NEUROBORRELIOSIS IN CHILDHOOD: TREATMENT WITH PENICILLIN SODIUM AND CEFTRIAXONE

M. M. Millner, G. H. Thalhammer

ABSTRACT

Beta-lactam antibiotics like ceftriaxone and penicillin G sodium have been shown to be active against *Borrelia burgdorferi in vitro*. Results of quantitative determinations of both antibiotic substances in cerebrospinal fluid of children are limited. 75 children (median age 96 months, range 10 to 176 months) with probable or definite neuroborreliosis were treated with ceftriaxone (1 x 50-90 mg/kg/day) or penicillin G sodium (4 x 80,000-120,000 I.U./kg/day) intravenously for 14 days. On day ten of therapy levels of penicillin G sodium (1, 1.5, 2, 3, 4, 5, or 6 hours after intravenous administration), and ceftriaxone (1, 2, 4, 6, 12, or 24 hours after intravenous administration) in serum and cerebrospinal fluid were measured using a micro agar diffusion bioassay. Results demonstrate that penicillin G sodium concentrations in cerebrospinal fluid were above minimum inhibitory concentration after five hours, but below the limit of determination in 60% after six hours. All ceftriaxone results in cerebrospinal fluid - even after 24 hours - were above minimum inhibitory concentration.

Penicillin G sodium serum values ranged from 46.6 to 0.1μg/ml (1 to 6 hours post dose) and ceftriaxone serum values from 261 to 5 μg/ml (1 to 24 hours post dose).

The role of administration intervals in antibiotic therapy of neuroborreliosis in children is discussed.

KEY WORDS

neuroborreliosis, antibiotic therapy, cerebrospinal fluid, ceftriaxone, penicillin

INTRODUCTION

Since Lyme Borreliosis (LB) is known to be a self limiting disease in some cases, the efficacy of antibiotic treatment cannot be discussed by looking at the clinical outcome of patients alone. Penicillin G sodium and ceftriaxone, a broad-spectrum b-lactamase-resistant third generation cephalosporine, are demonstrated to be active against *Borrelia burgdorferi* (*Bb*) *in vitro* (1-5). Although it is a bacterial agent, *Bb* spirochetes cause an aseptic type of meningitis.

A low-capacity, facilitated diffusion system at the blood-brain barrier and a transport from cerebrospinal fluid (CSF) back into blood via the choroid plexus have been described for penicillin G sodium and ceftriaxone in case of inflamed menin-

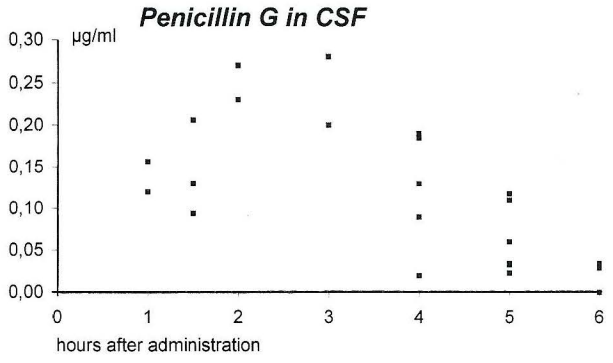

Figure 1. Penicillin G sodium concentrations in cerebrospinal fluid (CSF) on day 10 of therapy.

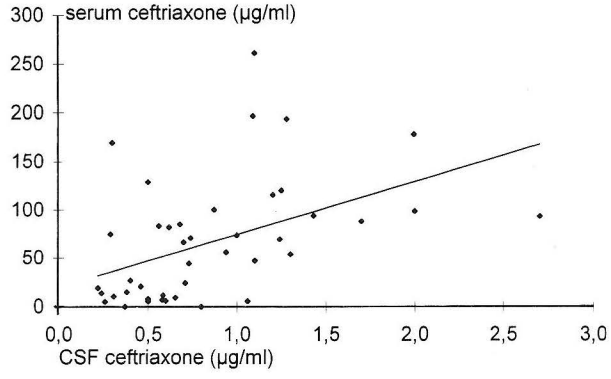

Figure 3. Correlation of ceftriaxone concentrations in serum and cerebrospinal fluid (CSF).

ges (6). Less is known about CSF penetration and pharmacokinetics of both substances in case of an aseptic meningitis in which antibiotics have to penetrate an intact blood-brain barrier. Therefore, concentrations of antibiotics are supposed to be lower. Since results of quantitative determinations of both antibiotic substances in CSF of children are very limited, pharmacokinetics of these substances in case of intact blood-brain barrier were studied by our group.

PATIENTS AND METHODS

Inclusion criteria over a 3-year period were:

- children with aseptic meningitis, with probable or definite central nervous system infection caused by *Bb*,

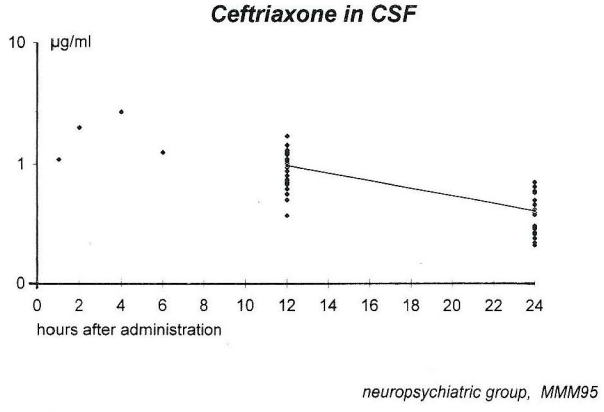

Figure 2. Ceftriaxone concentrations in cerebrospinal fluid (CSF) on day 10 of therapy.

- intact blood-brain barrier, investigated by the method of Reiber (7),

- treatment with 4 x 80,000-120,000 I.U. penicillin G sodium/kg/day, or 1 x 50-90 mg ceftriaxone/kg/day for 14 days intravenously, and

- availability of paired CSF and serum samples on day ten of treatment to measure concentration of both antibiotics.

75 children (median age 96 months, range 10 to 176 months) with probable or definite neuroborreliosis were treated at random with penicillin G sodium or ceftriaxone intravenously. On day ten of therapy paired serum and CSF samples were taken from each patient to control the course of the disease and the effect of antibiotic therapy. On this occasion these samples taken randomly 1, or 1.5, or 2, or 3, or 4, or 5, or 6 hours after intravenous administration (penicillin), and 1, or 2, or 4, or 6, or 12, or 24 hours after intravenous administration (ceftriaxone), respectively, were analyzed with a micro agar diffusion bioassay as a standard procedure (8).

RESULTS

The data in figure 1 demonstrate that 5 hours after administration of penicillin, the concentrations were above the minimum inhibitory concentration (MIC) of 0.005 µg/ml (3) in all cases. However, six hours after administration - which means exactly before giving teh next dose - concentration in 60% was fallen already below the determination limit - which may mean below its MIC.

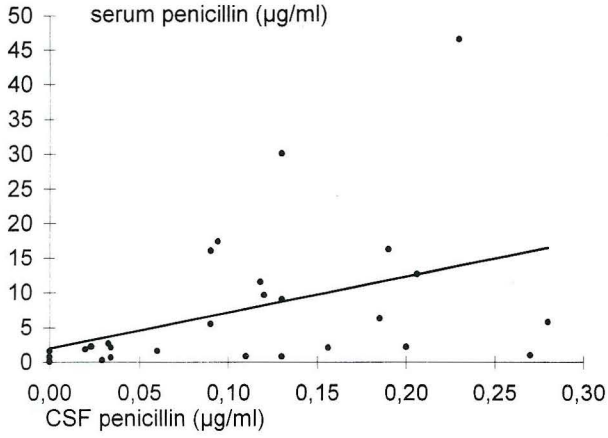

Figure 4: Correlation of penicillin G sodium concentrations in serum and cerebrospinal fluid (CSF).

Figure 2 shows all ceftriaxone levels in CSF to be above the MIC for *Bb*, which was reported to be 0.01 to 0.04 µg/ml (2,5).

In our study the elimination half-life of ceftriaxone was measured to be 9.7 hours.

Penicillin G sodium serum values ranged from 46.6 to 0.1µg/ml (1 to 6 hours post dose), and ceftriaxone serum values from 261 to 5 µg/ml (1 to 24 hours post dose). Thus, a good correlation between CSF and serum levels of both antibiotic substances are demonstrated (Figures 3 and 4).

DISCUSSION

Drugs administered for the treatment of LB have to be active against *Bb* in vitro which is undoubtedly the case for penicillin G sodium and ceftriaxone. Since 72 to 96 hours of an effective antibiotic concentration are necessary to eradicate 99% of the *Bb* spirochetes (5), effective therapy needs continuos levels of the antibiotic substances above its MIC. Moreover, penetration of antibiotics through blood-brain barrier is important not only for neuroborreliosis but also for early forms of the disease (i.e. dermatoborreliosis) as early dissemination of the infectious agent has been demonstrated (9). The presented data give clear evidence for such a good penetration of both antibiotics through blood-brain barrier even in case of aseptic meningitis in which the blood-brain barrier is fully intact. CSF concentrations above its MIC are demonstrated for both antibiotics. The long half life of ceftriaxone when given once a day guarantees therapeutic levels even after 24 hours. Penicillin G sodium was already below determination limit in 60% of our patients. This may indicate that penicillin G sodium with its short half life is not available continuously in CSF and thus, eradication of *Bb* could be insufficient in some cases. Further measurements of concentrations of penicillin in CSF samples will be necessary to determine whether it should be given at intervals of 6 hours or preferably 5 hours in the treatment of neuroborreliosis in children to guarantee continuous therapeutic levels in the CSF.

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