Consistent Global Approach on Reporting of Colistin Doses to Promote Safe and Effective Use

TO THE EDITOR—Colistin, an “old” polymyxin antibiotic, is being used increasingly as a last-line therapy against infections caused by gram-negative bacteria that are resistant to other available antibiotics. Unfortunately, a multiplicity of ways of expressing doses is confounding the clinical use of colistin around the world. This is impacting the ability of clinicians to use the drug optimally to maximize the antibacterial effect, and it is compromising patient safety. At the First International Conference on Polymyxins, held in Prato, Italy, from 2 to 4 May 2013, this was one
of the important issues raised and agreed upon by attendees in the last session of the conference (the Prato Polymyxin Consensus) as requiring urgent attention. The First International Conference on Polymyxins was an opinion-leader conference with invited speakers who are international leaders in research and clinical use of polymyxins. The final session of the conference, the Prato Polymyxin Consensus, was for consideration of recommendations regarding key aspects impacting the future clinical use of polymyxins and high-priority areas for research. The conference was attended by participants from 27 countries. The list of invited speakers and other details may be found at: www.pharm.monash.edu/events/polymyxins.

In large measure, the problem relating to colistin doses arises because of confusing terminology used in articles published in journals. Colistin is administered parenterally as its inactive prodrug, colistin methanesulfonate (CMS); the prodrug is also known as colistimethate. Two primary conventions are used in different global regions to describe the contents of parenteral vials and corresponding doses for CMS products. Both conventions rely on in vitro microbiological standardization assays. The conventions are as follows:

1. Number of international units (IU). This convention is used in Europe, the United Kingdom, India, and a relatively small number of other global regions. Summary of product characteristics/product information documents for some of the many (generic) brands available in these areas have introduced mention of vial contents and/or dose in terms of the number of milligrams of the chemical CMS, in addition to number of IU.
2. Number of milligrams of colistin base activity (CBA). This convention is used in the remaining global regions where parenteral colistin is available, including North and South America, Southeast Asia, and Australia.

One million IU is equivalent to approximately 30 mg of CBA. This corresponds to approximately 80 mg of the chemical CMS. Thus, a given number of milligrams of CBA corresponds to approximately 2.7 times (ie, 80 ÷ 30) that number of milligrams of CMS. Clearly, the existence of 2 ways of describing a colistin dose in milligrams (ie, milligrams of CBA and milligrams of the chemical CMS) creates significant potential for errors, thereby jeopardizing patient safety.

The problem that is occurring increasingly in journal articles is best exemplified by the provision of a nonspecific example. In the Methods section of a paper, the authors describing a study conducted in Europe report use of a daily dose of 10 million IU in patients with normal kidney function, and subsequently in the Results and/or Discussion describe the daily dose as being 800 mg of CMS. Upon reading this article, a clinician from a region of the world where vials and doses are expressed using the alternative convention (ie, milligrams of CBA) decides to prescribe what he/she believes is the same daily dose. The doctor prescribes 800 mg of CBA (equivalent to approximately 2130 mg of CMS), which is approximately 2.7 times higher than the daily dose used in the European study mentioned above, and approximately 2.7 times higher than the daily dose upper limit (300 mg CBA) for products labeled in terms of CBA.

This is just one of many possible scenarios. It should be stressed that the problem does not only relate to papers arising from the regions where IU is the primary labeling convention. The scenario above is an example of factors leading to a medication error that can have a tragic outcome; this scenario has already occurred in a patient who received higher than intended doses, developed acute renal failure, and later died [1]. Even without such a tragic outcome, substantial confusion exists among clinicians around the world due to the existence of 3 different ways of expressing colistin doses; 2 of these 3 methods express dose in milligrams, but of different entities.

Given the reporting in journals of clinical studies from various global regions and the guidance those reports provide to clinicians around the world, we make the following recommendations in regard to publishing of papers on clinical use of colistin:

1. In the Methods section, authors should provide an equivalence between the 2 primary conventions (eg, 1 million IU is equivalent to approximately 30 mg CBA). For a clinical pharmacokinetic type of study, it would be appropriate and important to also provide an equivalence to the number of milligrams of the chemical CMS (eg, 1 million IU is equivalent to approximately 30 mg CBA and to approximately 80 mg CMS).
2. In the other sections (eg, Introduction, Results, Discussion) of any clinical article, authors and journals should cease reporting doses in terms of milligrams of CMS. Colistin doses should be expressed in terms of the primary convention used in the region of the world where the study was performed (ie, number of IU or milligrams of CBA).

We are confident that such an approach will decrease confusion and promote optimal and safe use of colistin as an important last-line antibiotic.

Note

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