

Penetration of Doxycycline into Cerebrospinal Fluid in Patients Treated for Suspected Lyme Neuroborreliosis

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Twelve patients were treated orally with 100 mg of doxycycline twice a day (b.i.d.) and 10 patients were treated with 200 mg b.i.d. for suspected tick-borne neuroborreliosis (Lyme borreliosis). At 5 to 8 days after the start of therapy, the mean concentrations in serum were 4.7 µg/ml for the doxycycline dose of 100 mg b.i.d. and 7.5 µg/ml for 200 mg b.i.d., 2 to 3 h after the last drug administration. The corresponding levels for cerebrospinal fluid were 0.6 and 1.1 µg/ml. Since a doxycycline concentration in cerebrospinal fluid above the estimated MIC for *Borrelia burgdorferi* (0.6 to 0.7 µg/ml) is wanted in patients treated for severe neuroborreliosis, the higher dose is preferable.

Neuroborreliosis, a central nervous system infection caused by *Borrelia burgdorferi*, is the most common complication to tick-borne spirochetosis (Lyme borreliosis) in Sweden (11). Intravenous penicillin G, 15×10^6 to 20×10^6 U daily for 10 to 14 days, has been effective in most cases (10-12), although its ability to penetrate the blood-brain barrier (BBB) is poor. Furthermore, the spirochete has been estimated to be only moderately susceptible to penicillin G (6, 7).

Oral tetracyclines shorten the duration of erythema chronicum migrans, the skin manifestations of early tick-borne borreliosis, and have been shown to reduce the risk of later illness (9). Because of its lipophilic quality, doxycycline gives a higher concentration in the brain than other tetracyclines (2). The rapidity and degree of gastrointestinal absorption of doxycycline permit oral dosages that in less than 2 h reach the same concentrations as those seen after intravenous administration (8). Oral doxycycline has therefore been used in the treatment of neurosyphilis (13). On the basis of these findings, we have previously treated mild cases of neuroborreliosis successfully with 100 mg of oral doxycycline twice a day (b.i.d.) for 10 to 20 days (4). Analyses of the antibiotic concentrations in cerebrospinal fluid (CSF), however, showed that only the lower limit for the estimated MIC of doxycycline for *B. burgdorferi*, i.e., 0.6 to 0.7 µg/ml, was reached. Concentrations of doxycycline above the MIC would be desired in the CSF of patients treated for severe neuroborreliosis. The present study was therefore designed to compare concentrations in serum and CSF after an increased dosage of doxycycline in patients treated for suspected neuroborreliosis.

MATERIALS AND METHODS

Twenty-two patients, aged 22 to 80 years (mean age, 55), were treated with doxycycline for suspected neuroborreliosis at the Department of Infectious Diseases, Östra Hospital, Göteborg, Sweden, from February 1987 to August 1988. Of these patients, 10 had radicular pains, 3 had facial paresis (Bell's palsy), 3 had peripheral paresis, 2 had muscle fatigue, 2 had ascending paresis, 1 had vertigo, and 1 had meningism

as the main symptom. Neuroborreliosis was suspected because of a history of preceding erythema chronicum migrans or tick bite in 11 patients, because of borderline or increased antibody titer in serum against *B. burgdorferi* before admission to the Department of Infectious Diseases in 7 patients, and because of pleocytosis in CSF in 2 patients without history of tick bite or erythema chronicum migrans. In two patients, neuroborreliosis was suspected only on clinical grounds.

A dose of 100 mg of doxycycline (Vibramycin; Pfizer Inc.) was taken orally b.i.d. for 10 days by 10 patients, while 200 mg was taken orally b.i.d. for 10 days by 12 patients. On days 5 through 8 of treatment, CSF was collected 2 to 3 h after the last drug administration. In one patient, an intraspinal catheter was inserted for treatment of severe chronic pains, and repeated CSF samples were taken through the catheter during the doxycycline treatment. On the day of lumbar puncture, the patients were questioned regarding adverse reactions to the drug. No other antibiotics were given simultaneously.

The CSF analyses included cell count, determinations of protein and glucose concentrations, electrophoresis on agar, and isoelectric focusing. Sera and CSF were examined for antibodies against *B. burgdorferi* by indirect immunofluorescence standard methods. In serum a titer of 1/320 was regarded as positive, and 1/160 was regarded as borderline. In CSF, a titer of 1/5 was regarded as positive.

Doxycycline in serum and CSF was measured by an agar diffusion assay (5). The samples were stored at -70°C until analyzed. The agar medium was Diagnostic Sensitivity Test Agar (Oxoid Ltd.) (pH 7.3). The test organism was a doxycycline-susceptible laboratory strain of *Bacillus* species (BAB94). Standards were prepared by weighing doxycycline-hydrochloride, with a potency of 865 µg/mg (lot no. 636-58001; Pfizer), dissolving it in phosphate buffer (pH 7.3), and further diluting it in pooled human serum (pH 7.3) or in 0.067 M phosphate buffer (pH 7.3) to final concentrations ranging from 0.25 to 8 µg/ml. The limit for sensitivity was 0.25 µg/ml. An internal control (in serum or buffer) was prepared by separately weighing and diluting doxycycline-hydrochloride to a final concentration of 5.0 µg/ml.

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TABLE 1. Concentrations of doxycycline in serum and CSF after 5 to 8 days of oral treatment

| Daily dose (mg) | No. of patients | Mean concn ($\mu\text{g/ml}$) \pm SD ^a of doxycycline in: | |
|-----------------|-----------------|--|----------------------------|
| | | Serum | CSF |
| 200 | 12 | 4.7 \pm 1.5 | 0.6 \pm 0.1 |
| 400 | 10 | 7.5 \pm 2.7 ^b | 1.1 \pm 0.4 ^b |

^a 2 to 3 h after drug administration.

^b Significantly higher concentrations than with 200 mg daily ($P < 0.01$).

RESULTS

All patients stated that they had followed the drug regimen as described. Two patients complained of mild phototoxic reactions, but none of the patients were suffering from adverse gastrointestinal reactions.

The mean concentrations of doxycycline in serum were 4.7 $\mu\text{g/ml}$ (range, 3.1 to 6.6 $\mu\text{g/ml}$) for the dose of 100 mg b.i.d. and 7.5 $\mu\text{g/ml}$ (range, 4.3 to 12 $\mu\text{g/ml}$) for 200 mg b.i.d. ($P < 0.01$). The corresponding levels for CSF were 0.6 $\mu\text{g/ml}$ (range, 0.4 to 0.8 $\mu\text{g/ml}$) for the dose of 100 mg b.i.d. and 1.1 $\mu\text{g/ml}$ (range, 0.6 to 1.9 $\mu\text{g/ml}$) for 200 mg b.i.d. ($P < 0.001$) (Table 1). Penetration into the CSF varied from 8 to 35% of concentration in plasma, with a mean of 15%. Eight patients had signs of BBB dysfunction, measured as an increased CSF/serum albumin ratio (mean albumin ratio, 18.0×10^{-3}). The penetration of doxycycline into CSF in these patients was 18.0% of concentration in plasma compared with 13.4% in patients without BBB dysfunction (mean albumin ratio, 5.1×10^{-3}). This was not a statistically significant difference.

The serum and CSF doxycycline concentrations in the patient who was monitored with repeated CSF analyses reached levels of 5.2 and 0.6 $\mu\text{g/ml}$, respectively, 2 h after the second dose of 200 mg of doxycycline. The concentrations varied between 6.2 and 12 $\mu\text{g/ml}$ in serum and between 0.6 and 1.5 $\mu\text{g/ml}$ in CSF during the following days (Table 2). The levels in CSF were stable on day 7, and they were not related to the time of drug administration (Table 2).

The mean ages were 52 years for the 100-mg-dose group and 58 years for the 200-mg-dose group. On days 5 through 8, three patients in the 100-mg-dose group and five patients in the 200-mg-dose group had CSF pleocytosis. The corresponding numbers for increased CSF/serum albumin ratio were five and three patients, respectively.

TABLE 2. Concentration of doxycycline after 200-mg dose b.i.d. in patient^a treated for suspected neuroborreliosis

| Total dose (mg) | Medication period (days) | Time of sample (h after drug administration) | Doxycycline concn ($\mu\text{g/ml}$) in: | |
|-----------------|--------------------------|--|--|-------|
| | | | Serum | CSF |
| 200 | 0.5 | 2 | 3.9 | <0.25 |
| 400 | 1 | 2 | 5.2 | 0.6 |
| 2,000 | 5 | 2 | 12.0 | 1.3 |
| 2,600 | 7 | Before | 5.8 | 0.6 |
| 2,800 | 7 | 0.5 | | 0.8 |
| 2,800 | 7 | 1 | 6.2 | 0.7 |
| 2,800 | 7 | 2 | | 0.8 |
| 2,800 | 7 | 3 | | 0.6 |
| 2,800 | 7 | 4 | | 0.8 |
| 4,000 | 10 | 2 | 8.5 | 1.5 |

^a Normal BBB measured as CSF/serum albumin ratio.

In seven patients, elevated CSF immunoglobulin G antibody titers against *B. burgdorferi* confirmed the diagnosis of neuroborreliosis. Three of these patients were in the 100-mg-dose group, and four were in the 200-mg-dose group. All of these patients improved after doxycycline treatment, while 9 of the 15 patients in whom neuroborreliosis was not confirmed showed no effects from the antibiotic therapy. Two of the seven patients with confirmed neuroborreliosis who improved had concentrations of doxycycline in CSF below 0.6 $\mu\text{g/ml}$.

DISCUSSION

At 5 to 8 days after initiation of therapy, doxycycline concentrations in CSF were found to exceed the estimated MIC for *B. burgdorferi* (above 0.6 $\mu\text{g/ml}$) in 9 of 10 patients treated with 200 mg b.i.d. but in only 3 of 12 patients treated with 100 mg b.i.d. Although the lower dose had been successful in a previous small study (4) and had a good clinical effect in the patients with confirmed neuroborreliosis in the present study, the higher dose is preferable in the treatment of severe neuroborreliosis.

The penetration of doxycycline into CSF compared with penetration into serum noted in this study (15%) was lower than the 26% reported in a previous study (13). This difference is probably explained by the time of sampling. In the earlier study, CSF and serum samples were taken simultaneously, 4 to 6 h after drug administration, while the samples in the present study were collected 2 to 3 h after the last dose. Peak levels in serum have been found about 2 h after oral administration (8), whereas CSF levels seemed to be stable after prolonged administration.

The time required to reach adequate doxycycline levels in CSF with the higher dose was short. Doxycycline concentrations had reached the 0.6- $\mu\text{g/ml}$ level in CSF after the second dose of 200 mg. With lower doses of doxycycline, it has taken 3 to 5 days to reach the same level (1). Since the risk of irreversible neurologic symptoms is increased with duration of infection, it is desirable to reach a therapeutic level in CSF as rapidly as possible.

It is generally agreed that patients with a damaged BBB have increased CSF concentrations of antibiotics. The penetration of doxycycline into CSF in our patients with elevated concentrations of CSF-albumin was only slightly increased, however. In patients with BBB dysfunction, the serum/CSF concentration ratio increased to 18.0% (not significant) compared with 13.4% in patients without signs of BBB impairment.

The aim of this study was to analyze doxycycline levels in serum and CSF and not to evaluate the clinical effect of the drug. Therefore, patients were admitted to the study when the diagnosis of neuroborreliosis was only suspected. In 15 patients, the diagnosis was subsequently not confirmed.

The optimal treatment for neuroborreliosis is not yet established. It has been suggested that ceftriaxone is more effective than penicillin G (3). Doxycycline has potential advantages over both penicillin G and ceftriaxone since it can be taken orally. Furthermore, *B. burgdorferi* is more susceptible to doxycycline than to penicillin G, and doxycycline penetrates the BBB better than penicillin does. The use of oral doxycycline at 200 mg b.i.d. offers the possibility of treating mild cases of neuroborreliosis in outpatient clinics, and it may also be a good alternative in severe cases.

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