Reviewer's report

Title: Evaluation of Intravenous Voriconazole in Patients with Compromised Renal Function

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Reviewer: Nikolaos Sipsas

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Due to relatively poor aqueous solubility of voriconazole, the parenteral formulation incorporates sulfobutylether-b-cyclodextrin sodium salt (SBECID), as an excipient for solubilization of voriconazole. Some cyclodextrins have been associated with drug-associated nephrotoxicity. Therefore, the package insert of voriconazole restricts the use of intravenous voriconazole (containing SBECID) in patients with estimated creatinine clearances less than 50 mL/min. SBECID accumulates in systemic circulation of patients with kidney impairment, but there is no evidence that it causes further renal dysfunction.

In this retrospective, observational study, funded by Pfizer, Lilly and coworkers analyzed data from a database of patients hospitalized in a single academic center, including adults with compromised renal function (baseline estimated Clcr < 50 mL/min), with fungal infections that were treated with an intravenous antifungal agent. Fifty-five patients received caspofungin, 54 patients received fluconazole, and 19 patients received voriconazole.

The main findings of the study were:

• non-SBECID containing agents caused significantly greater increases from baseline Scr levels than the SBECID containing agent.
• There were no significant differences among the groups in the incidence of renal dysfunction at the end of antifungal treatment.
• The differences in 28-day mortality among the three treatment groups were not statistically significant.
• Regression analysis showed that the only factor associated with deterioration of renal function was the infecting organism (probably candida vs. molds? Or specific candida species considered as causing more severe disease, such as C. glabrata or C. kruzei?)

The authors conclude that treatment of fungal infections in patients with compromised renal function with an SBECID-containing antifungal agent was not associated with acute renal toxicity and decisions on the appropriate AF Tx should not take into consideration the incorporation of SBECID in the IV formulation.

Major points to be addressed

The conclusions of the authors are not fully supported by the presented data. This is a retrospective, single center, observational study carrying all the
limitations of such studies, as the authors acknowledge. The numbers of
patients, especially those treated with voriconazole, are too low to jump to
collusions and make strong statements. Moreover, it seems that there is a
selection bias: Patients were excluded from analyses if they had “unstable renal
function” at baseline, assessed as a 50% difference in Scr or estimated Clcr on
two measurements within 4 days of starting IV antifungal therapy. How the
authors know that the difference in Scr values is due to “unstable” renal function
and not to the nephrotoxicity of the antifungal agent? How many patients were
excluded using this criterion? On the other hand, patients eligible for analysis had
been dosed for a minimum of 4 days of IV antifungal therapy and had serum
creatinine (Scr) levels while on therapy and at the end of IV antifungal therapy.
That means at least in some of these patients, differences of Scr levels on day 4
of AF Tx were attributed to the drug and not to “unstable” renal function. On what
basis?

On table 1, underlying fungal disease has been diagnosed in only 9 (47%) of 19
pts on voriconazole. Probably the rest 10 patients received vorinz empirically for
probable or possible IFI. On the contrary, a specific IFI has been diagnosed in 46
(83%) of 55 pts on caspofungin and 42 (77%) of 54 pts on fluconazole. These
data contradict with the statement that a specific fungus is the major factor
associated with renal deterioration. Interestingly, 3 patients with aspergillosis
received fluconazole, which is not active against molds.

Moreover, patients receiving voriconazole had significantly better Scr and BUN
values at baseline. Maybe the caring physicians preferred to give voriconazole
only to patients with better Scr – BUN. It would be more meaningful to examine
two subsets of patients: with moderate (creatinine clearance 30-50 mL/min) or
severe (CrCl <30 mL/min) renal insufficiency.

Regarding the concomitant nephrotoxic agents, there was one or more per
patient? If some patients received more than one nephrotoxic agents they were
in greater risk for deterioration of renal function.

One major drawback is that the underlying disease of the study patients is not
mentioned. Patients in the ICU, with candidemia/sepsis, malignancy under
chemotherapy are at greater risk for acute kidney injury.

All study patients had compromised renal function at baseline. What was the
cause? Chronic renal failure due to diabetes or hypertension? Acute injury due to
previous treatment? This clinical information is important to assess the effect of
antifungals on further deterioration of renal function.

The only factor associated with AKI was the infecting organism. What was the
organism associated with the greatest risk for AKI? It is not clear what the
authors imply: candida vs. molds? Or specific candida species, such as C.
glabrata or C. kruzei, causing more severe disease?

Although differences in 28-day mortality among the three treatment groups were
not statistically significant, patients receiving voriconazole had higher mortality
(42% vs. 26 vs. 29%). This reflects the differences in the severity of underlying
diseases between the 3 study groups, making the results less interpretable.
Authors should comment on it.
Level of interest: An article of limited interest

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests