Prophylactic Treatment of Rocky Mountain Spotted Fever

RICHARD H. KENYON,* RONALD G. WILLIAMS,† CHARLES N. OSTER,‡ AND CARL E. PEDERSEN, JR.§

United States Army Medical Research Institute of Infectious Diseases, Fort Detrick, Frederick, Maryland 21701

Received for publication 14 March 1978

Prophylactic treatment of Rocky Mountain spotted fever with a single dose of oxytetracycline was investigated in guinea pigs. Disease was prevented when treatment was administered shortly before expected onset. Relapses occurred when treatment preceded expected onset by 48 h or more.

There were 1,115 reported cases of Rocky Mountain spotted fever (RMSF) in the United States in 1977 (3). Due to confusion in recognition of the disease clinically, death-to-case ratios have not changed since the 1940s despite the susceptibility of rickettsiae to antibiotics (5). The question of prophylactic treatment of possible RMSF exposure after known tick bite is frequently addressed by physicians. Perine et al. (9), Boese et al. (1), and Huys et al. (6) showed that a single-dose regimen of doxycycline successfully treated epidemic typhus (*Rickettsia prowazekii*) in humans. Investigations with scrub typhus (*R. tsutsugamushi*) revealed that chloramphenicol administered at regular intervals for about a month after exposure prevented disease, whereas drug treatment for a shorter period resulted in onset of illness about 1 week after cessation of the antibiotic (10). To date definite studies have not been performed on chemoprophylaxis of RMSF. The purpose of this investigation was to determine whether: (i) the disease process could be eliminated by a single prophylactic dose of oxytetracycline; (ii) treatment given prior to onset of symptoms would prevent or modify disease; and (iii) treated animals were protected against subsequent challenge.

Hartley strain male guinea pigs, 400 to 450 g (Buckberg Labs), were infected subcutaneously with chicken yolk sac-grown *R. rickettsii* (Sheila Smith strain) diluted to 10^6 , 10^4 , or 10^2 plaque-forming units in sucrose-phosphate-glutamate buffer (2). Viable rickettsiae were quantified by plaque titration (11). Guinea pigs were treated at the indicated time by a single intramuscular injection of 25 mg of oxytetracycline hydrochloride (Lederle, Pearl River, N.Y.) per kg. Rectal

temperatures were measured daily and expressed as guinea pig degree-days. Microagglutinating antibody (4) and lymphocyte transformation (7) assays were performed 3 weeks postinfection. Surviving guinea pigs were rechallenged 4 weeks postinfection with 10^7 plaque-forming units of *R. rickettsii* grown in chicken fibroblast cultures.

Results of prophylactic antibiotic treatment of guinea pigs are shown in Table 1. Early treatment prevented development of recognizable disease in all guinea pigs injected with 10^6 rickettsiae. Untreated guinea pigs showed fever by day 2 and developed typical RMSF (8). Animals receiving antibiotic on days 2 through 5 were cured of their infection and did not relapse. All animals in this group developed significant microagglutinating antibody and in vitro lymphocyte transformation responsiveness to rickettsial antigen; there was no correlation between magnitude of the immune response and time of treatment or febrile response. Two animals receiving antibiotic on day 7 died later the same day, but the other two recovered and did not relapse. All surviving treated guinea pigs became refractory to challenge.

Untreated guinea pigs inoculated with 10^4 rickettsiae first showed fever on day 3. Several guinea pigs treated early showed delayed, mild fever for 1 or 2 days or were susceptible to the disease when rechallenged. Animals receiving antibiotic on days 3 through 7 recovered and did not relapse.

Untreated guinea pigs infected with 10^2 rickettsiae became febrile on day 5. Most treated on days 0 to 2 experienced delayed disease onset. Those that were treated at the onset of symptoms or which later recovered did not relapse and were protected against challenge.

Our data show that a single dose of oxytetracycline can abort signs of RMSF in guinea pigs, but this effect is dependent upon the dose of rickettsiae injected and the time between challenge and treatment. Those animals infected

† Present address: Department of Pediatrics, Fitzsimons Army Medical Center, Denver, CO 80240.

‡ Present address: National Institute of Allergy and Infectious Diseases, Laboratory of Parasitic Diseases, Bethesda, MD 20014.

§ Present address: U.S. Army Medical Research and Development Command, Fort Detrick, Frederick, MD 21701.

TABLE 1. *Oxytetracycline treatment of RMSF in guinea pigs*^a

Challenge dose (PFU)	Treatment ^b	Fever (degree-days) ^c		No. of relapses	No. of deaths	Immune response of survivors ^d		No. ill at re-challenge ^e
		Before treatment	After treatment			LT	MA	
10 ⁶	0		0	0	0	4	4	0
	0.5	0	0	0	0	4	4	0
	1	0	0	0	0	4	4	0
	2	0.6	0	0	0	4	4	0
	3	1.1	0.7 ^f	0	0	4	4	0
	5	1.9	0	0	0	4	4	0
	7	1.7	0	0	2	2	2	0
	None ^g		3.2		2	2	1	0
10 ⁴	0		1.7	3	0	4	3	0
	0.5	0	0.2	2	0	3	3	1
	1	0	0.8	3	0	4	2	1
	2	0	0.6	2	0	4	4	0
	3	0.1	0	0	0	3	4	0
	5	1.3	0	0	0	4	4	0
	7	2.3	0	0	0	4	4	0
	None ^g		3.3		0	4	4	0
10 ²	0		2.3	3	1	2	2	1
	0.5	0	2.0	4	0	4	4	0
	1	0	1.7	2	1	2	2	1
	2	0	1.1	2	0	2	2	2
	3	0	0.4	1	0	3	3	1
	5	0.5	0.3 ^f	0	0	4	4	0
	7	2.1	0	0	0	4	4	0
	None ^g		6.2		3	1	1	0
Controls								4

^a *n* = 4. PFU, Plaque-forming units.^b At days postinoculation.^c Degree-days of fever are calculated by adding the number of degrees above 39.8°C for all guinea pigs in a particular group during the period of time under consideration, and dividing by the total number of guinea pigs in that group.^d Lymphocyte transformation (LT) stimulation index ≥ 3.0 or microagglutinating antibody (MA) titer ≥ 1:8 was considered positive.^e No deaths in experimental groups; three of four controls died.^f Fever was exhibited 24 h after treatment.^g Untreated guinea pigs showed first fever on day 2 for 10⁶ group, day 3 for 10⁴ group, and day 5 for 10² group.

with large doses and treated immediately showed no signs of disease, developed cell-mediated (lymphocyte transformation) and humoral (microagglutinating) immune responses, and were refractory to rechallenge. This combination of large numbers of rickettsiae with oxytetracycline treatment appeared to constitute a vaccination with a nonreplicating immunogenic mass of rickettsiae. Those animals infected with small doses and treated immediately frequently experienced delayed onset of disease or were susceptible to rechallenge.

The use of chemoprophylaxis pertains to situations where either a tick shown to be infected or to be from a geographically endemic area has been removed from a patient, or a suspected accidental laboratory exposure has occurred.

Even if humans and guinea pigs respond identically to treatment, the data presented here indicate that chemoprophylaxis with a single dose of antibiotic is useful only when administered no more than 24 to 48 h prior to fever onset. Since the incubation period after reported tick bite can vary from 3 to 12 days (12), prediction of fever onset is impossible. Therefore, the usual practice of closely observing the individual at risk and initiating a standard course of broad-spectrum antibiotic at the onset of fever is still the best course of RMSF disease management.

LITERATURE CITED

- Boese, J. L., C. L. Wisseman, Jr., W. T. Walsh, and P. Fiset. 1973. Antibody and antibiotic action on *Rickettsia prowazekii* in body lice across the host-vector

- interface, with observations on strain virulence and retrieved mechanisms. *Am. J. Epidemiol.* **98**:262-282.
2. **Bovarnick, M. R., J. C. Miller, and J. C. Snyder.** 1950. The influence of certain salts, amino acids, sugars, and proteins on the stability of rickettsiae. *J. Bacteriol.* **59**:509-522.
 3. **Center for Disease Control.** 1978. Summary: cases of specified notifiable diseases: United States. *Morbidity and Mortality Weekly Rep.* **27**:2.
 4. **Fiset, P., R. A. Ormsbee, R. Silberman, M. Peacock, and S. H. Spielman.** 1969. A microagglutination technique for detection and measurement of rickettsial antibodies. *Acta Virol.* **13**:60-66.
 5. **Hattwick, M. A. W., R. J. O'Brien, and B. F. Hanson.** 1976. Rocky Mountain spotted fever: epidemiology of an increasing problem. *Ann. Intern. Med.* **84**:732-739.
 6. **Huys, J., P. Freyens, J. Kayihigi, and G. Van Den Berghe.** 1973. Treatment of epidemic typhus. A comparative study of chloramphenicol, trimethoprim-sulphamethoxazole and doxycycline. *Trans. R. Soc. Trop. Med. Hyg.* **67**:718-721.
 7. **Kenyon, R. H., M. S. Ascher, R. A. Kishimoto, and C. E. Pedersen, Jr.** 1977. In vitro guinea pig leukocyte reactions to *Rickettsia rickettsii*. *Infect. Immun.* **18**:840-846.
 8. **Moe, J. B., D. F. Mosher, R. H. Kenyon, J. D. White, J. L. Stookey, L. R. Bagley, and D. P. Fine.** 1976. Functional and morphologic changes during experimental Rocky Mountain spotted fever in guinea pigs. *Lab. Invest.* **35**:235-245.
 9. **Perine, P. L., S. Awoke, D. W. Krause, and J. E. McDade.** 1974. Single-dose doxycycline treatment of louse-borne relapsing fever and epidemic typhus. *Lancet* **ii**:742-744.
 10. **Smadel, J. E., T. E. Woodward, H. L. Ley, Jr., and R. Lewthwaite.** 1949. Chloramphenicol (chloromycetin) in the treatment of tsutsugamushi disease (scrub typhus). *J. Clin. Invest.* **28**:1196-1215.
 11. **Weinberg, E. H., J. R. Stakebake, and P. J. Gerone.** 1969. Plaque assay for *Rickettsia rickettsii*. *J. Bacteriol.* **98**:398-402.
 12. **Woodward, T. E., and E. B. Jackson.** 1965. Spotted fever rickettsiae, p. 1095-1129. In F. L. Horsfall, Jr., and I. Tamm (ed.), *Viral and rickettsial infections of man*, 4th ed. J. B. Lippincott Co., Philadelphia.