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

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Running head: Voriconazole-induced skeletal disease
Abstract

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 <0.001 for all comparisons against voriconazole). We conclude that serum fluoride levels were elevated on average five-fold above normal levels in hematological patients receiving voriconazole. Clinically relevant skeletal disease was associated with renal insufficiency and above ten-fold elevated fluoride levels, and was reversible upon termination of voriconazole treatment.
Introduction

Invasive fungal infections are an important cause of morbidity and mortality among patients with hematologic malignancies undergoing intensive chemotherapy with or without autologous or allogeneic hematopoietic stem cell transplantation.\(^1\) The incidence of invasive aspergillosis (IA) in this patient population ranges from 4 to 12%.\(^2\) In most patients the diagnosis of IA triggers prolonged antifungal treatment. Voriconazole, a fluorinated triazole compound, is an established first line treatment for IA and is recommended by most international guidelines.\(^3,4\) Its most common side effects are well known and comprise visual disturbances, hallucinations, edema, hepatotoxicity, phototoxicity, cutaneous carcinogenesis and drug interactions due to cytochrome p450 inhibition.\(^5\) In addition, recent case reports of periostitis and skeletal disease in solid organ recipients with long-term voriconazole treatment have been published.\(^6-8\) It was suggested that the fluorinated moieties of voriconazole might play a pathogenetic role, as the radiological picture resembled that of ‘subacute fluorosis’. However, up to now only one study assessed fluoride levels in a small cohort (n=10) of primarily solid transplant patients including only one patient after bone marrow transplantation.\(^9\) Furthermore, the effect of posaconazole, a newer fluorinated triazole drug, on serum fluoride levels is unknown.

We here describe fluoride levels, renal function and musculoskeletal symptoms in a cohort of hematologic patients receiving treatment with voriconazole, posaconazole, or itraconazole and compare these to similar hematologic patients receiving no antifungal therapy.
Methods

Patients and clinical data

We report three 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.

Radiological assessment and laboratory measurements

The presence of skeletal disease was assessed by two independent radiologists who were blinded for the patient’s clinical data. Radiographic signs of periostal reaction and skeletal disease consisted of periostal thickening, periostal calcification, calcification of ligaments and osteosclerosis. Discordant interpretations were resolved by consensus in a second readout. The analysis included the conventional radiographs (n=60), CT scans and low dose CT scans (n=67) taken between January 2011 and August 2011. In patients with fungal infections only radiological 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, SevenMulti™). 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 seven days before or after the fluoride measurement took place. Drug levels were measured by HPLC mass spectrometry (Finnigan™ TSQ® LC/MS) at baseline.

The glomerular filtration rate (GFR) was calculated according the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula.

**Definition of medication-induced skeletal disease**

Diagnosis of medication-induced skeletal disease required (i) typical clinical findings such as a subacute disseminated musculoskeletal pain syndrome, (ii) radiographic findings such as periostal appositions or disseminated focal tracer uptake in a bone scintigraphy, (iii) absence of an alternative diagnosis such as relapse, secondary cancer, arthritis, etc., (iv) prompt improvement after drug cessation.

**Statistical Analysis**

Data were reported as proportions, means with standard deviations, or medians with interquartile ranges (IQR). Fluoride levels were compared by the Kruskal-Wallis test. All reported p-values are two-sided, and p<0.05 were considered to be significant. The Spearman's rank correlation coefficient was used to estimate the correlation between the serum fluoride level and the glomerular filtration rate.
Results

Case descriptions

We report three patients on long-term voriconazole treatment who developed clinically significant skeletal disease, which was completely reversible after termination of voriconazole (Table 1). All three patients were female allogeneic stem cell transplant recipients with cyclosporine-related moderate chronic renal failure. Disseminated bone pain started between 3 and 7.5 months of voriconazole treatment. Laboratory findings included an elevated alkaline phosphatase and bone-specific alkaline phosphatase, normal levels of calcium, phosphate, parathyroid hormone, 25-hydroxyvitamin D and a slightly elevated urinary deoxypyridinoline/creatinine quotient. Conventional radiographs, CT scans and bone scintigraphy revealed periostal appositions and focal tracer uptake, respectively (Figure 1 and 2). CT scans of the chest and abdomen showed no signs of secondary malignancies, and bone marrow biopsies ruled out recurrence of the acute leukemia. Patients one and two were initially misdiagnosed as having an unusual musculoskeletal presentation of graft-versus-host disease and hence the immunosuppression was intensified. However, the pain was only temporarily attenuated by corticosteroids and methotrexate but disappeared almost completely in all three patients within four days of voriconazole cessation. The diagnosis of voriconazole-induced skeletal disease was made only retrospectively in patient one, 20 months after occurrence of the first symptoms in patient two and without delay in patient three. Serum fluoride measurements at diagnosis were available for patients two and three with more than ten-fold elevated levels and a marked decrease within 3 weeks of voriconazole cessation (81% and 57% of pre-cessation values, respectively). Long-term follow up of
5.5 years after the initial diagnosis revealed complete resolution of the skeletal changes in patient one (Figure 1).

*Results of the cohort with hematological 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 as Supplemental data. The three 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; interquartile range (IQR) 97μg/l), when compared to 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<0.001 for all comparisons) (Figure 3). The fluoride level in the voriconazole treatment group was inversely correlated to the GFR (Spearman's rank correlation coefficient = 0.74; p<0.001) (Figure 4). Radiologically typical skeletal disease (periostal appositions, abnormal calcifications) was seen in the CT scan of one asymptomatic patient (5%) in the voriconazole group and none in the other treatment groups. Disseminated bone pain consistent with skeletal disease was present in three (15%) patients in the voriconazole group and none in the other treatment groups. No signs of skeletal disease were detected in two of these patients by chest CT scan, while the third patient had no radiological examinations performed during the observation phase. Additional fluorinated
drugs were given in only one 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 is relatively rare and most probably due to prolonged therapy, impaired renal function, and consecutively persistent high fluoride serum levels.

The clinical presentation and the radiological 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 graft-versus-host disease.

Voriconazole-induced skeletal disease shares many features of skeletal fluorosis, a condition which has been known for decades. In western countries, fluoride poisoning is rare but has been linked to occupational exposure, ingestion of tainted wine, excessive inhalation of fluorinated anaesthetics, and iatrogenic due to the prescription of fluoride supplements. The World Health Organisation states that a daily fluoride intake of more than 6 mg bears a risk of skeletal events.

Voriconazole contains three 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 tenfold the fluoride toxicity threshold defined by the WHO.

But why do only some patients on voriconazole treatment develop clinically relevant skeletal disease? (i) Fluoride is mainly excreted by the kidneys and an impaired renal function leads to higher circulating fluoride levels. In fact, the fluoride level in
our voriconazole treatment group was inversely correlated to the GFR and all our patients with proven voriconazole-induced skeletal disease had moderate to severe chronic renal failure (CRF). However, CRF alone does not necessarily translate into skeletal disease, as e.g. six additional patients with voriconazole treatment and moderate CRF did not show evidence of toxicity; (ii) 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 lacks the statistical power to test this; (iii) We hypothesize that pharmacogenetics and drug-drug interactions may account in part for the inter-individual differences; (iv) 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 two patients on long-term posaconazole treatment (≥20 days) and chronic renal failure (glomerular filtration rate < 90ml/min) no fluoride excess was observed.

There are limitations of our study. Firstly, it is a retrospective single-centre 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. Secondly, due to the retrospective nature of the radiological assessment, no systematic radiographic screening was available. This might have led to
a bias regarding the detection rate of skeletal disease. Thirdly, more data for long-term posaconazole treatment must be obtained to draw definite conclusions on fluoride levels and possible associated clinical implications for patients receiving this drug.

So far no treatment of voriconazole-induced periostitis or chronic fluoride intoxication has been established except withdrawal of the causing agent. While antifungal treatment was stopped permanently in two of our patients, the third was put on itraconazole, another triazole drug yet containing chlorinated, but not fluorinated, moieties (Figure 5). Bone pain resolved rapidly in all patients.

We conclude that voriconazole-induced periostitis and skeletal disease can occur in hematologic patients and even though causality cannot yet be fully proven, fluoride is very 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. Upon discontinuation of voriconazole, skeletal disease seems to be fully reversible over time.
Acknowledgments:
We would like to thank Dr. Pietro Butti for critical review of the manuscript and helpful comments.

Authorship Contributions
B.G. and U.S. conceived and designed the study; B.G., R.G., D.F. and G.N. collected and assembled the data; B.G., M.G.M., G.S. and U.S. analyzed and interpreted the data; B.G. prepared the first draft of the manuscript; and all authors contributed to writing of the manuscript and gave final approval of the manuscript.

Conflict of Interest Disclosures
B.G., G.N., U.S. and M.G.M. received research grants from MSD unrelated to this study.
R.G., D.F. and G.S. reported no potential conflicts of interest.

Funding
No funding source involved
References


Tables

Table 1. Clinical and laboratory characteristics of patients with voriconazole-induced skeletal disease.

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Diagnosis</strong></td>
<td>AML</td>
<td>AML</td>
<td>ALL</td>
</tr>
<tr>
<td><strong>Age at diagnosis (years)</strong></td>
<td>46</td>
<td>37</td>
<td>55</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td>female</td>
<td>female</td>
<td>female</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td>17.5</td>
<td>24.4</td>
<td>19.4</td>
</tr>
<tr>
<td><strong>Allogeneic stem cell transplantation</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Conditioning</td>
<td>Cy/TBI</td>
<td>Cy/TBI</td>
<td>Cy/TBI</td>
</tr>
<tr>
<td>Donor</td>
<td>MSD</td>
<td>MSD</td>
<td>MSD</td>
</tr>
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<td>GvHD prophylaxis</td>
<td>CsA/MTX</td>
<td>CsA/MTX</td>
<td>CsA/MTX</td>
</tr>
<tr>
<td><strong>Voriconazole treatment days until onset of skeletal disease</strong></td>
<td>100</td>
<td>177</td>
<td>226</td>
</tr>
<tr>
<td><strong>Total voriconazole dose until onset of skeletal disease (g)</strong></td>
<td>55</td>
<td>97.4</td>
<td>133.6</td>
</tr>
<tr>
<td><strong>Median voriconazole level (IQR) $^\dagger$/number of measurements</strong></td>
<td>1.6 (0.85)/12</td>
<td>1.95 (0.9)/14</td>
<td>1.2 (1.35)/15</td>
</tr>
</tbody>
</table>

**Laboratory values during voriconazole treatment/ 3 weeks after voriconazole cessation**

<table>
<thead>
<tr>
<th></th>
<th>Patient 1</th>
<th>Patient 2</th>
<th>Patient 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Glomerular filtration rate (ml/min)$^2$</strong></td>
<td>57/65</td>
<td>31/50</td>
<td>32/46</td>
</tr>
<tr>
<td><strong>ALP (U/l)$^3$</strong></td>
<td>195/102</td>
<td>384/214</td>
<td>202/125</td>
</tr>
<tr>
<td><strong>ALT(U/l)$^4$</strong></td>
<td>106/92</td>
<td>38/30</td>
<td>9/13</td>
</tr>
<tr>
<td><strong>Fluoride level (µg/l)$^5$</strong></td>
<td>NA</td>
<td>363/70</td>
<td>316/136</td>
</tr>
<tr>
<td><strong>CsA level (µg/l)</strong></td>
<td>154/NA</td>
<td>106/50</td>
<td>226/179</td>
</tr>
</tbody>
</table>

$^\#$Cy/TBI = Cyclophosphamide and total body irradiation (12 Gy), MSD = HLA-matched sibling donor, CsA/MTX = cyclosporine and methotrexate; $^\$IQR = interquartile range; $^\dagger$Target serum levels for voriconazole 1.0-6.0 mg/l, posaconazole >1.0 mg/l and for itraconazole >1.0 mg/l, respectively; $^\|$according the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula; $^\|$$^\|$ALP = Alkaline phosphatase (normal 35-104 U/L); $^\|$$^\|$$^\|$ALT = Alanine aminotransferase (normal 10-35 U/L); $^\|$$^\|$Normal <30µg/l; NA = non applicable
Table 2. Clinical and laboratory characteristics of patients with hematologic malignancies taking voriconazole, posaconazole, and itraconazole, and a hematologic patient control group not receiving antifungal therapy.

<table>
<thead>
<tr>
<th></th>
<th>Voriconazole (n=20)</th>
<th>Posaconazole (n=8)</th>
<th>Itraconazole (n=4)</th>
<th>control group (n=11)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (years)</td>
<td>55.1</td>
<td>54.9</td>
<td>49.5</td>
<td>56.6</td>
</tr>
<tr>
<td>Male gender (%)</td>
<td>10 (50)</td>
<td>3 (37.5)</td>
<td>3 (75)</td>
<td>7 (63.6)</td>
</tr>
<tr>
<td>Stem cell transplantation (%)</td>
<td>15 (75)</td>
<td>3 (37.5)</td>
<td>4 (100)</td>
<td>10 (90.9)</td>
</tr>
<tr>
<td>Median antifungal treatment days (IQR)</td>
<td>98 (220)</td>
<td>13 (576)</td>
<td>587 (1400)</td>
<td>NA</td>
</tr>
<tr>
<td>Median drug serum concentration (IQR)</td>
<td>1.7 (1.8)</td>
<td>0.24 (1.17)</td>
<td>1.95 (1.75)</td>
<td>NA</td>
</tr>
<tr>
<td>Median glomerular filtration rate (IQR)</td>
<td>77.5 (43.6)</td>
<td>92.2(33.8)</td>
<td>70.8 (45.7)</td>
<td>74.2 (18.9)</td>
</tr>
<tr>
<td>Cyclosporine treatment (%)</td>
<td>9 (45)</td>
<td>2 (25)</td>
<td>0</td>
<td>6 (54.5)</td>
</tr>
<tr>
<td>Median cyclosporine blood concentration μg/l (IQR)</td>
<td>92 (102.5)</td>
<td>53.5</td>
<td>NA</td>
<td>104 (141.5)</td>
</tr>
<tr>
<td>Median ALP³ (IQR)</td>
<td>111 (76.5)</td>
<td>66 (103)</td>
<td>120 (138)</td>
<td>71 (31)</td>
</tr>
<tr>
<td>Median ALT⁴ (IQR)</td>
<td>30 (12.5)</td>
<td>36 (30)</td>
<td>70.5 (90)</td>
<td>20 (18)</td>
</tr>
<tr>
<td>Median fluoride level⁵ (IQR)</td>
<td>156.5 (96.8)</td>
<td>&lt;30 (0)</td>
<td>&lt;30 (28)</td>
<td>&lt;30 (32)</td>
</tr>
<tr>
<td>Median number of radiographic studies (IQR)</td>
<td>2 (3.5)</td>
<td>0.5 (1)</td>
<td>1 (0.25)</td>
<td>3 (3.5)</td>
</tr>
<tr>
<td>Median number of CT scans (IQR)</td>
<td>1 (1)</td>
<td>0.5 (1)</td>
<td>1 (0.25)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Radiographic evidence of periostitis (%)</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Bone pain (%)</td>
<td>3 (15)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

*IQR = interquartile range; ¹Target serum levels for voriconazole 1.0-6.0 mg/l, posaconazole >1.0 mg/l and for itraconazole >1.0 mg/l, respectively; ² according the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula. ³ALP = Alkaline phosphatase (normal 35-104 U/L); ⁴ALT = Alanine aminotransferase (normal 10-35 U/L); ⁵ Normal <30μg/l; NA = non applicable
Figure legends

Figure 1. Radiographic findings and bone scintigraphy in Patient 1

(A) Technetium 99m-methyl-diphosphonate bone scintigraphy showing marked tracer uptake in the entire skeleton, most pronounced in the spine and pelvis (left). Also note multiple active spots in bones of both hands (right). (B) Plain film showing marked periostal bone apposition on diaphysis of the phalanges of the left hand (arrows). Findings are typical for hypertrophic osteoarthropathy. The image was taken after 9 months of voriconazole therapy. (C) Plain film showing resolution of periostal bone appositions on diaphysis of the phalanges (arrows). The image was taken five years after cessation of voriconazole therapy.

Figure 2. Radiographic findings and bone scintigraphy in Patient 2

(A) Plain film showing marked periostal bone apposition on radial and distal diaphysis of the first metacarpal bone of the right hand (arrow). (B) Technetium 99m-methyl-diphosphonate bone scintigraphy showing marked tracer uptake in the entire skeleton, most pronounced in the spine and pelvis. Also note active spots in bones of both hands and feet. (C) Computed Tomography (CT) scan of the entire skeleton revealed bone appositions in various sites of the skeleton (arrows): at the caudal margin of the glenoid (top), at the dorsal ribs (mid) and periacetabular on both sides (bottom). Findings are typical of hypertrophic osteoarthropathy.
Figure 3. Serum fluoride levels

The boxplots represent median, interquartile range, and the whiskers 95% confidence intervals. Serum fluoride levels were significantly elevated in patients receiving voriconazole (median 157 μg/l; interquartile range (IQR), 97 μg/l), when compared to 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<0.001 for all comparisons).

Figure 4. Correlation between the glomerular filtration rate and the serum fluoride levels for the patients taking voriconazole.

Correlation between the glomerular filtration rate as calculated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula and the serum fluoride levels for the patients taking voriconazole. Spearman’s rank correlation coefficient = 0.74; p<0.001.

Figure 5. Chemical structures of posaconazole, itraconazole, and voriconazole.

(A) posaconazole, (B) itraconazole, (C) voriconazole
Figure 2
Figure 3

Fluoride level (μg/L)

No triazole
Voriconazole
Posaconazole
Itraconazole

p < 0.001
Figure 4

The scatter plot shows a negative correlation between creatinine clearance (ml/min) and fluoride levels (μg/L). The regression line indicates a statistically significant relationship with a p-value less than 0.001.
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