Reviewer’s report

Title: Cotrimoxazole plasma levels, dialyzer clearance and total removal by extended dialysis in a patient with acute kidney injury - Risk of under-dosing using current dosing recommendations

Version: 2 Date: 28 January 2013

Reviewer: Alice Ceacareanu

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Major Compulsory Revisions:

1. Given the multiple doses received by this patient, authors should define Cmax more clearly. The Cmax to which they refer has a range as it is an average of values. This raises the question of what are the actual values averaged. The authors state that these values were over 3-days, but were those the first 3 days or at steady state? If the values that were averaged were all from steady state, then this should be stated to avoid confusion as to whether peak concentrations achieved as steady state was approached were included or not. If peak concentrations that come from before steady state was achieved were included in this average, then the Cmax value reported becomes a confounded metric. I suggest stating that the values were from “three consecutive days at steady state with a dose of…”. If, however, sampling was not done at steady state the authors should consider a model based approach for multiple dosing to estimate a steady state Cmax or state this as a limitation.

2. Based on Figure 1, the extended dialysis session each day lasted longer than 6 hours. However, the authors state that dialysis lasted 442 + 101 min. It is my understanding that the concentration “at the end of dialysis”, therefore, has little significance, in which case the trough concentration is likely to be a more useful metric. This is due to the stated large day-to-day variation in dialysis time meaning that the concentration “at the end of dialysis” is potentially from anytime from before a second Cotrimoxazole infusion or from anytime between the start of a second infusion or up to approximately 3 hours thereafter. Another metric that might be of interest is the peak concentrations achieved from the infusions that occurred during dialysis compared to the peak concentrations achieved between dialysis.

3. On page 9 the authors state “In a work from Paap clearances varied from 1.13-103.6 ml/min for TMP…”. Reference number 7 is quoted, however a work by Kliestein et al. is listed instead under references. Furthermore, I was unable to find Paap in any of the references.

Minor Essential Revisions:

1. All units should be uniform in letter case (e.g. some concentrations are reported as mg/l while others are mg/L).

2. In describing the findings by Curkovic et al. the authors list the clearances they
found as “21.5 to 28.9 ml/min” and then state the normal range as “20-80 ml/min”, so again consistency in format should be addressed (i.e. either state “21.5-28.9” or “20 to 80”).

3. On line 17-18 of page 3 in the background the word “is” is repeated.

4. Last line on page 5 the word “represents” is misspelled as “represntes”.

5. The TMP and SMX labels in Figure 2 B appear to be switched, I also did not find a description of this graph in the legend.

Discretionary Revisions:

1. In the opening paragraph, the start of the 3rd sentence states “Modern means of renal replacement therapy are…”. Suggest “Modern high-flux dialysis is…” instead.

2. In the background section, the 5th line, the authors state “It (Cotrimoxazole) is approved for treatment of… PCP prophylaxis and treatment as well as for …”. It is unclear whether they mean prophylaxis and treatment of all listed conditions or just PCP, or all including PCP and those listed after PCP. I realize that local guidelines may be slightly different from a country to another.

3. A number of abbreviations (e.g. CVVH, KDIGO, cANCA, etc.) are not initially defined. Though they may be common and understood in medicine or hemodialysis, Pharmacology & Toxicology journal may reach a broader audience, thus being defined in text would be of benefit.

4. In the discussion the authors state that Cotrimoxazole “belongs to…”, perhaps consider, “is one of the…”. The end of the sentence is “especially given the fact that it is used for half a century”. I suggest using “this is especially surprising given the fact that…”.

5. In describing the Craig and Kunin study the authors state “Craig and Kunin studied four hemodialysis patients, they did however not …”. If I understood this correctly, I suggest stating “Craig and Kunin studied four hemodialysis patients, however, they did not…” or , they did not however…”. The following sentence states “Current dosing recommendation in chronic hemodialysis patients is therefore solely based on…”. Recommendation is singular and must, therefore, either be prefaced as “The current dosing recommendation…is therefore solely based on…” or there are more than one recommendations and it should be “Current dosing recommendations…are therefore solely based on”.

6. The authors’ description of work by Curkovic et al. could be stated as “Recently, Curkovic et al. reported two patients undergoing CVVHD showed clearances of TMP (21.5-28.9 ml/min) that were within the range observed in patients with normal renal function (20-80 ml/min).”

**Level of interest:** An article whose findings are important to those with closely related research interests

**Quality of written English:** Needs some language corrections before being published
**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.