a two-fold increased risk (OR = 1.76, 95% CI 1.02–3.03, P = 0.043). However, we found no significant association between the duration of aciclovir treatment or concomitant use of co-trimoxazole and IRC.

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>74 weeks remained significantly associated with the development of IRC (OR = 0.23, 95% CI 0.09–0.57, \(P = 0.001\)), as did the use of aciclovir (OR = 1.99, 95% CI 1.14–3.51, \(P = 0.016\)). In contrast to our findings in the univariate analysis, we found an increasing risk for the development of IRC as the duration of aciclovir therapy increased. The use of aciclovir for up to 26 weeks was associated with a two-fold increased risk (OR = 1.93, 95% CI 1.04–3.57, \(P = 0.036\)), and use of aciclovir for >26 weeks was associated with a 2.5-fold increased risk of IRC (OR = 2.46, 95% CI 0.99–6.07, \(P = 0.05\)) compared with no aciclovir therapy. In the Cox proportional hazards model, no variables were significantly associated with time to development of IRC.

**Clinical outcome**

Thirty-six (63%) of the 57 cases of IRC resulted in a hospital admission, and 14 of these (39%) were referred for urological assessment. Five (9%) required stent insertion, and three (5%) had lithotripsy. Only seven (12%) required permanent cessation of indinavir, and in five cases (9%) the dose was modified (from a twice daily to a thrice daily regimen). Twenty (35%) cases experienced recurrence of symptoms on at least one further occasion, and seven (12%) on three or more occasions, often requiring hospital admission.

**Discussion**

This study represents the largest and most comprehensive analysis to date of risk factors for the development of IRC. Our incidence rate of 7.3% is only slightly higher than the rates reported from clinical trials (2.5–5%), but is substantially lower than the incidence rate of 18.6% documented in a recent study undertaken by Boubaker et al., where IRC was defined as a sustained creatinine level of >20% above the normal range. Consistent with most previous studies, flank pain or renal colic were the commonest presenting symptoms (occurring in 74–100% of cases).

<table>
<thead>
<tr>
<th>Variable</th>
<th>OR</th>
<th>95% CI</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Duration of indinavir (weeks)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 30 \text{ (ref.)})</td>
<td>1.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>31–74</td>
<td>1.01</td>
<td>0.54–1.87</td>
<td>0.99</td>
</tr>
<tr>
<td>&gt;74</td>
<td>0.23</td>
<td>0.09–0.57</td>
<td>0.001</td>
</tr>
<tr>
<td>Use of aciclovir</td>
<td>1.99</td>
<td>1.14–3.51</td>
<td>0.016</td>
</tr>
<tr>
<td>Use of co-trimoxazole</td>
<td>1.40</td>
<td>0.79–2.49</td>
<td>0.25</td>
</tr>
</tbody>
</table>

*Also included in the model: age (=33, 34–39, >39 years).

**Table 2. Multivariate logistic regression model of variables associated with the development of IRC**

<table>
<thead>
<tr>
<th>Variables</th>
<th>IRC patients ((n = 57))</th>
<th>Non-IRC ((n = 724))</th>
<th>OR for development of IRC</th>
<th>95%CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years)</td>
<td>37 (IQR: 33–44)</td>
<td>36 (IQR: 32–42)</td>
<td>3.08</td>
<td>0.74–12.92</td>
</tr>
<tr>
<td>Male</td>
<td>55 (96%)</td>
<td>651 (90%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Ethnic origin</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian (ref.)</td>
<td>43 (86%)</td>
<td>534 (80%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>black African/Caribbean</td>
<td>6 (12%)</td>
<td>108 (16%)</td>
<td>0.69</td>
<td>0.29–1.66</td>
</tr>
<tr>
<td>other</td>
<td>1 (2%)</td>
<td>27 (4%)</td>
<td>0.46</td>
<td>0.06–3.47</td>
</tr>
<tr>
<td>Risk group</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>homosexual (ref.)</td>
<td>48 (87%)</td>
<td>549 (78%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>heterosexual</td>
<td>3 (6%)</td>
<td>92 (13%)</td>
<td>0.37</td>
<td>0.11–1.22</td>
</tr>
<tr>
<td>other</td>
<td>4 (7%)</td>
<td>60 (9%)</td>
<td>0.76</td>
<td>0.27–2.19</td>
</tr>
<tr>
<td>AIDS diagnosis</td>
<td>39 (68%)</td>
<td>445 (61%)</td>
<td>1.36</td>
<td>0.76–2.42</td>
</tr>
<tr>
<td>Median CD4 cell count ((\times 10^3/L))</td>
<td>(87)</td>
<td>118</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median viral load ((\text{copies/mL}))</td>
<td>(21460)</td>
<td>(47616)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Duration of indinavir (weeks)*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\leq 30 \text{ (ref.)})</td>
<td>23 (40%)</td>
<td>249 (34%)</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>31–74</td>
<td>27 (48%)</td>
<td>238 (33%)</td>
<td>1.23</td>
<td>0.69–2.21</td>
</tr>
<tr>
<td>&gt;74</td>
<td>7 (12%)</td>
<td>237 (33%)</td>
<td>0.32</td>
<td>0.13–0.76</td>
</tr>
</tbody>
</table>

*aCensored at IRC date.*
Indinavir-associated renal complications

Only one study has found dysuria to be the sole presenting symptom of IRC.9 Our finding that 26% of our cases with IRC had abnormal abdominal X-rays is also broadly consistent with previous reports. The results of other imaging investigations undertaken (ultrasound, intravenous urogram and contrast CT scan) have generally confirmed the diagnosis, showing sludging of indinavir crystals in the renal tubule, evidence of obstruction with hydronephrosis, or dilated tubules, which is in agreement with previous studies. The urine microscopy findings in our cases are also similar to most other studies, which have been consistent in their reporting of microscopic haematuria in the majority of patients. However, a study by Dieleman et al.23 found high rates of sterile leucocyturia, associated with albuminuria and a raised serum creatinine level, which the authors felt were indicative of an interstitial nephritis secondary to indinavir. The incidence of impaired renal function varies between studies. We found an incidence of 26%, but rates from other studies have ranged from 26% to as high as 57%,9,20 In all cases these have been transient rises in creatinine, with values subsequently returning to normal, regardless of whether or not the drug was stopped. Although in our study patients’ urine was not routinely monitored, asymptomatic crystalluria has been found in a significant number of patients on indinavir in other studies, despite adequate hydration, with rates varying between 11%18 and 20%.9 This raises the question of whether routine screening of urine of patients receiving indinavir would help identify those at risk of IRC at an early stage.

We identified two independent risk factors for the development of IRC: duration of indinavir therapy and concomitant use of aciclovir. If indinavir was tolerated for >74 weeks, there was a reduced risk of developing IRC. In contrast, Boubaker et al.20 found that the longer the duration of therapy, the greater the risk of IRC (as defined by elevated serum creatinine levels >20% above normal). They found that the greatest risk was after 54 weeks of indinavir exposure with a seven-fold increased risk (OR = 7.1, 95% CI 1.8–27.7, P < 0.05). Other studies have not examined duration of indinavir as a risk factor, but have simply described the median or mean duration of therapy at the time of developing IRC, which has varied between 3 and 43 weeks.9,11,20,21

The other striking association we found was that concomitant use of aciclovir with indinavir significantly increased the risk of IRC by two-fold. Furthermore, there was a trend, with the risk of IRC increasing the longer the duration of aciclovir therapy. This is not unexpected as aciclovir is known to cause crystalluria, and it is postulated that indinavir may precipitate around these crystals.17 It is noteworthy that patients on chronic aciclovir treatment were in fact excluded from the original clinical trials of indinavir because of this potential interaction. This new finding warrants further investigation and confirmation in other cohort studies. It is noteworthy that co-trimoxazole, which in common with other sulfa-containing drugs, also forms urinary crystals, did not show a statistically significant association with the development of IRC, nor was an association apparent among long-term users of co-trimoxazole. This again is in contrast to the findings of Boubaker et al.,20 who found that the use of co-trimoxazole was associated with a four-fold increased risk of IRC. The one other risk factor for IRC that has been described is hepatitis C infection.21 From clinical trial data, it is known that patients with mild to moderate hepatic insufficiency and clinical evidence of cirrhosis have reduced metabolism and an increased half-life of indinavir,1 which could potentially influence the development of IRC. A study by Brodie et al.24 found that patients with hepatitis C infection (mainly haemophiliacs and intravenous drug users) had an increased incidence of IRC (37% in patients with hepatitis C versus 13% in uninfected patients, P = 0.02).

In summary, this represents the largest cohort study evaluation of IRC to date. We identified an overall incidence of IRC of 7.3%, with most episodes occurring within 74 weeks of starting indinavir therapy. Although the majority of patients were hospitalized, mainly for intravenous hydration and analgesia, only 14% required urological intervention. In most patients, indinavir treatment was continued, and there was no progressive rise in their serum creatinine levels. Concomitant use of aciclovir significantly increased the risk of IRC by approximately two-fold. Finally, a significant proportion of cases identified precipitating events, many of which could have been avoided.

Acknowledgements

This project was supported by a grant from the British Society for Antimicrobial Chemotherapy (no. 223).

References

7. Merck & Co. (1997). Crixivan (indinavir sulphate) product mono-
    graph. Merck & Co., West Point, PA.
8. Grases, F., Costa-Bauza, A., Garcia-Gonzalez, R., Payeras, A.,
    Bassa, A., Torres, J. J. et al. (1999). Indinavir crystallization and
9. Kopp, J. B., Miller, K. D., Mican, J. A., Feuerstein, I. M., Vaughan,
    E., Baker, C. *et al.* (1997). Crystalluria and urinary tract abnormal-
10. Dieleman, J. P., Gyssens, I. C., van der Ende, M. E., de Marie,
11. Hermieu, J.-F., Prevot, M.-H., Ravery, V., Sauty, L., Moulinier,
    F., Delmas, V. *et al.* (1999). Urolithiasis and the protease inhibitor
    **327**, 1141–52.
    Cadrobbi, P. (2000). Severe hypertension and renal atrophy asso-
    associated with long-term treatment with indinavir. *New England
18. Reiter, W. F., Schon-Pernerstorfer, H., Dorfinger, K., Hofbauer,
    seropositive for human immunodeficiency virus treated with indinavir
    navir urolithiasis: an emerging cause of renal colic in patients with
20. Boubaker, K., Sudre, P., Bally, F., Vogel, G., Meuwly, J.-Y.,
22. Centers for Disease Control. (1987). Revision of the CDC sur-
    villance case definition for acquired immunodeficiency syndrome.
23. Dieleman, J., van Rossum, A.-M., van der Ende, M., Blok, W.,
    nephrotoxicity with indinavir. *XIII International AIDS Conference,
    Durban, South Africa, July 2000*. Abstract WePeB4264.

Received 20 September 2000; returned 27 February 2001; revised
2 May 2001; accepted 21 May 2001