

## Penetration of Oral Doxycycline into the Cerebrospinal Fluid of Patients with Latent or Neurosyphilis

CONNIE WHITESIDE YIM,\* NEIL M. FLYNN, AND FAITH T. FITZGERALD

Division of General Medicine, Department of Internal Medicine, University of California, Davis School of Medicine, Sacramento, California 95817

Received 10 December 1984/Accepted 29 April 1985

**Five patients with laboratory evidence of latent or neurosyphilis were treated orally with doxycycline (200 mg) twice a day for 21 days. After the seventh dose, the mean level of doxycycline in serum was 5.8  $\mu\text{g}/\text{ml}$ , with a mean drug level in cerebrospinal fluid of 1.3  $\mu\text{g}/\text{ml}$ . The mean penetration into cerebrospinal fluid was 26%. These preliminary findings suggest that doxycycline, administered orally at a dose of 200 mg twice a day, reaches a sufficient concentration in cerebrospinal fluid to be worthy of further evaluation as an alternative regimen to penicillin therapy for latent or neurosyphilis.**

Tetracycline is recommended for the treatment of syphilis in penicillin-allergic patients (7). Doxycycline, which has also been studied in the therapy of primary and secondary stages of syphilis (5, 8; L. J. Alexander and A. G. Schoch, Sixth Scientific Conference on Antimicrobial Agents and Chemotherapy; October 1966, Philadelphia, Pa.), has potential advantages. Due to its lipophilic quality, doxycycline achieves five times the concentration in the brain as do equal doses of tetracycline (3). Tetracycline has a half-life of 6 to 9 h, requiring a dosage schedule of four times daily (11). The longer half-life of doxycycline (20 h) permits twice daily dosing (11).

Doxycycline might also offer advantages in the therapy of latent and neurosyphilis if it proves to be effective. There are currently no accepted regimens for the use of oral penicillin in the treatment of latent or neurosyphilis (7). The various parenteral regimens advocated are time-consuming and uncomfortable for patients and, in certain cases, have been associated with treatment failure or have produced undetectable levels of penicillin in cerebrospinal fluid (CSF) (4, 6, 12). This study was designed to examine the penetration of oral doxycycline into the CSF of patients with latent or neurosyphilis. This dose was chosen on the basis of patient tolerance and pharmacokinetics of the drug and was suggested by Rein (10) as a possible regimen.

Participants were selected for this study from patients seen in the clinics or hospital of the University of California, Davis Medical Center, who had serological evidence for latent or neurosyphilis. Patients were asked to participate if they had a positive serum rapid plasma reagin, positive microhemagglutination test for *Treponema pallidum*, no evidence of primary or secondary syphilis, and no history of treatment for syphilis in the previous year. The study protocol was reviewed and approved by the Human Subjects Review Committee at the University of California, Davis Medical Center, and informed consent was obtained from all patients. Doxycycline, 200 mg, was taken orally twice daily with meals for 21 days. Patients were asked to keep a record of when each dose was taken and to contact the investigators if nausea, vomiting, abdominal pain, or diarrhea occurred. Patients were questioned on days 4 and 7 of therapy regard-

ing symptoms. Compliance was evaluated by review of the dosing record and by drug levels. CSF cell count and differential, protein, and glucose levels were determined. Simultaneous doxycycline levels in serum and CSF were determined at the time of lumbar puncture, 4 to 6 h after the seventh dose of doxycycline, by a large-plate well-diffusion assay as described by Barry (2). Specimens were stored frozen for up to 1 month and assayed in batches.

Five patients were studied (three men and two women), who ranged in age from 23 to 70 years (Table 1). Patient 1, who denied recent sexual contact, had a positive CSF Venereal Disease Research Laboratory culture which went untreated ca. 1 year prior. Patient 2 gave a history of syphilis years before. Patient 3 was referred because of a positive rapid plasma reagin titer of ca. 1:32 which has persisted several years despite treatment with penicillin. Patient 4 had a 50-year history of syphilis and was last treated 6 years ago. Patient 5, who denied knowledge of syphilis infection, stated that her last sexual contact was several years ago. The CSF of two patients revealed leuko-

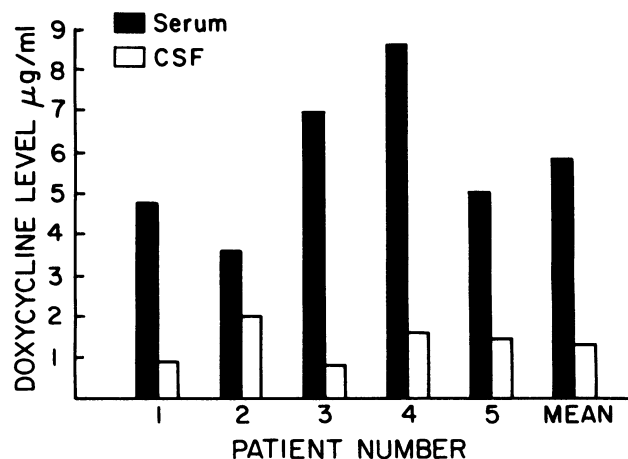


FIG. 1. Doxycycline levels in serum and CSF 4 to 6 h after the seventh dose of 200 mg twice a day.

\* Corresponding author.

TABLE 1. Clinical characteristics and antibiotic levels in five patients with latent or neurosyphilis<sup>a</sup>

Patient no.	Age (years)	Sex	Initial RPR <sup>b</sup>	CSF values <sup>c</sup> for:		Doxycycline level (µg/ml) in:		Penetration (%)
				WBC	VDRL	Serum	CSF	
1	23	M	1:32	94	1:4	4.8	0.9	19
2	59	M	1:32	0	neg.	3.6	2.0	56
3	61	M	1:64	19	1:8	7	0.8	11
4	70	F	1:1	0	neg.	8.6	1.6	19
5	65	F	1:1	1	neg.	5.0	1.4	28

<sup>a</sup> Microhemagglutination test for *T. pallidum* was positive in all five patients.

<sup>b</sup> RPR, Rapid plasma reagin.

<sup>c</sup> WBC, Leukocyte cell count; VDRL, Venereal Disease Research Laboratory; neg., negative.

cytes and a positive Venereal Disease Research Laboratory test which were confirmatory of neurosyphilis. The lumbar puncture on the other three patients showed normal CSF. All patients stated that they had taken the regimen as prescribed, and none reported side effects.

Figure 1 shows simultaneous CSF doxycycline levels in CSF and serum. Drug levels in serum ranged from 3.6 to 8.6 µg/ml (mean of 5.8), a greater than twofold difference. The mean doxycycline level in CSF was 1.3 µg/ml (range, 0.8 to 2.0). Penetration into the CSF varied from 11 to 56%, with a mean of 26%. There was poor correlation between the drug levels in serum and CSF in this small study (correlation coefficient, 0.25).

Oral doxycycline offers a potential advantage over tetracycline in the therapy of syphilis, since it can be given twice daily and is well absorbed after a meal. We have documented that compliance with and tolerance of the regimen used were excellent. The mean doxycycline level in serum achieved in this study is 76% higher than the peak level of tetracycline in serum expected from the current dosage recommended for treatment of latent or neurosyphilis (9). The mean level of doxycycline in CSF was 26% of the simultaneous drug level in serum, which is higher than the 14% penetration reported in a previous small study (1). The drug level in CSF might be expected to be even greater in patients with active neurosyphilis and inflamed meninges, but surprisingly, the two lowest drug levels in CSF in our cohort of patients were in the two patients with neurosyphilis.

Our small study shows good penetration of doxycycline into the CSF of patients with latent and neurosyphilis. Because penicillin treatment of the late stages of syphilis has been associated with treatment failure and because of the prevalence of penicillin allergy, further studies evaluating the efficacy of alternative regimens are warranted. The spirochetocidal level of doxycycline in humans, both in CSF and serum, needs to be determined in evaluating the potential clinical value of this regimen. Moreover, larger numbers of patients and long-term clinical and serological follow-up are necessary in using the established Centers for Disease Control guidelines (7). Our patients have been followed for

so short a time that we can as yet draw no conclusions as to the actual clinical efficacy of doxycycline.

This work was supported in part by a grant from Pfizer Laboratories.

#### LITERATURE CITED

1. Andersson, S. H., and K. Alestig. 1976. The penetration of doxycycline into CSF. *Scand. J. Infect. Dis.* 9(Suppl.):17-19.
2. Barry, A. L. 1981. Microbiological methods for monitoring antibiotics in body fluids, p. 204-219. *In* D. Bauer (ed.), *Interpretations in therapeutic drug monitoring*. American Society of Clinical Pathologists, Chicago, Ill.
3. Barza, M., R. B. Brown, C. Shanks, C. Gamble, and L. Weinstein. 1975. Relation between lipophilicity and pharmacological behavior of minocycline, doxycycline, tetracycline, and oxytetracycline in dogs. *Antimicrob. Agents Chemother.* 8:713-730.
4. Greene, B. M., N. R. Miller, and W. E. Bynum. 1980. Failure of penicillin G benzathine in the treatment of neurosyphilis. *Arch. Intern. Med.* 140:1117-1118.
5. Kim, Y. P., and S. D. Park. 1977. An evaluation of the therapeutic effectiveness of vibramycin (doxycycline) in early syphilis. *Korean J. Dermatol.* 15:45-46.
6. Mohr, J. A., W. Griffiths, R. Jackson, H. Saadah, P. Bird, and J. Riddle. 1976. Neurosyphilis and penicillin levels in cerebrospinal fluid. *J. Am. Med. Assoc.* 236:2208-2209.
7. *Morbidity and Mortality Weekly Report*. 1982. Sexually transmitted diseases treatment guidelines. *Morbid. Mortal. Weekly Rep.* 31(Suppl.):50-53.
8. Onoda, Y. 1979. Therapeutic effect of oral doxycycline on syphilis. *Br. J. Vener. Dis.* 55:110-115.
9. Ory, E. M. 1980. The tetracyclines, p. 119. *In* B. M. Kagan (ed.), *Antimicrobial therapy*. The W. B. Saunders Co., Philadelphia, Pa.
10. Rein, M. F. 1976. Biopharmacology of syphilotherapy. *J. Am. Vener. Dis. Assoc.* 3:109-127.
11. Sande, M. A., and G. L. Mandell. 1980. Antimicrobial agents, p. 1184. *In* L. S. Goodman and A. Gilman (ed.), *The pharmacological basis of therapeutics*. MacMillan Publishing Co., Inc., New York.
12. Tramont, E. C. 1976. Persistence of *Treponema pallidum* following penicillin G therapy. *J. Am. Med. Assoc.* 236:2206-2207.