Comparison of Single-Dose Tetracycline Hydrochloride to Conventional Therapy of Urinary Tract Infections

JOEL ROSENSTOCK,† L. PATRICK SMITH, MICHAEL GURNEY, KEN LEE, WINKLER G. WEINBERG, JENICE N. LONGFIELD, WILLIAM B. TAUBER, AND WALTER W. KARNEY

Division of Infectious Diseases, Department of Internal Medicine, Naval Hospital, Uniformed Services University of the Health Sciences, Bethesda, Maryland 20814

Received 24 August 1984/Accepted 28 December 1984

Sixty-two women with signs and symptoms compatible with lower urinary tract infections were randomized to receive single-dose tetracycline (2 g), multi-dose tetracycline (500 mg four times per day for 10 days), or single-dose amoxicillin (3 g). Urine cultures were obtained upon entry into the study and on days 4, 14, and 28 after therapy. Single-dose tetracycline cured 12 of 16 (75%) of women with documented urinary tract infections, compared with 15 of 16 (94%) in the multi-dose tetracycline group and 7 of 13 (54%) receiving single-dose amoxicillin. Mild nausea in 3 of 20 patients (15%) was the only complication in the single-dose tetracycline group. Two grams of single-dose tetracycline is as effective as other reported regimens regardless of the susceptibility of the initial pathogen and has minimal toxicity.

Symptomatic lower urinary tract infections (UTI) in women are a common problem in the United States. It affects approximately 20% of women during child-bearing years and generates approximately 6 million office visits annually. In recent years, numerous studies have attempted to define an effective, easily administered, nontoxic, inexpensive therapeutic regimen, deliverable in a single oral dose (2, 5-7, 9, 14-16, 18, 19, 23). Although these studies tested a variety of single-dose agents, tetracycline (TCN) has certain properties that make it particularly attractive as a single-dose regimen. TCN is active against most common bacterial urinary pathogens (17) and is also one of the most effective antimicrobial agents available for treatment of Chlamydia trachomatis, the etiological agent in perhaps 20% of women with the acute urethral syndrome (22). TCN is inexpensive ($0.16 for 2 g at our pharmacy), has a low incidence of toxicity in nonpregnant adults, and is largely excreted through urine (12). TCN has been used successfully without significant toxicity in single-dose regimens for shigellosis (4, 13) and gonorrhea (3, 11). We previously evaluated the efficacy of a 2.5-g single-dose tetracycline (SDT) in uncomplicated UTI and reported that although it was efficacious, frequent gastrointestinal toxicity limited its use (unpublished data). In this study, we compared the efficacy and adverse side effects of a 2-g SDT in the therapy of UTI to single-dose amoxicillin (SDA) (3 g) and to 10 days of TCN (500 mg four times per day) in a single-blind, randomized clinical trial.

(This work was presented at the 23rd Interscience Conference on Antimicrobial Agents and Chemotherapy, Las Vegas, Nev., 24 to 26 October 1983.)

Patients were women (age, 14 years or older) with uncomplicated cystourethritis attending the Medical Acute Care Clinic, Naval Hospital, Bethesda, Md. Criteria for exclusion from the study were pregnancy, diabetes mellitus, use of antimicrobial agents in the preceding 2 weeks, clinical evidence of an upper UTI, history of three or more documented UTI in the preceding 2 years, or allergy to penicillin or TCN. Informed consent was obtained from all patients.

At the initial visit, the following specimens were obtained: a urethral swab, two cervical swabs, and a clean-catch midstream urine (MSU) sample. The MSU was examined chemically by dipstick (N-Multistix-C; Ames Co., Elkhart, Ind.) and cultured by standard microbiological techniques. Antimicrobial susceptibility testing was determined by the Kirby-Bauer disk method. Positive MSU cultures had colony counts greater than or equal to 1,000 organisms per ml of a single isolate (20). The MSU sediment was prepared in duplicate by centrifuging 10-ml portions for 10 min at 1,500 × g. One sediment was suspended in 0.5 ml of supernatant and split and used for microscopic urinalysis, Gram stain, and Chlamydia cultures. The other MSU sediment was used for the antibody-coated bacteria (ACB) test, using the microscopic slide method of Matuscak et al. (10). A positive ACB test showed more than five flocculating bacteria in 100 fields.

Wire-mounted calcium alginate swabs were inserted into the cervix and urethra and rotated for 10 s. These swabs and the MSU sediment were frozen at −70°C in 1 ml of standard 2-sucrose phosphate transport medium and thawed immediately before culture. Chlamydia isolates were cultured in untreated McCoy cells (MS Bioproducts, Walkersville, Md.) as outlined by Bird and Forester (1). Another cervical swab was placed in transport media and cultured on modified Thayer-Martin medium for Neisseria gonorrhoeae. Serum for Chlamydia antibodies by the indirect fluorescent technique (Electronucleonics, Silver Spring, Md.) was obtained on the day of entry into the study and at the end of 28 days. By using a table of random numbers, patients were given one of three regimens: 2 g of TCN followed by identical-appearing placebos four times per day for 10 days, eight TCN look-alike placebo capsules followed by 500 mg of TCN four times per day for 10 days, or 3 g of amoxicillin followed by amoxicillin look-alike placebos three times per day for 10 days. On return visits (days 4, 14, and 28), a detailed history was obtained, focusing on symptoms and their duration, compliance, and side effects of therapy. At each follow-up visit, an MSU was cultured.

Responses to therapy were classified as cure, failure,
TABLE 1. Quantitative culture results in 62 symptomatic women

<table>
<thead>
<tr>
<th>No. of bacteria per ml</th>
<th>Organism</th>
<th>No. (%) of women infected</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;10&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Escherichia coli</td>
<td>29 (47)</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis</td>
<td>4 (6)</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus saprophyticus</td>
<td>3 (5)</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Citrobacter amalonanatis</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Streptococcus agalactiae</td>
<td>1 (2)</td>
</tr>
<tr>
<td>10&lt;sup&gt;2&lt;/sup&gt;-10&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Escherichia coli</td>
<td>2 (3)</td>
</tr>
<tr>
<td></td>
<td>Proteus mirabilis</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Klebsiella pneumoniae</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus saprophyticus</td>
<td>1 (2)</td>
</tr>
<tr>
<td></td>
<td>Staphylococcus aureus</td>
<td>1 (2)</td>
</tr>
<tr>
<td>&lt;10&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Sterile</td>
<td>5 (8)</td>
</tr>
<tr>
<td></td>
<td>Mixed flora</td>
<td>10 (16)</td>
</tr>
<tr>
<td></td>
<td>Contaminants</td>
<td>2 (3)</td>
</tr>
</tbody>
</table>

relapse, or reinfecrion. Cure was defined as a disappearance of both symptoms and the infecting organisms on culture at all follow-up visits. Failure was defined as persistence of a positive MSU culture at the day 4 visit. A relapse was a transient disappearance of symptoms and the initial pathogen. Reinfecrion was defined as disappearance of symptoms and pathogens with subsequent return of symptoms associated with a new pathogen.

The chi-square statistic was used to compare proportions between the treatment groups for both efficacy and toxicity rates.

Sixty-two women were enrolled (age range, 15 to 82; mean, 44). There were no significant age differences in treatment groups. Complete follow-up was obtained on all patients.

Pyuria, defined as greater than 10 leukocytes per high-power field on examination of an MSU sediment, was present in 36 of 45 (80%) patients with positive cultures, compared with 10 of 17 (59%) patients with negative culture results (P not significant). Although the nitrate test (N-Multistix-C) was 100% specific, the sensitivity of the test was low (negative results in 84% of patients who had a positive culture).

The 45 patients (73%) with MSU-positive cultures were almost equally distributed by treatment group. A total of 10 cultures (16%) had mixed flora, 5 (8%) were sterile, and 2 (3%) had contaminants (diphteroids) (Table 1). All cervical cultures were negative for N. gonorrhoeae and Chlamydia species. No patient demonstrated a rising chlamydial antibody titer during the course of the study.

Table 2 summarizes the final outcome in the three treatment groups. No significant differences in cure rate by treatment, including the two single-dose regimens, were found. The cure rates for the SDT, multi-dose TCN, and SDA groups were 75, 94, and 54%, respectively. Adding patients who were cured of the initial pathogen but acquired a second pathogen during the month of follow-up, the cure rates were 88, 94, and 69%, respectively (P not significant).

In those patients receiving SDT, 9 of 11 (82%) whose entry urine was ACB positive and all the patients with ACB-negative tests were cured. The pathogen in both cases failing therapy was Proteus mirabilis resistant to TCN. Of the 15 patients cured in the multi-dose TCN group, 13 (87%) were ACB negative. The single treatment failure in the multi-dose TCN group was a woman with ACB-positive MSU containing Escherichia coli resistant to TCN. No patient receiving TCN who was either ACB negative or proved to have a TCN-susceptible organism failed therapy. All patients initially cured by SDA had amoxicillin-susceptible organisms. One patient infected with a susceptible E. coli isolate (ACB positive) failed SDA.

Mild nausea was defined as insufficient to cause any change in therapy. Moderate nausea required taking the medication with meals, and severe nausea required discontinuation of the drug. The nausea associated with the SDT was mild in 3 of 20 cases (15%) and did not occur in any other treatment group (P < 0.05). Severe nausea, beginning after day 5 in seven of eight patients, occurred with the daily administration of 2 g of TCN. The drug had to be stopped in 8 of 25 (32%) patients. Only one patient in the SDA group had late onset nausea (6%), but six other patients complained of diarrhea or vaginal discharge.

SDT cured 75% of patients with dysuria and a positive MSU culture in our study. All ACB-negative patients were cured, and 9 of 13 (69%) ACB-positive patients remained disease-free after 1 month. This is comparable to success rates reported by researchers with amoxicillin or trimethoprim-sulfamethoxazole in ACB-negative patients (6, 16) and is higher than their results in ACB-positive patients. As none of our patients had a positive Chlamydia culture, the efficacy of SDT for Chlamydia cysto-urethritis could not be assessed.

The median age in our study population was greater than the original study of Stamm et al. (21) of the acute urethral syndrome, and our group was more affluent and probably less sexually active than were the women in other similar studies. This possibly accounts for the absence of Chlamydia species in our study group.

Cure rates in the SDA group (54%) were lower than two studies reported in the literature (6, 16). However, in both of these studies patients infected with organisms resistant to amoxicillin were excluded from analysis. One study that did not exclude drug-resistant organisms obtained a cure rate of 61% at 1 week of follow-up (18), which is comparable to our rate of 69%. Since antimicrobial susceptibilities are not available at the time of initial consultation, fair comparisons of single-dose regimens should be made with all isolates and not just susceptible organisms.

The low incidence of toxicity from SDT also has been reported by Pickering et al. (13) after the administration of 2.5 g and by Karney et al. (8), who used 1.5 g. The 64% incidence of nausea in our study group taking 10 days of TCN was unexpected and is significantly different than reported in the literature. Seven of our middle-aged patients experienced nausea after day 5 of therapy, which suggests that older patients have a lower tolerance for gastrointestinal side effects of TCN when taken over a period of several days.

The small numbers of patients in our three treatment groups limited the statistical power to detect differences in the incidence of these reactions.

TABLE 2. Cure rates by treatment regimen in 62 symptomatic women

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Total no. treated</th>
<th>No. with &gt;10&lt;sup&gt;3&lt;/sup&gt; bacteria in MSU</th>
<th>Cured</th>
<th>Failed</th>
<th>Reinfeeted</th>
</tr>
</thead>
<tbody>
<tr>
<td>SDT</td>
<td>20</td>
<td>16</td>
<td>12 (75)</td>
<td>2 (13)</td>
<td>2 (13)</td>
</tr>
<tr>
<td>Multi-dose TCN</td>
<td>25</td>
<td>16</td>
<td>15 (94)</td>
<td>1 (6)</td>
<td>0</td>
</tr>
<tr>
<td>SDA</td>
<td>17</td>
<td>13</td>
<td>7 (54)</td>
<td>4 (31)</td>
<td>2 (15)</td>
</tr>
</tbody>
</table>
groups do not allow firm conclusions to be drawn at this time. However, we feel that the potential advantages demonstrated in this study warrant further investigation of TCN as a single-dose agent in the treatment of uncomplicated UTI.

We gratefully acknowledge the secretarial assistance of B. Small, E. Klein, and B. J. Holland. Portions of this work were supported in part by project CIP 8106157800 from the Bureau of Medicine and Surgery, Navy Department, Washington, D.C.

LITERATURE CITED


