Use of Low-Dose Trimethoprim-Sulfamethoxazole Thrice Weekly for Primary and Secondary Prophylaxis of *Pneumocystis carinii* Pneumonia in Human Immunodeficiency Virus-Infected Patients

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We conducted an open prospective clinical trial to evaluate the efficacy and toxicity of trimethoprim-sulfamethoxazole given as one double-strength tablet thrice weekly for primary and secondary prophylaxis of *Pneumocystis carinii* pneumonia (PCP) in human immunodeficiency virus-infected (HIV+) patients. A total of 104 HIV+ patients were evaluated, with 74 being in the primary prophylaxis group and 30 being in the secondary prophylaxis group. All except six patients received concomitant zidovudine; five patients on primary prophylaxis and one patient on secondary prophylaxis refused zidovudine. There were 70 patients evaluated for the efficacy of primary prophylaxis. The mean CD4 count was 124.4 ± 110.1 cells per µl. The mean follow-up time was 11.8 ± 5.8 months (median, 12 months; range, 1 to 32 months). Two noncompliant patients developed PCP after 1 and 3 months of chemoprophylaxis. The failure rate (under the intention to treat principle) was 2 of 70 patients (2.9%; 95% confidence interval, 0.35 to 10%), or 1 per 413 patient-months of observation. There were 27 patients evaluated for the efficacy of secondary prophylaxis. The mean follow-up time was 12.4 ± 7.2 months (median, 11 months; range, 1 to 29 months). Two patients, one of whom was noncompliant, were treatment failures, developing PCP after 14 and 15 months of chemoprophylaxis; this gave a failure rate of 2 of 27 patients (7.4%; 95% confidence interval, 0.9 to 24.3%), or 1 per 167 patient-months of observation. Adverse reactions sufficient to permanently terminate therapy occurred in 9 of 104 patients (8.7%; 95% confidence interval, 4 to 15.7%) overall. The serum trimethoprim, sulfamethoxazole, and N-acetylsulfamethoxazole concentrations measured by high-pressure liquid chromatography were uniformly low. One double-strength tablet of trimethoprim-sulfamethoxazole taken weekly on Monday, Wednesday, and Friday appeared to be well tolerated and efficacious for the prophylaxis of PCP in HIV+ patients at high risk and deserves further investigation.

*Pneumocystis carinii* pneumonia (PCP) is the most common life-threatening opportunistic infection in human immunodeficiency virus-infected (HIV+) patients. The mortality from a first episode of PCP is still 5 to 20% with current therapy (1). The introduction of zidovudine therapy has prolonged the time until the first occurrence of PCP, but it has not prevented its recurrence after an initial episode of PCP (1, 4, 5, 19). In June 1989, a Centers for Disease Control panel of experts recommended the use of aerosolized pentamidine or trimethoprim-sulfamethoxazole (two double-strength [DS] tablets daily with leucovorin) for patients with CD4 counts of <200 cells per µl, or <20% of lymphocytes, and for those who had had a prior episode of PCP (1). However, neither of these regimens is optimal. The apparent high incidence of adverse reactions with trimethoprim-sulfamethoxazole (2) and the high cost and inconvenience of use with aerosolized pentamidine have limited the use of chemoprophylaxis in certain patients.

In our institutions, the use of one DS tablet of trimethoprim-sulfamethoxazole (co-trimoxazole; 160 mg of trimethoprim and 800 mg of sulfamethoxazole) thrice weekly for PCP prophylaxis became common practice in early 1988. The rationale for this approach was based on the clinical evidence that a lower dose could reduce adverse reactions but maintain the drug’s efficacy. Several studies support this supposition. An intermittent regimen of trimethoprim-sulfamethoxazole thrice weekly had an efficacy comparable to that of daily dosing for primary prophylaxis in pediatric oncology patients (7). These children received trimethoprim (150 mg/m²) and sulfamethoxazole (750 mg/m²) up to the equivalent of two DS tablets daily. However, this dosing scheme cannot be directly extrapolated to adult patients. The volumes of distribution of trimethoprim and sulfamethoxazole per body weight or body surface area are larger in children compared with those in adults, resulting in higher dose requirements in the former population (12, 17). Sibert et al. (17) demonstrated that, on a milligram per kilogram of body weight basis, adults need only 60% of the pediatric dose of intravenous trimethoprim-sulfamethoxazole to achieve equivalent concentrations of each drug component.
in serum. Therefore, we rationalized that a chemoprophylactic dose of trimethoprim-sulfamethoxazole in adults would be approximately 60% of the dosage requirements documented by Hughes et al. (7). In light of the need for an effective, convenient, and inexpensive chemoprophylaxis for PCP, we report our experience with the use of one DS tablet of trimethoprim-sulfamethoxazole taken orally on Monday, Wednesday, and Friday of each week without concomitant leucovorin. This regimen was used for both primary and secondary prophylaxis of PCP in HIV+ individuals who were at high risk for developing this disease and who were known not to be allergic to trimethoprim-sulfamethoxazole.

(This study was presented in part at the 30th Interscience Conference on Antimicrobial Agents and Chemotherapy [18].)

MATERIALS AND METHODS

Patient population. The patients were evaluated and followed up at the following sites: the Adult Special Care Clinic of the Regional Medical Center, a tertiary-care county hospital; the private ambulatory care clinic of the University of Tennessee Medical Group; and private physicians’ offices at the Baptist Memorial Hospital. Therapy was initiated and discontinued at the discretion of the patient’s treating physician. Follow-up examinations and laboratory hematology and biochemistry evaluations were done at intervals determined by each patient’s physician, generally between 1 week and 2 months depending on the clinical indications. Primary prophylaxis was defined as therapy initiated in those patients at risk for PCP who had not had a prior episode. Secondary prophylaxis was defined as therapy initiated after a patient had recovered from an episode of PCP. Patients were first started on this therapy in January 1988, and all patients known to be eligible for study were started on therapy through July 1990. Follow-up was done through 31 January 1991. This was initially a pilot study of activity and tolerance, but with subsequent reports of effective PCP prophylaxis (3), it was thought that a comparison placebo group was not feasible.

A patient was considered eligible for taking trimethoprim-sulfamethoxazole if there was no history of adverse reactions to trimethoprim-sulfamethoxazole or one of its individual components, was known to be positive for HIV antibodies by enzyme-linked immunosorbent assay and Western blot (immunoblot), and either had a verified history of prior PCP or was considered by the physician to be at high risk for developing PCP secondary to having a CD4 count of ≤250 cells per μl, symptoms of HIV infection, or both. The patient’s risk for acquiring HIV was noted in the patient’s chart by an interviewing nurse or physician. Endpoints defined for evaluation were the end of therapy secondary to discontinuation by the patient or physician, development of PCP, death, or loss to follow-up. In the case of loss to follow-up, the date of the last known contact of the patient with a physician or nurse was used. Attempts to ascertain the status of patients that were lost to follow-up were made by a research nurse who used telephone and personal contacts. All cases of PCP were confirmed histologically. A patient was evaluated for adverse reactions to therapy if he or she was known to have started therapy. Efficacy was evaluated if therapy had been prescribed (intention to treat) for at least 3 weeks. The CD4 lymphocyte count used for assessing a patient’s risk of developing PCP while he or she was on primary prophylaxis was the value obtained closest (<6 months, usually <2 months) to the time that trimethoprim-sulfamethoxazole therapy was initiated. If no CD4 count was available, then the total lymphocyte count was used as a conservative estimate. CD4 lymphocyte counts were determined by flow cytometry using standard laboratory protocols.

Pharmacology. A subgroup of 12 patients from the population described above gave informed consent for a separate study approved by the Institutional Review Board of the University of Tennessee for determination of concentrations of trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole in serum by an ion-paired high-pressure liquid chromatography assay with solid-phase extraction (8). The limits of detectability for this assay were as follows: trimethoprim, 25 ng/ml; sulfamethoxazole, 250 ng/ml; and N4-acetylsulfamethoxazole, 25 ng/ml. The intra- and interassay coefficients of variation were <6% and <9%, respectively.

Statistics. All means are expressed as ± standard deviations. Categorical data were compared by the chi-square test with the Yates correction. Exact 95% confidence intervals (exact confidence limits for P) were obtained from standard tables (9).

RESULTS

There were 75 patients eligible for primary prophylaxis and 37 patients eligible for secondary prophylaxis with low-dose thrice-weekly trimethoprim-sulfamethoxazole therapy determined by chart review. All except six patients were on concomitant zidovudine therapy. Five patients receiving primary prophylaxis and one patient receiving secondary prophylaxis refused zidovudine therapy. The zidovudine dosage was generally 1,200 mg/day prior to August 1989 (the time of the National Institutes of Health’s A Note to Physicians [14]) and generally 500 mg/day thereafter, with dosage and therapy determined by the patient’s tolerance.

Primary prophylaxis. Of the 75 eligible patients on primary prophylaxis, drug efficacy could be evaluated in 70 of them and toxicity could be evaluated in 74 of them. Four were excluded from the efficacy evaluation because all had CD4 counts of >380 cells per μl at the time of initiation of prophylactic therapy. One patient was excluded from both efficacy and toxicity evaluation since he was receiving concomitant therapy with another agent with antipneumocystis activity (pyrimethamine-sulfa).

The demographic characteristics of the patients in the primary prophylaxis group (n = 70) are given in Table 1. The mean CD4 count was 124.4 ± 110.1 cells per μl. This included three patients for whom no CD4 count could be documented. In these three patients, total lymphocyte counts of 510, 420, and 28 were used as conservative reference estimates of the CD4 counts, since this would tend to underestimate the group’s overall immune depletion and risk for developing PCP. In addition, one patient’s only CD4 count had been 327 cells per μl 6 months earlier, with no zidovudine therapy in the interim. Exclusion of these four patients gave a mean CD4 count of 112.5 ± 91.2 cells per μl, with a range of 2 to 264 cells per μl (only five patients had CD4 counts of between 250 and 264 cells per μl). Of these 70 patients, 28 developed an AIDS-defining condition either at the time of initiation of chemoprophylaxis or during the follow-up period.

On follow-up of the 70 patients, 13 patients died, but none of these patients had suspected PCP at the time of death (as noted by a review of their records, discussions with their

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attending physicians, or both), and 11 patients were lost to follow-up. The mean follow-up time for the group (as of 31 January 1991) was 11.8 ± 5.8 months, with a median follow-up time of 12 months (range, 1 to 32 months). There were only two patients who developed PCP, after 1 and 3 months on therapy, with CD4 counts of 33 and 220 cells per μL 1 and 3.5 months earlier, respectively. In both cases, the treating physician felt that the patients were noncompliant with their medications. In the failure at 3 months, the pharmacy records and the patient confirmed the physician’s evaluation. In the failure at 1 month, no pharmacy records indicating that the prescription was filled could be found, but an outside pharmacy may have been used. The failure rate was (under the intention to treat principle) 2 of 70 patients (2.9%, 95% confidence interval [CI], 0.35 to 10%), or 1 per 413 patient-months of observation.

**Secondary prophylaxis.** Of the 37 patients eligible for secondary prophylaxis, 30 started trimethoprim-sulfamethoxazole, 3 elected therapy with aerosolized pentamidine, and 4 refused any therapy. Two patients were lost to follow-up in <1 month. In addition, for one patient, trimethoprim-sulfamethoxazole was stopped in <3 weeks secondary to increased liver function tests; trimethoprim-sulfamethoxazole was subsequently restarted at twice a week by his physician without a recurrence of symptoms. Therefore, 27 patients on secondary prophylaxis were evaluated for the efficacy of therapy and 30 were evaluated for the toxicity of therapy. The demographic characteristics for the secondary prophylaxis group (n = 27) are given in Table 1. Since the results would not affect treatment decisions, CD4 counts were obtained for only 11 of the 27 patients (mean, 80.9 ± 79.6 cells per μL; range, 5 to 234 cells per μL).

On follow-up of the 27 patients, 16 patients died and 3 (including the 2 described above) were lost to follow-up. The mean follow-up time for the group (as of 31 January 1991) was 12.4 ± 7.2 months, with a median follow-up time of 11 months (range, 1 to 29 months). One patient had PCP at the time of death, but this was 5 months after the discontinuation of trimethoprim-sulfamethoxazole and zidovudine for chemotherapy for cancer. Two patients were treatment failures, developing PCP after 14 and 15 months on therapy. The patient who relapsed at 14 months died of an apparent pulmonary embolus, but PCP had been diagnosed and the patient was being treated for PCP at the time of death. It was noted in this patient’s medical records that on prior clinic visits he was taking his medications only intermittently. This is a failure rate of 2 of 27 patients (7.4%; 95% CI, 0.9 to 24.3%), or 1 per 167 patient-months of observation. The patients who elected to use aerosolized pentamidine or who refused therapy did not fare well. The three patients on aerosolized pentamidine died. Deaths were after three PCP relapses over 15 months; after 7.5 months from respiratory cause not specified in the medical record; and after 8 months from histoplasmosis, dementia, and severe wasting. Follow-up was available for three of the four patients who refused therapy. The patients died at 6, 9, and 12 months after their first episode of PCP.

**Toxicity.** Trimethoprim-sulfamethoxazole therapy was stopped for presumed adverse reactions in 5 of 74 patients (6.8%; 95% CI, 2.2 to 15.1%) in the primary prophylaxis group and 4 of 30 patients (13.3%; 95% CI, 3.8 to 30.7%) in the secondary prophylaxis group. The reasons for discontinuation of trimethoprim-sulfamethoxazole in the five patients in the primary prophylaxis group were described as rash (two patients) at 4 and 1 months, pruritus (two patients) at 13.5 and 3.5 months, and declining hematocrit (one patient) at 10 months (zidovudine was also discontinued). For two other patients in the primary prophylaxis group, trimethoprim-sulfamethoxazole was stopped temporarily for a suspected reaction, but it was later restarted without incident. The reasons for stopping trimethoprim-sulfamethoxazole therapy in the four patients in the secondary prophylaxis group were nausea and vomiting at 3 months, fever at 1 month, and rashes at 4 and 11 months of therapy. For four other patients in the secondary prophylaxis group, trimethoprim-sulfamethoxazole was stopped for various reasons, but trimethoprim-sulfamethoxazole was restarted in each case without a recurrence of symptoms. Therefore, adverse reactions sufficient to permanently terminate therapy occurred in 9 of 104 patients (8.7%; 95% CI, 4.0 to 15.7%) overall. There was no significant difference between the adverse reaction rates found in patients in the primary and secondary prophylaxis groups (P > 0.25, χ² = 0.48).

**Pharmacology.** The concentrations of trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole in serum were measured by high-pressure liquid chromatography and are given in Table 2. The sampling times were chosen to coincide with the predicted highest and lowest trough concentrations, on Friday and Monday, respectively, and the highest peak levels (2 h after the dose on Friday). The concentrations of the compounds in serum were undetectable in the majority of the patients sampled at the trough periods. The concentrations of the compounds were low but detectable in all the patients at the peak sampling time (Friday). There was no accumulation of drug components or metabolites on this dosing schedule.

**DISCUSSION**

The results of this open prospective community experience indicate that low-dose trimethoprim-sulfamethoxazole without leucovorin is effective and is well tolerated by HIV+ patients at high risk of developing PCP. Although there was not a comparative concurrent control group, these results can be compared with data on the incidence of PCP from
large controlled studies (Table 3). Data from the Multicenter AIDS Cohort Study (15) indicate that 18.4% of HIV+ patients develop PCP within 1 year when the CD4 lymphocyte count (as measured at 6-month intervals) is <200 cells per µl, or <20% of lymphocytes. The primary prophylaxis study of Hirschel et al. (6), with 78% of the patients receiving placebo having a CD4 cell count at the time of entry into the study of <200 cells per µl, more closely resembles our primary prophylaxis group and had a PCP incidence of 27.1% per year of observation. A small percentage of patients with CD4 cell counts of >200 cells per µl do develop PCP, as noted in this and prior studies (6, 10, 15). In contrast to the data from the Multicenter AIDS Cohort Study (15) and Hirschel et al. (6), in our primary prophylaxis group (mean follow-up time, 11.8 months; median follow-up time, 12 months) we observed a PCP occurrence of 2.9%. However, this comparison is limited by the effect of zidovudine on the progression of disease, as up to 93% of the patients in the primary prophylaxis group of this study were on zidovudine, whereas only 9% of the patients in the Multicenter AIDS Cohort Study (15) and up to 78% of the patients in the study of Hirschel et al. (6) were on zidovudine. If compliance and the probability that the development of PCP in <1 month of therapy is likely to be due to preexisting infection are considered, then there were no treatment failures in the primary prophylaxis group in this study. The relapse rate at 8 months after the first episode of PCP in the absence of prophylaxis in patients on zidovudine therapy is approximately 50%, and at 12 months it is 66% (1, 13); our observed rate was 7.4% at a mean of 12.4 months.

Adverse reactions were mild and, overall, lead to therapy being permanently discontinued in 8.7% of patients (Table 3). Although the incidence of adverse reactions was higher in the secondary prophylaxis group, it did not achieve statistical significance (P > 0.25). In an additional six patients (5.8%), suspected adverse reactions did not recur on rechallenge with trimethoprim-sulfamethoxazole and were therefore unlikely to be drug related. It is unknown whether the overall incidence of adverse reactions that were presumed to be drug related would have been lower if all patients had been rechallenged.

The concentrations of trimethoprim, sulfamethoxazole, and N4-acetylsulfamethoxazole in serum, as measured by high-pressure liquid chromatography, were uniformly low. These results may indicate that for a slowly replicating organism such as P. carinii, only intermittently inhibitory concentrations are needed to substantially slow its growth. The efficacy noted with these low concentrations indicates that we do not know what the minimal effective chemoprophylactic dose of trimethoprim-sulfamethoxazole is.

One DS tablet of co-trimoxazole taken on Monday, Wednesday, and Friday each week appears to be well tolerated and efficacious for the prophylaxis of PCP in HIV+ patients at high risk. Our results are in overall agreement with those published by Ruskin and LaRiviere (16). Those investigators had no treatment failures in 71 patients on secondary prophylaxis and 45 patients on primary prophylaxis with mean follow-up times of 18.5 months (median, 17 months) and 24.2 months (median, 25 months), respectively. Therapy was permanently discontinued for adverse reactions in 15 of 116 (13%) patients, most commonly within the first month for rash with fever. However, these data were from patients in a health maintenance organization and were obtained by review of pharmacy records, so compliance likely was high. Our efficacy data are probably more representative of a largely indigent population commonly encountered under usual practice conditions and likely include some element of breakthrough failure. The overall adverse reaction rate for our study population (8.7%; 95% CI, 4.0 to 15.7%) was similar to that of the study of Ruskin and LaRiviere (16).

Our results are also comparable to those obtained by other methods of prophylactic therapy. Fischl et al. (3) used two DS tablets of trimethoprim-sulfamethoxazole per day with 5 mg of leucovorin for primary prophylaxis in patients with AIDS in a placebo-controlled study. There were no treatment failures for patients on trimethoprim-sulfamethoxazole, but toxicity was higher than what we observed, with 50% of patients having an adverse reaction and 17% discontinuing therapy secondary to the adverse reaction. The higher dose and the use of leucovorin also make this method of prophylaxis more expensive than the one used in this study.

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<thead>
<tr>
<th>Table 2. Concentrations of drug and metabolite measured in the sera of 12 patients</th>
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<td><strong>Conc (µg/ml)</strong></td>
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<tr>
<td><strong>Time</strong></td>
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<td></td>
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<tr>
<td>Trough, Friday</td>
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<tr>
<td>Peak, Friday</td>
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<tr>
<td>Trough, Monday</td>
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*Concentrations were measured by high-pressure liquid chromatography. TMP, trimethoprim; SMX, sulfamethoxazole; N-SMX, N4-acetylsulfamethoxazole.

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<th>Table 3. Incidence of PCP</th>
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<td><strong>Group</strong></td>
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<td>Primary prophylaxis</td>
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<td>Secondary prophylaxis</td>
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* The rates are reported under the intention to treat analysis.
| * Data were presented previously (1, 6, 15).
| * The difference in adverse reactions between patients in the primary and secondary prophylaxis groups was not significant (P > 0.25).
The use of dapsone at a dosage of 100 mg daily is an inexpensive alternative therapy reported to have a failure rate of 2 of 173 patients (1.2%) over a mean observation period of 9.4 months, with 10% of patients experiencing an adverse reaction (11). Aerosolized pentamidine therapy at a dosage of 300 mg once monthly has reported failure rates of 28 of 139 patients (22%) in both primary and secondary prophylaxis strata combined over 18 months. In those with a prior episode of PCP, 21 of 80 patients (26%) had a relapse on therapy. Therapy was discontinued because of adverse effects in 2.2% of patients (10). In patients on primary prophylaxis in the study of Hirschel et al. (6), the failure rate was 8.6% per year of observation for patients on aerosol pentamidine; therapy was discontinued in 3.5% of patients because of adverse reactions. In the study of secondary prophylaxis of Montaner et al. (13) (in which a hand-held nebulizer was used), the relapse rate was 9% within 6 months for patients on aerosol pentamidine compared with 50% for patients on placebo. The estimated relapse rates at 48 weeks were 20 and 67% for the therapy and placebo groups, respectively.

The open nature of this study precluded an evaluation of whether the low-dose trimethoprim-sulfamethoxazole prophylaxis increased the patients' survival. Prophylaxis with trimethoprim-sulfamethoxazole was indicated by Fischl et al. (3) to increase survival compared with the survival of patients in a control group. No effect on survival was indicated in a comparison of the different dosage arms in the study of Leong et al. (10) or the placebo and treatment arms of the studies of Montaner et al. (13) or Hirschel et al. (6). Although adverse reactions resulting in the discontinuation of therapy with aerosolized pentamidine were low (6, 10), the expense, inconvenience, and higher failure rate in patients on secondary prophylaxis (10, 13) and a possible short-term survival benefit with trimethoprim-sulfamethoxazole would favor the use of low-dose trimethoprim-sulfamethoxazole as the initial method of prophylaxis. If our results are corroborated by other investigators in larger comparative controlled studies of longer duration, then this method of chemoprophylaxis, which is both inexpensive and convenient, should become a standard regimen for the chemoprophylaxis of PCP.

REFERENCES


