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Minocycline in the Chemoprophylaxis of Meningococcal Disease

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An outbreak of meningococcal disease occurred among basic combat trainees at Fort Lewis, Wash., in the first 3 months of 1971. After five recruits developed meningitis within a 2-week period, 8,721 recruits were given 100 mg of minocycline every 12 hr for 5 days. No new cases of meningococcal disease occurred for almost 5 weeks. Then six additional cases occurred among recruits who had entered training after the initial course of minocycline and who had not received the drug. Minocycline was given to all 6,130 of these men, and again occurrence of new cases was halted abruptly. One week later, group C polysaccharide vaccine was administered to all recruits in the first 6 weeks of training and subsequently to all new entering trainees. No new cases of meningitis occurred in the next 3 months. Surveys showed that minocycline significantly lowered the meningococcal carrier rate for 4 to 5 weeks. No strains of *Neisseria meningitidis*, among 341 isolated after minocycline treatment, were resistant to the drug. Prophylaxis with minocycline clearly interrupted the course of this outbreak due to sulfa-resistant meningococci. Although immunization is the preferred method of prophylaxis, minocycline may be useful until a suitable polyvalent vaccine is available.

Between 1943 and 1963, sulfadiazine was used successfully to abort outbreaks of meningococcal disease among military recruits. However, for the past several years, chemoprophylaxis with sulfadiazine has been ineffective because a high proportion of meningococci isolated now are resistant to the drug. It was logical, therefore, to search for another suitable agent for prophylaxis. Among the antibiotics used in the treatment of meningococcal disease, notably penicillin G, chloramphenicol, and tetracycline, all are uniformly ineffective in preventing infection. Several recent studies have shown that two new antimicrobial agents, rifampin and minocycline, have an effect on the nasopharyngeal carriage of meningococci which is similar to that of the sulfonamides (2, 3, 5). However, it remains to be proved whether either of these agents can halt an established outbreak of meningococcal disease in a closed population.

Because the potential of rifampin for mass prophylaxis is limited by the rapid development of resistance by strains of *Neisseria meningitidis* (5), minocycline was selected for further study. This report describes its use as a prophylactic agent during an outbreak of meningococcal disease at Fort Lewis, Wash., in the winter of 1971.

MATERIALS AND METHODS

Background. The United States Army Infantry Training Center at Fort Lewis has a daily complement of between 8,000 and 12,000 basic combat trainees. Upon their arrival at the training center, inductees are formed into companies of 150 to 250 men, and they remain in these units during their week of orientation and 8 weeks of training. Each company is rigidly segregated from all other training units, and during the first 4 weeks of training a recruit's only contact outside his company is through his training cadre, i.e., the 20 to 30 officers and men responsible for the training of each company.

Outbreaks of meningococcal disease have occurred among basic combat trainees during 4 of the 6 years the Training Center has been in operation. There were 14 cases in 1968, 70 in 1969, 47 in 1970, and, as will be discussed in detail below, 12 in the first 4 months of 1971. Virtually all of these 143 cases and all of those encountered in 1971 were caused by group C meningococci which were resistant to sulfadiazine; 83% of all cases occurred in the months of January through June. Routine surveillance of carriage of meningococci is conducted monthly by obtaining nasopharyngeal cultures from 10% of the recruits in their sixth week of training. During the summer months, about 25% of trainees harbor the organisms, but the rate of carriage usually increases to the range of 70% during outbreaks of meningococcal disease.

Description of the outbreak and study design. On 14 December 1970, a recruit in his fourth week of training died of meningitis caused by a group C meningococcus resistant to sulfadiazine. Because of previous experience in the Training Center and the fact that the routine meningococcal surveillance in November had shown an increase in the rate of carriage from 27% to 70%, an outbreak of meningococcal disease was anticipated. Routine surveillance was increased, and it was decided that, if two or more additional recruits developed meningococcal disease within 1 week, prophylaxis with minocycline would be attempted. (These decisions were made conjointly by medical officers of Madigan General Hospital, the Preventive Medicine Department of Madigan General Hospital, and a Civilian Advisory Committee on Meningococcal Disease whose members were R. G. Petersdorf, W. M. M. Kirby, and H. N. Beaty, Department of Medicine, University of Washington; B. J. Francis, State Department of Health; H. P. McNutt, County Health Department; and E. B. Cooper, Department of Medicine, Madigan General Hospital. The protocol for the study was approved by the Office of the Surgeon General, U.S. Army.) On 12 January, two men from separate units in their seventh and third weeks of training developed meningitis. Final preparations for the administration of minocycline had not been completed, and, before chemoprophylaxis was begun on 23 January, meningitis developed in three more recruits and was fatal in two. After informed consent was obtained from all but 28 basic combat trainees in accordance with Army Regulation 40-7, 8,721 recruits received 100 mg of minocycline (supplied free of charge by Lederle Laboratories) every 12 hr for 5 days. Each dose of antibiotic was administered under the supervision of one of the authors (R.G.) and his staff. The men were questioned repeatedly regarding untoward reactions to the drug, and when necessary antibiotic was discontinued. The more troublesome reactions were evaluated by medical officers assigned to the Training Center. The training cadre also received antibiotic, but for one reason or another, 233 recruits were not treated; one of these men developed meningitis on 26 January. Recruits entering training after 23 January did not receive chemoprophylaxis and constituted an untreated group.

To assess the effect of this effort at prophylaxis on the rate of carriage of meningococci, nasopharyngeal cultures were obtained from 350 men in their sixth week of training 2.5 and 4.5 weeks after the course of minocycline had been completed. In addition, the rate of meningococcal carriage among 217 trainees in a separate company (B-2-2) was determined before and at weekly intervals for 7 weeks after minocycline was given.

On 21 February, four weeks after the regimen of prophylaxis had been completed, an individual in his second week of training developed meningitis. Within the next 10 days, five additional cases of meningococcal disease occurred among the untreated recruits, which by this time consisted of 6,121 individuals and constituted 61% of all of the basic combat trainees. Beginning on 3 March, minocycline was administered to these men in a dosage of 100 mg every 12 hr. At the same time, a second course of minocycline, 200 mg in one daily dose for 3 days, was administered to recruits of company B-2-2 which was in its seventh week of training, to determine whether this regimen effectively reduced the rate of meningococcal carriage. This is the only company which received this simplified regimen and the only group to receive minocycline twice. On 8 March, the Surgeon General of the Army ordered the administration of the group C polysaccharide vaccine to all recruits in the first 6 weeks of basic training and to all inductees entering Fort Lewis through May 1971. Consequently, about 6,800 men received both minocycline and vaccine, and 2,100 men, who were in their seventh and eighth weeks of training on 8 March, were given neither vaccine nor additional minocycline for prophylaxis. Two of these men developed meningococcal meningitis 7 and 13 weeks after receiving the first course of minocycline. Both had graduated from basic combat training to advanced infantry training by the time they became ill. No subsequent cases of meningococcal disease were encountered at Fort Lewis through June 1971.

Laboratory procedures. All the cases of meningococcal disease described in this report were confirmed in the Department of Pathology of Madigan General Hospital, Fort Lewis, by isolation of group C meningococci from blood or cerebrospinal fluid. Nasopharyngeal cultures taken to determine rates of meningococcal carriage were obtained in the field according to procedures described previously (5). Those acquired for routine surveillance were incubated locally for 24 hr in 5% CO_2 at 37 C before being sent to the Sixth U.S. Army Area Laboratory where meningococci were identified and grouped serologically by standard techniques. Cultures obtained from company B-2-2 were processed in the laboratory of one of the authors (H.B.). All of the meningococci isolated from these cultures and 28% of those recovered in the Sixth Army Laboratory in January, February, and March were tested for susceptibility to minocycline and sulfadiazine by the agar-dilution method described previously (5).

RESULTS

Effect of minocycline on the attack rate of meningococcal disease. In the 2 weeks prior to the first course of minocycline, five basic combat trainees developed meningococcal disease (Table 1). Following prophylaxis, the number of men and the proportion of the total population of recruits who had received minocycline decreased progressively, because at the end of each week a battalion of recruits was graduated and was replaced by an untreated group entering training. New occurrences of meningitis were not encountered until almost 5 weeks after the first dose of minocycline was given and at a time when 50% of the recruits were untreated. After the second course of minocycline and institution of the vaccine program, no additional outbreaks of meningococcal disease occurred among basic combat trainees. The two men who developed meningitis

7 and 13 weeks after the first course of minocycline are not included in Table 1 because they had graduated from basic training by the time they became ill.

Statistical analysis of these results was accomplished with calculations based on man-weeks and the assumption that the probability of meningococcal disease occurring was small and relatively constant for each man-week. The first of these assumptions is justified by the fact that, in the 15,030 man-weeks before prophylaxis, the epidemic incidence per 1,000 man-weeks was 0.333. The second assumption is difficult to prove, but is supported by the fact that the 12 recruits who developed meningococcal disease were in their first, second, third, sixth, seventh, and eighth week of training at the time they became ill.

Application of the epidemic attack rate of 0.333 per 1,000 man-weeks to the 18,886 man-weeks in the untreated group for weeks 0 through 5 (Table 1) leads to an expected number of cases of 6.3. There were in fact seven cases in this group during this period (Table 2). In the treated group, 38,063 man-weeks were observed in weeks 0 through 5 with an expected number of cases of 12.7. However, no meningococcal disease occurred in this group, and the difference between the expected and observed occurrence was highly significant ($P < 0.001$). Data from weeks 6 through 8 were not used in these calculations because, shortly after the second course of minocycline, another prophylactic agent, the vaccine, was used.

When the same data are analyzed with the binomial test of the hypothesis that the treated and untreated group are different with respect to the occurrence of meningococcal disease, the results are similar. For the weeks 0 through 5, the proportion of cases in the treated group, 0/7 = 0%, differs significantly from the proportion of man weeks of exposure for the treated group, 38,063/56,949 = 66.8%.

Effect of minocycline on the rate of carriage of meningococci. In the months of August through October 1970, the rate of nasopharyngeal carriage of meningococci among recruits in the sixth week of basic training averaged 26% (Fig. 1). Of meningococci isolated in this period, 27% were group C. During November, December, and January, the mean rate of carriage was 68%, and 30% of the isolates were group C organisms. For the 3 months following the initial course of minocycline, the mean rate of carriage was 35%, with 21% group C strains. The surveys in February and March were performed before the second course of minocycline, and the cultures done in April were 5 weeks after the second course of minocycline and vaccination with group C polysaccharide. This may account for the apparent discrepancy between the effect of the two courses

TABLE 1. *Effect of minocycline prophylaxis on the occurrence of meningococcal disease*

Week	No. of recruits		
	Treated	Untreated	With disease[a]
−2	0	7,534	2
−1	0	7,496	3
0[b]	8,721	233	1
1	7,625	1,303	0
2	6,736	2,672	0
3	5,933	3,584	0
4	5,058	4,973	3
5	3,990	6,121	3
6[b]	9,066	945[c]	0
7	8,362	2,309[c]	0
8	7,356	3,342[c]	0

[a] None of the treated recruits developed meningococcal disease.

[b] Denotes timing of the two courses of minocycline.

[c] Received vaccine but not minocycline.

TABLE 2. *Effect of minocycline prophylaxis on the occurrence of meningococcal disease during weeks 0 through 5*

Determination	Treated group		Untreated group	
	Observed, O	Expected, E	Observed, O	Expected, E
Man-weeks without cases	38,063	38,050.3	18,879	18,879.7
Man-weeks with cases	0	12.7[a]	7	6.3
Total	38,063	38,063.0	18,886	18,886.0
χ_1^2	$= \Sigma(O - E)^2/E = 12.7$ ($P < 0.001$)		$= \Sigma(O - E)^2/E = 0.08$ (not significant)	

[a] Expected values calculated under the binomial assumption that the probability of a case in any man-week is 0.000333, probability for no case is 1 − 0.000333, and the probabilities are independent for any two man-weeks (4).

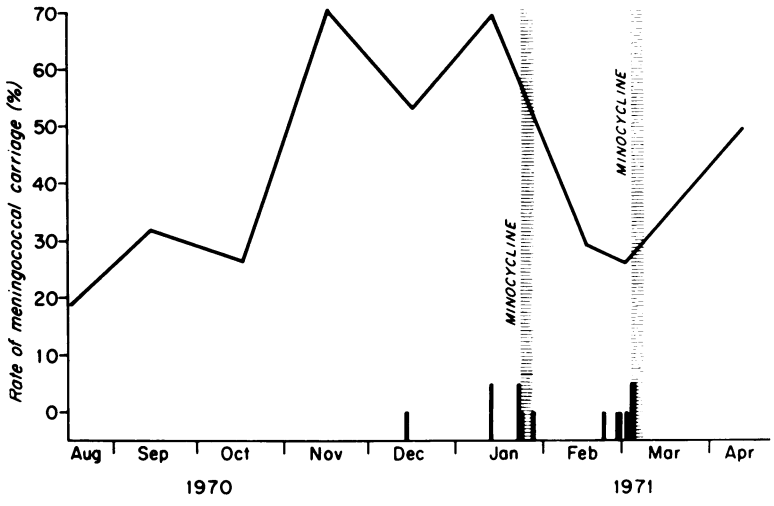

FIG. 1. *Rate of carriage of meningococci among recruits in their sixth week of training. Vertical bars denote timing of attempts at prophylaxis with 100 mg of minocycline every 12 hr for 5 days. The distribution of cases of meningococcal disease is shown along the abscissa; a short vertical bar is one case and a long vertical bar is two cases.*

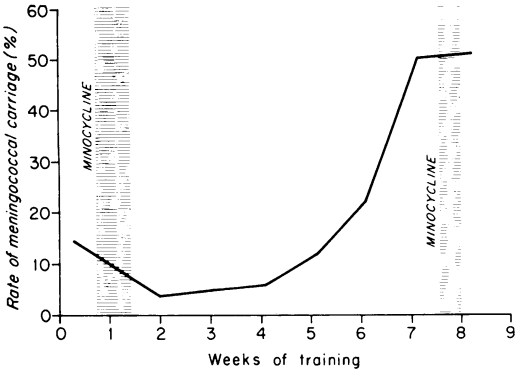

FIG. 2. *Effect of minocycline on the rate of carriage of meningococci among recruits of company B-2-2. Vertical bars denote timing and duration of two courses of minocycline treatment; the first was 100 mg every 12 hr for 5 days and the second was 200 mg a day in a single dose for 3 days.*

on the carrier rate, because previous studies have shown that minocycline influences the carrier rate for only 4 to 5 weeks (5).

The rate of carriage of meningococci in the single company followed weekly after the first course of minocycline is shown in Fig. 2. Treatment with antibiotics reduced the rate of carriage to about 4%, and by the fifth week of training it had risen only to 12%. Two weeks later, however, the rate of carriage had climbed to 55% and remained high despite the fact that these men received a second course of minocycline in a different dosage.

TABLE 3. *Susceptibility of meningococci to minocycline before and after treatment*[a]

Time	No. of strains	Minimal inhibitory concn (μg/ml)	
		Mean	SE of mean
Before treatment.....	62	0.192	0.08
After treatment.....	341	0.220	0.04

[a] $P = 0.10$, determined from the ratio of the difference of the means to the standard error of the difference.

Susceptibility of meningococci to minocycline and sulfadiazine. The minimal inhibitory concentration (MIC) of sulfadiazine for 83% of 403 strains of meningococcus isolated from nasopharyngeal carriers was 0.5 mg or more per 100 ml. The MIC of minocycline for 62 strains of meningococci isolated before the first course of treatment ranged from 0.06 to 1.0 μg/ml with a mean of 0.192 μg/ml. The mean and range of MIC for 341 isolates recovered after prophylaxis with minocycline were 0.22 and 0.03 to 0.50 μg/ml, respectively, and did not differ significantly from the values obtained before treatment (Table 3).

One hundred five isolates of meningococcus were recovered from 188 recruits in company B-2-2 3 days after they received their second course of prophylaxis. All of these strains were sensitive to 0.5 μg or less of minocycline per ml,

and the mean MIC for the group was 0.25 μg/ml.

Side effects and toxicity. Minocycline was well tolerated by the 14,800 recruits who received prophylaxis. Hypersensitivity reactions, consisting of rash or fever or both, necessitated discontinuing the drug in 0.14% of the men treated. About 7% of the recruits had minor reactions consisting of headache, dizziness, or nausea. These were not sufficiently bothersome to require interruption of treatment.

DISCUSSION

The prophylactic administration of minocycline clearly influenced the course of this outbreak of meningococcal disease. The attack rate of meningitis among treated recruits and those who entered training after the first course of minocycline was zero for almost 5 weeks. The fact that new cases occurred when the proportion of untreated recruits in training reached 50% indicates that the conditions favoring the outbreak persisted, strengthening the argument that prophylaxis with minocycline provided protection for the men treated. Furthermore, the fact that no new cases occurred after the second course of minocycline attests to its effectiveness, because vaccination of the recruits was not completed until 13 March, and it is likely that several days are required for protection to be conferred by the polysaccharide vaccine.

If the results of this study are compared with those reported by Bristow and co-workers (1), the advantage of minocycline over other agents used for chemoprophylaxis is apparent. They found that, during an outbreak of meningitis due to organisms resistant to sulfadiazine, seven separate attempts at prophylaxis with sulfadiazine, penicillin V, or oxytetracycline failed. In fact, over the 16-week period in which these efforts at prophylaxis were made in a population of recruits about equal to that at Fort Lewis, no more than one calendar week passed without a new case of meningococcal disease.

The observed effect of 100 mg of minocycline every 12 hr for 5 days on the rate of carriage of meningococci is consistent with results which have been published previously (5). For about 4 weeks, the rate remains low and then increases sharply. A single daily dose of 200 mg was not effective in the one company which was treated a second time. The reason for this failure is not apparent, but the meningococci isolated from these men were fully sensitive to minocycline. Therefore, this simplified regimen consisting of 200 mg daily in a single dose for 3 days should not be employed for prophylaxis without further study

While it is likely that minocycline is less effective as a prophylactic agent than sulfadiazine, their relative value cannot be assessed from this study. Kuhns and co-workers concluded that the effectiveness of sulfadiazine in prophylaxis depended upon (i) treating all individuals in the group simultaneously, (ii) treating all persons who joined the group subsequent to initiation of prophylaxis before they were incorporated into the group, and (iii) keeping the treated group closed to reinfection from outside sources (6). Two of these criteria for effective prophylaxis were not adhered to in this study, and, if minocycline is needed for prophylaxis in the future, each group entering training should receive drug before they begin the training cycle. It is possible that new cases would not have occurred within 5 weeks of the first course of minocycline if this prodedure had been followed.

Strains of *N. meningitidis* resistant to minocycline were not observed. However, if the drug is used for a long time in this setting, the possibility of resistant isolates occurring should be evaluated.

The ultimate control of the outbreak of meningococcal disease at Fort Lewis can probably be attributed to the use of the polysaccharide vaccine. This is the preferred method of preventing meningococcal disease, and, when an effective polyvalent vaccine becomes available, chemoprophylaxis on a large scale will be unnecessary. If, however, it is decided to administer the group C vaccine routinely throughout the military before vaccines against meningococci of groups A and B are ready for use, minocycline may be an important interim measure for controlling outbreaks due to sulfonamide-resistant organisms.

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LITERATURE CITED

1. Bristow, W. M., P. F. D. Van Peenen, and R. Volk. 1965. Epidemic meningitis in naval recruits. Amer. J. Public Health 55:1039–1045.
2. Deal, W. D., and E. Sanders. 1969. Efficacy of rifampin in

treatment of meningococcal carriers. N. Engl. J. Med. 281: 641–645.
3. Devine, L. F., D. P. Johnson, C. R. Hagerman, W. E. Pierce, S. L. Rhode, and R. O. Peckinpaugh. 1970. Rifampin Levels in serum and saliva and effect on meningococcal carrier state. J. Amer. Med. Ass. 214:1055–1059.
4. Goldstein, A. 1964. Biostatistics—an introductory text. Macmillan, New York.
5. Guttler, R. B., G. W. Counts, C. K. Avent, and H. N. Beaty. 1971. The effect of rifampin and minocycline on meningococcal carrier rates. J. Infect. Dis. 124:199–205.
6. Kuhns, D. M., C. T. Nelson, H. A. Feldman, and C. R. Kuhn. 1943. The prophylactic value of sulfadiazine in the control of meningococcic meningitis. J. Amer. Med. Ass. 123:335–339.