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Care Needed in Interpreting Mouse-Model Study

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We read with much interest the paper by Thompson et al., describing the efficacy of several rifampin-based antibiotic regimes in a mouse model with a periprosthetic joint infection (PJI) caused by methicillin-resistant *Staphylococcus aureus*. The authors demonstrated that, for most antibiotics, monotherapy was not sufficient to eradicate the infection, but all rifampin-based regimes showed high efficacy in bacterial clearance. Moreover, the authors demonstrated excellent results with oral linezolid plus rifampin, and they propose this combination as a potential treatment option in patients.

There are several aspects we feel are important to address before extrapolating the observed findings to patients. First, rifampin causes a pronounced reduction in linezolid serum levels in humans. Gandelmann et al. demonstrated a decrease in serum linezolid levels of 30% in human volunteers [1], and subtherapeutic trough- and area under the curve (AUC) levels were observed in multiple patients treated with the linezolid-rifampin combination [2-4]. In addition, myelosuppression is less frequently reported when the two drugs are co-administered compared to linezolid monotherapy, supporting a significant interaction [5]. As linezolid is a time-dependent antibiotic and its efficacy depends on the 24-hour AUC-to-MIC [minimal inhibitory concentration] ratio, this observation is worrisome, especially when considering difficult-to-treat infections like infected prosthetic joints with formation of biofilm.

Although the clinical relevance of the interaction between linezolid and rifampin has not been clearly demonstrated, patients with a PJI who were treated with this combination showed moderate treatment

outcomes, with success rates varying between 50% and 85% [5-7]. These success rates appear to be the same or even higher when patients are treated with linezolid monotherapy [7-8]. As serum levels of linezolid show high inter-individual variability [9], this might explain why the linezolid-rifampin interaction may be detrimental in some patients, while in others the interaction is less relevant. These findings show the importance of therapeutic drug monitoring when linezolid is prescribed to patients.

Another concern of low serum levels of linezolid when co-administered with rifampin is the development of rifampin resistance. This induction of resistance has been recently demonstrated in patients with a PJI who were treated with fusidic acid plus rifampin [10]. Rifampin reduced the AUC of fusidic acid by 45% and subsequently, 3 out of 7 patients failed, and in 1 case a MRSA infection resistant to rifampin was isolated. As rifampin is one of the cornerstones in the treatment of a PJI caused by staphylococci, selection of resistant mutants to this drug greatly reduces the chance of curing the infection, particularly when the implant is not removed [11].

The mechanism of interaction between linezolid and rifampin is not yet fully elucidated, and it is not known whether the interaction also occurs in mice. The high cure rate observed in the Thompson et al. study compared to other regimes could be due to a different drug metabolism. Unfortunately, serum levels of linezolid were not measured in this study. Another explanation for the high cure rate in the mouse model may be the lack of follow-up, as the mice were sacrificed at the end of the antibiotic treatment. Indeed, studies have shown that more than 75% of failures occur due to a relapse of infection, and only a minority fail during antibiotic treatment [7,12]. Although no bacteria were isolated in the sonication fluid of the implant at the end of antibiotic treatment, cultures were incubated for a relatively short period, which may have underestimated the culture yield.

Based on the aforementioned concerns, we highly recommend close therapeutic drug monitoring of serum levels when linezolid is prescribed to patients, especially when combined with rifampin. With MIC levels of ± 2 mg/L for MRSA, trough levels between 4 to 8 mg/L should be maintained. Serum levels > 8 mg/L should be avoided due to a higher risk of toxicity and adverse events [4].

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