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ORIGINAL ARTICLE

Experimental study of cerebrospinal fluid tumor necrosis factor-alpha release in penicillin- and cephalosporin-resistant pneumococcal meningitis treated with different antibiotic schedules

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Abstract *Background/Purpose:* To measure the inflammatory response in terms of tumor necrosis factor-alpha (TNF-α) levels in cerebrospinal fluid (CSF), using bacteriolytic versus non-bacteriolytic antibiotic therapy and adjunctive treatment with dexamethasone in an experimental rabbit model of pneumococcal meningitis.
Methods: In a rabbit model of pneumococcal meningitis, we tested CSF TNF-α levels in several samples from rabbits infected with the HUB 2349 strain and treated with ceftriaxone 100 mg/kg/d, ceftriaxone plus vancomycin 30 mg/kg/d, or daptomycin at 15 mg/kg or 25 mg/kg. Daptomycin schedules were compared with the same doses in combination with dexamethasone at 0.125 mg/kg every 12 hours over a 26-hour period.
Results: The ceftriaxone group had the highest levels of TNF-α. TNF-α levels were significantly higher after ceftriaxone administration than in both daptomycin groups. The high-dose daptomycin group presented the lowest inflammatory levels in CSF samples. Adjunctive treatment with dexamethasone in this group modulated the inflammatory response, bringing down CSF TNF-α levels.
Conclusion: CSF TNF-α levels were significantly lower in rabbits treated with daptomycin than in rabbits treated with ceftriaxone. Daptomycin avoided the inflammatory peak after

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administration observed in ceftriaxone-treated rabbits. The use of daptomycin plus dexamethasone achieved a significantly larger reduction in CSF TNF-α levels.

Introduction

Inflammation has been related to neuronal damage and sequelae in patients with bacterial meningitis. Inflammation generated during antibiotic therapy may be dependent on the antibiotic's mechanism of action. Finding a therapy without a significant host inflammatory cascade would be particularly useful.

Certain bactericidal antibiotics that inhibit the synthesis of the cell wall, such as β-lactams, cause bacterial lysis and the release of proinflammatory bacterial products, leading to an increased inflammatory response.[1]

Tumor necrosis factor alpha (TNF-α) is an important early proinflammatory cytokine associated with inflammation-related complications of bacterial meningitis; patients with bacterial meningitis present increased cerebrospinal fluid (CSF) TNF-α levels early in the course of the disease.[2] An early study by Saukkonen et al[3] determined the role of cytokines in the CNS, including TNF-α, using a rabbit model of meningeal inflammation. The results suggested that cytokines have multiple inflammatory activities in the CNS and contribute to tissue damage.[3]

Several reports in an infant rat model by Barichello et al[4,5] evaluated the levels of TNF-α in the hippocampus and prefrontal cortex, showing that the cytokine was produced mainly in the first 6—24 hours of the immune response. TNF-α played an important role in the pathophysiology and might be related to brain damage in the first hours of pneumococcal meningitis.[4,5]

Daptomycin is a nonbacteriolytic antibiotic with elevated bactericidal activity against a wide range of gram-positive pathogens and may have minimal effects on cytokine production.[6]

In experimental models of meningitis comparing its effectiveness with that of ceftriaxone therapy, daptomycin has already demonstrated a highly bactericidal effect and its ability to attenuate inflammation in the CSF without causing cortical damage.[7,8]

The aim of this study was to measure the inflammatory response in terms of the release of TNF-α in the CSF, comparing bacteriolytic and nonbacteriolytic antibiotic therapy and adjunctive treatment with dexamethasone in an experimental rabbit model of meningitis.

Methods

Bacterial strain

A HUB 2349 penicillin- and cephalosporin-resistant strain of *Streptococcus pneumoniae* belonging to serotype 23F and isolated from a patient with meningitis was used. Minimum inhibitory concentration (MIC) and minimum biocidal concentration (MBC; mg/L) were as follows: penicillin 4/4; ceftriaxone 2/4; vancomycin 0.25/0.25; and daptomycin 0.09/0.18.

Meningitis model

The experimental protocol was in keeping with Spanish legislation on animal experimentation and was approved by the Ethics Committee for Animal Experiments at the University of Barcelona, Barcelona, Spain. The rabbit model of meningitis described originally by Dacey and Sande[9] was used, with slight modifications. Young female New Zealand white rabbits were anesthetized intramuscularly with 35 mg/kg of ketamine (Ketolar; Parke-Davs, Prat de Ll., Spain) and 5 mg/kg of xylazine (Rompum; Bayer AG, Leverkusen, Germany). Meningitis was induced using an intracisternal injection of 250 μL of a saline suspension containing 106 colony forming units/mL of inoculum, and therapy was started 18 hours postinoculation. Rabbits were anesthetized using urethane (Sigma Chemical Company, St Louis, MO, USA) at 1.75 g/kg subcutaneously and thiopental sodium (Tiopental; B. Braun Medical S.A., Rubí, Spain) at 5 mg/kg intravenously (iv). Animals were placed in the stereotactic frame and a baseline CSF sample was taken (0 hours). A dose of dexamethasone (Fortecortin; Merck, Mollet del Vallés, Barcelona, Spain) of 0.25 mg/24 h divided every 12 hours was given intravenously. Ten minutes later, antibiotic therapy was administered. CSF samples were taken after 2 hours, 6 hours, 24 hours, and 26 hours of therapy. Hydration was ensured throughout the experiment. Mortality was assessed at 26 hours. Surviving animals were euthanized using a lethal dose of thiopental sodium at the end of each experiment.

Therapeutic groups

Antibiotic iv therapy was then administered for 26 hours using one of the following therapy schedules: ceftriaxone ($n = 8$ rabbits) at 100 mg/kg once daily, vancomycin at 15 mg/kg every 12 hours plus ceftriaxone ($n = 9$ rabbits), daptomycin ($n = 8$ rabbits) at 15 mg/kg given once daily, daptomycin ($n = 9$ rabbits) 15 mg/kg given once daily plus dexamethasone at 0.125 mg/kg every 12 hours, daptomycin ($n = 9$ rabbits) at 25 mg/kg given once daily, and daptomycin ($n = 10$ rabbits) 25 mg/kg given once daily plus dexamethasone at 0.125 mg/kg every 12 hours. Untreated controls received saline. The pharmacokinetics and pharmacodynamics studies and the dosing regimens for antibiotics and dexamethasone have been previously described.[10,11]

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