Combination of Daptomycin plus Ceftriaxone Is More Active than Vancomycin plus Ceftriaxone in Experimental Meningitis after Addition of Dexamethasone

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We examined the cerebrospinal fluid penetration of daptomycin after the addition of dexamethasone and its bactericidal efficacy with and without ceftriaxone in an experimental rabbit model of pneumococcal meningitis. The combination of daptomycin with ceftriaxone was the most efficacious regimen for pneumococcal meningitis. The previous addition of dexamethasone affected the antibacterial activity of daptomycin only marginally, either as monotherapy or combined with ceftriaxone, although the penetration of daptomycin into inflamed meninges was significantly reduced from 6 to 2%. Daptomycin with ceftriaxone might be a potential candidate for the empirical therapy of bacterial meningitis, although the activity of this regimen against Listeria monocytogenes remains to be demonstrated.

The worldwide continuous spread of penicillin-resistant pneumococci represents one of the major challenges for clinicians and infectiologists. The epidemiological situation in Europe varies considerably with a global tendency of increasing penicillin resistance rates from 6% in 1997 to 22% in 1999 (8). In the United States and Canada, the combined rate of penicillin intermediate plus resistant strains varied between 24% and 67% as reported in the multinational SENTRY antimicrobial resistance surveillance program (5). Based on a recent study, the rates of highly resistant strains were 14.7%, 12.7%, and 15.9% for Europe, Latin America, and North America, respectively (9). In adults, pneumococci are the most frequent pathogens causing meningitis (1, 11). In meningitis due to highly resistant strains, high-dose vancomycin has been recommended, either alone or in combination with third-generation cephalosporins (1, 14). In adults, the addition of steroids, now established as standard adjunctive therapy, reduces the penetration of vancomycin into the cerebrospinal fluid (CSF) by 29% (10, 12).

We have previously shown that daptomycin, a cyclic lipopeptide, was very efficacious in experimental pneumococcal meningitis due to a penicillin-resistant strain. The comparator regimen was ceftriaxone combined with vancomycin, which is the standard empirical regimen.

MATERIALS AND METHODS

Pneumococcal strain. The pneumococcal strain Streptococcus pneumoniae WB4 was isolated from a patient at the Inselspital in Bern, Switzerland, and has been routinely used in this experimental model. The MICs for this strain were as follows: 4 mg/liter for penicillin, 0.5 mg/liter for ceftriaxone, 0.12 to 0.25 mg/liter for vancomycin, and 0.06 mg/liter for daptomycin.

Experimental meningitis model. The experimental rabbit meningitis model described by Dacey and Sande (4) was used in this project. The experimental protocols were approved by the Kantonales Veterinairamt des Kantons Bern. Pathogen-free New Zealand rabbits were provided by the Zentralstelle der Medizinischen Fakultät der Universität Bern, where all the experiments were performed.

One day before an experiment, rabbits were anesthetized with intramuscular injections of ketamine (30 mg/kg of body weight) and xylazine (15 mg/kg) to fit prostheses on their calvaria to facilitate subsequent placement within a stereotactic frame. On the day of the experiment, rabbits received 1.75 g/kg ethylcarbamate (urethane) subcutaneously and then 10 mg/kg pentobarbital intravenously to induce deep anesthesia. The animals were fixed in a stereotactic frame, and a 3.5-in. (25-gauge) spinal needle was introduced in the cisterna magna. Following the withdrawal of 0.2 ml of CSF, pneumococci (1 × 107 CFU in 0.2 ml of saline solution) were injected into the subarachnoid space. After inoculation, the animals were brought back to the cages for the night. The next day the rabbits were fitted again in the frames using the techniques and anesthesia described above. A catheter was fixed in the femoral artery for serum sampling. A spinal needle was fixed again in the subarachnoid space. Antibiotics were injected intravenously at doses published in the literature (12, 13) (100 mg/kg for ceftriaxone and 20 mg/kg for vancomycin). Daptomycin was tested at a dose of 15 mg/kg, as suggested, in order to mimic serum levels measured in humans. Vancomycin was given at hours 0 and 4 and ceftriaxone was given at hour 0 according to their pharmacokinetic properties. Daptomycin was administered in one dose at hour 0. CSF (0.2 ml) was sampled at 6, 1, 2, 4, 6, and 8 h after initiation of the antibiotic treatment. Dexamethasone (1 mg/kg) was administered 15 min before antibiotics were injected (10). Untreated controls received saline solution.

Blood was sampled at 0, 0.25, 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 h. Each group included untreated controls. All antibiotics and dexamethasone were purchased from commercial sources.

The antibacterial activities of the different regimens are presented as killing
RESULTS AND DISCUSSION

The kinetics of daptomycin (15 mg/kg) in the CSF when daptomycin was injected 15 min after dexamethasone (1 mg/kg) is presented in Fig. 1. The penetration of daptomycin through inflamed and noninflamed meninges has been described in previous studies (2, 3, 6). Interestingly, the penetration of daptomycin is affected by the addition of dexamethasone. In the present study, after the addition of dexamethasone, the daptomycin CSF levels increased progressively and peaked around 2 mg/liter at 4 hours after intravenous injection and remained stable until the end of the experimental period. Measured by comparison of AUC for serum/AUC for CSF, the penetration of daptomycin into the CSF was significantly more active than the comparator based on a combination of vancomycin and ceftriaxone (−1.01 versus −0.68 log10 CFU/ml · h), as shown in previous studies (3). Only three CSF samples were sterile at the end of the experimental period in this group. As expected, the addition of ceftriaxone to daptomycin did not increase the antibacterial effect against this penicillin-resistant strain. Nine out of 10 CSF samples were sterile after 4 h in this group.

The effect of dexamethasone alone has not been tested in uninfected controls in this study.

The addition of dexamethasone affected the efficacy of daptomycin with or without dexamethasone over 8 h. Killing activity was presented as log10 CFU/ml ± SD. The broken line represents the limit of detection. The points that are significantly different (P < 0.05) between the two curves are indicated by the asterisks.

In Table 1, the efficacies of the different regimens are summarized. In the control group, the bacterial titer increased only modestly during 8 h (+0.25 log10 CFU/ml). One injection of daptomycin produced a highly bactericidal activity with a decrease of 1 log10 CFU/ml per hour and managed to stabilize the CSF samples of all rabbits at the end of the treatment period. Eight out of 10 CSF samples were already sterile after 4 h in the treatment group. Daptomycin monotherapy was significantly more active than the comparator based on a combination of vancomycin and ceftriaxone (−1.01 versus −0.68 log10 CFU/ml · h), as shown in previous studies (3). Only three CSF samples were sterile at the end of the experimental period in this group. As expected, the addition of ceftriaxone to daptomycin did not increase the antibacterial effect against this penicillin-resistant strain. Nine out of 10 CSF samples were sterile after 4 h in this group. The effect of dexamethasone alone has not been tested in uninfected controls in this study.

The addition of dexamethasone affected the efficacy of daptomycin monotherapy by delaying the sterilization of the CSF by 2 hours (all CSF samples were sterile only after 6 hours in this group). Although differences were significant at hour 2 and 4 (Fig. 2), the activity was similar at hour 8, the end of the treatment period. The combination of daptomycin with ceftri-
axone was not significantly superior to daptomycin monotherapy but restored the rapid killing activity of daptomycin (8 out 10 CSF samples were sterile already after 4 h). The addition of dexamethasone did not influence the activity of these regimens (Fig. 3). The standard regimen (ceftriaxone plus vancomycin) produced the lowest decrease of the viable cell count in this study (Fig. 4). The addition of dexamethasone affected only slightly the efficacy after 8 h, although the difference was not significant. No CSF sample was sterile by this regimen at the end of the experimental period.

In summary, this study reveals several interesting aspects about the role of daptomycin in the treatment of bacterial meningitis. It is noteworthy that the penetration of daptomycin into meninges was reduced significantly (from 6 to 2%) by the previous addition of dexamethasone. However, despite the low MIC of daptomycin for this penicillin-resistant strain (0.06 mg/liter) with CSF level/MIC ratio around 30 during the entire treatment period, the addition of dexamethasone affected the antibacterial activity of daptomycin by delaying the sterilization of the CSF. Nevertheless, with or without the addition of dexamethasone, all CSF samples were sterile at the end of the treatment period by daptomycin monotherapy.

Daptomycin monotherapy (with or without dexamethasone) was significantly superior to ceftriaxone combined with vancomycin, the least efficacious regimen. The least active regimen was the standard regimen (vancomycin plus ceftriaxone) after the addition of dexamethasone (Fig. 4). One conceivable explanation might be the reduced penetration of vancomycin into the CSF due to the addition of dexamethasone (10).

As expected, the addition of a β-lactam antibiotic (ceftriaxone) did not improve the efficacy of daptomycin monotherapy because the CSF samples of rabbits were already sterile by daptomycin monotherapy.

However, on the basis of its antibacterial spectrum, this combination treatment could be evaluated as a potential candidate for the empirical treatment of bacterial meningitis, covering the major gram-positive and gram-negative human pathogens. However, in cases of meningitis due to Listeria monocytogenes, the efficacy of daptomycin might be questionable because of a higher MIC of daptomycin for this microorganism (0.25 to 4 mg/liter) reported in the literature (2), especially if dexamethasone is added. On the other hand, the nonlytic activity of daptomycin, recently demonstrated in pneumococcal meningitis (15), led to a reduced inflammatory response of the host and prevented brain injury during pneumococcal meningitis (7).

These preliminary data suggest the potential role of daptomycin combined with β-lactam antibiotics as empirical treatment of bacterial meningitis, although the efficacy of this regimen against Listeria monocytogenes needs to be clarified.

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REFERENCES


