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Defining the Dosage Units for Colistin Methanesulfonate: Urgent Need for International Harmonization

In a recent letter in *Antimicrobial Agents and Chemotherapy*, Falagas and Kasiakou (2) made reference to the difference in the contents of and recommended dosage regimens for different parenteral colistin methanesulfonate (CMS, also known as colistimethate) products available in various parts of the world. This significant problem was first revealed in an invited symposium presentation (R.L. Nation, Abstr. 45th Intersci. Conf. Antimicrob. Agents Chemother., abstr. 1341, 2005) at the 45th Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC) (Washington, D.C., 16 to 19 December 2005) and was discussed further in our review article (6).

Several aspects in the recent letter (2) require comment and clarification. First, great care is needed to avoid confusion between colistin and CMS, the latter being a derivative of the former rather than a different salt of colistin; it is essential not to use the terms interchangeably (for details of the difference between colistin and CMS, refer to recent reviews [5, 6]). It has been demonstrated recently that CMS is a nonactive prodrug of colistin (1); following parenteral administration, CMS undergoes hydrolysis to generate colistin, which also circulates in the body (5). Second, it is incorrectly suggested in the letter (2) that the parenteral product of Parkedale in the United States (7) contains 150 mg "colistin base" in each vial. In fact, each vial contains approximately 400 mg of sodium CMS (equivalent to approximately 5 million international units [IU]) but, unfortunately, is labeled using confusing terminology as containing 150 mg "colistin base activity" (based on microbiological standardization). The European product also contains CMS and is labeled in IU (500,000 IU, 1 million IU, or 2 million IU per vial) (3); since there is approximately 12,500 IU per mg of CMS, there is 40, 80, or 160 mg of CMS (sodium salt) per vial, depending on vial size. Thus, whether the parenteral product of CMS is from Europe (3) or the United States (7), there is no directly available "colistin base" in the vials, in contrast to what was suggested in the letter (2). Third, the chemical structure of CMS indicated in the letter (2) is not correct; the methanesulfonate moiety should be linked through a secondary amine.

As also discussed in the aforementioned symposium presentation at the 45th ICAAC, there is a substantial difference in the recommended doses of the European and U.S. products. The recommended upper limit dosage for a 60-kg patient with normal renal function is 480 mg of CMS per day for the European product and approximately 800 mg of CMS per day for the U.S. product. We have called for international harmonization with respect to CMS parenteral products. First, the dichotomy in the labeling conventions for different products is illogical and extremely confusing. In particular, the use of the term "colistin base activity" as a way of expressing the content of vials and the dosage ranges has the potential to cause significant confusion, as is evident in the recent letter (2). In regard to the suggestion to use IU (2), it should be noted that there is not any direct relationship between IU determined for this prodrug in vitro and the pharmacodynamics of the colistin formed in vivo. There are compelling reasons to consider the number of milligrams of CMS per vial as the appropriate unit of measurement to use. Second, it is time that the dosage regimens in the product information for the different brands (3, 7) are the subject of further investigation and, hopefully, harmonization, especially in view of the different dosage ranges discussed above. Clear and rational approaches to the clinical use of CMS are mandatory if we are to retain its usefulness in an era where there are virtually no novel antibiotics active against gram-negative bacteria in the drug development pipeline (4, 8).

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Author's Reply

The authors of the submitted letter basically elaborate further on the need to specify whether dosing recommendations for a formulation of colistin refer to colistin base or colistimethate sodium. I believe that these points are sufficiently made in the letter published in *Antimicrobial Agents and Chemotherapy* to which the letter above refers. Also, it

should be noted that the authors of the reviewed letter have made important contributions in the literature on several pharmacokinetic/pharmacodynamic aspects of polymyxins in which the main points included in the submitted letter regarding the appropriate dosing of colistin have already been made.

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