NOTES

Influence of Environmental Temperature on Incidence of Indinavir-Related Nephrolithiasis

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We analyzed the influence of temperature, humidity, and atmospheric pressure on the 1-year incidence of nephrolithiasis among human immunodeficiency virus type 1–infected patients treated with indinavir. One hundred three patients (13.6%) developed 326 episodes of nephrolithiasis. Eighty-two patients (79.6%) had more than one episode (range, two to seven episodes). The overall incidence ranged from 0 to 10.2 episodes per 100 patients exposed per month. There was a significant correlation between temperature and the overall incidence of nephrolithiasis and the incidence of recurrences but not with the incidence of first episodes. Nephrolithiasis was not related to humidity or atmospheric pressure. Our data support the standard recommendation of drinking at least 1.5 L of water daily to prevent nephrolithiasis in most patients treated with indinavir irrespective of meteorologic factors. However, the risk of nephrolithiasis is higher for a certain subgroup of patients when the environment is hot irrespective of adequate water intake.

Indinavir is the only HIV type 1 (HIV-1) protease inhibitor with significant renal elimination. Its water solubility sharply decreases when the pH is >5.5 [1], and nephrolithiasis may result from precipitation of the drug in the renal tubules [2]. A daily fluid intake of at least 1.5 L is recommended to prevent nephrolithiasis [1], although several investigators have suggested increasing that amount [3–6].

We noticed that the incidence of nephrolithiasis in an indinavir compassionate program substantially increased during the summer months irrespective of compliance with water intake. Because excessive sweating in a hot climate may itself predispose to kidney stones [7], we decided to prospectively analyze the influence of meteorologic factors on the incidence of nephrolithiasis among HIV-1–infected patients who were treated with indinavir and cared for at our hospital during the first year of commercial use of indinavir in Spain.

Methods

Patients with no history of nephrolithiasis who were treated with indinavir from November 1996 to October 1997 were included in the study. Indinavir was prescribed at dosages of 2,400 mg/d either b.i.d. or t.i.d. After a pilot study [8], most patients were taking indinavir b.i.d. by February 1997. Nevertheless, this practice is no longer supported since an interim analysis of the 069 Study comparing indinavir t.i.d. with indinavir b.i.d. as part of a triple antiretroviral regimen disclosed a lower virological effect in the b.i.d. treatment group (Merck Sharp & Dohme de España S.A. [Madrid, Spain], unpublished data).

Nephrolithiasis was defined as acute flank pain or dysuria with or without hematuria [9]. Episodes were considered different if there was at least a 3-day symptom-free interval between them. Compliance with water intake was based on self-reporting by patients. To ensure an adequate daily fluid intake [1], patients were requested to drink at least one 1.5-L bottle of water from those commercially available. Discontinuation of indinavir therapy because of side effects was decided on the basis of either the patient’s request or the physician’s judgment. For those patients continuing indinavir therapy after an episode of nephrolithiasis, the standard recommendation of daily water intake was reemphasized [1].

The incidence of nephrolithiasis was calculated as the number of episodes per 100 patients exposed per month. The average monthly values of temperature, humidity, and atmospheric pressure in the city of Barcelona (Spain) were provided by the National Institute of Meteorology (table 1). The relationship between every one of those variables and the incidence of nephrolithiasis was calculated by simple linear regression [10].

Results

In the study period, 758 patients had been or were being treated with indinavir. There were 326 episodes of nephroli-
Thiostiasis in 103 patients (13.6%). Eighty-two patients (79.6%) had more than one episode (range, two to seven episodes). The first episode developed after a median time of 16 weeks (range, 1–41 weeks). The median interval between episodes was 5 weeks (range, 1–25 weeks). The time between recurrences tended to be shorter as the number of episodes per patient increased. Indinavir therapy for 96 patients (12.7%) was withdrawn because of side effects. The main reason for discontinuation was nephrolithiasis (56 patients [58.3%]). Most (51 [91.1%]) of the patients whose indinavir therapy was withdrawn because of nephrolithiasis had had recurrent episodes.

The incidence of nephrolithiasis is shown in table 2. The overall incidence of nephrolithiasis closely correlated with temperature ($r = .894; P = .0001$) (figure 1) but not with humidity ($r = .074; P = .39$) or atmospheric pressure ($r = .003; P = .87$). The overall incidence of indinavir-related nephrolithiasis increased 0.6 episode per 100 patients exposed per month per 1°C increase in the average monthly temperature. The incidence of first episodes of nephrolithiasis did not correlate with temperature ($r = .009; P = .68$) (figure 1), humidity ($r = .018; P = .64$), or atmospheric pressure ($r = .022; P = .77$). The incidence of recurrences also correlated with temperature ($r = .886; P = .0001$) but not with humidity ($r = .058; P = .45$) or atmospheric pressure ($r = .00009; P = .98$).

Overall, lack of compliance with water intake was recognized in 54% of the episodes of nephrolithiasis. Paradoxically, compliance with water intake in patients with nephrolithiasis was better in the hot months (only 32% of patients with nephrolithiasis in the period July to October 1997 did not comply with water intake).

### Discussion

Most (86.4%) of the patients in this study did not have nephrolithiasis. We think that most of the episodes of nephrolithiasis were drug associated, as 0.5% of the population is estimated to have kidney stones every year [7]. The incidence of indinavir-related nephrolithiasis among our patients was higher than rates reported in premarketing clinical trials (3%–4%) [1, 11] and was similar to rates reported in other clinical studies with indinavir t.i.d. [12, 13]. Despite higher peak plasma levels of indinavir with b.i.d. dosing [14], this regimen has shown to be as safe as the t.i.d. regimen [15].

Our study shows that the incidence of indinavir-related nephrolithiasis...
nephrolithiasis is associated with environmental temperature. Some epidemiological surveys demonstrated a higher prevalence of nephrolithiasis in hot environments [16–19]. This effect was partly attributed to low urinary volume due to excessive sweating [20]. In fact, highly concentrated urine was found in urine samples from indinavir-treated patients with crystalluria [2, 21].

The effect of temperature on the incidence of nephrolithiasis centered mainly on patients who had had a previous episode. The higher incidence of nephrolithiasis during hotter months did not seem to be due to a lack of compliance with water intake. Our data suggest that the risk of nephrolithiasis is specially higher for a subgroup of patients and that the risk for those patients increases proportionally with temperature. An increased risk of indinavir-related nephrolithiasis was linked with certain conditions such as chronic viral hepatitis [22]. Unfortunately, the design of our study did not allow us to know which risk factors, if any, distinguished those patients with indinavir-related nephrolithiasis from those without it.

In summary, our data support the recommendation of drinking at least 1.5 L of water a day to prevent nephrolithiasis in most patients treated with indinavir irrespective of meteorologic factors. However, the risk of nephrolithiasis is higher for a subgroup of patients when the environment is hot despite compliance with water intake.

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References

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