Studies of Early Bactericidal Activity: New Insights into Isoniazid Pharmacokinetics

Stephen H. Gillespie
Department of Medical Microbiology, University College of London, United Kingdom

(See the article by Donald et al. on pages 1425–30)

Studies of early bactericidal activity (EBA) have an important place in the experimental investigation of tuberculosis treatment. Although there are several variations in the clinical protocols used, patients with newly diagnosed drug-susceptible tuberculosis are treated with a single drug or combination of drugs for 2–14 days, and the number of viable colony-forming units (CFUs) in sputum samples is measured serially. Although monotherapy is thought to possibly increase the risk of drug resistance emerging during a given trial, there are no examples of this having occurred in the course of an EBA study. The first such study was performed in Nairobi in the late 1970s and investigated all of the components and drug combinations available for use in antituberculosis therapy. It provided evidence of the relative activity of the different antituberculosis drugs and drug combinations available at that time [1, 2]. The data that emerged from this study [1] have been important in underpinning thinking about how different antituberculosis agents contribute to treatment. For example, Jindani’s original study [1] demonstrated that isoniazid had the most bactericidal activity of the antituberculosis drugs; this and other data were important in framing the “special populations” hypothesis of antituberculosis treatment [3].

From these beginnings, EBA studies have been used to investigate the in vivo activity of new agents—notably the fluoroquinolones—and their potential as antituberculosis agents [4–6]. On the other hand, some drugs or formulations have been shown to have little bactericidal activity in studies using this technique [7, 8]. The ability of EBA studies to show significant differences between patients treated with different drugs with use of relatively small study sizes has been enhanced by methods that record the decrease in CFU count in sputum samples for ≥5 days and use nonlinear regression analysis [9, 10]. EBA studies now form an essential part of the development process for new antituberculosis drug development [11]. However, care must be taken in the design of a trial, because the use of another drug in combination with isoniazid may not significantly increase the bactericidal activity. This was demonstrated in a study of patients who received rifalazil in combination with isoniazid, which failed to show a significant difference in the bactericidal activity of this drug combination, compared with isoniazid alone [8].

As well as demonstrating whether a drug has bactericidal activity, EBA studies can be used to quantify the degree of such bactericidal activity. With use of a consistent protocol and calculation method, it has also proved possible to accurately compare the results obtained with a new drug with current and historical control results [6, 12], enabling the activity of the novel compound to be compared with that of existing agents. Some studies have demonstrated a dose-related response, as in the study reported here [13], by administering increasing doses. This experimental approach may prove to be useful in determining the dose for future clinical trials [10, 14, 15].

Isoniazid is metabolized mainly by hepatic N-acetyltransferase 2 (NAT2)– and cytochrome P450 2E1 (CYP2E1)–producing intermediates that are potentially hepatotoxic [16]. More than 80% of isoniazid is excreted in the urine as unchanged drug or its metabolites. Acetylator status in humans is an autosomal recessive trait, and patients who are phenotypically “slow” acetylators are homozygous for a NAT2 protein with reduced enzymic activity. Previous studies that have compared outcome at the end of full antituberculosis treatment have suggested that acetylator status is not associated with response if the isoniazid is given at least twice weekly. Fast acetylators given isoniazid only once weekly do have poorer outcomes of treatment than slow acetylators [17]. More importantly, recent evidence suggests that

Received 16 July 2004; accepted 21 July 2004; electronically published 25 October 2004.
Reprints or correspondence: Dr. Stephen H. Gillespie, Dept. of Medical Microbiology, University College of London, Royal Free Campus, Rowland Hill St., NW3 2PF London, United Kingdom (stepheng@rfc.ucl.ac.uk).
Clinical Infectious Diseases 2004;39:1431–2
© 2004 by the Infectious Diseases Society of America. All rights reserved.
1058-4838/2004/3910-0004$15.00
slow acetylators are more prone to severe hepatotoxicity than rapid acetylators, and this is an important reason for discontinuing isoniazid therapy [18]. The fact that acetylator status is not generally associated with a poor outcome in clinical trials is reassuring, but this may not translate into routine clinical practice in all cases, because clinical trials usually select patients carefully and monitor them closely. In contrast, clinicians are interested in individual patients whose clinical course may be complicated by toxicity or drug resistance. This study [13] is welcome, because it helps us understand how drugs work differently in each patient.

The treatment of tuberculosis is unusual in that all of the antituberculosis drugs are given only once per day, even though some of these drugs have a short half-life and are given more frequently when used for other indications. Several investigators have explored the influence of dosage intervals on the risk of emergence of drug resistance. For example, in a treatment trial that contained a study arm that received once-weekly rifapentine and isoniazid in the consolidation phase [19], 2 patients who experienced relapse with a Mycobacterium tuberculosis strain that was monoresistant to rifampicin had very low serum concentrations of isoniazid. Of interest, in this same study [19], acetylator status as determined by NAT2 genotype was associated with poorer outcome in the study arm that received once-weekly isoniazid/rifapentine, confirming the findings of previous studies.

The study presented in this issue of Clinical Infectious Diseases [13] is of considerable interest to those investigating ways to optimize antituberculosis therapy. It expands the ways in which EBA methodology can be used by demonstrating that it is capable of answering important pharmacokinetic questions. Although Donald et al. [13] only monitored their patients for 2 days, making the study less sensitive than one in which the patients are monitored for ≥5 days [10], they have been able to demonstrate significant differences between fast and slow acetylators in terms of the bactericidal effect of isoniazid. Isoniazid is central to the success of antituberculosis therapy and, as an agent that inhibits Mycobacterium tuberculosis cell wall metabolism, it is thought to be active mainly against bacteria that are rapidly dividing. All of the EBA studies demonstrate that isoniazid has more bactericidal activity than other first-line antituberculosis drugs and is responsible for bringing about a rapid decrease in the CFU count in sputum [1, 4]. This rapid reduction in bacterial load not only helps the patient to feel better, but by reducing the number of viable bacteria available for mutation, it also reduces the risk that drug resistance will emerge [20]. This study [13] suggests that acetylator status may be a more important factor in patient well-being, the risk of toxicity, and the emergence of drug resistance than was previously recognized. Clinicians should consider determining the acetylator status of patients more frequently, particularly in cases of poor response to therapy or toxicity.

Acknowledgments

Potential conflicts of interest. S.H.G. has received research funding from Bayer AG and has been employed as a consultant for Monsanto, Os- solving the problem of drug resistance. For example, in a treatment trial that contained a study arm that received once-weekly rifapentine and isoniazid in the consolidation phase [19], 2 patients who experienced relapse with a Mycobacterium tuberculosis strain that was monoresistant to rifampicin had very low serum concentrations of isoniazid. Of interest, in this same study [19], acetylator status as determined by NAT2 genotype was associated with poorer outcome in the study arm that received once-weekly isoniazid/rifapentine, confirming the findings of previous studies.

The study presented in this issue of Clinical Infectious Diseases [13] is of considerable interest to those investigating ways to optimize antituberculosis therapy. It expands the ways in which EBA methodology can be used by demonstrating that it is capable of answering important pharmacokinetic questions. Although Donald et al. [13] only monitored their patients for 2 days, making the study less sensitive than one in which the patients are monitored for ≥5 days [10], they have been able to demonstrate significant differences between fast and slow acetylators in terms of the bactericidal effect of isoniazid. Isoniazid is central to the success of antituberculosis therapy and, as an agent that inhibits Mycobacterium tuberculosis cell wall metabolism, it is thought to be active mainly against bacteria that are rapidly dividing. All of the EBA studies demonstrate that isoniazid has more bactericidal activity than other first-line antituberculosis drugs and is responsible for bringing about a rapid decrease in the CFU count in sputum [1, 4]. This rapid reduction in bacterial load not only helps the patient to feel better, but by reducing the number of viable bacteria available for mutation, it also reduces the risk that drug resistance will emerge [20]. This study [13] suggests that acetylator status may be a more important factor in patient well-being, the risk of toxicity, and the emergence of drug resistance than was previously recognized. Clinicians should consider determining the acetylator status of patients more frequently, particularly in cases of poor response to therapy or toxicity.

Acknowledgments

Potential conflicts of interest. S.H.G. has received research funding from Bayer AG and has been employed as a consultant for Monsanto, Os- cient, and Johnson & Johnson.

References