Stability of Antituberculosis Drugs Mixed in Food

To the Editor—Tablet or capsule administration is difficult in young children or patients with dysphagia, and most antituberculosis drugs are not available in liquid formulations. Pharmacies can prepare extemporaneous dosage forms, but stability data are limited for such preparations [1]. Therefore, we tested the stability of tuberculosis drugs in common foods that might be palatable for children.

Tablets (or capsules) of isoniazid, rifampin, rifapentine, pyrazinamide, ethambutol, ethionamide, and cycloserine were individually crushed (or opened), and their contents, mixed with several different types of foods to improve acceptability to selected patients. We tested oral antituberculosis drugs in a variety of mixtures that might be acceptable to children. These tuberculosis drugs proved to be stable for up to 4 h in sugar-free chocolate pudding and, in most cases, remained stable in the other mixtures tested. These data suggest that mixtures should be administered as soon as possible after preparation to avoid decay. We did not test the oral bioavailability of these mixtures in healthy volunteers. Our previous studies suggest that high-fat meals reduce the peak concentrations and, to a lesser extent, the area under the curve for isoniazid, rifampin, and cycloserine [2–4]. Because of their lower fat content, the vehicles studied here, with the exception of peanut butter, would not be expected to produce the same reductions in bioavailability. These data suggest that tuberculosis drugs may be mixed in sugar-free chocolate pudding or grape jelly and, if necessary, in peanut butter prior to administration.

Acknowledgments

Financial support. The Centers for Disease Control and Prevention Tuberculosis Trials Consortium.

Potential conflicts of interest. All authors: no conflicts.

Charles A. Peloquin,1 David Durbin,1 James Childs,1 Timothy R. Sterling,2 and Marc Weiner4
1 National Jewish Medical and Research Center and 2 University of Colorado Schools of Pharmacy and Medicine, Denver, Colorado; 3 Division of Infectious Diseases, Department of Medicine, Vanderbilt University School of Medicine, Nashville, Tennessee; and 4 Veteran’s Affairs Medical Center, San Antonio, Texas

References


Addition of Trimethoprim-Sulfamethoxazole to Ceftazidime during Parenteral Treatment of Melioidosis Is Not Associated with a Long-Term Outcome Benefit

To the Editor—In October 2005, we published an article in Clinical Infectious Diseases about the comparative efficacy of ceftazidime alone versus ceftazidime plus trimethoprim-sulfamethoxazole (TMP-SMX) for the treatment of severe melioidosis [1]. The primary end point of this meta-analysis of 2 independent prospective randomized trials in Ubon Ratchath-
Table 1. Oral antibiotic eradication treatment and outcome in 190 patients with culture-confirmed melioidosis who survived until hospital discharge, by study location and treatment group.

<table>
<thead>
<tr>
<th>Treatment and outcome</th>
<th>Khon Kaen (n = 87)</th>
<th>Ubon Ratchathani (n = 154)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftazidine (n = 46)</td>
<td>Ceftazidine plus TMP-SMX (n = 41)</td>
</tr>
<tr>
<td>Survived</td>
<td>39 (84.8)</td>
<td>33 (80.5)</td>
</tr>
<tr>
<td>Conventional 4-drug</td>
<td></td>
<td>18 (34.0)</td>
</tr>
<tr>
<td>Doxycycline plus TMP-SMX</td>
<td>38 (97.4)</td>
<td>32 (97.0)</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td></td>
<td>14 (26.4)</td>
</tr>
<tr>
<td>None</td>
<td>1 (2.6)</td>
<td>1 (3.0)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>32 (82.1)</td>
<td>26 (78.8)</td>
</tr>
<tr>
<td>Culture-confirmed recurrence</td>
<td>1 (3.1)</td>
<td>1 (3.9)</td>
</tr>
<tr>
<td>Clinical recurrence</td>
<td>3 (9.7)</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>All cause deaths</td>
<td>3 (9.4)</td>
<td>4 (15.4)</td>
</tr>
<tr>
<td>Overall late treatment failure</td>
<td>4 (12.5)</td>
<td>5 (19.2)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Combination oral treatment consisted of chloramphenicol, doxycycline, and TMP-SMX.

b Death and/or culture-confirmed recurrence.

ani and Khon Kaen, in northeast Thailand, was in-hospital mortality. There was no difference in death rate for all deaths (stratified $P = .70$; OR, 0.88; 95% CI, 0.48–1.6) or death occurring after 48 h (stratified $P = .73$; OR, 0.88; 95% CI, 0.41–1.9). However, this study did not address whether the 2 treatment groups differed in terms of recurrent infection, which occurs in 6% of patients within the first 12 months following primary melioidosis. It is plausible that the addition of TMP-SMX to the initial phase of parenteral therapy is associated with a higher rate of bacterial eradication. To investigate this possibility, we extended the parenteral treatment period for an additional 12 months after trial completion and compared the overall mortality rate and rate of recurrent melioidosis between the 2 groups.

One hundred ninety patients with culture-confirmed melioidosis survived until discharge from the hospital, 92 patients (48%) in the ceftazidime group and 98 patients (52%) in the ceftazidime plus TMP-SMX group. Patients were followed up every 1–3 months for at least 6 months and every 4–6 months thereafter. Patients who were lost to follow-up were contacted by mail or visited at home. The outcome measure was time to culture-confirmed recurrent melioidosis and/or death, as measured from hospital discharge. If patients were lost to follow-up, the record was censored at the last known contact.

The total duration of follow-up was 17,804 patient-weeks, with a median duration of follow-up of 71 weeks (interquartile range, 25–154 weeks). The proportion of patients who were lost to follow-up was similar in both groups (10 [11%] of 92 patients in the ceftazidime group and 8 [8%] of 98 in the ceftazidime plus TMP-SMX group; stratified $P = .75$). Table 1 indicates that choice of oral antimicrobial eradication therapy (a strong predictor of recurrence) was the same in both treatment arms. There was no difference between the 2 parenteral treatment groups with regard to mortality and the number of patients experiencing culture-confirmed melioidosis recurrences after discharge (15 [18.3%] of 82 patients in the ceftazidime group and 16 [17.8%] of 90 in the ceftazidime plus TMP-SMX group; stratified $P = .35$).

Figure 1. Kaplan-Meier survival plot illustrating time to death or culture-confirmed melioidosis during follow-up of 190 patients treated for acute melioidosis with ceftazidime alone or ceftazidime plus trimethoprim-sulfamethoxazole (TMP-SMX).
A Kaplan-Meier graph of disease-free and/or survival duration after hospital discharge showed no statistically significant difference between the groups (stratified \( P = .12 \), by Wilcoxon test) (figure 1). A second analysis, in which the starting point was the first day of parenteral therapy (and thereby included in-hospital deaths), also failed to show a difference between the 2 groups (stratified \( P = .34 \), by Wilcoxon test). The total case-fatality rates for the ceftazidime and ceftazidime plus TMP-SMX groups were 33.3% (36 of 108 patients) and 30.4% (35 of 115 patients), respectively (stratified \( P = .62 \)). These findings, combined with the in-hospital mortality results described previously, suggest that the addition of TMP-SMX to the acute treatment regimen for severe melioidosis has neither a short-term nor long-term benefit.

Acknowledgments

We thank the directors, medical staff, and nursing staff of the Department of Medicine at Sappasitpirasong (Ubon Ratchathani, Thailand) and Sirirajind Hospital (Khon Kaen University, Khon Kaen, Thailand); Drs. P. Mootsikapun, J. M. Short, A. J. H. Simpson, D. Linnmathurotsakul, A. C. Cheng, and P. N. Newton, who participated in patient enrollment; and V. Wuthiekanun, N. Getchalarat, and J. Suwannapruk, for laboratory and administrative support.

Financial support. Khon Kaen University and the Mahidol-Oxford Research Unit were supported by the Wellcome Trust of Great Britain. S.P. was supported by a Wellcome Trust Career Development Award in Clinical Tropical Medicine.

Potential conflicts of interest. All authors: no conflicts.

Wirongrong Chierakul,1,2 Siriluck Anumnatsiri,2 Wipada Chaowagul,4 Sharon J. Peacock,2,5 Ploenchan Chetchotisakd,2 and Nicholas P. Day2,5

1Department of Clinical Tropical Medicine and 2Mahidol-Oxford Research Unit, Faculty of Tropical Medicine, Mahidol University, Bangkok; 3Department of Medicine, Faculty of Medicine, Khon Kaen University, Khon Kaen, and 4Medical Department, Sappasitpirasong Hospital, Ubon Ratchathani, Thailand; and 5Centre for Clinical Vaccinology and Tropical Medicine, Nuffield Department of Clinical Medicine, University of Oxford, Churchill Hospital, Oxford, United Kingdom

References


Correspondence — In 2005, we reported the short-term outcome of treatment with metronidazole for Clostridium difficile colitis (CDAD) in 207 patients. Ninety days after completion of therapy, 103 patients (50%) appeared to be cured, therapy failed for 46 patients (22%), and 58 patients (28%) had recurrent disease [1]. Pepin et al. [2] simultaneously reported a nearly identical experience in Canada. Our ongoing clinical experience has suggested, however, that CDAD is a more chronic condition than we previously recognized, and that it tends to recur in persons who meet short-term definitions of apparent cure. Accordingly, we used the excellent patient follow-up and fully computerized medical records at the Michael E. DeBakey Veterans Affairs Medical Center (Houston, TX) to review the long-term outcomes for patients whom we reported as cured.

We initially regarded 103 patients as having been cured because they completed therapy, exhibited a good clinical response in <9 days, and remained free of recurrent symptoms for >90 days after the completion of therapy or until death if it occurred within that time [1]. Of these 103 patients, 79 (77%) experienced no further diarrheal disease (figure 1), but 42 (53%) of these 79 patients died (median time to death, 3 months and 10 days). Twenty patients (19%) had ≥1 documented late recurrence of CDAD, of whom 13 died (median time to death, 5 months and 23 days); 4 patients (3%) had recurrent diarrheal disease, with ≥3 negative results of C. difficile toxin assays; 2 of these patients died.

Had we used the newly proposed definitions for CDAD surveillance [3], which define a new case as recurrence of symptoms and a positive toxin assay result >8 weeks after the last positive fecal toxin assay result, 16 additional patients would have been considered to have had early apparent cures. Among these 119 patients, the rates of lasting cure, recurrent CDAD, and recurrent diarrheal disease would have been 66%, 30%, and 3%, respectively.

The overall burden of C. difficile colitis is, therefore, huge. Patients with CDAD are at risk of not only treatment failure and/or early recurrence [1, 2], but, as we show here, also long-term, debilitating, re-