Dosing Ethambutol in Obese Patients

Deshpande et al. conclude that ethambutol (EMB) doses of ≥50 mg/kg of body weight twice a week would be the optimal clinical dose for the treatment of *Mycobacterium avium* (2). This was based on pharmacokinetic-pharmacodynamic studies using a hollow-fiber system model of intracellular *M. avium*, mimicking ethambutol human-like pharmacokinetics. This adds important information on the relationship between ethambutol exposure, dose schedule, and *M. avium* response.

Indeed the authors are concerned about the ocular toxicity of EMB in higher doses but suggest that safety is less of a concern because intermittent dosing yields lower toxicity than does daily administration (4), as toxicity is driven by area under the concentration-time curve (AUC) and not by maximum concentration of drug in serum (*C*_ max) (2). Based on their modeling results, the authors suggest testing their proposed schedule in humans. Clinicians may therefore try this schedule to treat their patients with *M. avium* infections.

However, we are concerned about ocular toxicity in obese patients who may receive EMB in a dose of 50 mg/kg. Earlier we investigated ocular toxicity of EMB and noticed that dosing on the basis of total body weight instead of ideal body weight led to serious overdosing in obese patients (6). This stems from the lower volume of distribution per kg of body weight due to the water-fat partition coefficient of EMB. As the studies cited by the authors lack obese patients (1, 7), the statement that 50 mg/kg is safe cannot be generalized. As with other drugs, not only the volume of distribution but also the clearance of EMB is likely to be different in obese patients, and a weight-normalized maintenance dose, using a size descriptor that corrects for differences in body mass index (BMI), should be given to obese patients (5). As the pharmacokinetics of EMB in obese patients has not been addressed in prospective studies and, therefore, the best size descriptor has not been retrieved, we propose/suggest that chronic drug dosing in the obese subject should be based on lean body weight (3). Since body water is reduced (e.g., from 60% to 30%) in obese patients, it is suggested to use the Devine formula to which a dosing weight correction factor of 0.3 is added to base dosage of hydrophilic antibiotics (8). These weight-based dose corrections result in a significant total dose reduction. For example, the total dose for a male patient of 1.7 m and 90 kg based on 50 mg/kg would result in 3,155 mg using lean body weight, 3,300 mg for ideal body weight, 3,360 mg for adjusted ideal body weight, and 4,500 mg for total body weight. Taking into account the difference of about 30% in total doses, we suggest that the dose of 50 mg/kg should be based on ideal body weight and not on total body weight.

Considering that obesity is increasing worldwide, it is important to keep in mind that weight-based dosing in patients with an altered body composition results in higher plasma levels, which can lead to adverse events. A prospective study should evaluate actual pharmacokinetic parameters of EMB and make these empirical dose adjustments superfluous.

**REFERENCES**


Jan-Willem Alffenaar*
Department of Clinical and Hospital Pharmacy
University Medical Center Groningen
University of Groningen
P.O. Box 30.001
9700 RB Groningen, Netherlands

Tjip van der Werf
Departments of Internal Medicine and Pulmonary Diseases and Tuberculosis
University Medical Center Groningen
University of Groningen
Groningen, Netherlands

*Phone: 31 503614070
Fax: 31 503614087
E-mail: j.w.c.alffenaar@apoth.umcg.nl

Authors’ Reply

We thank Dr. Alffenaar and Dr. van der Werf for their interest in our paper. The authors are to be commended for keeping the focus on treatment of disseminated *Mycobacterium avium* infection, a focus unfortunately abandoned by many researchers. We also thank them for highlighting an important concept, which is that of complexity of dosing in obese patients. We agree with many of their suppositions but would also like to challenge one part of their assertions.

The authors’ main point in the foregoing letter is that obese patients may be at greater risk of toxicity from ethambutol. We concur, based on the theoretical grounds that they advance. Obesity profoundly alters pharmacokinetics of drugs, sometimes increasing the clearance of drugs as weight increases and sometimes increasing the volume of distribution as weight increases. This would reduce drug concentrations in obesity rather than increase them. However, while ethambutol is metabolized by alcohol dehydrogenase to an aldehyde, 80% of parent drug is excreted unchanged by the kidney, so that the effect of weight on ethambutol clearance either via oxidation or via alteration of renal function is likely to be minimal. On the other hand, their argument of a lower volume of distribution per kg of body weight due to water-fat partition coefficient is valid, so that higher concentrations could be achieved per mg/kg of ethambutol dose. Given that the pharmacokinetics of the drug are likely driven by distribution and redistribution of the drug (in addition to renal function), obesity could lead to a different concentration-time profile shape. This brings us to a central toxicodynamic question: what part of the ethambutol...
concentration-time curve (time above threshold or area under the concentration-time curve [AUC] or maximum concentration of drug in serum [C\text{max}]) correlates with the ocular toxicity? Indeed, the effect of dosing schedule on toxicity is well known, and intermittent dosing has been used to reduce the toxicity of drugs whose efficacy is concentration driven but for which toxicity is driven by time above threshold (4–7). Based on our analysis of earlier clinical studies by others (1, 2), we suspect that as long as high ethambutol doses are administered intermittently as opposed to a daily regimen, the high doses would likely be associated with less ocular toxicity. Obviously, this needs prospective evaluation.

Where we differ with them is on the solution. We are concerned about the proposed ethambutol dosing algorithm for obese patients using ideal body weight. Although their study demonstrated ethambutol-based ocular toxicity in 6 patients, only 2 of the 6 had a body mass index (BMI) of >20 kg/m, and all 6 received daily therapy regimens (3). We are concerned about generalizing from such a small data set. Since the pharmacokinetic parameter associated with ethambutol toxicity is still unknown, as are the population and compartmental pharmacokinetic parameters of ethambutol in obese patients, using their proposed formula to calculate ethambutol doses that would reduce toxicity is still premature. We first need to understand the extent to which the obesity contributes to pharmacokinetic variability of ethambutol and to what extent the obesity contributes to the ethambutol concentration exposure threshold associated with toxicity. With that knowledge more deliberate dose adjustments could then be made. Nevertheless, their concern about potential toxicity during dosing of obese patients is important to note and will be studied further.

REFERENCES