Equivalence Between Oral and Intravenous Antibiotics When Treating Serious Staphylococcal Infections?

Sir—I read with interest the article by Schrenzel et al. [1], which compared intravenous and oral antibiotic regimens for the treatment of severe staphylococcal infection. The aim of the study was to show “the equivalence of the treatments” [1, p. 1287]. Equivalence studies have been plagued by methodological deficiencies [2, 3], and this study is no exception.

First, such studies require that a predefined range of equivalence be established [4]. The range has to be wide enough to ensure a reasonable sample size but narrow enough to ensure practical significance. If the authors allow the outcomes in the oral and intravenous antibiotic treatment groups to differ by 30%, is it still meaningful to call the 2 treatment arms equivalent? The fact that, midway through the study, the differences between the 2 groups were noted to be much smaller does not mean that the original sample size could be decreased. On the contrary, the smaller the range, the larger the sample size needed to establish equivalence.

This leads us to the major deficiency of this study: it was underpowered to detect equivalence at clinically relevant ranges (i.e., 5%–20%), and because the investigators were unable to recruit 260 participants, the study was even underpowered to detect equivalence at clinically dubious ranges (i.e., 30%–40%). A P value >0.05 (i.e., not significant) for the 3 outcomes measured does not imply equivalence. This highlights 2 important points: first, the shortcomings of P values, and second, the importance of 95% CIs to demonstrate uncertainty. For example, the relative risk for the intention-to-treat population was 1.1, with a 95% CI of 0.7–1.6 (i.e., the range of effectiveness of the oral regimen varied from being 30% less effective to being 60% more effective than the intravenous regimen in treating staphylococcal infections) and a P value of .66. If we are to believe the P value, then we cannot reject the null hypothesis that a significant difference exists between the 2 treatment groups. Thus, we must deduce that there is a difference between intravenous and oral therapy. The 95% CIs, however, tell the real story. For all 3 outcomes (intention-to-treat, clinically evaluable, and microbiologically evaluable), the range of the 95% CIs far exceeds even the excessive pre-hoc range of equivalence of 30%. This article [1] shows how easily an underpowered study can be misinterpreted as showing equivalence. The results of this important study are, unfortunately, inconclusive. A reasonable clinician should not make a decision to use an oral regimen to treat a serious staphylococcal infection in one of his patients on the basis of this study. Although the authors should be commended for undertaking a most difficult trial, the conclusions presented in their article are misleading. The major benefit of this study is that it provides estimates that can be used to power a more definitive trial.

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References