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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 transferred to beakers containing 30 g of chocolate pudding (Hunt’s Snackpack, no sugar added), grape jelly (Safeway Concord), or peanut butter (Safeway Creamy) or to a beaker containing a 1:1 concentration of methanol and water as the control. In addition, isoniazid and rifapentine were tested in 7-Up soda and orange juice. Each drug-food mixture was blended thoroughly. Paired samples for each mixture were frozen at 0, 1, 2, and 4 h after preparation. Final dilutions were extracted and assayed according to standard operating procedures at the National Jewish Medical and Research Center (Denver, CO). For each drug, the median percent-recovery for each pair of samples at each time point was calculated, and the median and range of recovery for all pairs and time points were calculated. Drug stability over time was assessed by plotting median recovery versus time.

For all drugs and time points, there was 93% recovery from pudding, 89% recovery from jelly, and 80% recovery from peanut butter. Recoveries of <90% were seen for pyrazinamide mixed with jelly or peanut butter and for either rifampin or ethambutol mixed with peanut butter. Recovery was close to 100% for isoniazid and rifapentine mixed with orange juice or 7-Up soda, although isoniazid recovery was as low as 85% in the latter. Recovery over 4 h trended downward for isoniazid, pyrazinamide, and cycloserine mixed in grape jelly and for pyrazinamide and rifapentine mixed in peanut butter.

In clinical practice, tablets are crushed (or capsules are opened), and their contents are 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.

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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>No. (%) of patients</th>
<th>Khon Kaen (n=87)</th>
<th>Ubon Ratchathani (n=103)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ceftazidime</td>
<td>Ceftazidime plus TMP-SMX</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Survived</td>
<td>39 (84.8)</td>
<td>33 (80.5)</td>
<td>53 (73.6)</td>
<td>65 (79.3)</td>
</tr>
<tr>
<td>Conventional 4-drug(^a)</td>
<td>...</td>
<td>...</td>
<td>...</td>
<td>...</td>
</tr>
<tr>
<td>Doxycycline plus TMP-SMX</td>
<td>38 (97.4)</td>
<td>32 (97.0)</td>
<td>17 (32.1)</td>
<td>25 (38.5)</td>
</tr>
<tr>
<td>Co-amoxiclav</td>
<td>...</td>
<td>...</td>
<td>14 (26.4)</td>
<td>13 (20.0)</td>
</tr>
<tr>
<td>None</td>
<td>1 (2.6)</td>
<td>1 (3.0)</td>
<td>4 (7.6)</td>
<td>2 (3.1)</td>
</tr>
<tr>
<td>Follow-up</td>
<td>32 (82.1)</td>
<td>26 (78.8)</td>
<td>50 (94.3)</td>
<td>64 (98.5)</td>
</tr>
<tr>
<td>Culture-confirmed recurrence</td>
<td>1 (3.1)</td>
<td>1 (3.9)</td>
<td>6 (12.0)</td>
<td>7 (10.9)</td>
</tr>
<tr>
<td>Clinical recurrence</td>
<td>3 (9.7)</td>
<td>2 (8.0)</td>
<td>5 (10.6)</td>
<td>3 (5.1)</td>
</tr>
<tr>
<td>All cause deaths</td>
<td>3 (9.4)</td>
<td>4 (15.4)</td>
<td>7 (14.0)</td>
<td>6 (9.4)</td>
</tr>
<tr>
<td>Overall late treatment failure(^b)</td>
<td>4 (12.5)</td>
<td>5 (19.2)</td>
<td>11 (22.0)</td>
<td>11 (17.2)</td>
</tr>
</tbody>
</table>

\(^a\) 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 patient follow-up 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 \(P = .35\)).

![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).](https://academic.oup.com/cid/article-abstract/45/4/521/428248)

Figure 1.
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.

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The Long-Term Outcome of Treatment of Clostridium difficile Colitis

To the Editor—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-

Figure 1. Long-term outcomes for 103 patients who were initially regarded as having been cured of Clostridium difficile colitis on the basis of a good clinical response in <9 days and absence of recurrent diarrheal disease during 90 days or until death, if it occurred within that time. +, Positive; −, negative.