Therapeutic drug monitoring

Pranger, Anna Diewerke

4C

Chapter

Rifampicin and moxifloxacin for tuberculous meningitis

O.W. Akkerman, A.D. Pranger, R. van Altena, T.S. van der Werf, and J.W.C. Alffenaar

Lancet Infectious Diseases. 2013 July;13(7):568-9

Letter to the editor

Ravina Ruslami and colleagues presented a study assessing pharmacokinetics, safety, and survival benefit of different treatment regimens containing high-dose rifampicin and moxifloxacin in patients with tuberculous meningitis in a hospital setting (1).

Their findings that a treatment regimen containing a higher dose of rifampicin and standard-dose or high-dose moxifloxacin during the first 2 weeks is safe in patients with tuberculous meningitis, and that high-dose intravenous rifampicin could be associated with a survival benefit in patients with severe disease are important to note.

We agree with the authors that, on the basis of the small number of patients per group, clinical results should be interpreted carefully. To compensate for small group sizes, one could consider a different strategy with drug exposure as a continuous variable. Additionally, isoniazid concentrations should also be measured since isoniazid contributes to rapid culture conversion and penetrates well in cerebrospinal fluid. Receiver operating characteristic analysis could show the extent to which cumulative drug exposures of rifampicin, moxifloxacin, and isoniazid relate to outcome. Resultant potentially crucial values for positive treatment outcome could be detected and related to the antagonistic effect on cell kill as observed after co-administration of rifampicin and moxifloxacin in *in vitro* and *in vivo* studies (2,3).

Another consideration is the potential benefit of a higher oral dosage to reach similar drug exposure as achieved with intravenous dosing. The proposed alternative strategy to analyse the data would also compensate for the difference in drug exposure due to intravenous administration compared with oral dosing, especially in the presence of predisposing factors for poor drug absorption like HIV co-infection.

We therefore would like to encourage the authors to do further analyses of their data to generate additional hypotheses.

References

1. Ruslami R., Ganiem A.R., Dian S. et al. 2013. Intensified regimen containing rifampicin and moxifloxacin for tuberculous meningitis: an open-label, randomised controlled phase 2 trial. Lancet Infect Dis. 13: 27-35.
2. Drusano G.L., Sgambati N., Eichas A., Brown D.L., Kulawy R., and Louie A.. 2010. The combination of rifampin plus moxifloxacin is synergistic for suppression of resistance but antagonistic for cell kill of *Mycobacterium tuberculosis* as determined in a hollow-fiber infection model. mBio. 1:e00139-10.
3. Balasubramanian V., Solapure S., Gaonkar S. et al. 2012. Effect of coadministration of moxifloxacin and rifampin on *Mycobacterium tuberculosis* in a murine aerosol infection model. Antimicrob Agents Chemother. 56: 3054-57.