Plasma Fluoride Level as a Predictor of Voriconazole-Induced Periostitis in Patients With Skeletal Pain

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Background. Voriconazole is a triazole antifungal medication used for prophylaxis or to treat invasive fungal infections. Inflammation of the periosteum resulting in skeletal pain, known as periostitis, is a reported side effect of long-term voriconazole therapy. The trifluorinated molecular structure of voriconazole suggests a possible link between excess fluoride and periostitis, as elevated blood fluoride has been reported among patients with periostitis who received voriconazole.

Methods. Two hundred sixty-four patients from Michigan were impacted by the multistate outbreak of fungal infections as a result of contaminated methylprednisolone injections. A retrospective study was conducted among 195 patients who received voriconazole therapy at St Joseph Mercy Hospital during this outbreak. Twenty-eight patients who received both bone scan and plasma fluoride measurements for skeletal pain were included in the statistical analyses. Increased tracer uptake on bone scan was considered positive for periostitis. The primary outcome measure was the correlation between plasma fluoride and bone scan results.

Results. Blood fluoride ($P < .001$), alkaline phosphatase ($P = .020$), daily voriconazole dose ($P < .001$), and cumulative voriconazole dose ($P = .027$) were significantly elevated in patients who had periostitis compared with those who did not. Discontinuation or dose reduction of voriconazole resulted in improvement of pain in 89% of patients.

Conclusions. High plasma fluoride levels coupled with skeletal pain among patients who are on long-term voriconazole therapy is highly suggestive of periostitis. Initial measurement of fluoride may be considered when bone scan is not readily available. Early detection should be sought, as discontinuation of voriconazole is effective at reversing the disease.

Keywords. contaminated methylprednisolone injection; fluorosis; fungal infection; periostitis; voriconazole.

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Voriconazole was the first-line therapy recommended by the CDC due to its excellent oral bioavailability and central nervous system penetration [6–10]. Visual disturbances, skin rash, prolongation of QT interval, and hepatic enzyme elevation have been frequently observed among patients taking voriconazole [11–15]. Periostitis, skeletal fluorosis, and exostoses have also been reported [16–28]. Because of its trifluorinated molecular structure, several studies have suggested a link between excess fluoride intake from voriconazole therapy and the development of periostitis [19, 25, 27]. Patients who are taking the Food and Drug Administration–recommended voriconazole maintenance dose of 200 mg every 12 hours are consuming an average of 65 mg of fluoride per day [19, 27]. This is 15...
times greater than what is outlined by the United States Department of Agriculture as an adequate daily intake (3–4 mg) [12, 29, 30]. Most patients who received voriconazole at SJMH during the outbreak required much higher doses to maintain the CDC-recommended therapeutic blood voriconazole trough levels of 2–5 µg/mL (Table 1) [5].

Although excess fluoride intake has been proposed as a cause of voriconazole-related periostitis, the exact relationship remains unclear. Of 195 patients treated at SJMH, at least 25% reported skeletal pain concerning for periostitis. This relatively large population allowed us to test the hypothesis that, in the presence of pain, plasma fluoride and voriconazole dose are positively correlated with development of periostitis.

METHODS

Design and Data Collection

This retrospective study was approved by the SJMH institutional review board. Data collection of variables including voriconazole dose and blood laboratory and bone scan results, if available, occurred in all patients who received either a bone scan, plasma fluoride level measurement, or both (n = 68/195). To determine the relationship between skeletal pain, excess fluoride, and the development of periostitis, patients with reported skeletal pain who received orders for whole-body bone scan together with plasma fluoride concentration measurement were included in the statistical analyses (n = 28/195). To eliminate provider bias and unpaired test results, patients were excluded from the statistical analysis if orders for the bone scan and fluoride did not occur together or if the time between bone scan and plasma fluoride measurement was >1 month.

Data abstracted from the medical record included age and comorbid conditions including coronary artery disease, cerebrovascular disease, diabetes mellitus, chronic kidney disease, dementia, hypertension, hyperlipidemia, pulmonary disease, malignancy, and bisphosphonate use as well as the location of pain. Variables including voriconazole dose; cumulative voriconazole dose; plasma concentrations of fluoride, creatinine, alanine aminotransferase (ALT), total bilirubin, and alkaline phosphatase (ALP); and bone scan results were also collected. Prior to analysis, plasma fluoride units were converted from milligrams per liter to the more widely used micromoles per liter. Changes to voriconazole dose after diagnosis of periostitis, including reduction or discontinuation, were recorded based on SJMH electronic medical record documentation. Evolution of pain after dose reduction or discontinuation of voriconazole was also recorded for analysis. The summation of daily voriconazole dose from the date of initiation through the date of bone scan was recorded as an estimate of cumulative voriconazole dose. The primary outcome measure was the correlation between plasma fluoride and bone scan results.

RESULTS

Demographics

During the multistate outbreak of fungal infections, a total of 195 patients received care at SJMH (Figure 1). Sixty-eight patients received at least 1 bone scan or plasma fluoride measurement. Of the 68 patients, 9 received only a whole-body bone scan and 24 patients only received a plasma fluoride measurement. Thirty-five received both tests, and 28 in that group met our inclusion criteria for statistical analysis. Within this group, 21 patients had periostitis and 7 did not. Common locations of skeletal pain involved the chest or ribs, followed by arms or forearms and, less commonly, the hip and lower extremities (Table 1). None of the patients without periostitis reported rib pain. Nineteen of 21 patients (90.5%) with periostitis correctly identified at least 1 location of periostitis when the reported pain location was compared with the results of the bone scan (Table 1).

The average age for those without and those with periostitis was 59 ± 3.7 and 68 ± 2.6 years, respectively (P = .098; Table 2). We did not find any significant associations between the analyzed comorbidities and periostitis (Table 1).

Blood Laboratory Values and Periostitis

The average plasma fluoride concentration among patients without periostitis was 3.61 ± 1.29 µmol/L, whereas those with periostitis had an average value of 12.78 ± 0.96 µmol/L (laboratory reference <5.26 µmol/L) (P < .001). Serum ALP was 117 ± 15.7 in those without periostitis and 273 ± 35.6 in those with periostitis (laboratory reference 27–120 IU/L) (P = .020).

Diagnosis of Periostitis

In the context of reported voriconazole intake and skeletal pain, the presence of abnormal linear uptake of tracer along the skeleton on a whole-body bone scan with technetium-99 m labeled methyl diphosphonate was considered positive for periostitis [31, 32]. Bone scan results as documented within the electronic medical records were recorded for analysis. A second radiologist who was blinded to plasma fluoride concentrations confirmed the diagnosis and recorded the location(s) of periostitis.

Statistical Analysis

A 2-tailed homoscedastic t test was used to compare daily voriconazole dose, estimated cumulative voriconazole dose through the time of bone scan, and plasma fluoride, voriconazole, creatinine, ALT, total bilirubin, and ALP concentrations to the bone scan results. Results are reported as average ± the standard error. Correlation among variables was tested in GraphPad Prism 6 statistical computing software. A P value <.05 was considered statistically significant.
Table 1. Detailed Clinical Information

| Patient | Age | Comorbidities | Bone Scan Location of Pain | Location of Periostitis | Fluoride, µmol/L | Voriconazole Reduced Cumulative Dose, mg | Daily Voriconazole Dosage, mg | Creatinine, mg/dL | ALT, IU/L | Total Bili, IU/L | ALP, IU/L | Pain Improved | Reduction Helped |
|---------|-----|---------------|-----------------------------|------------------------|-------------------|-------------------------------|-----------------------------|----------------------------|----------------|----------------|----------------|-------------|-----------------|-----------------|
| 1 F     | 57  | HTN           | –                           | –                      | 133.2             | 600                           | 1.8                         | 0.58                       | 21             | 0.5           | 89             |             |                 |                 |
| 2 F     | 49  | None          | –                           | –                      | 6.84              | .                             | 91.0                        | 500                        | 0.8            | 0.6           | 90             |             |                 |                 |
| 3 F     | 55  | None          | –                           | –                      | 5.26              | .                             | 60.9                        | 350                        | 1.7            | 0.37          | 110            |             |                 |                 |
| 4 F     | 70  | None          | –                           | –                      | 6.84              | .                             | 97.4                        | 500                        | 3.3            | 0.79          | 157            |             |                 |                 |
| 5 F     | 49  | DM            | –                           | –                      | 0                 | .                             | 109.3                       | 600                        | 2.8            | 0.7          | 99             |             |                 |                 |
| 6 F     | 59  | DM, HTN       | –                           | –                      | 6.32              | .                             | 76.6                        | 600                        | 0.9            | 0.98          | 139            |             |                 |                 |
| 7 M     | 74  | CAD, CVD      | –                           | –                      | 0                 | .                             | .                           |                            |                 | 0.1           | 0.93          |             |                 |                 |
| 8 F     | 73  | HTN + Hip, knee | Ulna | Ulna, clavicle, humerus, fibula | 11.05 | No | 193.7 | 800 | 4 | 0.93 | 58 | 0.7 | 114 | 0.6 | Yes | No |
| 9 F     | 65  | None + Rib, leg, humerus | Rib, ulna, Radius, ulna | 10.53 | Yes | 131.4 | 800 | 2.6 | 1.18 | 17 | 0.5 | 89 | 0.7 | Yes | Yes |
| 10 F    | 60  | CKD, HLD, HTN | –                           | –                      | 10.00             | No                            | No                          | 700                        | 2.3            | 0.82          | 236            |             |                 |                 |
| 11 F    | 33  | None + Shoulder, elbow, hand | Ulna, tibia, clavicle | 14.74 | Yes | 98.5 | 700 | 3.3 | 0.82 | 17 | 0.5 | 48 | 0.7 | 281 | No |
| 12 F    | 69  | CVD, DM, HLD, HTN, MAL, PD | Arm, hand, Ulna, clavicle | 14.74 | Yes | 109.8 | 700 | 1.4 | 0.86 | 157 | 0.5 | 48 | 0.7 | 114 | Yes |
| 13 F    | 68  | HLD, HTN + Rib, forearm | Rib, ulna, Radius, ulna | 13.16 | Yes | 131.4 | 800 | 2.6 | 1.18 | 17 | 0.5 | 89 | 0.7 | Yes | Yes |
| 14 F    | 66  | None + Forearm | Rib, ulna, Femur, clavicle, tibia | 0 | No | 98.9 | 500 | 3 | 0.82 | 15 | 0.4 | 168 | Yes | Yes |
| 15 F    | 56  | None + Forearm | Ulna | 12.63 | No | 102.4 | 700 | 1.8 | 0.58 | 21 | 0.5 | 89 | . | Yes | No |
| 16 F    | 82  | HLD + Rib, hip | Rib, ulna, cubitalis, rib | 12.11 | Yes | 89.3 | 700 | 1.6 | 0.58 | 21 | 0.5 | 89 | . | Yes | No |
| 17 F    | 82  | HLD + Rib, clavicle | Rib, ulna | 14.21 | Yes | 95.6 | 700 | 1.6 | 0.58 | 21 | 0.5 | 89 | . | Yes | No |
| 18 F    | 77  | None + Thorax, rib, hand, feet | Ulna, Radius, clavicle | 10.00 | Yes | 131.4 | 800 | 2.6 | 1.18 | 17 | 0.5 | 89 | 0.7 | Yes | Yes |
| 19 F    | 76  | None + Thorax, rib, hand, feet | Ulna, Radius, clavicle | 10.00 | Yes | 131.4 | 800 | 2.6 | 1.18 | 17 | 0.5 | 89 | 0.7 | Yes | Yes |
| 20 F    | 73  | None + Thorax, rib, hand, feet | Ulna, Radius, clavicle | 10.00 | Yes | 131.4 | 800 | 2.6 | 1.18 | 17 | 0.5 | 89 | 0.7 | Yes | Yes |
| 21 F    | 83  | None + Thorax, rib, hand, feet | Ulna, Radius, clavicle | 10.00 | Yes | 131.4 | 800 | 2.6 | 1.18 | 17 | 0.5 | 89 | 0.7 | Yes | Yes |
| 22 F    | 59  | Dementia, DM, PD | Ulna | 13.69 | Yes | 147.3 | 900 | 1.6 | 0.58 | 21 | 0.5 | 89 | . | Yes | No |
| 23 M    | 73  | CAD, HLD, HTN | –                           | –                      | 8.42              | Yes                           | 132.8                       | 700                        | 3.2            | 0.8           | 272            |             |                 |                 |
| 24 F    | 47  | None          | –                           | –                      | 8.42              | Yes                           | 132.8                       | 700                        | 3.2            | 0.8           | 272            |             |                 |                 |
| 25 F    | 71  | None          | –                           | –                      | 8.42              | Yes                           | 132.8                       | 700                        | 3.2            | 0.8           | 272            |             |                 |                 |
The 28 patients who were included in the statistical analyses are shown. To determine the relationship between skeletal pain, excess fluoride, and the development of periostitis while eliminating provider-biased and unpaired test results, only those with reported skeletal pain who received orders for whole-body bone scan together with plasma fluoride concentration measurement were included (n = 28/195).

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; Bili, total bilirubin; CAD, coronary artery disease; CKD, chronic kidney disease; CVD, cerebrovascular disease; DM, diabetes mellitus; HLD, hyperlipidemia; HTN, hypertension; MAL, malignancy; PD, pulmonary disease.

The daily voriconazole dose was positively correlated with plasma fluoride (r = 0.26, P = .002). Cumulative voriconazole dose was not correlated with blood laboratory parameters (Table 2). All other correlations between daily voriconazole dose, cumulative voriconazole dose, or blood voriconazole level with blood laboratory parameters were negative (Supplementary Table 1).

Site-Specificity of Voriconazole-Induced Periostitis

Periostitis was present throughout the appendicular and axial skeleton, with the most common locations being ulna and ribs (Figures 3 and 4). Less common locations included tibia, clavicle, femur, radius, or fibula, and scapula or humerus. All patients with periostitis had either ulna or rib periostitis, whereas 48% of the patients had both locations involved (Tables 1 and 2).

Relationship Between Discontinuation of Voriconazole and Resolution of Symptoms

Identification of periostitis resulted in reduction or discontinuation of voriconazole in all 21 patients. Discontinuation of voriconazole resulted in improvement or resolution of pain in 8 of 11 patients over a period of 2 weeks to 5 months. Two patients had continued skeletal pain despite discontinuation of voriconazole, and symptoms were not followed in one patient. Among 10 patients whose dose was reduced, 5 reported improvement of pain over a period of 2–8 weeks, and voriconazole was continued until the planned discontinuation date. Skeletal pain in 4 patients continued despite dose reduction, resulting in subsequent discontinuation of voriconazole. After discontinuation, pain improved in all 4 patients over 3–6 weeks. Symptoms were not followed in 1 patient whose dose was reduced. Overall, pain symptoms were followed in 19 of 21 patients after reduction or discontinuation of voriconazole. Seventeen of 19 patients (89%) had improvement of pain, whereas 2 patients continued to have pain despite reduction or discontinuation of voriconazole (Table 2). In 1 patient, resolution of periostitis

Table 1 continued.

Serum voriconazole trough, creatinine, ALT, and total bilirubin did not differ significantly between the 2 groups (Table 2).

Voriconazole Dose, Plasma Fluoride, and the Development of Periostitis

The daily voriconazole dose at the time of blood draw was 450 ± 82 mg for patients without periostitis and 780 ± 43 mg for those with periostitis (P < .001). For patients at SJMH, voriconazole dose was adjusted every 1–6 weeks after evaluation of serum voriconazole trough if the levels were not within the recommended range (2–5 µg/mL). The estimated cumulative voriconazole dose through the date of the bone scan was 94.7 ± 9.5 g for those without periostitis and 130.5 ± 7.3 g in patients positive for disease (P = .024; Table 2). Cumulative dose calculation was not possible for 2 patients who received care at a different institution prior to transferring to SJMH. The daily voriconazole dose was positively correlated with plasma fluoride (P < .001) and ALP (P = .002), whereas the cumulative voriconazole dose was not (P = .062 and .143) (Figure 2, Supplementary Table 1).
was confirmed 11 months after discontinuation of voriconazole with an additional bone scan (Figure 4).

**DISCUSSION**

Voriconazole-induced periostitis has been described in case reports and small studies in the fields of radiology, oncology, and transplant medicine [16–28]. In the only prospective study to date, Wermers et al followed a total of 20 patients, 10 who were taking voriconazole and 10 who were not. They found that fluoride levels were elevated in the group that was taking voriconazole. Five of the 10 patients who were taking voriconazole also had evidence of periostitis [27]. In another retrospectively performed but larger study, Gerber et al compared a group of 20 patients receiving voriconazole to those receiving other antifungal medications. One out of 20 patients had

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Breakdown of the patients who received voriconazole therapy. Total number of patients who received therapy with voriconazole at St Joseph Mercy Hospital for fungal infections caused by contaminated methylprednisolone injections and their subsequent clinical evaluations. “Bone Pain”: number of patients who reported skeletal pain; “No Pain”: number of patients who had no reported skeletal pain; “Fl > 8”: plasma fluoride levels >8 µmol/L; “Fl < 8”: plasma fluoride level <8 µmol/L; “Bone Scan (+)”: number of bone scans positive for periostitis and its percentage; “Pain Unknown”: number of patients who did not receive either bone scan or fluoride measurement and therefore were excluded from data extraction; “Fl Not Measured” and “Bone Scan Not Ordered”: these tests were not obtained during the treatment period.

![Table 2](https://example.com/table2.png)

**Table 2. Comparison of Patients Without and Those With Periostitis**

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Negativea</th>
<th>Positivea</th>
<th>P Value</th>
<th>Reference Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average age, y</td>
<td>59 ± 3.7</td>
<td>68 ± 2.6</td>
<td>.098</td>
<td></td>
</tr>
<tr>
<td>Daily voriconazole dose, mg</td>
<td>450 ± 82</td>
<td>780 ± 43</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Cumulative voriconazole dose through bone scan date, g</td>
<td>94.7 ± 9.5</td>
<td>130.5 ± 7.3</td>
<td>.024</td>
<td></td>
</tr>
<tr>
<td>Plasma fluoride, µmol/L</td>
<td>3.61 ± 1.29</td>
<td>12.78 ± 0.96</td>
<td>&lt;.001</td>
<td>&lt;5.26</td>
</tr>
<tr>
<td>Serum voriconazole trough, µg/mL</td>
<td>1.63 ± 0.43</td>
<td>2.37 ± 0.28</td>
<td>.188</td>
<td>1–5.5</td>
</tr>
<tr>
<td>Serum creatinine, mg/dL</td>
<td>0.71 ± 0.08</td>
<td>0.84 ± 0.06</td>
<td>.309</td>
<td>Females: 0.44–1.03 Males: 0.64–1.27</td>
</tr>
<tr>
<td>Serum alanine transaminase, mg/dL</td>
<td>32.1 ± 11.9</td>
<td>29.8 ± 4.8</td>
<td>.830</td>
<td>Females: 10–54 Males: 10–63</td>
</tr>
<tr>
<td>Serum total bilirubin, IU/L</td>
<td>0.52 ± 0.1</td>
<td>0.54 ± 0.04</td>
<td>.876</td>
<td>Females: 0–2 Males: 0–1.6</td>
</tr>
<tr>
<td>Serum alkaline phosphatase, IU/L</td>
<td>117 ± 15.7</td>
<td>273 ± 35.6</td>
<td>.020</td>
<td>27–120</td>
</tr>
<tr>
<td>Periostitis involving rib</td>
<td>15 of 21 (71%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periostitis involving ulna</td>
<td>16 of 21 (76%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Periostitis involving rib and ulna</td>
<td>10 of 21 (48%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved pain after voriconazole reduction or discontinuation</td>
<td>17 of 19 (89%)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The averages of each independent variable are recorded along with the standard error. Location of periostitis and symptom follow-up is recorded as No. (%).

* Negative bone scan results represent those without periostitis, whereas positive bone scan results represent patients with periostitis.
evidence of periosteal disease, whereas 3 of 20 had bone pain [19]. In our study, there were 29 diagnosed cases of periostitis among 195 patients (15%), placing our results within the rather wide range established by the literature (5%–50%). At least 49 of the 195 patients experienced bone pain (25%). All patients with periostitis had involvement of either ribs or ulna (Table 1). This site is in contrast to lower-extremity pain previously reported in patients who were treated with sodium fluoride [33]. We observed that those with both pain and periostitis were prescribed a significantly higher average daily (P < .001) and cumulative voriconazole dose (P = .024) than those without (Table 2). Although the retrospective nature of this study did not allow us to verify patient compliance, dose reduction as documented in the medical record resulted in improvement of symptoms in 5 of 10 patients whereas immediate discontinuation of voriconazole resulted in improvement of pain in 8 of 11 patients. This observation is consistent with the previously reported reversibility of periostitis caused by excess fluoride intake [19, 22, 26–28]. Although immediate discontinuation of voriconazole resulted in a greater number of patients with improved pain, the observation of pain improvement in 50% of patients on a reduced dose suggests that it is reasonable to try dose reduction in patients who require voriconazole as an antifungal agent prior to discontinuation.

Humans are widely exposed to fluoride from natural, systemic, and topical sources. Although low levels of supplemental fluoride are beneficial for prevention of tooth decay, chronic intake of an excessive dose can result in dental or skeletal fluorosis, exostoses, and pain [33–36]. Following ingestion, plasma fluoride concentrations peak after 20–60 minutes and then fall rapidly, reaching baseline within 3 to 11 hours [34]. Approximately 35%–50% of circulating fluoride is incorporated into the surface of the bone, <1% resides temporarily in soft tissues, and the rest is excreted in the urine, sweat, and feces [34, 37]. If excess fluoride has been stored, it will be released when plasma levels fall, resulting in a prolongation of the plasma fluoride elevation. The 28 patients shown in Table 1 were prescribed 350–1300 mg of voriconazole, corresponding to 57–211 mg of daily ingested fluoride. Consistent with this, we observed a significant positive correlation between daily voriconazole dose and plasma fluoride (P < .001; Figure 2).

In the presence of patient-reported skeletal pain, our statistical analyses also indicate a strong association between plasma fluoride concentration and the presence of periostitis (P < .001). Twenty of 21 patients with periostitis had plasma fluoride levels exceeding 8 µmol/L (laboratory reference <5.26 µmol/L). When considering all 28 subjects who met our inclusion criteria, a plasma fluoride level >8 µmol/L in the presence of pain yielded a sensitivity and specificity for periostitis of 0.95 (95%
Figure 3. Computed tomography (CT) and whole-body bone scan of periostitis. A, Chest CT was obtained in this patient to further evaluate for rib pain. B and C, Magnified images of the bilateral ribs. B, Magnified image of right posterior rib has evidence of periosteal inflammation and thickening consistent with periostitis (arrowheads). C, Left midshaft of the rib in an uninvolved area that does not have periostitis does not show periosteal layer thickening as shown in (B). D, Posterior whole-body bone scan of the same patient showing bilateral posterior rib periostitis.

Figure 4. Posterior view of the whole-body bone scan, before and after voriconazole discontinuation. This patient had evidence of right rib periostitis approximately 5 months after beginning voriconazole (A). Approximately 11 months after discontinuation of voriconazole, a repeat bone scan shows no evidence of periostitis (B).
Confidence interval [CI], .76–.99) and 1.0 (95% CI, .59–1.0), respectively.

Consistent with previous reports, we also observed elevated fluoride levels in some patients without periostitis [19, 25, 27] (Figure 1). Among 17 patients without pain who received a fluoride level test, but not a bone scan, 8 of 17 had a fluoride level >8 µmol/L (Figure 1). Two patients without pain received both a fluoride level and a bone scan. Neither had evidence of periostitis, with 1 fluoride level >8 µmol/L and 1 level <8 µmol/L (Figure 1). This further suggests that patient-reported symptoms of bone pain significantly add to the diagnostic evaluation. For example, if a patient on voriconazole reports skeletal pain, measurement of plasma fluoride is a relatively inexpensive and noninvasive first-line assessment. If the fluoride is >8 µmol/L, a follow-up bone scan could be used to confirm the presence of periostitis leading to dose reduction or discontinuation of voriconazole.

Hepatic enzyme elevation is a common side effect of voriconazole. We observed statistically significant elevations in blood ALP in patients with both pain and periostitis (P = .020) that positively correlated with daily voriconazole intake (P = .002; Figure 2) [6, 11, 13, 27]. However, we did not observe differences in ALT or total bilirubin. Isolated elevation of ALP in the absence of ALT or aspartate aminotransferase elevation has been reported previously among patients on long-term voriconazole [19, 26, 27]. Given the relationship between fluoride and skeletal metabolism, it is likely that increases in ALP signify an elevation of the bone isozyme. Future studies to measure ALP subtypes are needed to evaluate their clinical utility as biomarkers for development of periostitis in patients taking voriconazole.

Limitations of this study include the absence of a control population that was not taking voriconazole. We were also limited by the retrospective nature of the analysis and could not assess parameters such as patient compliance. Also, although we did not observe any relationship between the assessed comorbidities and periostitis, the sample size is relatively small and it is still largely unclear why some individuals are more likely to develop periostitis than others. Last, although diagnosis of periostitis by bone scan in the context of pain and voriconazole intake has been well defined in previous reports, it is possible that other conditions such as osteomalacia and fracture can cause increased tracer uptake.

CONCLUSIONS

Our study shows that high plasma fluoride concentration coupled with skeletal pain among patients who are on long-term voriconazole therapy is highly suggestive of periostitis. Obtaining a plasma fluoride level may be a cost-effective first-line alternative to obtaining a bone scan for patients who have skeletal pain and are unable to afford the cost of a bone scan or for institutions where nuclear imaging is not readily accessible. Future studies are needed to determine if biomarkers of changes in bone metabolism, such as ALP isozymes, can also be used to predict development or risk of periostitis. It is extremely important to diagnose voriconazole-induced periostitis early, because discontinuation is effective at reversing the disease. If discontinuation of voriconazole is not possible, a trial dose reduction may be reasonable as 50% of the patients reported improvement of pain.

Supplementary Data

Supplementary materials are available at Clinical Infectious Diseases online (http://cid.oxfordjournals.org). Supplementary materials consist of data provided by the author that are published to benefit the reader. The posted materials are not copyedited. The contents of all supplementary data are the sole responsibility of the authors. Questions or messages regarding errors should be addressed to the author.

Notes

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Potential conflicts of interest. A. N. M. has been part of the speaker’s bureau for Cubist Pharmaceuticals and is a shareholder of Pfizer Pharmaceuticals. V. M. has been a consultant for Gilead and Merck and has received payment for lectures from Cubist Pharmaceuticals. E. L. S. has received personal fees through Biomet Biologics. All other authors report no potential conflicts.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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