Making optimal use of available anti-tuberculosis drugs

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EDITORIAL

Making optimal use of available anti-tuberculosis drugs: first steps to investigate terizidone

ACCORDING TO the recently updated World Health Organization (WHO) treatment guidelines for rifampicin-resistant or multidrug-resistant tuberculosis (MDR-TB), an effective treatment regimen consists of at least five effective drugs. The combination consists of a fluoroquinolone (group A), an injectable (group B) and two drugs from group C, in combination with pyrazinamide.[1] Group C consists of ethionamide/prothionamide, cycloserine/terizidone, linezolid and clofazimine. Cycloserine is considered to be the last option in group C due to its limited bactericidal activity and poor tolerability.[2] Specifically, many patients experience some form of central nervous system disturbance, ranging from tiredness and lethargy to more serious behavioural changes or seizures. The incidence of these various adverse reactions may vary in different populations around the globe, but this has not been well studied. Despite this unfavourable profile, cycloserine is widely used.

Terizidone, a drug consisting of two coupled cycloserine molecules, has been introduced with the aim of increasing tolerability. Due to their introduction on the market more than four decades ago, the development of these drugs lacked modern pharmacokinetics and pharmacodynamic studies to guide the dose selection, and the relation between drug concentration and efficacy and toxicity is therefore poorly understood. As the pharmaceutical industry is not interested in spending resources on the optimisation of these old drugs, research is dependent on public funding.

The first step in the dose optimisation of a drug is often to study its pharmacokinetics in clinical practice. In this issue of the *Journal*, Court and his team studied the pharmacokinetics of 250–750 mg terizidone daily as part of standard treatment regimens for pulmonary MDR-TB in 35 patients in Cape Town, South Africa.[3] They collected blood samples over a period of 10 h and analysed the samples using mass spectrometry. An important finding was the long half-life of the drug, which enabled a once-daily dosing strategy. Unfortunately, the design of the sampling scheme and the small sample size did not allow an in-depth covariate analysis to find factors that determined the pharmacokinetics. Although this study did not provide final answers, it is an important first step in the dose optimisation of cycloserine/terizidone. This is comparable with another group C drug, linezolid, being evaluated in MDR-TB patients.[4] The current study will hopefully encourage investigators to initiate more operational research in the quest for the optimal dose of cycloserine/terizidone to find the balance between efficacy and toxicity. Considering the variability in cycloserine drug concentrations at the same dose, therapeutic drug monitoring may find its use in further tailoring the dose in patients who experience treatment response or side effects.[5,6]

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