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The influence of dosing schedules and cerebrospinal fluid bactericidal activity on the therapy of bacterial meningitis

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Bacterial meningitis represents an infection in an area of impaired host defence. Optimal therapy of meningitis requires attaining bactericidal activity within cerebrospinal fluid (CSF). Studies in experimental animal models of meningitis suggest that maximal rates of bacterial killing *in vivo* and optimal cure rates are achieved when CSF antibiotic concentrations exceed the MBC of the test strain by $\geqslant$ten-fold. The results of clinical trials support this conclusion. In addition, a variable post-antibiotic effect occurs *in-vivo* after short periods of exposure to antimicrobial activity, thus maintaining therapeutic efficacy with intermittent dosage regimens These basic principles of therapy are outlined in this review and serve as a basis for rational treatment regimens. For most antibiotics, the optimal dose, dosage interval, and duration of therapy for bacterial meningitis remain to be established.

Introduction

The optimal therapy of bacterial meningitis appears to require attaining bactericidal activity in the cerebrospinal fluid (CSF) against the responsible pathogen (Sande, 1981), as suggested by clinical evidence and a large amount of data from experimental animal models. Eradication of bacteria from the CSF serves as the definition of bacteriological response to or cure during therapy of meningitis. Multiple factors determine whether antibiotics achieve bactericidal activity within CSF, including the dosage regimen chosen. The major determinants of optimal dosing of antibiotics for the therapy of meningitis are as follows: (1) factors influencing drug entry or passage (i.e. "penetration") into the CSF; (2) factors determining antimicrobial activity within purulent CSF *in vivo*; (3) the critical need for achieving bactericidal activity within the CSF; (4) the mode of drug administration (i.e. intermittent vs. continuous regimens) and the potential importance of "post-antibiotic effects" *in vivo*; and (5) the duration of therapy. These and other factors have been reviewed recently (Scheld, 1984*a*; Tauber & Sande, 1984).

This symposium has emphasized the important correlations between *in-vitro* models and the results of therapy *in vivo* both in experimental animal models of infection and

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in humans. For the therapy of meningitis, these relationships are most relevant to two of the five areas outlined above, (1) the relationship between *in-vitro* determination of the MBC and quantitative time-kill studies and peak CSF and rate of bactericidal activity *in vivo*, and (2) the influence of *in-vitro* post-antibiotic effects (PAE) on appropriate intermittent dosage regimens and the response to therapy *in vivo*. These two concepts of *in vitro-in vivo* interactions are emphasized in this brief review.

The necessity for bactericidal activity in CSF

Bacterial meningitis, like bacterial endocarditis or bacteremia in a granulocytopaenic host, represents an infection in an area of impaired host defence. Once bacteria gain access to the subarachnoid space (SAS), host defences are, in general, inadequate (Scheld, 1981, 1984*b*). Antibody and complement concentrations are low or absent in normal or purulent CSF; functional opsonic or bactericidal activity is usually undetectable early in the disease course (Scheld & Brodeur, 1984; Simberkoff, Moldover & Rahal, 1980; Zwahlen *et al.*, 1982). As a result of these deficiencies, phagocytosis of the major encapsulated meningeal pathogens is inefficient and the organisms attain enormous population densities in purulent CSF, often exceeding 10^8 cfu/ml (Feldman, 1977). Studies in leucopaenic animals support these conclusions (Ernst, Decazes & Sande, 1983). After the intracisternal inoculation of pneumococci into rabbits, maximal bacterial concentrations were nearly identical in leucopaenic animals when compared to normal controls. In addition, other altered CSF parameters (increased protein and lactate and decreased glucose) were similar in the two groups, suggesting that a CSF pleocytosis does not contribute substantially to these changes in the CSF during meningitis. Surface phagocytosis is also inefficient in the fluid medium of the CSF. These defects in host defence within the CSF suggest that bactericidal activity at the site of infection within the SAS is necessary for optimal therapy of bacterial meningitis.

Early studies in a rabbit model of bacterial meningitis clearly documented that eradication of the organisms from purulent CSF *in vivo* was dependent upon achieving maximal CSF concentrations in excess of the MBC of the pathogen inoculated (Strausbaugh & Sande 1978; Scheld, Brown & Sande 1978; Schaad *et al.*, 1981). Rapid bacterial killing *in vivo* was observed only when CSF concentrations of β-lactams or aminoglycosides exceeded the MBC by 10- to 20-fold. The poor *in-vivo* activity of aminoglycosides was partially related to the acid pH (mean = 6·98) of purulent CSF in the animals, since the MBC rises approximately 16- to 32-fold as pH declines from 7·8 to 7·0 (Strausbaugh & Sande 1978).

The effect of bactericidal activity in CSF on the cure rate of experimental pneumococcal meningitis was examined recently in a rabbit model (Scheld & Sande, 1983). Two different strains of *Streptococcus pneumoniae* were employed; they had identical susceptibility to ampicillin *in vitro* (MBC = 0·125 mg/l) but with divergent chloramphenicol MBCs of 16 and 2 mg/l, respectively. The ampicillin dosage (250 mg) produced mean peak CSF concentrations of 6·6–6·8 mg/l, approximately 50-fold greater than the MBC of both test strains. In contrast, two different dosages of chloramphenicol were used; one achieved a bacteriostatic effect in CSF against strain_1 (i.e. peak CSF concentration = 4·4 mg/l; MBC = 16 mg/l) but was bactericidal against strain_2. The second chloramphenicol regimen resulted in mean peak CSF concentrations of over 30 mg/l, bactericidal against both isolates. All drugs were given

Table I. Results of therapy of experimental pneumococcal meningitis in rabbits Dependence on bactericidal activity within CSF *in vivo*

Inoculum	Drug	MBC (mg/l)	Mean 'peak' CSF conc.	Mean ± S.D. $\Delta\log_{10}$ *Str pneumoniae* cfu/ml CSF after 48 h of therapy	Cure rate %
$Strain_1$	Ampicillin	0 125	6·6	$^{-}5{\cdot}5 \pm 1{\cdot}1$	77
	Chloramphenicol	16	4·4	$^{-}2{\cdot}4 \pm 1{\cdot}7$	17
	Chloramphenicol	16	32 0	$^{-}5\,3 \pm 1{\cdot}5$	64
$Strain_2$	Ampicillin	0·125	6 8	$^{-}5\,6 \pm 1{\cdot}2$	80
	Chloramphenicol	2	4·9	$^{-}4{\cdot}6 \pm 1{\cdot}4$	70

Adapted from Scheld & Sande (1983)

intramuscularly every 8 h for five days beginning 18 h after intracisternal inoculation; the CSF was sampled daily and again three days after cessation of therapy to assess rapidity of response and ultimate cure rates.

The results (Table I) clearly document that cure was associated only with regimens that achieved bactericidal activity in CSF. More than 90% of animals on bactericidal regimens demonstrated greater than 5 log decreases in CSF bacterial concentrations after 48 h and sterile CSF samples after five days of treatment. Bacteriostatic CSF concentrations (i.e. peak CSF concentrations between the MIC and MBC of $strain_1$) produced slower declines in CSF pneumococcal counts after 48 h and none of the surviving rabbits had sterile CSF after five days (Table I). Thus, bactericidal activity in CSF was associated with rapid bacterial killing *in vivo* and an optimal response to therapy in this experimental model (Scheld & Sande, 1983). The inhibition of bactericidal activity *in vivo* by the coadministration of bacteriostatic antibiotics in animal models (Strausbaugh & Sande, 1978) and humans (Lepper & Dowling, 1951; Mathies *et al.*, 1967) supports this concept.

Recent short-term studies in a variety of experimental animal models of bacterial meningitis suggest that peak CSF concentrations greater than ten times the MBC of the pathogen are necessary for optimal rates of bacterial killing *in vivo*. In one recent analysis (Decazes, Ernst & Sande, 1983), ceftriaxone was administered to rabbits with experimental *Escherichia coli* meningitis. The drug was given by intravenous (iv) bolus and was followed 4 h later by a continuous infusion of 0·1, 0·5, 1, 5, or 10 mg/kg per hour; steady-state ceftriaxone concentrations in CSF were achieved by this method. Although the percentage penetration ([CSF]/[serum] × 100) into CSF was only 2·1–8·9%, the CSF concentration of ceftriaxone ranged from less than the MBC (0·06 mg/l) for the test strain to more than ten times this value. As shown in Table II, maximal rates of eradication of *E. coli* from CSF occurred when the mean ceftriaxone concentration in CSF was $\geqslant 10 \times$ the MBC. More important, the rate of bacterial killing did not increase further when CSF concentrations were 20- to 100-fold greater than the MBC of the test strain (data not shown). In addition, *in-vitro* quantitative "time-kill" curves were more accurate than the MBC alone in predicting the maximal rate of bacterial eradication from CSF *in vivo* These results suggest that CSF antibiotic concentrations should exceed the MBC of the responsible pathogen by 10- to 20-fold to ensure maximum efficacy. Similar studies performed by McCracken and colleagues in Dallas support this conclusion (Schaad *et al.*, 1980, 1981; McCracken &

Table II. Results of therapy of experimental *E. coli* meningitis: correlation between mean ceftriaxone concentration in CSF and rate of bacterial killing *in vivo*

Mean CSF ceftriaxone concn. (mg/l) (× MBC)	Mean $\Delta \log_{10}$ cfu *E. coli*/ml CSF/h of therapy
Controls	$^{+}0.4$
<0·06 (<1)	$^{-}0.15$
0·06–0·6 (1–10)	$^{-}0.7$
>0·6 (>10)	$^{-}1.5$

Decazes *et al* (1983)

Schaad, 1982; McCracken, Nelson & Grimm, 1982; Sakata, Boccazzi & McCracken, 1983). A large number of antimicrobials were evaluated in rabbits with meningitis induced by the intracisternal inoculation of *Str. pneumoniae, Str. agalactiae, Haemophilus influenzae,* or various Gram-negative aerobic bacilli. The drugs were given by continuous intravenous infusion; serum concentrations closely approximated those found in man. The results (mean $\Delta \log_{10}$ cfu/ml CSF) were analyzed after 9 h of therapy. In general, when CSF bactericidal titres exceeded 1:32 (e.g. with third-generation cephalosporin therapy of experimental *E. coli* meningitis), maximum reductions of CSF bacterial concentrations of 4·1–4·8 logs were noted after 9 h of intravenous infusion. In contrast, when CSF bactericidal titres achieved values of only 1:2 to 1:4 (e.g. netilmicin and ampicillin in the *E. coli* model, latamoxef (moxalactam) therapy of experimental group B streptococcal meningitis), the mean decrease in CSF bacterial concentrations was only 1·6 to 2·7 logs after the same treatment interval. Maximal rates of bacterial killing *in vivo* were achieved only when CSF bactericidal titres were greater than 1:16, similar to the results presented in Tables I and II. Latamoxef (moxalactam) was also ineffective when administered intermittently for three days in another model of experimental group B streptococcal meningitis (Khurana & Deddish, 1983). The poor *in-vitro* activity of latamoxef (moxalactam) (relative to that of other third-generation cephalosporins) results in low CSF bactericidal titres against these organisms (Schaad *et al.*, 1981) and correlates with its suboptimal efficacy in humans with serious infections caused by Gram-positive cocci (Salzer, Pegram & McCall, 1983).

The need for CSF bactericidal activity to achieve maximal rates of bacterial killing *in vivo* is also suggested by clinical experience. This principle was first suggested by French investigators (Chabbert, 1967; Armengaud *et al.*, 1979) following retrospective review of the results of therapy in large numbers of patients treated with various regimens. Recently careful review of results has supported this position. For example, the mortality rate for patients with Gram-negative aerobic bacillary meningitis treated during the past decade in New York City with regimens including chloramphenicol was 83% (Cherubin *et al.*, 1981). Chloramphenicol is bacteriostatic against these organisms *in vitro* (Rahal & Simberkoff, 1979) and negates the bactericidal activity of aminoglycosides *in vivo* in experimental proteus meningitis in rabbits (Strausbaugh & Sande, 1978). Thus, bactericidal activity in the CSF against members of the Enterobacteriaceae is not attainable with chloramphenicol, and the poor therapeutic results reflect this property. In contrast, as noted in the above discussion of experimental models, the third-generation cephalosporins readily produce CSF

bactericidal titres of 1 : 32 to 1 : 64 against this group of organisms. These new agents have been evaluated extensively in the therapy of Gram-negative bacillary meningitis in humans, and the initial results are encouraging, with cure rates of 78–94% in adults (Landesman *et al.*, 1981; Cherubin *et al.*, 1982) versus mortality rates of 40–90% in patients receiving traditional therapy of aminoglycosides (by various routes of administration), chloramphenicol, ampicillin, or combinations of these agents (Cherubin *et al.*, 1981).

This type of analysis suggests that some of the newer third-generation cephalosporins may prove useful in the therapy of meningitis due to the more common meningeal pathogens, including ampicillin-resistant *H. influenzae*. For example, several clinical trials have compared ceftriaxone alone (usually 50 mg/kg q 12 h) to ampicillin plus chloramphenicol for the therapy of acute bacterial meningitis in children (Del Rio *et al.*, 1983; Congeni, 1984; Steele & Bradsher, 1983). The outcome (e.g. cure rate, mortality rate, neurologic sequelae, toxicity) in both regimens was equivalent in these carefully performed studies. The CSF was sterilised more quickly during ceftriaxone therapy when compared with ampicillin plus chloramphenicol (57% vs. 42% sterile after 4–12 h of treatment, respectively) (Del Rio *et al.*, 1983). In addition, the median CSF bactericidal titres were 1 : 512–1 : 1024 for patients receiving ceftriaxone and 1 : 8 for the ampicillin plus chloramphenicol group ($P < 0{\cdot}001$). Although ceftriaxone may prove extremely useful in the therapy of meningitis due to a convenient q 12 h (or q 24 h) dosage regimen, the results of current studies suggest that increasing the CSF bactericidal titre above 1 : 8 is unlikely to produce enhanced clinical efficacy in humans. This conclusion is identical to that reached in the studies with experimental models of meningitis discussed above.

The mode of drug administration, dosage intervals, and the post-antibiotic effect (PAE) *in vivo*

The optimal route and mode of antibiotic administration for the therapy of serious infections (e.g. meningitis) has been the subject of considerable debate. The parenteral route is preferred, but unpredictable absorption due to shock or hypotension and clotting abnormalities renders the intramuscular route undesirable. Although higher CSF concentrations were achieved in the first 20 min following intracarotid administration of penicillin when compared to the intravenous route, the former was not practical, and the experimental technique employed may have inadvertently opened the blood-brain barrier thus accounting for enhanced drug entry into CSF (Kourtopoulos, Holm & Norrby, 1983).

The intravenous route is currently favoured for the therapy of bacterial meningitis, but the mode of administration is controversial. Experimental studies in animals support both continuous infusion with serum levels constantly above the MBC of the responsible pathogen (Eagle, Fleischmann & Levy, 1953) and intermittent "bolus' infusions, since higher extracellular fluid (including CSF) antibiotic concentrations are achieved by the latter method (Barza *et al.*, 1974; Plorde, Garcia & Petersdorf, 1964). Intermittent infusions may also produce periods of bacterial exposure to subinhibitory concentrations with subsequent rapid regrowth and enhanced susceptibility of the remaining bacterial population to antimicrobial activity (McDermott, 1958); this is of particular importance with β-lactam agents. In addition, as discussed elsewhere in this symposium, the post-antibiotic effect (PAE) may permit successful therapy with

infrequent dosages of antibiotics. None of the above studies evaluated the influence of the mode of drug administration or the PAE *in vivo* on the rate of bacterial elimination from CSF.

We investigated these concepts in a recent series of experiments with a rabbit model of experimental pneumococcal meningitis. The first studies (Sande *et al.*, 1981) compared the effect of penicillin delivered by intermittent bolus (q 4 h) and continuous intravenous infusion. Both groups received a total dose of 800,000 units over an 8 h treatment period; CSF was sampled frequently for quantitative bacterial counts and penicillin concentrations. Serum penicillin concentrations closely approximated those found in humans during therapy with standard parenteral regimens of penicillin. Higher penicillin concentrations were detected earlier in CSF in animals receiving intermittent bolus infusions but the rate of bacterial killing was nearly identical in both groups. Rapid bacterial killing was observed despite trough CSF penicillin concentrations below the MBC in 60% of the rabbits receiving intermittent therapy (Sande *et al.*, 1981).

The CSF was sterile after 8 h of therapy in 10 of 15 and 11 of 15 rabbits treated with intermittent or continuous infusions, respectively. Both modes of penicillin administration resulted in a straight-line logarithmic decrease in CSF bacterial counts, an effect independent of pre-therapy CSF bacterial counts. All rabbits with CSF bacterial counts less than 10^5 cfu/ml before therapy had sterile CSF 8 h later. Because the CSF penicillin concentrations were above the MBC for nearly the entire 8 h exposure period, the effect of a PAE could not be assessed with these regimens.

The influence of the PAE on bacterial viability in CSF was examined in a second series of studies. After induction of experimental pneumococcal meningitis, treatment was commenced 18 h later with a single intravenous bolus infusion of ampicillin at the following dosages: 1, 2, 3, 4, 6, 12·5, 20, and 62·5 (mg/kg). The CSF was sampled for quantitative bacterial and ampicillin concentrations every 2 h for the next 24 h. When ampicillin dosages achieved CSF concentrations below the MBC of the test strain (0·12 mg/l), a significant PAE was observed *in vivo*, characterized by a continued decline or stable pneumococcal counts in CSF for variable periods. All animals demonstrated an early bactericidal period of 1·5–2 h with decline in CSF bacterial counts of approximately 2·5 logs, followed by a variable 'static' phase of 4 to 20 h with slower decline or stable bacterial counts. This PAE *in vivo* was longer (4–12 h) than that observed *in vitro* under similar conditions (1–4·3 h), it occurred even after exposure to subinhibitory concentrations of ampicillin (an effect not observed *in vitro*), and there was no definite relationship between peak CSF ampicillin concentration or area under the CSF concentration-time curve and its duration (Sande *et al.*, 1981; Tauber *et al.*, 1984). The longer PAE *in vivo* may be related to the longer generation time of pneumococci in CSF when compared with that in broth (Ernst *et al.*, 1983). The PAE *in vitro* clearly differed from that observed *in vivo*, since the addition of β-lactamase influenced only the latter. In these studies, β-lactamase was given at a dosage of 300,000 units intravenously plus 100,000 units intracisternally 2 and 4·5 h following the administration of ampicillin. Bacterial regrowth in CSF began immediately following β-lactamase, suggesting a prolonged 'gamma' phase of ampicillin elimination from the CSF and continued antibacterial activity *in vivo* at subinhibitory concentrations below the lower limit of detectability of our bioassay ($\simeq$0·06 mg/l). In contrast, as shown in other studies (McDonald, Craig & Kunin, 1977), the enzyme did not influence the course of the PAE *in vitro*.

Table III. Results of ampicillin (MBC = 0·1 mg/l) therapy in experimental pneumococcal meningitis

Dose (mg/kg)	Mean peak [CSF] (mg/l)	Cure rate (%) after. 2 × q 12 h	4 × q 4 h
6 25	0·25	21	43
12 5	0·53	57	79
25	1·28	95	100
37.5	1·49	92	100

Tauber *et al* (1984)

These issues were examined further in a recent study (Tauber *et al.*, 1984) employing 186 rabbits with experimental pneumococcal meningitis. Treatment was begun 18 h following intracisternal inoculation with ampicillin at the following dosages: 4·17, 6·25, 12·5, 25, and 37·5 mg/kg. Two treatment regimens were employed: two injections 12 h apart and four injections at 4 h intervals with both regimens being completed in 12 h. The CSF was then sampled every 4 h, and cure was defined as a sterile CSF 36 h after the last dose of ampicillin. Due to rapid elimination, the CSF ampicillin concentration fell below the MBC (0·1–0·12 mg/l) of the test strain within 4 h. Thus, subinhibitory or undetectable ampicillin concentrations were present for approximately 2/3 of the treatment interval for the q 12 h regimen but the q 4 h schedule maintained CSF concentrations greater than the MBC for the entire 12 h.

A compilation of the results is shown in Table III. A consistent PAE was again demonstrated. Both regimens produced similar results in this model as judged by cure rate 36 h following the last injection of ampicillin; no statistically significant differences (by Chi-square analysis) were found (Table III). The only parameter that determined the cure rate was the mg/kg dosage per injection; the number of injections (two or four) over the 12-h treatment interval did not affect the outcome (Tauber *et al.*, 1984). It is also apparent (Table III) that once peak ampicillin concentrations exceeded the MBC by greater than ten-fold (25 and 37·5 mg/kg doses), cure rates of more than 90% were obtained. This result is in excellent accordance with the general principle that greater than 1 : 10 bactericidal activity in CSF gives maximal bacterial killing *in vivo*.

These studies suggest that bactericidal activity ($\geq 1:10$) in CSF is the critical variable for efficacy in meningitis and that the mode of drug administration is irrelevant as long as this criterion is fulfilled. The PAE may permit continued efficacy even when CSF antibiotic concentrations fall below bactericidal levels for portions of the dosing interval. This principle has already been demonstrated in African studies with cures of meningococcal meningitis after a single dose of penicillin or ceftriaxone (MacFarlane *et al.*, 1979; Cadoz *et al.*, 1982) or five days of chloramphenicol therapy (Whittle *et al.*, 1973). Further studies are necessary to determine the optimal dosing interval and duration of therapy for bacterial meningitis which are of immense practical importance in developing countries.

Another important variable, the CSF half-life or area under the CSF concentration-time curve for various antibiotics, deserves further emphasis. The persistence of drugs in the CSF is variable and dependent on multiple factors. For example, following a single injection, the time interval during which drug concentrations in CSF exceeded the MBC for 90% of relevant Enterobacteriaceae was 462, 312, and 55 min for

cefoperazone, latamoxef (moxalactam), and cefotaxime, respectively, in animals with experimental *H. influenzae* meningitis (Perfect & Durack, 1981). This type of analysis, together with the studies outlined in this review, may place the antimicrobial therapy of bacterial meningitis on a more scientific and rational foundation.

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