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Intermittent Chemoprophylaxis for *Pneumocystis carinii* Pneumonia

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An intermittent regimen of trimethoprim-sulfamethoxazole was tested in the corticosteroid-treated rat model to learn whether or not administration for 3 consecutive days a week would provide prophylaxis equal to continuous daily doses. Although all of the untreated control animals acquired *Pneumocystis carinii* pneumonia, none of the animals given either continuous or intermittent trimethoprim-sulfamethoxazole became infected.

An animal model has been found to correlate closely with human disease from *Pneumocystis carinii*. Rats maintained for 2 to 3 months on corticosteroids and antibiotics will regularly acquire extensive *P. carinii* pneumonitis. In 1974, this animal model was used to determine that trimethoprim-sulfamethoxazole administered daily was highly effective in the prevention of the pneumonitis (5). Subsequently, clinical studies in cancer patients showed results identical to those in animals (3, 4, 6). Although the continuous daily use of trimethoprim-sulfamethoxazole provides a satisfactory approach to prophylaxis, some advantages might be realized with the use of a schedule of intermittent doses of the drug. Aside from convenience for the patient, reduction in drug cost, and minimization of antibacterial effects on the microbial flora, the possibility of reducing dose-related adverse effects would be desirable. This report describes animal experiments to determine whether or not intermittent courses of trimethoprim-sulfamethoxazole are as effective as continuous doses in the prevention of *P. carinii* pneumonitis.

Three groups of rats were immunosuppressed with dexamethasone to provoke *P. carinii* pneumonitis. One group received no prophylactic medication. A second group was given trimethoprim-sulfamethoxazole daily throughout the period of immunosuppression, and the third group received the drug combination only on Monday, Tuesday, and Wednesday of each week. After 2 months of corticosteroid immunosuppression, the animals were sacrificed, and the lungs were examined histologically for *P. carinii* infection.

Sprague-Dawley male rats weighing ca. 200 g each were used. The animals were housed as groups of five in wire-top plastic cages placed on racks in a conventional animal facility. They had access to water and food ad libitum. A total of 30 rats were randomly assigned to three groups of 10 each.

All drugs were administered in drinking water. A basic solution was prepared by adding 500 mg of tetracycline hydrochloride (E. R. Squibb & Sons, Princeton, N.J.) and 2.0 mg of dexamethasone sodium phosphate (Merck Sharp & Dohme, West Point, Pa.) to 1 liter of distilled water. All animals received this solution in the amount of 30 ml per rat per day. Trimethoprim-sulfamethoxazole was administered by adding 335 mg of the former drug and 1,675 mg of the latter drug (Hoffmann-LaRoche Inc., Nutley, N.J.) to each liter of the dexamethasone-tetracycline solution. This dosage provided about 10 mg of trimethoprim and 50 mg of sulfamethoxazole per rat per day, or 50 and 250 mg of the respective drugs per kg of body weight per day. The tetracycline was used to prevent early deaths from bacterial infections.

At the end of 2 months of immunosuppression, all of the surviving rats were sacrificed by carbon dioxide.

Autopsies were done at the time of death. Sections of the right lungs were taken for histopathology. The Formalin-fixed specimens were sectioned for slides and stained with Gomori's methenamine silver nitrate technique. Also, imprints of the cut surface of fresh lung specimens were made on microscope slides and stained with toluidine blue O. An animal was considered free of *P. carinii* if no organisms were found on two lung sections or on lung imprint preparations. At least two unequivocal *P. carinii* cysts were required for an infected animal. However, all infected animals had at least several hundred cysts on a single lung section as well as imprints.

The results are summarized in Table 1. Two animals in group 1, four in group 2, and two in group 3 died between 6 and 8 weeks of immuno-

TABLE 1. Prevention of *P. carinii* pneumonitis

Group	No. tested	Administration of following drug:		*P. carinii* pneumonitis (no. of animals infected/ no. studied)
		Dexamethasone-tetracycline	Trimethoprim-sulfamethoxazole	
1	10	Yes	None	10/10[a]
2	10	Yes	Daily	0/10
3	10	Yes	3 days/wk	0/10

[a] All animals had extensive *P. carinii* infections with diffuse alveolitis and masses of cysts filling the alveolar lumina.

suppression. The others were sacrificed at 8 weeks of dexamethasone and tetracycline administration. The two rats in group 1 died with *P. carinii* pneumonitis. Those in groups 2 and 3 had bacterial or fungal infections or both, as revealed by septate mycelia, cocci, or bacilli forms in the histological sections.

The results of this study show clearly that intermittent administration of trimethoprim-sulfamethoxazole for periods of 3 days, between 4-day intervals without the drug prophylaxis, is effective in the prevention of murine *P. carinii* pneumonitis. Furthermore, the effect is equal to continuous administration of the drug combination for this purpose. Although this animal model has been highly representative of the human infection in previous studies, one cannot assume the intermittent regimen would be equally successful when used in humans.

It has been demonstrated that trimethoprim-sulfamethoxazole treatment does not eradicate *P. carinii* from the host. In a previous study, we found that rats treated continuously for 6 weeks with the drugs and then placed in barrier isolators to prevent acquisition of *P. carinii* during immunosuppression had exacerbation of latent *P. carinii* infections in 90% of the animals (1).

Although the incubation period for *P. carinii* pneumonitis is not well delineated, it is believed to be about 3 to 6 weeks, based on the acquisition of the disease in endemic nurseries and studies in germfree rats (2). This rather long incubation period perhaps accounts for the success of the intermittent prophylactic regimen observed in our study. The 3-day courses of trimethoprim-sulfamethoxazole, interrupted at 4-day intervals without the drug, seem adequate to maintain the organism in a latent, subclinical state. Whether variations of this scheme might be equally successful is not known.

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