UNDERSTANDING THE DISEASE

Understanding central nervous system efficacy of antimicrobials

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Introduction

The requirements for antimicrobial treatment to reach the central nervous system (CNS) are of maximal importance, for two major reasons: (i) the brain is an immuno-privileged site, with virtually no leukocytes in the brain parenchyma or cerebrospinal fluid (CSF) at baseline; (ii) the blood–brain barrier (BBB) drastically reduces the diffusion of antimicrobials into the CNS [1]. Treatment of CNS infections has been a major area of research since the discovery of the first antimicrobials. Treatment regimens recommended for encephalitis [2, 3], meningitis [4], and brain abscess [5], have to comply with the pharmacokinetic (PK), and pharmacodynamic (PD) characteristics of available antibacterial, antiviral, antifungal, and antiparasitic agents [6]. Due to the numerous constraints created by the BBB, therapeutic options are quite limited, so that current practices for treatment of CNS infections are remarkably similar worldwide, with much less heterogeneity than for other major infectious diseases (e.g. pneumonia, abdominal, or skin and skin structure infections). This paper summarizes the main parameters that must be taken into account to ensure efficacy of antimicrobial agents in the CNS, with an emphasis on antibacterial drugs.

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Physiology of the cerebrospinal fluid

CSF is an ultrafiltrate of plasma that supports brain cells and eliminates waste products, acting as an alternate circulation system. The rate of CSF production in adult humans is 0.5 mL/min, two-thirds originating from the choroid plexus, and one-third from extracellular spaces of the brain and the spinal cord. Complete exchange of CSF occurs 5 times a day [7]. CNS infections have three major effects on CSF dynamics: (i) increase in BBB permeability, proportionally to the extent of inflammation; (ii) reduction of CSF flow, in association with higher intracranial pressure; (iii) blockage of CSF flow, sometimes occurring when there is obstruction, for example due to exudate at the basal cisterns. Antibiotics are not metabolized in the CSF, so that their concentrations and half-lives in the CNS compartment depend on the balance between penetration, and elimination. No tight barrier exists between the CSF and the interstitial fluid of the brain, so that even large molecules enter the brain from the CSF by diffusion [8]. Although drug concentrations in nervous tissue, extracellular space, and CSF may differ, CSF concentrations provide reliable estimates of drug concentrations in the CNS compartment as a whole [1].

Blood–brain barrier

The functionality of the BBB has been illustrated by landmark experiments conducted by Ehrlich and colleagues 130 years ago (reviewed in [1]). The intravenous injection of anilin dyes in animals was able to stain all organs except the CNS. Conversely, injection of trypan blue in the CSF homogeneously tainted the brain and the spinal cord, but no other organ. The BBB consists of cerebral vascular endothelium of the arachnoid membrane and the choroid plexus epithelium, which form a barrier of cells linked by tight junctions and surrounded by lipid layers. Diffusion of antimicrobials into the CNS mostly depends on their ability to cross the BBB and is inversely proportional to molecule size. The lipophilicity of a drug is another major determinant of CNS

penetration. Diffusion of highly (fluoroquinolones, rifampin), or moderately (cefotaxime or ceftriaxone) lipophilic drugs is much higher than that of hydrophilic drugs (penicillins). Other factors determining CNS penetration include active transport, meningeal inflammation, and protein binding. The impact of the latter is major in uninflamed meninges, with CNS diffusion rates 15 times lower for ceftriaxone (plasma protein binding > 90%), as compared to cefotaxime (protein binding < 40%). However, in patients with meningitis, protein binding has a limited impact on CNS diffusion. Dexamethasone, recommended as an adjunctive treatment for community-acquired bacterial meningitis, significantly reduces the CNS diffusion of large hydrophilic molecules (e.g. vancomycin), but has a limited impact for smaller, and/or lipophilic molecules [9]. CNS infections with limited or no meningeal inflammation (e.g. ventriculitis, brain abscess) may result in lower CNS diffusion of antimicrobial agents, as compared to meningitis.

PK/PD of antimicrobials in CSF

The PK of antimicrobials in the CNS has been investigated through complementary approaches. Simultaneous determination of the concentration of one antimicrobial agent in the plasma and in the CSF is often used to estimate its diffusion in the CNS, but such a simple calculation has many drawbacks, as it provides variable, and often inaccurate, estimates of CNS diffusion. Indeed, the timing of sampling has a major effect on these estimates, given that concentrations curves may be dramatically different in blood and in CNS. With most antibiotics, the peak in the CSF occurs a few hours after the plasma peak, and the half-life is much longer in CSF than in plasma (e.g., cefotaxime half-life is 9.3 h in CSF vs. 0.7–1.4 h in blood [10]). Hence, if CNS and plasma are sampled close to the plasma peak, the diffusion rate will appear as < 10%, while it would be estimated at > 100% if sampled a few hours later, by the time of plasma trough, when CSF concentrations are still close to the peak [11]. CNS diffusion can only be reliably estimated through the ratio of area under curves (AUC) for CSF and plasma concentrations (supplementary Table 1). This has been performed for a few antibacterial agents in animal models, and in patients with easy access to CNS (e.g. patients with external ventricular drain), but both approaches have limitations: (i) the PK of antimicrobial agents is often different in animals as compared to humans; (ii) patients with external ventricular drain have significant impairment in CSF production, and flow [12], so that data obtained in those patients may not be generalizable to the heterogeneous population of patients with CNS infections: CNS penetration of drugs may vary up to 1000-fold. In addition, CNS concentrations of antimicrobial agents may be heterogeneous, even within one compartment. Systemic administration of most drugs will lead to much higher concentrations in lumbar than in ventricular or cisternal CSF. Likewise, most drugs injected into the lumbar CSF do not reach therapeutic concentrations in ventricular CSF. Hence, in selected cases, intraventricular administration of antimicrobial agents may be the last resort, when intravenous administration is unlikely to be effective (e.g. predicted CNS concentrations below therapeutic target), see supplementary Table 3 [13].
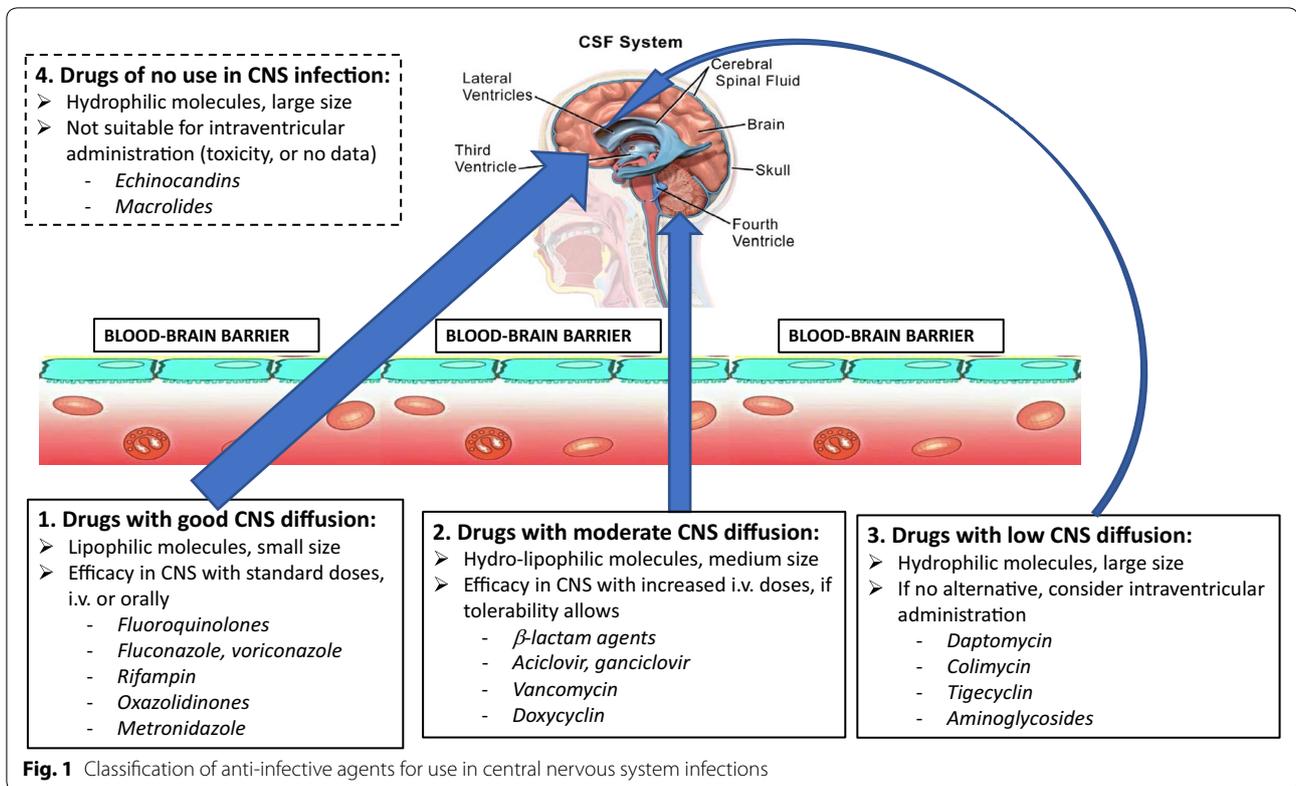
Selected examples (Fig. 1)

β-Lactam agents, although hydrophilic, are the backbone of most antibacterial treatment for CNS infections, despite a poor diffusion rate into the CSF at baseline (i.e., < 15%). CNS efficacy of β-lactam relies in two major assets: (i) diffusion rate may dramatically increase with meningeal inflammation (e.g., from 2 to 20% for penicillins); (ii) for selected β-lactams, tolerability allows the use of very high doses (e.g., until 24 g/day for cefotaxime, while the FDA-approved dose for uncomplicated infection is 2 g/day). Important exceptions must however be acknowledged: (i) Imipenem increases the risk of seizures and should not be used for CNS infections; (ii) β-lactamase inhibitors (clavulanate, sulbactam, and tazobactam) are not suitable for treatment of CNS infections, as their CNS diffusion is low even in patients with meningitis, and CSF concentration remains below the efficacy threshold; (iii) data suggest that the poor CNS diffusion of several major anti-staphylococcal β-lactams (e.g. cloxacillin, and cefazolin), precludes their use in this indication.

Fluoroquinolones cumulate the assets for efficacy in CNS infection (lipophilic drugs, small molecules). However, tolerability of most fluoroquinolones restricts the use of high doses, so that their indications remain limited in CNS infection (i.e. fluoroquinolone-susceptible bacteria, with no satisfactory alternative), at the maximal dose tolerated in humans (e.g. 1200 mg/day for intravenous ciprofloxacin, 1000 mg/day for levofloxacin, or 800 mg/day for moxifloxacin).

Amphotericin B remains a mystery in terms of CNS efficacy; although this compound is almost undetectable in CSF or brain tissues, even in patients with meningeal inflammation treated with high doses, clinical studies have found that this is the most active agent for the treatment of cryptococcal meningitis. The particular metabolism of this antifungal agent may play a role in this unsolved enigma.

Future developments

Bactericidal, non-bacteriolytic antibiotics, such as daptomycin and rifampicin, may reduce the neuronal injury

4. Drugs of no use in CNS infection:
➢ Hydrophilic molecules, large size
➢ Not suitable for intraventricular administration (toxicity, or no data)
   - *Echinocandins*
   - *Macrolides*

CSF System

Lateral Ventricles
Cerebral Spinal Fluid
Brain
Third Ventricle
Skull
Fourth Ventricle

BLOOD-BRAIN BARRIER   **BLOOD-BRAIN BARRIER**   **BLOOD-BRAIN BARRIER**

1. Drugs with good CNS diffusion:
➢ Lipophilic molecules, small size
➢ Efficacy in CNS with standard doses, i.v. or orally
   - *Fluoroquinolones*
   - *Fluconazole, voriconazole*
   - *Rifampin*
   - *Oxazolidinones*
   - *Metronidazole*

2. Drugs with moderate CNS diffusion:
➢ Hydro-lipophilic molecules, medium size
➢ Efficacy in CNS with increased i.v. doses, if tolerability allows
   - *β-lactam agents*
   - *Aciclovir, ganciclovir*
   - *Vancomycin*
   - *Doxycyclin*

3. Drugs with low CNS diffusion:
➢ Hydrophilic molecules, large size
➢ If no alternative, consider intraventricular administration
   - *Daptomycin*
   - *Colimycin*
   - *Tigecyclin*
   - *Aminoglycosides*

Fig. 1 Classification of anti-infective agents for use in central nervous system infections

caused by bacterial products [14]. Innovative approaches have been identified in recent years for delivering drugs into the CNS, such as adenovirus-associated viruses mediated gene delivery, or nano-carriers for antibody treatment in neurodegenerative disease [15, 16]. Examples of nano-carriers include lipo-carriers, carbon nanotubes, metal based carriers, polymers and emulsions, but the majority of these have been tested only in vitro, and none were designed to transport anti-infectives across the BBB [16]. These new drug delivery methods may eventually also be used to improve penetration of anti-infectives in the CNS.

Conclusion

Defining the optimal treatment of CNS infections is one of the most challenging tasks for the intensivists; the therapeutic window is narrow, and the alternative drug options more limited than with any other severe infectious diseases. Progress has been achieved, especially with clinical studies on drug concentrations into the plasma and the CSF, but many unresolved issues remain to better define optimal treatment of major CNS infections.

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Compliance with ethical standards

Conflicts of interest
On behalf of all authors, the corresponding author states that there is no conflict of interest.

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