Reversible skeletal disease and high fluoride serum levels in hematologic patients receiving voriconazole

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We here investigate the occurrence of fluoride intake-associated alterations in patients with hematologic disease on triazol antifungal medication. Clinical, laboratory, and radiology data of overall 43 patients with hematologic malignancies taking voriconazole (n = 20), posaconazole (n = 8), and itraconazole (n = 4), and a hematologic patient control group (n = 11) are described. Bone pain and radiologic evidence of periostitis were exclusively observed in patients receiving long-term voriconazole. Cessation of treatment led to clinical improvement in all cases. In line with clinical evidence, fluoride serum concentration was elevated in patients receiving voriconazole (median, 156.5 µg/L; interquartile range, 96.8 µg/L; normal < 30 µg/L) but not in the other treatment groups (P < .001 for all comparisons vs voriconazole). We conclude that serum fluoride levels were elevated on average 5-fold above normal levels in hematologic patients receiving voriconazole. Clinically relevant skeletal disease was associated with renal insufficiency and above 10-fold elevated fluoride levels, and was reversible on termination of voriconazole treatment. (Blood. 2012; 120(12):2390-2394)

Methods

Patients and clinical data

We report 3 patients with bone pain under antifungal therapy with voriconazole and an additional cohort of hematologic patients (n = 43) treated with antifungal therapy between June 2011 and August 2011 at the Division of Hematology, University Hospital Zurich. Inclusion criteria were a history of intensive chemotherapy and/or allogeneic stem cell transplantation. We included all patients treated with voriconazole, itraconazole, and posaconazole and a control group that was treated during the same time but did not receive antifungal treatment. Clinical information was extracted from the patient’s charts. Bone pain was assessed by patient interview on the day of fluoride measurement. The retrospective study was approved by the local ethical committee of the Canton Zurich, Switzerland.

Radiologic assessment and laboratory measurements

The presence of skeletal disease was assessed by 2 independent radiologists who were blinded for the patient’s clinical data. Radiographic signs of periosteal reaction and skeletal disease consisted of periosteal thickening, periosteal calcification, calcification of ligaments, and osteosclerosis. Discordant interpretations were resolved by consensus in a second readout. The analysis included the conventional radiographs (n = 60) and CT scans and low-dose CT scans (n = 67) taken between January 2011 and August 2011. In patients with fungal infections only, radiologic studies taken after initiation of the antifungal treatment were included.

Fluoride levels were determined from patient serum and measured by potentiometry with an ion-selective electrode (Mettler Toledo, Seven-Multi). Laboratory values were assessed on the date of fluoride measurement, with the exception of drug serum levels, which were allowed to be assessed during a time frame of 7 days before or after the fluoride measurement took place. Drug levels were measured by HPLC mass spectrometry (Finnigan TSQ LC/MS) at baseline.


The online version of this article contains a data supplement.
Results of the cohort with hematologic malignancies receiving antifungal therapy and the control group

The main patient characteristics of overall 32 patients with hematologic malignancies taking voriconazole (n = 20), posaconazole (n = 8), and itraconazole (n = 4), as well as a hematologic patient control group (n = 11) not receiving antifungal therapy are shown in Table 2 and in more detail in Supplemental Tables 1 and 2 (available on the Blood Web site; see the Supplemental Materials link at the top of the online article). The 3 patients with proven voriconazole-induced skeletal disease were not included in this analysis. Serum fluoride levels were significantly elevated in patients receiving voriconazole (median, 157 µg/L; IQR, 97 µg/L) compared with itraconazole (median, < 30 µg/L; IQR, 28 µg/L), posaconazole (median, < 30 µg/L; IQR, 0 µg/L), and the control group without antifungal medication (median, < 30 µg/L; IQR, 28 µg/L; P < .001 for all comparisons; Figure 3). The fluoride level in the voriconazole treatment group was inversely correlated

showed no signs of secondary malignancies, and bone marrow biopsies ruled out recurrence of the acute leukemia. Patients 1 and 2 were initially misdiagnosed as having an unusual musculoskeletal presentation of GVHD; hence, the immunosuppression was intensified. However, the pain was only temporarily attenuated by corticosteroids and methotrexate but disappeared almost completely in all 3 patients within 4 days of voriconazole cessation. The diagnosis of voriconazole-induced skeletal disease was made only retrospectively in patient 1, 20 months after occurrence of the first symptoms in patient 2, and without delay in patient 3. Serum fluoride measurements at diagnosis were available for patients 2 and 3 with > 10-fold elevated levels and a marked decrease within 3 weeks of voriconazole cessation (81% and 57% of precessation values, respectively). Long-term follow up of 5.5 years after the initial diagnosis revealed complete resolution of the skeletal changes in patient 1 (Figure 1).
to the glomerular filtration rate (Spearman rank correlation coefficient = 0.74; \( P < .001 \); Figure 4). Radiologically typical skeletal disease (periosteal appositions, abnormal calcifications) was seen in the CT scan of 1 asymptomatic patient (5%) in the voriconazole group and none in the other treatment groups. Disseminated bone pain consistent with skeletal disease was present in 3 (15%) patients in the voriconazole group and none in the other treatment groups. No signs of skeletal disease were detected in 2 of these patients by chest CT scan, whereas the third patient had no radiologic examinations performed during the observation phase. Additional fluorinated drugs were given in only 1 patient (posaconazole group), and no increase in serum fluoride level was noted.

**Discussion**

To the best of our knowledge, this is the first study to systematically analyze the impact of voriconazole on fluoride levels and skeletal disease in hematologic patients. Fluoride levels are elevated in all patients taking voriconazole irrespective of treatment duration. However, severe periostitis and skeletal disease are relatively rare and most probably result from prolonged therapy, impaired renal function, and consecutively persistent high fluoride serum levels.

The clinical presentation and the radiologic findings of the affected patients are impressive and can lead to considerable confusion as, for example, in our institution where the first affected patients have been mistakenly treated for chronic musculoskeletal GVHD.

Voriconazole-induced skeletal disease shares many features of skeletal fluorosis, a condition that has been known for decades.\(^10-12\) In Western countries, fluoride poisoning is rare but has been linked to occupational exposure, ingestion of tainted wine, excessive inhalation of fluorinated anesthetics, and iatrogenic because of the prescription of fluoride supplements.\(^13-16\) The World Health Organization states that a daily fluoride intake of > 6 mg bears a risk of skeletal events.\(^17\)

Voriconazole contains 3 fluoride atoms, which account for 16.3% of the total molecular weight of the compound. It has an oral bioavailability of 96%. Thus, in theory, the calculated daily fluoride intake at a standard dose may be as high as 62.6 mg and therefore exceeds 10-fold the fluoride toxicity threshold defined by the World Health Organization.

But why do only some patients on voriconazole treatment develop clinically relevant skeletal disease? (1) Fluoride is mainly...
excreted by the kidneys, and an impaired renal function leads to higher circulating fluoride levels. Indeed, the fluoride level in our voriconazole treatment group was inversely correlated to the glomerular filtration rate, and all our patients with proven voriconazole-induced skeletal disease had moderate to severe chronic renal failure. However, chronic renal failure alone does not necessarily translate into skeletal disease as, for example, 6 additional patients with voriconazole treatment and moderate chronic renal failure did not show evidence of toxicity. (2) It is known from endemic fluorosis that prolonged intake promotes toxicity, and it seems reasonable to assume that this also holds true for patients exposed to fluorinated drugs, even though our data lack the statistical power to test this. (3) We hypothesize that pharmacogenetics and drug-drug interactions may account in part for the interindividual differences. (4) We speculate that inflammatory processes play an additional role as the symptoms in our patients were temporarily attenuated by adding corticosteroids and methotrexate and the pain rapidly resolved after cessation of voriconazole, even though the radiographically visible skeletal changes clearly needed more time to resolve.

Posaconazole, another triazole drug containing fluorinated moieties, did not cause fluoride excess in our patient cohort. However, the number of patients receiving posaconazole was rather small, the treatment duration short, and the median serum level low. Nevertheless, in 2 patients on long-term posaconazole treatment (<20 days) and chronic renal failure (glomerular filtration rate < 90 mL/min), no fluoride excess was observed.

There are limitations of our study. First, it is a retrospective single-center study, which lacks the power to draw firm conclusions regarding the prevalence of the disorder and its observational, descriptive character does not allow statements about the precise mechanism of disease. Second, because of the retrospective nature of the radiologic assessment, no systematic radiographic screening...
In conclusion, voriconazole-induced periostitis and skeletal disease can occur in hematologic patients; and even though causality cannot yet be fully proven, fluoride is likely to contribute to the clinical picture. Physicians caring for patients on long-term voriconazole should be aware of this side effect, as it severely affects the quality of life and, when misdiagnosed, may lead to inappropriate therapy. In our experience, bone scintigraphy is a useful test when a voriconazole-induced periostitis is suspected, but other causes of skeletal disease still have to be ruled out. On discontinuation of voriconazole, skeletal disease seems to be fully reversible over time.

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Authorship

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References

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