Difficulties in the assay of cefamandole highlight the importance of specific methodologies in pharmacokinetic studies

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Sir,

In developing and implementing assay methodology it is usual to make assumptions about the purity of standard materials used in the method, which, as we have recently found, may not necessarily be true. In conducting a pharmacokinetic study involving cefamandole we purchased cefamandole, as the sodium salt, from a well-known major chemical supplier. Having set up our liquid chromatographic method to assay this agent<sup>1</sup> we were therefore surprised to find that, other than in the samples taken immediately post-dose, there was no drug present in the patients. As the cefamandole was being co-administered with another agent, drug interactions appeared to be a possibility. In a series of stability studies we were able to establish that our standard material, although stable in water, had a half-life of only 36 min at room temperature in serum, irrespective of the presence of the second agent. As this was so different from stability data from our earlier studies<sup>1,2</sup> and other published data<sup>3</sup> where a serum half-life at room temperature in excess of 6 h was found, we were left with the inescapable conclusion that our standard material was not the sodium salt of cefamandole. We were able to demonstrate that the standard material was chromatographically indistinguishable and exhibited an identical breakdown profile to cefamandole nafate. Interestingly, when we brought our concerns to the attention of the original supplier, they responded by sending us another vial of the same material.

In bringing this problem to the attention of the readership we would like to highlight two particular issues. The first, and most obvious, relates to the degree of trust we place in suppliers of standard material. While the second, and more important one, relates to the assay methodologies that are currently employed in pharmacokinetic, and similar, studies. Owing to the specific nature of the methodology used, we quickly identified that there was a problem with the standard material. However, this was unlikely to have been the case had a non-specific method, such as microbiological assay, been used. On the assumption of stoichiometric conversion of cefamandole nafate to free cefamandole, use of a microbiological assay would have resulted, at best, in an overestimation of cefamandole levels of some 12%. This could have been substantially more, depending on the rate of breakdown of cefamandole nafate under the assay conditions used. We believe the unusual observations we report here further illustrate the importance of using a specific technique, such as liquid chromatography, when conducting pharmacokinetic, or similar, studies.

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References


