Letters to the Editor

Development and validation of a reversed-phase high-performance liquid chromatography assay for polymyxin B in human plasma—authors’ response

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Sir,

We thank Tam et al.1 for their comments. This provides an opportunity to further clarify several important issues relating to the analysis of polymyxin B for pharmacokinetic and pharmacodynamic studies.

At the outset, we would make the general observation that polymyxin B is not alone in being a multi-component antibiotic. Indeed, a number of antibiotics comprise multiple components. For gentamicin, the analytical methods that have been used in the vast majority of studies to define the clinical pharmacokinetics and pharmacodynamics allowing optimization of dosing regimens, and also used for routine therapeutic drug monitoring, are assays that do not discriminate between the various components. Notwithstanding, it is important to consider the implications of the multi-component nature of an antibiotic when determining drug concentrations in biological fluids.

We do not believe that the pharmacokinetics of polymyxin B based on polymyxin B1 and B2 are misleading. It is clear that there are multiple components in polymyxin B, with polymyxin B1 and B2 as the two major components.1–4 Polymyxin B1 and B2 generally account for >85% of total polymyxin B.2,4 and the ratio of polymyxin B1 to B2 can vary from ~1.5 to 4 from batch to batch and product to product.2,5 Our recent unpublished data have demonstrated that colistin A (polymyxin E1) and B (polymyxin E2) have comparable MICs. Because there is only one amino acid difference between colistin and polymyxin B,6 it is very likely that polymyxin B1 and B2 have similar MICs (work in progress). Importantly, polymyxin B MICs in clinical laboratories are measured using a mixture, rather than polymyxin B1 alone. Therefore, if only polymyxin B1 concentration is measured without knowing the ratio of polymyxin B1 to B2 and the total proportion of these two major components in the product/batch administered, derived pharmacokinetic data based on quantification of polymyxin B1 alone7 can be very misleading in terms of pharmacokinetics/pharmacodynamics, particularly for a product/batch with a low ratio of polymyxin B1 to B2 (e.g. ratio of ~1.5). Thus, in chromatographic assays, we believe that it is a better and more accurate approach to use the summed peak area of polymyxin B1 and B2 for the quantification of polymyxin B in biological samples.

Tam et al.1 allude to the possible difference in pharmacokinetics between polymyxin B1 and B2 and suggest that it may be prudent to characterize them as separate entities (although in their recently reported clinical pharmacokinetic study, polymyxin B1 only was quantified following administration of polymyxin B1). In our clinical pharmacokinetic study,2 the ratios of chromatographic peak areas of polymyxin B1 to B2 in plasma were 3.97 ± 0.44 (unpublished results), and there was no apparent change over time during the dosing interval. Therefore, it is very likely that no major differences exist in key pharmacokinetic parameters between polymyxin B1 and B2, as suggested previously.7 The currently available data, therefore, would not support the comment by Tam et al.1 that a more rapid clearance of one component could have been compensated by a more gradual clearance of its counterpart. Further evaluation of the pharmacokinetics and pharmacodynamics of polymyxin B1 and B2 is currently being undertaken in our laboratory.

It should be noted that it is uncommon in pharmacokinetic studies that the product administered to patients is used as the analytical standard in the method for quantifying concentrations in biological fluids; indeed, it would be unwise to use this approach. There is no pure standard provided by the USP of each component of polymyxin B. In their clinical pharmacokinetic study in which polymyxin B1 was quantified in serum following administration of polymyxin B, Kwa et al.7 employed...
a polymyxin B1 analytical standard with >98% purity supplied by Professor Hoogmartens’ group. It appears that the purity of the polymyxin B1 standard was determined based on ultraviolet absorption and normalization,2 with the assumption that all polymyxin B components have similar molar absorptivity.

In summary, Dr Tam’s group7 has taken the approach of quantifying polymyxin B1 only in serum, while we1,3 have chosen to quantify based on the summed chromatographic peak areas of polymyxin B1 and B2. We believe that the second approach is more appropriate for pharmacoelastokinetic and pharmacodynamic studies to avoid substantial underestimation, which may occur if polymyxin B1 only is determined, especially for products/batches that have a relatively high proportion of polymyxin B2. Again, we wish to thank Dr Tam et al. for their letter and welcome the opportunity to discuss these important issues concerning the appropriateness of bioanalytical methods for the quantification of antibiotics that comprise multiple components.

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References

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Comment on: New guidance from NICE regarding antibiotic prophylaxis for infective endocarditis – response by the BSAC Working Party
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Sir,
The recent letter from the BSAC Working Party on Infective Endocarditis1 states that the BSAC has now abandoned its 2006 report recommendations,2 in favour of the nil prophylaxis strategy outlined in the National Institute of Clinical Excellence (NICE) guidelines for antibiotic prophylaxis for infective endocarditis.3 It is unfortunate that members of the BSAC had no opportunity to comment on this before this radical change. The NICE guidelines are largely based on a consensus opinion of the NICE guideline development group. This group acknowledged the difficulties of formulating guidelines as infective endocarditis is rare, the risk of dental procedures may be low and there is a lack of clinical trial evidence either to support or to refute the need for antibiotic prophylaxis.

The BSAC letter mentions up to 16 million cardiac patients potentially at risk with the old guidelines, but fails to state that far fewer patients in the UK might be given prophylaxis if only those with the highest risk cardiac lesions are included.

There is universal agreement that the main measure needed to prevent streptococcal endocarditis is the maintenance of good oral hygiene, but this does not preclude the opportunity to also offer scaled-back antibiotic prophylaxis to the highest risk cardiac patients. This was the approach in the original BSAC 2006 report and is still the approach in the current American Heart Association (AHA) guidelines.4 Every other European country and Australia,5 which rejected the NICE guidelines, have a scaled-back rather than a nil prophylaxis approach in their national guidelines.

The NICE guidelines suggest that there would be fewer deaths with a strategy of no prophylaxis, but this is based on inadequate estimates of the risk of fatal anaphylaxis after amoxicillin. There have never been any case reports of deaths from anaphylaxis following amoxicillin given for the prophylaxis of infective endocarditis, either in America or in the UK where such prophylaxis has been widely used for over 25 years. The AHA considered this question and concluded that amoxicillin is a safe drug provided it is not given to patients with suspected type 1 hypersensitivity reactions. A recent survey of fatal anaphylaxis in the UK6 noted that over 100 million treatment courses of oral amoxicillin were given in the UK during a 5 year period. Only one case of fatal anaphylaxis after oral amoxicillin (not associated with prophylaxis of infective endocarditis) had been observed during 35 years. It is probable that the risks of fatal amoxicillin anaphylaxis have been greatly exaggerated.

Surely, the NICE guidelines, based largely on opinion, should not be rigidly applied to all circumstances. If a cardiologist advises single-dose oral amoxicillin prophylaxis for an adult patient who previously had streptococcal endocarditis, followed by insertion of prosthetic valves, and who is about to undergo multiple dental extractions, there could be great problems for the patient if the dental practitioner refuses to cooperate because he/she is strictly following the NICE guidelines.

Perhaps, the BSAC should encourage the Department of Health to make infective endocarditis a notifiable disease as a matter of urgency in case the NICE guidelines become widely accepted. It would be preferable to have some data about the prevalence of streptococcal endocarditis before and after the