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Pharmacodynamics of antibiotics in the therapy of meningitis: infection model observations

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Detailed studies of pharmacodynamic principles relevant to the therapy of bacterial meningitis are difficult to perform in man, while the rabbit model of bacterial meningitis has proved to be extremely valuable and has led to insights that appear relevant for the treatment of humans. Most importantly in the light of the restricted penetration of antibiotics into the CSF, animal studies have shown that in meningitis there is a dose-response curve between the CSF concentrations achieved by antibiotics and their bactericidal activity. This appears to be true for all classes of antibiotics thus far examined, including the β-lactams, which do not show such a dose-response behaviour in other infections. Only CSF concentrations that exceed the MBC of the infecting organism by at least 10–30-fold achieve consistent and rapid bactericidal activity. Such rapid bactericidal activity is a requirement for successful therapy with β-lactams and can be impaired with certain antibiotics by the specific conditions in infected CSF (protein content; acidic pH; slow-growing bacteria). However, rapid antibiotic killing of the infecting organisms may not be without adverse effects either. Some antibiotics, particularly β-lactams lead to the brisk liberation of bacterial cell wall components (e.g. endotoxin, in the case of Gram-negative organisms) which have an inflammatory effect on the host and can lead to a temporary deterioration of the disease. Dexamethasone, when administered with the antibiotic, can prevent some of the adverse effects of rapid bacterial lysis.

Introduction

Several discriminative infection models of bacterial meningitis have proved to be valuable in the study of the pathophysiology and therapy of this disease. These experimental studies have elucidated many aspects that play a role in the successful treatment of clinical meningitis. These are the penetration into and bactericidal activity in the CSF of antibiotics and pharmacodynamic considerations of optimal dosing schedules. Recently, exciting links between the pathophysiology of meningitis and aspects of antibiotic therapy have become evident. It was observed that the initial bacterial lysis of meningeal pathogens by bactericidal antibiotics leads to the release of inflammatory bacterial products. This can be associated with an acute increase in pathophysiological abnormalities which can be harmful to the brain. The pathophysiological deterioration is at least in part mediated by inflammatory cytokines and can be

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counteracted by the use of dexamethasone before or concomitantly with the first antibiotic dose.

Infection models of meningitis

Among the different animal models of bacterial meningitis described (for a review see Scheld, 1986), the adult rabbit model originally described by Dacey & Sande (1974) has proved to be best suited to investigating the factors that influence efficacy of antibacterial agents. Our laboratory has used this model with some modifications for many years (Täuber, Khayam-Bashi & Sande, 1985*b*; Täuber, Borschberg & Sande, 1988). Briefly, New Zealand white rabbits are anaesthetized and a dental acrylic helmet containing a half turnbuckle is attached to the skull by four screws that do not penetrate the dura. This helmet secures the anaesthetized animals in a frame that holds a geared electrode introducer with a spinal needle and thus facilitates puncture of the cisterna magna. Animals are infected by direct instillation of a bacterial suspension into the CSF. Meningitis then develops with increasing CSF bacterial titres and an inflammatory response in CSF similar to that observed in humans, and with clinical signs of meningitis (fever, lethargy, ataxia). Antibiotics are administered to rabbits with fully developed meningitis, and antibiotic concentrations in CSF relative to serum, and the bactericidal effect of therapy can be measured easily in repetitive CSF samples that can be obtained through the spinal needle placed in the cisterna magna.

Antibiotic penetration into the CSF

The arachnoid membrane, the epithelium of the choroid plexus, and the cerebral capillary endothelium constitute what is known as the blood-brain barrier (BBB; strictly blood CSF barrier), a physiological barrier that largely restricts the exchanges of macromolecules between the blood and the central nervous system. In order to eradicate meningeal pathogens, antibiotics have to cross the BBB from serum into CSF and reach bactericidal concentrations at the site of infection. Several factors summarized below have been identified that determine the extent to which antibiotics can cross the BBB.

Meningeal inflammation

The inflammation caused by meningitis has a profound effect on the BBB and markedly increases its permeability by inducing an opening of the tight junctions responsible for the barrier function of the BBB (Quagliarello, Long & Scheld, 1986). As a result of this disruption the concentrations of most antibiotics in CSF relative to serum are increased by approximately five- to ten-fold (Sande *et al.*, 1978; Strausbaugh, Murray & Sande, 1980; McCracken, Nelson & Grimm, 1982; Scheld *et al.*, 1982*b*; Sakata, Boccazzi & McCracken, 1983; Täuber *et al.*, 1984*a*, 1985*a*; Meulemans *et al.*, 1989). CSF penetration across the BBB for most antibiotics appears to occur by passive diffusion. However, in the case of ceftriaxone, the presence of an active, energy-dependent transport system localizing in the choroid plexus has been suggested (Spector, 1987).

Hydrophobicity of antibiotics

The more lipophilic an antibiotic molecule, the higher concentration it achieves in the brain and CSF, because of the lipophilic character of the brain cell membranes and BBB (Sande, 1981*b*). Chloramphenicol, trimethoprim, and rifampicin are known for their good CSF penetration, which is largely attributed to the lipophilic character of these drugs (Sande, 1981*a*; Scheld, 1989). Another example of this principle has come from studies in rabbits with pneumococcal meningitis which have shown that esterification of the hydrophilic β-lactam antibiotic hetacillin enhanced the blood-CSF penetration by approximately eight-fold, from 0·7% to 5·5% (Bodine, Strausbaugh & Sande, 1976). Similarly, when we compared a quinolone, temafloxacin, and a macrolide, clarithromycin, with ceftriaxone in the same model, we found that the different classes of antibiotics, as a consequence of their chemical structures, differed remarkably in their CSF penetration. While ceftriaxone, typically for a relatively hydrophilic β-lactam, achieved CSF penetrations in the range of 5–10%, the quinolone and the macrolide, which are both more lipophilic, showed substantially better penetration in the range of 30% (T. Schmidt & M. G. Täuber, unpublished results).

Protein binding

Several studies have documented that the protein binding of an antibiotic inversely influences its CSF penetration (Reudy, 1965; Oppenheimer, Beaty & Petersdorf, 1969; Waterman, Scharfenberger & Raff, 1974; Sande *et al.*, 1978; Strausbaugh *et al.*, 1980; Sande, 1981*a*). Only free drug can penetrate into the CSF across the intact BBB, since the BBB almost completely excludes serum proteins from the CSF (Quagliarello *et al.*, 1986). Kunin (1965) reported that the CSF concentration of ancillin, which is 73% bound to protein, was increased by simultaneous treatment with orthocresotinic acid, a protein binding inhibitor of ancillin. Along the same line, it was reported that in rabbits with experimental uraemia penicillin G achieved increased CSF levels, at least in part as the consequence of its decreased binding to plasma proteins (Spector & Snodgrass, 1976). During meningitis, BBB disruption leads to influx of proteins from serum into the CSF (Kadurugamuwa, Hengstler & Zak, 1988), and this is associated with increased antibiotic penetration into the CSF. The increased CSF protein concentration during meningitis will, on the other hand, reduce the amount of free drug in the CSF available for antibacterial activity, which may be a factor for highly protein-bound drugs.

CSF-blood exit (efflux) pump

It is known that numerous ions, organic acids (such as β-lactams), and quaternary ammonium compounds are removed from the brain by an active transport system resembling the tubular epithelium secretion system of the kidneys (Fishman, 1964; Fishman, 1966). Blocking this active transport with probenecid leads to elevated CSF drug concentration (Dacey & Sande, 1974; Spector & Lorenzo, 1974; Schliamser *et al.*, 1989).

Other factors influencing antibiotic penetration

Besides the factors mentioned above, the molecular weight and charge affect CSF penetration of antibiotics. Small molecules and those without significant charges (less

ionized) seem to achieve higher CSF concentrations than large or highly charged compounds, such as polymyxin and teicoplanin, which poorly traverse the BBB (Stahl *et al.*, 1987). It has been demonstrated that teicoplanin concentrations in CSF dramatically increase after intrarterial infusion of 3 mg/kg mannitol plus 5 mg/kg teicoplanin (Manquat *et al.*, 1990), presumably because of an osmotically mediated opening of the BBB (Perkins & Strausbaugh, 1983; Syrogiannopoulos, Olsen & McCracken, 1987).

Bactericidal activity of antibiotics in the CSF

The need for bactericidal activity

Clinical evidence suggests that rapid sterilization of the CSF is prognostically favourable in patients with bacterial meningitis (Lebel & McCracken, 1989). However, the CSF is an area with scarce host defences, since both pathogen-specific antibodies and complement components are present only at very low concentrations even during meningitis and opsonization of the encapsulated pathogens is therefore insufficient to allow efficient phagocytosis and killing by granulocytes. This was experimentally supported by studies showing that the growth rates and final counts of pneumococci in CSF were identical in normal and neutropenic rabbits (Ernst, Decazes & Sande, 1983; Täuber *et al.*, 1988). In contrast, when non-encapsulated strains of either *Streptococcus pneumoniae* or *Haemophilus influenzae* were used as inoculum, bacteria were promptly eliminated from the CSF (Tuomanen *et al.*, 1985; Lesse *et al.*, 1988).

In the face of the requirement for prompt sterilization of the CSF and the absence of effective host defences, antibiotics have to exhibit rapid bactericidal activity for successful treatment of meningitis. This need for bactericidal activity was documented in rabbits with experimental meningitis due to two different strains of pneumococci with similar MIC and MBC values for ampicillin but different MBCs for chloramphenicol. Rabbits were cured only when CSF antibiotic concentrations clearly exceeded the MBC and thus achieved bactericidal activity (Scheld & Sande, 1983). The bactericidal activity of an antibiotic in the CSF, however, can be influenced by many factors, some of which are briefly discussed below.

In-vitro versus in-vivo activity

Many experimental studies have documented that antibiotics have to exceed the in-vitro MBC of the infecting pathogen by at least 10–30-fold (Täuber *et al.*, 1984*a*, 1985*a*; Kern *et al.*, 1990; Guerra-Romero *et al.*, 1991). The reasons for this reduced activity of antibiotics in CSF compared with that *in vitro* are not completely clear, but the specific milieu of the CSF may be a contributing factor, since time-kill curves performed in CSF *ex vivo* with penicillin G against *S. pneumoniae* showed that three to ten times higher concentrations were needed to reach the same maximal bacterial activity as in broth (Täuber *et al.*, 1984*a*).

Again, in contrast to in-vitro experiences, which show that β-lactams achieve maximal activity at concentrations only slightly above the MBC, infection model studies have found a strong dose-response curve between antibiotic concentration and bacterial killing rates in the CSF. The maximum attainable bacterial killing rate is approximately 1 $\log_{10}$ cfu/mL/h at very high doses, and is independently of the class of antibiotic and infecting pathogen examined (Täuber *et al.*, 1984*a*, 1985*a*; Kern *et al.*, 1990; Guerra-Romero *et al.*, 1991).

Acidic milieu. The relatively low pH of the CSF during meningitis (approximately 6·5–7·0) (Andersen *et al.*, 1989) reduces the bactericidal effect of drugs with pH-dependent activity, such as aminoglycosides (Strausbaugh & Sande, 1978) or macrolides (Fernandes *et al.*, 1986; Truffot-Pernot, Ji & Grosset, 1991). We found the newer macrolide clarithromycin to be very active against our *S. pneumoniae* strain *in vitro* (MBC 0·06 mg/L in Todd-Hewitt medium at pH 7·8), but the drug had absolutely no bactericidal activity in the CSF of infected animals, despite drug concentrations that exceeded the MBC several hundred-fold (T. Schmidt & M. G. Täuber, unpublished data). In-vitro time-kill curve studies revealed that at a concentration of clarithromycin equivalent to the MBC, cultures were sterilized within 24 h at pH 7·4, while the counts were not different from control cultures at pH 7·0. These results demonstrate that standard in-vitro tests can fail to predict the in-vivo efficacy of antibiotics.

Slow growth rate in CSF. The slow growth rate of bacteria in the CSF may also influence the activity of antibiotics, depending on the agent used (Cozens *et al.*, 1986). In general antibiotics are most active against actively dividing bacteria.

Experimental studies have documented that in febrile rabbits both pneumococci and *H. influenzae* grow very slowly with doubling times for the pneumococcus of 3 h, compared with 30 min in broth and 0·85 h in pooled ex-vivo CSF at 37°C (Small *et al.*, 1986; O'Reilly & Zak, 1992). In infected but afebrile rabbits, growth rates of pneumococci, but not *H. influenzae*, are still slower than those observed *in vitro* (Small *et al.*, 1986; O'Reilly & Zak, 1992).

Antagonistic and synergic antibiotic combinations

A few antibiotic combinations have been used in the treatment of meningitis, usually with the aim of increasing bactericidal activity. Tragically, the first such combination examined in a clinical study proved to be antagonistic. Lepper and colleagues showed that the combination of penicillin G with the bacteriostatic drug chlortetracycline resulted in failures in the treatment of pneumococcal meningitis (Lepper & Dowling, 1951). Similar results were later obtained in dogs with pneumococcal meningitis, when they were treated with chloramphenicol followed by penicillin G (Wallace *et al.*, 1965). Chloramphenicol and gentamicin were also antagonistic in the therapy of *Proteus mirabilis* meningitis in rabbits (Strausbaugh & Sande, 1978). It is evident that bacteriostatic antibiotics tend to antagonize the activity of bactericidal drugs. On the other hand, combinations of β-lactams and aminoglycosides generally reveal synergic effects, e.g. ampicillin and gentamicin in Group B streptococcal meningitis (Scheld *et al.*, 1982*a*), and penicillin G or ampicillin and gentamicin in *Listeria monocytogenes* meningitis (Scheld *et al.*, 1979*b*). The combination of two β-lactams that differ in PBP affinity profile, such as ampicillin (which binds to PBP 1 and 3) and mecillinam (PBP 2) is also synergic in experimental *Escherichia coli* meningitis (Scheld *et al.*, 1979*a*; Schaad *et al.*, 1982). More recently, we have shown that the addition of a β-lactamase inhibitor can preserve the CSF bactericidal activity of β-lactams against meningeal pathogens that produce β-lactamases (Kern *et al.*, 1990; Guerra-Romero *et al.*, 1991).

The other side of bactericidal activity

Despite the uncontested need for rapid bactericidal activity of antibiotics in the CSF, achievement of this aim is not without disadvantages. Studies in rabbits with pneumo-

coccal and Gram-negative meningitis have documented that rapid bacterial killing leads to the liberation of bacterial products that are inflammatory (Täuber *et al.*, 1987; Tuomanen *et al.*, 1987; Mustafa *et al.*, 1989*a*). In the case of Gram-negative organisms, endotoxin appears to be the primary inflammatory product, while cell wall fragments play a similar role in pneumococcal disease. These inflammatory bacterial products stimulate the release of cytokines and can thereby aggravate CSF inflammation and the pathophysiology of meningitis (Täuber *et al.*, 1987; Mustafa *et al.*, 1989*b*; Saukkonen *et al.*, 1990). Dexamethasone has been shown in experimental studies to prevent the cytokine release induced by bacterial products when given before or at the time of the first antibiotic dose (Mustafa *et al.*, 1989*a*), and clinical studies have confirmed this to be beneficial for the neurological outcome of the disease (Lebel *et al.*, 1988; Odio *et al.*, 1991).

Pharmacodynamics of antibiotics in experimental meningitis

Continuous vs intermittent therapy

Optimal dosing schedules for the therapy of meningitis are almost impossible to determine by clinical studies. However, experimental studies have provided some information. In experimental pneumococcal meningitis in rabbits it was found that the bacterial killing was unaffected when the total dose of penicillin G (800,000 U) was given as a constant infusion or as bolus injections at 4 h dosing intervals (Sande *et al.*, 1981). It is important to note that in the case of the bolus injection, CSF drug concentrations were less than the MBC for part of the dosing interval, without obvious loss of activity. Subsequent studies using the same model revealed that there was practically no difference in the effectiveness of therapy, whether animals received four bolus injections of ampicillin every 4 h or two injections 12 h apart, the latter regimen resulting in CSF drug concentrations below the MBC for two-thirds of the dosing interval (Täuber *et al.*, 1984*b*). This result was explained by prolonged growth inhibition caused by residual amounts of drug. When a β-lactamase was injected into the CSF bacterial regrowth started immediately. These results support the concept that bolus administration, even at relatively long dosing intervals, is not associated with a reduced efficacy when compared with constant infusion in the therapy of meningitis.

Dose, dose interval, duration of therapy

In another experiment using the same pneumococcal model, the amount of the individual dose of ampicillin and the total duration of the therapy emerged as factors of critical importance for outcome, while varying the dosing interval did not influence outcome (Täuber *et al.*, 1989). Individual doses resulting in CSF concentrations that sufficiently exceeded the MBC (see above) and duration of therapy longer than 48 h achieved the highest cure rates.

Conclusion

While it is difficult to apply the results obtained in infection models directly to the clinical situation, the basic principles appear to be valid for the treatment of patients with meningitis. As a rule, high doses of bactericidal antibiotics will achieve

cures in a large proportion of patients. Observations from infection models are likely to be transferable and relevant to the course and treatment of meningitis in man.

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