The Urgent Need for Clear and Accurate Information on the Polymyxins

To The Editor—We read with interest the recent invited article on polymyxins (colistin and polymyxin B) by Kassamali et al [1] and agree that wisdom does not always come with age. As discussed at the recent international conference on polymyxins in Prato, Italy [2], there is much to be done to improve the official pharmacopoeial monographs for the polymyxins, an important goal supported by Kassamali et al [1]. However, as also stated at the conference [2], it is essential that clinicians be provided with accurate and unambiguous information to promote the optimal use of these important last-line antibiotics. Unfortunately, the article by Kassamali et al [1] adds to existing confusion and provides incorrect information in several very important areas. We shall comment on our most serious concerns.

In both the text and Table 2, Kassamali et al [1] have provided very confusing information relating to the different labeling conventions for the parenteral products of colistin methanesulphonate (CMS; the inactive prodrug of colistin [3]) used in various parts of the world and the corresponding daily dose ranges. The 2 conventions for CMS products used in different global regions are (1) number of international units (IU) and (2) milligrams of colistin base activity (CBA); 1 mg of CBA is equivalent to approximately 2.7 mg of the chemical CMS [4]. Both the IU and CBA conventions rely on in vitro microbiological standardization assays. It is extremely unhelpful, as in Table 2 of the invited article [1], to report dosages of CBA-labeled products not only in terms of milligrams of CBA per kilogram per day (ie, the preferred approach because the vials and doses are expressed as milligrams of CBA) but also as units of CBA per kilogram per day and milligrams of CMS per kilogram per day.

The introduction of “units of CBA” clouds an already extremely confusing situation for clinicians. Indeed, even the current multiple ways of expressing dose have caused substantial confusion among clinicians and led to the issuing of an alert for “risk of serious or fatal medication error” arising from the CMS-to-CBA conversion factor of 2.7, mentioned above [5]. Doses for the CBA-labeled and IU-labeled products should be prescribed in terms of the respective labeling conventions, and authors and journals should cease reporting doses in milligrams of CMS [2] and should certainly not adopt “units of CBA.”

It has been reported elsewhere that the approved upper-limit daily dose of CMS is substantially lower for IU-labeled than for CBA-labeled products [4]. Kassamali et al suggested “potency differences between the two products” [1]. However, it was revealed at the polymyxin conference in Prato [2] that essentially all generic products of CMS now available around the world, whether labeled in international units or CBA, are from a single manufacturer. Because the clinical and scientific literature contains studies from various parts of the world, it is important that clinicians understand the relationship between the number of international units and the number of milligrams of CBA [4]. The approved upper-limit dosage for an adult patient with good renal function for most IU-labeled products is 6 million IU/d (equivalent to approximately 180 mg of CBA per day), and the corresponding upper-limit dosage for the CBA-labeled products is 300 mg of CBA per day (equivalent to approximately 10 million IU/d). It should be noted that it is now common for clinicians in Europe, where the IU-labeled product is available, to prescribe for adult patients with good renal function daily doses (9–10 million IU/d, or approximately 270–300 mg of CBA per day) [6] approximating the upper-limit daily dose used in the United States for the CBA-labeled products.

It is important to note that Table 2 in the article by Kassamali et al [1] contains very serious errors in regard to the approved dosages of polymyxin B. The approved dosage of polymyxin B is stated correctly as 15 000–25 000 units/kg/d, but unfortunately this dosage is incorrectly noted in the same table to be equivalent to 5–25 mg/kg/d [1]. Because for polymyxin B there are approximately 10 000 units per milligram, the correct dosage range is 1.5–2.5 mg/kg/d. Both ends of the mg/kg/d range reported by Kassamali et al [1] are incorrect, with the upper-limit dosage 10-fold higher than the correct value.

We also disagree with Kassamali et al [1] on the impact of lower minimum inhibitory concentration (MIC) values measured in the presence of polysorbate 80 on the interpretation of a given plasma colistin concentration relative to the MIC. It is important to note that views on the likely adequacy of a given plasma colistin concentration in patients [7, 8] are based on preclinical pharmacokinetic-pharmacodynamic findings in animal infection models in which MICs were measured in the absence of polysorbate 80 [9, 10], the current practice in clinical microbiology.
laboratories worldwide. A difference in MIC between measurements conducted without or with polysorbate only serves to affect the numerical value of the area under the curve (AUC)/MIC index and would affect the AUC/MIC value for a given level of bacterial killing equally in both animals and humans. Therapeutic target values of the AUC/MIC ratio would change, but target attainment rates would not.

Finally, among other concerns, we note the incorrect molecular weight range given by Kassamali et al for the polymyxins and also note that the structure shown in their Figure 2 is that of colistin base, not its sulfate salt, as mentioned in the caption [1]. In conclusion, it is essential that clinicians are provided with clear and accurate information on these important old antibiotics.

Notes

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