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REVIEW

Pharmacokinetic considerations in selecting optimal antibiotic therapy for *Mycoplasma pneumoniae* encephalitis

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Abstract

Effective antimicrobial therapy depends on several factors including degree of activity against the pathogen, antibiotic resistance, and when relevant, optimal tissue penetration factors. Central nervous system (CNS) infections illustrate these points well. The pharmacokinetic (PK) parameters important in antibiotic blood cerebrospinal fluid barrier (BCB) penetration that is important in meningitis are different and do not predict blood brain barrier (BBB) penetration. Recently, we had a case of *Mycoplasma pneumoniae* encephalitis (MPE) which prompted a review of the antibiotic PK determinants of BBB penetration which differ markedly from those of BCB penetration important in encephalitis. Using MPE as an illustrative example, this article reviews host and drug factors of therapeutic importance in optimally treating MPE.

Keywords CNS manifestations of *Mycoplasma pneumoniae* · Blood brain barrier (BBB) · Antibiotic lipid solubility · Tissue penetration of hydrophilic and hydrophilic antibiotics · Antibiotic penetration across brain barrier (BPB)

Recently, we had a case of *Mycoplasma pneumoniae* encephalitis (MPE) complicating *M. pneumoniae* pneumonia in an adult. The patient with *Mycoplasma pneumoniae* encephalitis was a healthy immunocompetent adult who presented with a *M. pneumoniae* CAP complicated by encephalitis. Encephalitis was confirmed by EEG showing diffuse global slowing. CSF and serum studies for other causes of encephalitis were negative. *M. pneumoniae* was confirmed serologically and accompanied by high titer cold agglutinin titers typical of M. pneumoniae encephalitis. The choice of antibiotic was discussed, i.e., macrolide (azithromycin) vs. doxycycline requiring encephalitis, but there was little data to guide selection. The patient was successfully treated with doxycycline therapy and made an uneventful recovery. This case raised questions regarding the optimal therapy of *M. pneumoniae* CNS infections, e.g., encephalitis.

Antibiotic selection for *M. pneumoniae* pneumonia is straightforward using a clinically effective antibiotic with anti-*M. pneumoniae* activity and dosed as recommended. In treating pneumonias, tissue penetration is not an issue since the lungs are well vascularized with an extensive capillary bed with no barriers to antibiotic lung penetration. In contrast, antibiotic tissue penetration is a critical consideration in treating certain infections, particularly CNS infection, e.g., leptomeninges (meningitis), brain parenchyma (encephalitis) [1–3]. With *M. pneumoniae* meningitis, the goal of therapy is to achieve therapeutic antibiotic concentrations in cerebrospinal fluid (CSF). Conversely, *M. pneumoniae* encephalitis has little or no meningeal component and the primary tissue target is brain parenchyma.

Pharmacokinetically (PK), tissue levels are dependent on site and several drug factors. With acute bacterial meningitis (ABM), the two key determinants of CSF penetration are the permeability of blood CSF barrier (BCB) and to a lesser extent, molecular drug size. BCB permeability is highly dependent on degree of meningeal inflammation. Degree of BCB permeability is directly proportional to the amount of protein (albumin) in the CSF. Drug molecular weight is also a consideration since small molecules penetrate the BCB more readily than larger molecules. The unbound portion of the antibiotic is

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therapeutically important. In the absence of meningeal inflammation, (BCB) penetration is minimal (sub therapeutic) and limited to the free (unbound) antibiotic component [2, 4–11].

Since brain parenchyma is primarily composed of lipids, lipid solubility is the primary factor that determines blood brain barrier (BBB) penetration. Clearly, the BCB and BBB are two distinct PK CNS drug compartments, and therefore, BCB penetration does not predict BBB penetration [2, 7, 10, 12].

The determinants of antibiotic BCB penetration are degree of meningeal inflammation (non-inflamed meninges vs. inflamed meninges), molecular size, and hydrophilicity. With acute bacterial meningitis (ABM), there is relatively little protein in the CSF. CSF protein may be mildly elevated in many cases of acute bacterial meningitis (ABM). However, causes of highly elevated CSF protein include CNS TB especially with subarachnoid block and CNS malignancies (primary and metastatic). ABM decreases CSF pH to less than serum pH and the activity of some antibiotics are influenced by pH. Relatively unimportant factors, in BCB penetration, are protein binding and CSF pH [1, 5, 12].

In contrast, BBB permeability depends on primarily on antibiotic lipid solubility which may be inferred from the antibiotic's volume of distribution (V_d) l/kg. Hydrophilic antibiotics with a low V_d, approximating body water ($V_d = 0.5$ l/kg), minimally penetrate the BCB in the presence of inflammation. In the presence of inflammation, some "meningeal dosed" hydrophilic antibiotics penetrate to BCB in low but therapeutically useful concentrations, e.g., meropenem [1, 3, 12]. Lipid soluble antibiotics with a higher V_d, e.g., doxycycline, readily penetrate the BBB and reach therapeutic levels in brain parenchyma [13, 14]. With highly lipid soluble antibiotics, brain perennial levels are not significantly higher than in the absence of inflammation, e.g., chloramphenicol [4]. Steroids given after initiation of therapy for ABM may influence antibiotic penetration into the CSF. In contrast, steroids have no effect on BBB penetration and brain parenchymal levels, e.g., chloramphenicol [13–17].

Capillary differences are the basis for the fundamental differences in BCB and BBB antibiotic permeability. The BCB is characterized by the selectively permeable capillaries of the choroid plexus which have a continuous non-fenestrated basement membrane (BM). These capillaries contain channels or pores which open in the presence of meningeal inflammation permitting antibiotic penetration into the CSF. For this reason, in ABM, the main determinant of BCB penetration is the degree of inflammation for hydrophilic (highly polar) drugs, but there is minimal CSF penetration in the absence of inflammation [2, 3, 6]. In the absence of BBB inflammation, there is minimal penetration of hydrophilic antibiotics. In contrast, brain capillaries lack the BM pores of systemic capillaries rendering them impermeable to large hydrophilic molecules, e.g., aminoglycosides [2, 7, 10]. The differences between choroid plexus and brain vasculature are not just the basement membrane. Intercellular tight junctions and astrocytic foot processes play an important role in BBB.

Serum CSF pH gradient influences the degree of ionization of weak acids (relative lipid solubility of the non-ionized fraction). The usual pH gradient between serum (pH = 7.4) and CSF (pH = 7.3) is increased by the lower CSF pH accompanying ABM [2, 4, 5, 12].

Since most causes of acute encephalitis are viral, there is little information on the optimal antibiotic treatment of non-viral encephalitis, e.g., *M. pneumoniae* encephalitis (MPE)

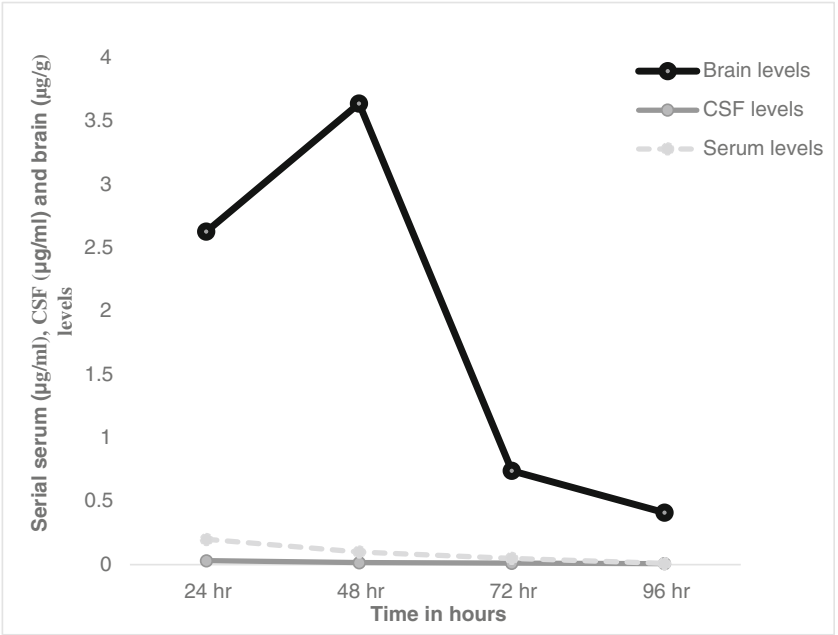

Fig. 1 Serial serum, CSF, and brain levels following a single 500-mg oral dose of azithromycin. Adapted from: Jaruratanasirikul S, Hortiwakul R, Tantisarasart T, Rheunpatham N, Tussanasunthornwong S. Distribution of Azithromycin into brain tissue, cerebrospinal fluid, and aqueous humor of the eye. Anti Agents and Chemo;40:825–26 [22]

Table 1 Pharmacokinetic considerations in selecting antimicrobial therapy for *Mycoplasma pneumoniae* in penetrating the blood CSF barrier (BCB) in meningitis and blood brain barrier (BBB) in encephalitis

Anti-mycoplasma antibiotics	*M. pneumoniae* MIC (mcg/ml)	Usual dose	Peak serum levels	Relative CSF penetration (% of simultaneous serum levels)	Meningitis (relative CSF penetration)†	Lipid solubility (V_d = volume of distribution)	Encephalitis (relative brain penetration)*
Erythromycin	0.004 mcg/ml	1 g (IV) q6h	12 mcg/ml	UM = < 1% IM = 10%	+	V_d = 0.5 l/kg	+
Azithromycin	0.0005 mcg/ml	250 mg (IV) q24h	1.1 mcg/ml	UM = 0% IM = 1%	0	V_d = 31 l/kg	++++
Tetracycline	1.0 mcg/ml	500 mg (PO) q6h	1.5 mcg/ml	UM = 5% IM = 5%	0	V_d = 0.7 l/kg	+
Doxycycline	0.5 mcg/ml	200 mg (IV) q12h	100 mg = 4 mcg/ml 200 mcg/ml = 8 mcg/ml	UM = 25% IM = 25%	++	V_d = 0.75 l/kg	++++
Minocycline	0.25 mcg/ml	100 mg (IV) q12h	4 mcg/ml	UM = 50% IM = 50%	+++	V_d = 1.5 l/kg	++++
Levofloxacin	0.13 mcg/ml	500 mg (IV) q24h 750 mg(IV) q24h	5 mcg/ml 8 mcg/ml	UM = < 1% IM = 15%	+++	V_d = 1.3 l/kg	++++
Moxifloxacin	0.19 mcg/ml	400 mg (IV) q24h	4.4 mcg/ml	UM = 0% IM = 1%	+++	V_d = 2.2 l/kg	++++

UM, uninflamed meninges. † Blood CSF Barrier

IM, inflamed meninges. *Blood brain barrier

Adapted from: Cunha CB, Cunha BA. Antibiotic Essentials (15th Ed) Jay Pee Medical Publishers, New Delhi [1]; Ristuccia A, Cunha BA (Eds) Antimicrobial Therapy Raven Press NY [2]; Grayson ML (Ed) Kucers The Use of Antibiotics (6th Ed) Arnold Publishers London [3]; Blasi F. Atypical pathogens and respiratory tract infections. Eur Respir J 24:171–81,2004; Bebear C, Pereyre S, Peruchant O. Mycoplasma pneumoniae: Susceptibility and resistance to antibiotics. Future Microbiol 6:423–31, 2011

[14]. Because of the relative rarity of MPE, there are only a few reports concerning antibiotic effectiveness in treating MPE. There are reports of erythromycin successes and failures (some may have been due to macrolide resistant strains). There are reported cases describing successful therapy of MPE with levofloxacin, moxifloxacin, erythromycin, tetracycline, and minocycline.

There are also limited data from animal studies with the usual problems of extrapolating animal to human data. Published case reports are unhelpful regarding selecting optimal dosing regimens for the treatment of MPE. While doxycycline has been used for a wide variety of CNS infections, i.e., neuroborreliosis, neurotoxoplasmosis, and neurobrucellosis, little information exists on the effects of PK based dosing [1, 3, 12, 18, 19].

Doxycycline, particularly using a "high dose" regimen, e.g., 200 mg (IV/PO) q12h, has the PK attributes to optimally penetrate brain parenchyma [1, 15]. Even more lipophilic than doxycycline is minocycline. At any given dose, minocycline has enhanced BBB penetration compared to doxycycline [18, 19]. There are reports of the treatment of MRE in children with minocycline [20]. However, most remarkable is the lack of azithromycin experience. It is likely that most physicians regard azithromycin as an antibiotic with very low serum levels, but a long half-life ($t_{½} = 68$ h) ideally suited to treat respiratory tract but not CNS infections [1, 2]. Interestingly, azithromycin has excellent BBB penetration and achieves high therapeutic brain levels well above the MIC of *M. pneumoniae*. Its high degree of activity against MP and its extremely high lipid solubility ($V_d = 31$ l/kg) assure optimal BBB penetration [21]. (Fig. 1) Clearly, azithromycin should be considered as one of the preferred antibiotics for the treatment of MPE (Table 1).

Some antibiotics have the requisite PK properties to penetrate the BBB, but lack the appropriate spectrum to treat MPE, e.g., clindamycin. Clindamycin does not penetrate the BCB well and therefore is not useful to treat ABM due to susceptible organisms [1–3]. However, clindamycin does penetrate the BBB well and has been used to treat CNS toxoplasmosis.

When physicians are confronted with antibiotic selection in adults with MPE, several factors should be considered. Firstly, the antibiotic should have a high degree of inherent anti-*M. pneumoniae* activity. Secondly, the antibiotic should be lipid soluble with a relatively high V_d predictive of BBB, not BCB, penetration. Thirdly, for optimal PK dosing, some antibiotics given in high doses result in higher tissue levels, e.g., doxycycline. Therefore, if there are no dose related adverse effects, then it is preferable to use "high dose" therapy for optimal BBB penetration, e.g., doxycycline.

Antibiotics most likely to be maximally effective for MPE are the macrolides, quinolones, or second-generation tetracyclines. Among the macrolides, azithromycin is preferred, among the quinolones, levofloxacin or minofloxacin is preferred, and among the tetracycline, high-dose doxycycline or minocycline is preferred. [23–27] There is insufficient reported experience to recommend one class or one antibiotic over another. Depending on severity, duration of therapy for MPE is to 2–3 weeks.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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