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Letter to the Editor

Linezolid is not suitable as internal standard

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Gordien et al. [1] describe the validation of a method of analysis for simultaneous determination of five systemic azoles in plasma by high-performance liquid chromatography with ultraviolet detection. Although this method is validated according to FDA guidelines we have to make two important remarks about the choice for linezolid as internal standard.

The authors describe that invasive fungal infections predominantly occur in patients with haematological malignancies, organ transplantation and HIV infection. Except for patients with HIV infection, the other two may be treated with linezolid [2,3]. Since in the laboratory the co-medication is not known, the choice for an internal standard is important. Using linezolid as an internal standard can result in the wrong interpretation of the analytical results. Because of the large observed inter- and intra-patient variability in serum concentrations of azole antifungal agents [4] the analytical flaw might stay unnoticed. Therefore it is mandatory to use an internal standard that is not used as co-medication in these patients.

Using linezolid could be advocated if specificity was assayed by adding linezolid to blank human plasma, but this evaluation was not performed.

Besides this, linezolid is neither a structure analogue of the azole agents nor isotope and should therefore not be used for correction of sample preparation and chromatography.

References

[1] J.B. Gordien, A. Pigneux, S. Vigouroux, R. Tabrizi, I. Accoceberry, J.-M. Bernadou, A. Rouault, M.-C. Saux, D. Breilh, Simultaneous determination of five systemic azoles in plasma by high-performance liquid chromatography with ultraviolet detection, J. Pharm. Biomed. Anal. 2009, doi:10.1016/j.jpba.2009.06.030.

[2] J. El Khoury, J.A. Fishman, Linezolid in the treatment of vancomycin-resistant *Enterococcus faecium* in solid organ transplant recipients: report of a multicenter compassionate-use trial, Transpl. Infect. Dis. 5 (2003) 121–125.

[3] B. Jaksic, G. Martinelli, J. Perez-Oteyza, C.S. Hartman, L.B. Leonard, K.J. Tack, Efficacy and safety of linezolid compared with vancomycin in a randomized, double-blind study of febrile neutropenic patients with cancer, Clin. Infect. Dis. 42 (2006) 597–607.

[4] W.W. Hope, E.M. Billaud, J. Lestner, D.W. Denning, Therapeutic drug monitoring for triazoles, Curr. Opin. Infect. Dis. 21 (2008) 580–586.

Response

Alffenaar and Greijdanus discuss the choice of linezolid as internal standard (IS) for determination of systemic azoles in patients with haematological malignancies or organ transplantations.

We have tested several internal standards, among them linezolid gave the best results in terms of stability and recovery with SPE extraction on Plexa cartridges. Our validation results are very good following FDA's guidance, showing that the chosen IS is suitable for this method; moreover, many validated and published HPLC methods use an IS with a different structure from analytes. For example Chhun et al. used diazepam for determination of posaconazole and voriconazole in plasma (S. Chhun, E. Rey, A. Tran, O. Lortholary, G. Pons, V. Jullien, Simultaneous quantification of voriconazole and posaconazole in human plasma by high-performance liquid chromatography with ultra-violet detection, J. Chromatogr. B. 852 (2007) 223–228).

Obviously we are aware of the fact that linezolid can be administered to patients in haematological units, and that this can be a limit to its use as IS. However, linezolid is not administered frequently in haematological units: in two years and more than 600 dosages, we did not find this case in our units; moreover in our laboratory we work directly with clinicians, and we receive samples always with information about co-medication.

Finally, for pharmacology laboratories who do not want to use linezolid, ketoconazole could be used as IS, as it is not usually used for prophylaxis or treatment of systemic fungal infections units, compared with the four other drugs.

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