Urban Trench Fever and Cat Scratch Disease

Str—I read with interest the article on urban trench fever by Safdar [1]. The article did not comment on cat contact, nor did it appear that PCR for Bartonella henselae (or Bartonella quintana) was performed on either blood or lymph node specimens. Since there is a great deal of cross-reactivity between these organisms, it would be prudent to perform PCR before diagnosing a case of trench fever on the basis of serological test results, particularly since cat scratch disease is far more common and could account for the patient’s symptoms.

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References

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Uncertain Generalizability of Switch Studies

Str—Drechsler and Powderly [1] review well the available studies on switching effective antiretroviral therapy. However, they do not note a flaw inherent in switch studies. Because entrance criteria for these studies produce study populations skewed in unclear ways, switch studies have uncertain generalizability to the entire population of persons who are HIV positive. This problem is not mitigated by randomizing subjects to continue the former therapy or to switch to the alternative therapy, nor is it mitigated by reproducibility.

When the regimen switched from is producing favorable results, the new regimen is disadvantaged in that it is unlikely to produce better results than did the former one. For instance, in the BID Efficacy and Safety Trial (BEST)[2], subjects with undetectable levels of HIV who were tolerating an indinavir regimen with doses administered every 8 h (hereafter, indinavir t.i.d.) were randomized to continue receiving indinavir t.i.d. or to receive a ritonavir-boosted indinavir regimen administered twice per day (hereafter, IDV/r b.i.d.). A greater proportion of subjects receiving the new regimen developed nephrolithiasis than did subjects who continued to receive the previous regimen. But the universe of HIV-positive persons might contain a greater number of persons who develop this complication while receiving the indinavir t.i.d. regimen but not while receiving the IDV/r b.i.d. regimen than the number of persons who develop this complication while receiving the IDV/r b.i.d. regimen but not while receiving the indinavir t.i.d. regimen. The former group could not participate in the BEST trial. The BEST trial result indicates that the IDV/r b.i.d. regimen caused more cases of nephrolithiasis among persons who tolerate the IDV t.i.d. regimen. It does not establish that the IDV/r b.i.d. regimen causes more cases of nephrolithiasis than does the IDV t.i.d. in the universe of HIV-positive persons.

Similarly, when the regimen switched from producing unfavorable results, a switch study may misleadingly favor the new regimen. Switch studies of persons with lipodystrophy who are receiving stavudine, for instance, have tended to show that subjects switched to abacavir therapy have less progression, or even remission, of the lipodystrophy. But the universe of HIV-positive persons might contain more persons who develop lipodystrophy when receiving abacavir but not when receiving stavudine than persons who develop lipodystrophy when receiving stavudine but not when receiving abacavir. The former group could not enter these trials. These studies indicate that abacavir therapy causes less lipodystrophy in persons who develop lipodystrophy when receiving stavudine. They do not establish that abacavir therapy causes less lipodystrophy in the universe of HIV-positive persons.

Only prospective, randomized studies in more-general populations provide generalizable results.

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Voriconazole Inhibition of Tacrolimus Metabolism

Sir—Voriconazole (Pfizer) is a new triazole antifungal agent used in the management of invasive infections caused by molds such as Aspergillus species, Fusarium species and Scedosporium apiospermum. This agent is known to inhibit the cytochrome P450 (CYP) isoenzymes 3A4, 2C9, and 2C19, and is consequently associated with a number of drug interactions [1]. Preliminary observations have demonstrated that voriconazole significantly increases the trough concentrations of tacrolimus [2]. The manufacturer recommends reducing the daily tacrolimus dose by one-third when it is concurrently administered with voriconazole [3]. We describe a patient who required a 90% reduction in the manufacturer’s recommended maintenance dose of tacrolimus.

A 44-year-old, 62-kg woman with a history of hepatitis C, alcoholic liver disease, and liver transplantation (6 years earlier)
Figure 1. Daily trough tacrolimus blood concentrations in a patient also receiving voriconazole.

presented to the emergency department of the University Hospital (Albuquerque, NM) with multiple complaints. The patient had a 10-day history of severe headaches, nausea, and anorexia with a 6-kg weight loss over that period. She also reported a loss of balance, light-headedness, and generalized weakness. Her vital signs were within normal limits, and the only abnormality detected by a physical examination was the patient's inability to walk across the room unassisted. With the exception of a low serum sodium level (126 mg/dL), all laboratory values, including those for CSF, were within normal limits. No abnormalities were noted on a head CT scan (without contrast), but an MRI of the head revealed multiple white matter changes consistent with a diagnosis of leukoencephalopathy. A chest radiograph revealed a right lower lobe mass. The patient was admitted for an additional diagnostic workup.

The patient's medications prior to admission included mycophenolate mofetil, lansoprazole, tacrolimus, promethazine, spironolactone, prednisone, allopurinol, citalopram, and furosemide. The tacrolimus concentration was assessed and was found to be elevated (29.9 ng/mL). Tacrolimus therapy was withheld, producing a dramatic resolution in the patient's symptoms within 48 h. A second MRI of the patient's head no longer demonstrated the previously observed white matter changes. These findings were consistent with the diagnosis of tacrolimus-induced multifocal leukoencephalopathy [4].

A history of coccidioidomycosis (valley fever) 4 years earlier was elicited from the patient and was confirmed through medical records. Treatment with liposomal amphotericin B (AmBisome; Fujisawa Healthcare; 3.5 mg/kg) was initiated on day 10 of her hospitalization, on the assumption that the patient had had a relapse of coccidioidomycosis (indicated by fevers and abnormal chest radiograph findings), but was discontinued because of nephrotoxicity. A needle-guided biopsy of the lesion was performed on day 30 of hospitalization, and treatment with voriconazole (400 mg po b.i.d.) and trimethoprim/sulfamethoxazole (5 mg/kg iv b.i.d.) was initiated empirically.

Tacrolimus therapy was started again, but the daily dose (1.5 mg po q.d.) was reduced by one-third, as recommended by the manufacturer of voriconazole. Tacrolimus trough concentrations in blood were monitored daily (figure 1) and, ultimately, the patients regimen was required to be reduced to 0.15 mg po q.d. to maintain the tacrolimus blood concentrations within the therapeutic range (5–15 ng/mL). This change in the tacrolimus dosage was performed 10 days after the initiation of voriconazole therapy. The patient’s condition worsened and was thought to be a combination of adult respiratory distress syndrome, pulmonary edema, and hepatorenal syndrome. The patient’s family decided to withdraw care, and the patient died on day 46 of hospitalization.
Voriconazole has recently been reported to elevate trough tacrolimus blood concentrations by 10-fold [2]. Such elevated levels have the potential to induce serious adverse events in patients who are not carefully monitored. The present case documents the consequence of elevated tacrolimus concentrations in a patient who developed multifocal leuкоencephalopathy. Daily monitoring of tacrolimus trough blood concentrations was performed to adjust the tacrolimus dosage and prevent a potential repetition of this adverse event. The current recommendation to reduce the daily tacrolimus dose by one-third may not maintain tacrolimus concentrations within the therapeutic range. In addition, the duration of inhibition of tacrolimus metabolism after voriconazole therapy is discontinued is not known. Careful monitoring of tacrolimus concentrations is crucial when voriconazole is coadministered with tacrolimus, especially for outpatients.

References


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Lack of Cross-Hepatotoxicity between Fluconazole and Voriconazole

Sir—A recent letter to the editor from Potski and Brown [1] addressed the issue of voriconazole hepatotoxicity. These authors nicely summarized the available data regarding the incidence of abnormal liver function test (LFT) results during voriconazole treatment. They also cited data suggesting the incidence of hepatotoxicity during voriconazole treatment is greater than that seen during fluconazole treatment for esophageal candidiasis. However, to our knowledge, no data are currently available addressing the issue of fluconazole and voriconazole cross-hepatotoxicity (Helen Boucher, personal communication). In this regard, we recently cared for a patient with coccidioidal meningitis who...