Evaluation of Sch 29,482 in the Eradication of *Neisseria meningitidis* from Nasopharyngeal Carriers

MARY P. PUGSLEY,* DAVID L. DWORZACK, CHRISTINE C. SANDERS, AND W. EUGENE SANDERS, JR.

Creighton University School of Medicine, Omaha, Nebraska 68131

Received 11 August 1983/Accepted 3 January 1984

Fifty-eight chronic carriers of *Neisseria meningitidis* were given 250 mg of Sch 29,482 or placebo orally every 6 h for 4 days. Although 22 of 29 subjects taking Sch 29,482 became culture negative while taking the drug, only five were culture negative 2 weeks posttherapy. There were no significant adverse reactions.

*Neisseria meningitidis* remains one of the leading causes of acute bacterial meningitis. Chemoprophylaxis of close contacts of patients can halt spread of the disease (13). Currently, rifampin and minocycline are the drugs of choice for this purpose (1). However, both agents have real and potential drawbacks. Minocycline use is associated with a high incidence of tinnitus and vertigo (9). The use of rifampin in closed populations has been followed by the isolation of rifampin-resistant strains (11, 14).

Sch 29,482, a new beta-lactam antibiotic, is an oral penem synthesized from 6-amino-penicillanic acid. The pharmacokinetics have been evaluated in normal volunteers by Gural et al. (10). The drug is rapidly absorbed from the gastrointestinal tract and has an elimination half-life of 0.95 to 1.37 h. After a dose of 250 mg is administered, a peak serum concentration of approximately 5 μg/ml is achieved after 1 h. Dillon et al. (7) studied 103 strains of *N. meningitidis* and found MICs of Sch 29,482 to range from 0.008 to >0.125 μg/ml. The minimum concentration inhibiting 90% of strains was 0.036 μg/ml.

After approval by the Creighton University Human Research Committee, we screened 555 healthy young men (the majority of which were college students) for the presence of nasopharyngeal *N. meningitidis* during March 1982 and found 139 (25%) to be colonized. Based on two consecutive positive cultures at weekly intervals, 81 of the 139 subjects (58%) were designated chronic carriers, and 59 of these men were entered into the study. Before entry, informed consent was obtained, a medical history was obtained from each subject, and a physical examination was performed. Laboratory screening tests (complete blood count, prothrombin time, urinalysis, urea nitrogen, creatinine, total and direct bilirubin, aspartate aminotransferase, and alkaline phosphatase) were also collected. No subject had evidence of penicillin allergy, antibiotic use within 3 weeks of the first culture, serious underlying disease, or concomitant infection.

In a double-blinded fashion, subjects were assigned to receive identical capsules containing either 250 mg of Sch 29,482 or placebo based on a random number table. Subjects were instructed to take one capsule every 6 h for 4 days (30 min before meals). The use of concomitant medication was limited to analgesics, decongestants, and antihistamines.

Each subject was questioned daily with regard to adverse reactions, and a daily nasopharyngeal culture was obtained. Cultures were also taken 7 and 14 days after drug administration was completed. Each subject underwent a repeat physical examination and laboratory tests 7 days after the conclusion of drug administration. Compliance was judged by the return of all capsules not taken and empty drug containers.

Nasopharyngeal swabs were streaked ontomodified Thayer-Martin agar and were incubated at 37°C in 10% CO₂ in air for 48 h. Colonies resembling *N. meningitidis* were identified by positive oxidase reactions and by the fermentation of glucose and maltose in the absence of sucrose and lactose fermentation. Cultures were considered positive if any *N. meningitidis* colonies were identified. The MICs of rifampin and Sch 29,482 were determined on pre- and posttherapy isolates by the agar dilution technique with an inoculum of 10⁸ CFU/ml incubated at 37°C in 10% CO₂. MBCs were not determined.

Serotypes of all isolates were also determined by the slide agglutination technique with cells suspended in physiological saline. Antisera were obtained from the Burroughs Wellcome Co.

Of the 59 men entering the study, 58 completed the period of drug administration and follow-up evaluations. Serotypes Z (21 strains) and B (14 strains) were the most common in our subjects. The remaining isolates were: serotype A (2 strains), C (1 strain), X (1 strain), and nontypable (19 strains). The MIC of rifampin for both pre- and poststudy isolates ranged from ≈0.007 to 0.5 μg/ml. The MIC of Sch 29,482 ranged from 0.015 to 0.25 μg/ml for pretherapy isolates and from ≈0.007 to 0.25 μg/ml for posttherapy isolates. In no subject was the poststudy MIC of either drug greater than twice the MIC of the pretherapy isolate.

Compliance was considered excellent; only one subject (placebo group) returned any unopened capsules. Of 29 subjects taking Sch 29,482, 22 (76%) were culture negative after taking the antibiotic for 3 full days (based on cultures taken at the beginning of the day 4 (Fig. 1). Only one subject among those who took the placebo was culture negative during the drug administration period. However, on day 7 after drug administration was completed, only 21% (6 of 29) of subjects who took Sch 29,482 were still culture negative as compared with 11% (3 of 29) of subjects who took placebo. Fourteen days after the completion of drug administration, 18% (5 of 29) of subjects who had taken Sch 29,482 were culture negative as compared with 3% (1 of 29) of the placebo group. The serotypes of pre- and poststudy isolates from each subject were the same, including those transiently culture negative while taking the capsules.

Adverse effects were minimal and transient. The most frequent complaint from subjects was malodorous urine, noted by all subjects taking Sch 29,482 and three subjects taking placebo.

* Corresponding author.
Diarrhea (four or more stools per day) occurred in two subjects taking Sch 29,482. Significant abnormal laboratory results found 7 days after Sch 29,482 administration included: (i) aspartate amino transferase six times normal in one subject; (ii) leukocyte count of 3,300/mm³ in one subject; and (iii) albuminuria of 30 mg/dl determined by Multistix (Miles Laboratories, Inc.) in one subject. All laboratory abnormalities had resolved by 3 to 5 days after they were noted, except for one subject who had persistent minimal albuminuria.

Many antibiotics with in vitro activity against *N. meningitidis* fail to eradicate its nasopharyngeal carriage, presumably because a concentration of the drug exceeding the MIC has not been achieved in nasopharyngeal secretions (4–6). Factors thought to favor nasopharyngeal penetration of an antibiotic are: small molecular weight, low charge at physiological pH, minimal binding to serum proteins, and lipid solubility (12). Although the MIC of Sch 29,482 inhibiting 90% of *N. meningitidis* is low (0.036 μg/ml), and the serum concentration achievable after a 250-mg oral dose is 5 μg/ml; the antibiotic does not appear to achieve sufficient concentrations in nasopharyngeal secretions to eradicate *N. meningitidis*. This may be a consequence of avid serum protein binding (95%), despite the relatively low molecular weight (297) and relative nonionization at physiological pH (pK 6.3), which should favor penetration of Sch 29,482 into saliva.

In the doses we used, the percentage of subjects culture negative 2 weeks after drug administration was no higher than that obtained with beta-lactam antibiotics studied in the past (2, 3, 8). In the majority of subjects taking Sch 29,482, enough antibiotic apparently reached the nasopharynx to suppress growth of *N. meningitidis*. However, the recovery of the same serotype in each subject before and after Sch 29,482 administration indicates that the organism was not eradicated. Higher doses of the antibiotic may be more effective; however, because of the extensive protein binding of Sch 29,482, very large doses may be necessary for efficacy.

This research was supported by a grant from Schering Corp. We thank Joan Fagnant and Laurier Couture for their assistance.

**LITERATURE CITED**


