INTRODUCTION

Treatment of infections in the central nervous system (CNS) is complicated due to different permeability of various antibiotics across the blood-cerebrospinal fluid (CSF)-barrier (B-CSF-B) and the blood-brain-barrier (BBB). In patients with brain abscesses, the therapy can be further complicated due to limited penetration of antibiotics into the abscess cavity. Other pharmacokinetic and pharmacodynamic properties of the antibacterial agents also affect their preference in treating infection in CNS. The choice of antibiotics for empirical therapy may be facilitated by the knowledge of location of the abscess in the brain, which may not be accessible for microbiological testing. The microbial flora colonising or infecting the extracerebral structure(s) near to the site of the abscess are likely to be involved in its pathogenesis. This update reviews the use of conventional antibacterial agents following more experience and data on their use and some of the newer agents.

BARRIERS TO THE PASSAGE OF DRUGS INTO THE BRAIN

The CNS is normally protected from free exposure to administered drugs due to a unique functional and morphological nature of brain capillaries. Agents are tested for their ability to cross these barriers to avoid toxicity to the CNS, and to measure their efficacy in treating CNS conditions. The CSF compartment is protected by B-CSF-B and in health the B-CSF-B permits the entry of simple, small molecules but the passage of more complex drugs is very limited. Inflamed meninges, however, enhance their entry into the CSF. This could be due to acidosis in the plasma-CSF pH gradient that facilitates the entry of the agents ionised at normal pH, e.g., β-lactams. Adjuvant therapy with anti-inflammatory agents might hinder the passage of drugs, particularly larger molecules, e.g., vancomycin, across the barriers. Lipid solubility of drugs, e.g., fluoroquinolones, also facilitates drug delivery to this compartment. Only the fraction of the drug free in serum, and not bound to serum proteins, is available for crossing the barrier. Most drugs are removed from the CSF compartment by active, energy-dependent mechanisms that are inhibited during meningitis. Hydrophilic drugs, e.g., β-lactams, have longer half life in CSF compared with serum, allowing longer dosing intervals.

Brain parenchyma is protected from free exposure to drugs by BBB. Distribution of antibiotics in the interstitial space of the brain is dependent on both the BBB and B-CSF-B. The BBB is important in delivery of drugs to brain parenchyma in cases of metabolic or parenchymal brain disease and in areas of the brain with cerebritis and abscess. It has been shown that passage of antibiotics across the BBB is enhanced in the areas of brain affected by inflammation. Interstitial space in the brain is contiguous with the CSF compartment and there is no anatomical CSF-brain barrier. Drugs delivered directly to the CSF do not, however, effectively penetrate brain tissue possibly due to tortuous nature of the interstitial space in the brain.

ANTIBIOTICS IN CNS INFECTIONS

Choice of antibiotic in the treatment of infection in CNS depends upon the availability of the antibiotic in the brain tissue, abscess fluid or CSF. Table I summarises the conventional antibiotics that can appear in therapeutic concentrations in the CSF compartment and abscess fluid.
NEW OR EXPERIMENTAL ANTIBACTERIAL AGENTS

Linezolid belongs to a novel group called oxazolidinones, which act in inhibiting the initiation of bacterial protein synthesis. Linezolid has been licensed in the UK for the treatment of pneumonia and skin and soft tissue infections. Being effective generally against Gram-positive organisms, this agent is also active against more resistant organisms, methicillin-resistant S. aureus, penicillin-resistant pneumococcus and vancomycin resistant enterococcus. It attains acceptable levels in CSF and brain tissue and has been employed to treat difficult brain infections caused by Gram-positive organisms. Effective levels in CSF of daptomycin, a lipopetide, another novel agent, in experimental pneumococcal-meningitis model have been demonstrated.

Fluoroquinolones achieve therapeutic levels in brain tissue and CSF owing to their lipophilic properties. Moxifloxacin, a newer fluoroquinolone, is active against penicillin-resistant and penicillin-sensitive pneumococci and vancomycin-tolerant pneumococci, in addition to the Gram-negative spectrum typical of fluoroquinolones.

Penetration of antibiotics in therapeutic concentrations into brain abscess is not, however, the only important factor in the management of these conditions. Factors that determine the antimicrobial activity of antibiotics in the purulent fluid, e.g., bacterial growth rate and inoculum size, and sequestration of the abscess and, most importantly, the nature of the antimicrobial activity of antibiotics under consideration must be taken into account. Larger doses of antibiotics are used in these cases to increase the availability of drugs to cross over the barriers, and length of treatment is usually guided empirically by the progress in the individual cases. Most studies recommend 4-6 weeks treatment with appropriate antibiotics in brain abscess. The choice between medical management with or without surgical intervention depends, among the other factors, on the initial size of abscess. Abscesses smaller than 1.7 cm (range, 0.8—2.5 cm) have been successfully treated with antibiotics alone, while medical treatment alone cannot be relied upon when the size is larger (4.2 cm, range 2.0-6.0).

There are two possible routes for the bacteria to cause brain abscesses: contiguous spread from the carrier sites in the nose and throat, sometimes facilitated by local trauma; and metastatic seeding during bacteremia. While a local extension of infection usually results in a single abscess with polymicrobial flora, bacteremia might be complicated with multiple abscesses involving only one type of organism.

Due to uncertainty about the issue of bioavailability in the CNS, cases of brain abscess might be preferably treated with multiple intravenous antibiotics, combined wherever possible with intraventricular antibiotics delivered through an EVD inserted to control the CSF pressure or for drainage of pus. We support the view that insertion of an EVD solely for antibiotic therapy might be justified in cases where the organisms are sensitive only to antibiotics with poor CNS penetration and an increase in the antibiotic dose is precluded by its toxicity, or where iv therapy alone has not been clinically effective or has not sterilised the CSF compartment.

Duration of therapy depends upon the size and site and number of abscesses, the organisms involved and availability of bactericidal agents with appropriate CSF penetration. In most cases, 8-12 weeks therapy is required. The progress needed to be closely monitored with inflammatory markers, repeated scanning, if necessary, and for adverse drug effects.

REFERENCES

9. Fenstermacher JD, Blasberg RG, Patlak CS. Methods for

Table 1: Activity of conventional antibiotics in the CNS.

<table>
<thead>
<tr>
<th>Antibiotic</th>
<th>Level in abscess fluid</th>
<th>CSF level</th>
<th>Reference</th>
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</thead>
<tbody>
<tr>
<td>Penicillin</td>
<td>Therapeutic with high dose regimen</td>
<td>10</td>
<td></td>
</tr>
<tr>
<td>Sub-therapeutic with usual doses</td>
<td>Therapeutic**</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Amoxicillin/Amoxicillin +clavulanic acid</td>
<td>NA</td>
<td>Therapeutic**</td>
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<tr>
<td>Fluoroquinolones*</td>
<td>Therapeutic</td>
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<td>12</td>
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<tr>
<td>Imipenem</td>
<td>Therapeutic</td>
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<tr>
<td>Cefotaxime</td>
<td>Therapeutic</td>
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</tr>
<tr>
<td>Cefuroxime</td>
<td>NA</td>
<td>Low***</td>
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</tr>
<tr>
<td>Cefazidime</td>
<td>NA</td>
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<tr>
<td>Other b lactams</td>
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</tr>
<tr>
<td>Aminoglycosides</td>
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<td>Erythromycin</td>
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<td>Chloramphenicol*</td>
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<td>Trimethoprim+ Sulfamethoxazole*</td>
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<td>Rifampicin</td>
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<tr>
<td>Metronidazole*</td>
<td>NA</td>
<td>Therapeutic**</td>
<td>25</td>
</tr>
</tbody>
</table>

NA, reliable data not available; * Lipid-soluble; ** therapeutic levels are achieved only with a barrier disorder; *** The authors argue against the use of cefuroxime in neurosurgical prophylaxis.


31. Jansson AK, Enblad P, Sjolin J. Efficacy and safety of cefotaxime