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Clinicopharmacological Evaluation of Amoxicillin and Probenecid Against Bacterial Meningitis

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Forty-three infants and children with bacterial meningitis were treated intravenously with 200 mg of amoxicillin sodium per kg per day for 10 days. (Patients were initially treated with ampicillin and chloramphenicol until the bacterial etiology was defined.) Patients were randomly treated with amoxicillin only or with amoxicillin and four doses of probenecid (10 mg/kg per dose) orally every 6 h for 24 h before the lumbar puncture at day 10. Serum and cerebrospinal fluid (CSF) were obtained on days 1, 5, and 10 of therapy for antibiotic assay. The mean peak serum concentration of amoxicillin of 49.2 μg/ml was increased to 61.4 μg/ml in patients who received probenecid. The half-life in serum (1.5 h) and area under the curve with probenecid (112.5 μg/ml·h) were increased compared with those of amoxicillin alone (1.3 h and 82.2 μg/ml·h). The mean peak CSF concentrations on days 1 and 5 were similar, but day 1 concentrations remained between 2.0 μg/ml and 5.0 μg/ml throughout the 4 h after a dose, whereas the day 5 values decreased at the same decay rate as that in serum. All CSF concentrations were lower on day 10, but patients receiving probenecid had peak values occurring at 1 h rather than at 0.5 h, and levels were significantly greater at 1 and 2 h after a dose. There were no deaths and patients responded well to treatment.

Amoxicillin sodium is the parenteral form of amoxicillin with an antibacterial spectrum and human pharmacology similar to those of ampicillin sodium (1, 7, 13, 14, 16, 18, 19, 22, 23). Ampicillin is safe and effective therapy for bacterial meningitis due to susceptible bacteria (3).

Concentrations of antibiotics attained in cerebrospinal fluid (CSF) are dependent on several factors (2, 3, 24-26). Levels are higher early in the course of treatment than later when inflammation has subsided (2, 24-26) and the CSF-to-serum ratio of ampicillin concentration is greater in patients with bacterial meningitis than in those with aseptic meningitis or without meningitis (2, 3, 24, 25). Increased intracranial pressure delays bulk-flow removal of antibiotic through the venous system, and the pump mechanism in the choroid plexus which actively removes antibiotics from CSF to the systemic circulation is relatively inoperative early in acute meningitis (2). Probenecid increases the levels of penicillin in CSF in the rabbit meningitis model and in patients with neurosyphilis (8, 9), principally by interference with the pump in the choroid plexus.

This study was done to evaluate the efficacy and pharmacology of amoxicillin in patients with bacterial meningitis and to determine whether probenecid would increase concentrations of amoxicillin in the CSF.

MATERIALS AND METHODS

Between March 1977 and May 1978 patients with bacterial meningitis admitted to Parkland Memorial Hospital and Children's Medical Center in Dallas, Tex., and to the Henrietta Egleston Hospital for Children and Grady Memorial Hospital in Atlanta, Ga., were treated with amoxicillin sodium after informed consent from the parents was obtained.

Patients were initially treated with ampicillin, 50 mg/kg intravenously (i.v.) every 6 h, and chloramphenicol, 25 mg/kg i.v. every 6 h. When beta-lactamase-negative *Haemophilus influenzae* type b, meningococci, or pneumococci were identified by culture of CSF, ampicillin and chloramphenicol treatment was discontinued, and amoxicillin sodium therapy was instituted. Patients were randomly assigned to one of two regimens. One group of patients received amoxicillin, 50 mg/kg i.v. as a 20-min i.v. infusion every 6 h (200 mg/kg per day) for 10 days. Patients in the second group received amoxicillin in the same schedule and, in addition, were given four oral doses of 10 mg of probenecid per kg every 6 h during the last 24 h of amoxicillin therapy.

Patients were examined daily for signs of improvement in state of alertness and other neurological signs and for complications such as rashes, vomiting, soft tissue reaction around i.v. sites, and prolonged fever. A complete blood cell count, routine urinalysis, blood urea nitrogen, creatinine, and serum glutamic oxaloacetic transaminase were done on admission and on days 5 and 10 of the study. Blood specimens for culture were obtained on admission, after 24 h of therapy, and later when clinically indicated.

Lumbar punctures were performed after 18 to 36 h of therapy (day 1) and again on days 5 and 10 of therapy at 0.5, 1, 2, or 4 h after a dose according to random assignment. Simultaneous blood specimens were obtained. CSF, leukocyte and erythrocyte counts, differential cell count, and protein and glucose concentrations were done, and the specimens were assayed for amoxicillin content by the microbioassay technique of Simon and Yin (21), using *Sarcina lutea* as the test organism. CSF specimens were stored at −70°C, and assays were done within 3 days.

CSF specimens were cultured on 5% sheep blood agar and chocolate agar and in thioglycolate broth. Counterimmunoelectrophoresis was done on all CSF specimens. Antisera to *H. influenzae* type b and meningococcal groups A, B, and C were supplied by John Robbins, Bureau of Biologics, Bethesda, Md. Pooled pneumococcal antiserum was obtained from the Staatens Serum Instituten, Copenhagen.

Serum specimens were taken from all patients at zero time and at 0.5, 1, 2, and 4 h after a dose of amoxicillin on days 5 and 10 of therapy for assay of amoxicillin content.

H. influenzae were tested for beta-lactamase production by using the 1-min iodometric paper strip test of Jorgensen, Lee, and Alexander (17). The minimal inhibitory concentrations of amoxicillin for inhibition of bacterial pathogens were determined by broth dilution using Mueller-Hinton broth (Difco) with 1% Supplement C (Difco). Twofold concentrations of amoxicillin from 20 μg/ml to 0.019 μg/ml were prepared and an inoculum of from 10^5 to 10^6 *Haemophilus* organisms was added. Minimal inhibitory concentrations of amoxicillin were defined as the smallest concentration preventing visible growth after incubation at 35°C for 18 h. Minimal bactericidal concentrations were determined by subculturing all clear tubes onto chocolate agar.

The statistical tests used were chi-square analysis and two-tailed Student's *t* test comparing the means of two small samples from normal populations (20).

RESULTS

A total of 43 patients were evaluated for efficacy, and pharmacological studies were performed in 34 patients (Table 1). Patients in the two groups were comparable regarding sex, race, and age. The mean age was 13.4 months in the amoxicillin-only group and 15.6 months in the amoxicillin-probenecid group. Most patients (63%) received ampicillin and chloramphenicol for less than a day before entering the study. The etiological bacteria isolated from CSF were *H. influenzae* type b in 38 patients, pneumococcus in 1 and meningococcus in 2 patients. One patient with negative CSF and blood cultures had meningococcal B antigen detected in CSF by counterimmunoelectrophoresis. The patient with negative cultures and CIE had received ampicillin orally before the diagnostic procedures and was presumed to have an amoxicillin-susceptible bacterial infection.

Initial blood cultures were positive in 35 (85%) patients. No blood cultures were positive in patients with negative CSF cultures. All blood cultures were negative 24 h after the start of therapy.

TABLE 1. *Clinical characteristics of study patients*

Observation	No. of patients treated with:	
	Amoxicillin	Amoxicillin-probenecid
Efficacy evaluation	18	25
Pharmacokinetic studies	16	18
Sex		
Male	11	16
Female	7	9
Race		
Black	7	10
White	9	14
Other	2	1
Etiological organisms		
H. influenzae type b	15	23
N. meningitidis group B	2	1
S. pneumoniae	0	1
Culture negative	1	0
No. of doses of chloramphenicol before amoxicillin therapy		
1–4	10	17
5–8	7	6
>8	1	2

Concentrations of amoxicillin in sera on days 5 and 10 in patients not given probenecid were similar (Table 2; Fig. 1). Ten minutes after completion of the 20-min i.v. infusion, mean serum concentrations were in the range of 40 to 50 μg/ml and fell to 4 μg/ml 4 h later. Patients given probenecid for 24 h before the tests on day 10 had higher serum concentrations at all time intervals but these were not significantly greater than in patients not treated with probenecid. The calculated mean half-life in serum, volume of distribution, area under the curve, and plasma clearance rates are shown in Table 2.

CSF concentrations of amoxicillin were substantially greater on days 1 and 5 than on day 10 (Table 3; Fig. 1). On day 1, CSF concentrations throughout the 4 h after a dose remained between 2.0 μg/ml and 5.0 μg/ml. The mean peak CSF concentration of amoxicillin on day 5 was similar to that seen on day 1, but levels decreased during the ensuing hours at a rate similar to that in serum. By day 10, peak concentrations were lower at the four time intervals studied. In patients receiving probenecid the peak value occurred at 1 h rather than at 0.5 h and levels were significantly greater at 1 and 2 h in those receiving probenecid than in those treated with amoxicillin alone.

CSF cultures were positive in two patients with *H. influenzae* type b infection between 18 and 36 h after starting therapy. All subsequent CSF cultures were negative.

Subdural collections of fluid causing symp-

TABLE 2. *Amoxicillin concentrations in plasma*

Treatment day	h after dose[a]					Half-life (h)	Vol distribution (ml/kg)	Area under the curve (μg/ml·h)	Plasma clearance (ml/min per 1.73 mm²)
	0	0.5	1	2	4				
5	4.0 ± 0.15	53 ± 0.48	37 ± 0.32	13 ± 0.11	3.8 ± 0.03	1.4	1,162	86.4	402
10									
Without probenecid	4.4 ± 0.25[b]	43 ± 1.1[c]	32 ± 0.61[c]	14 ± 0.30[c]	4.0 ± 0.04[c]	1.5	1,395	80.0	485
With probenecid	5.1 ± 0.16	61 ± 0.98	43 ± 0.68	21 ± 0.33	6.4 ± 0.11	1.48	947	112.5	378

[a] Values indicate mean micrograms per milliliter ± 1 standard error of the mean.
[b] $P > 0.5$.
[c] $P < 0.5$

toms were diagnosed in four patients between days 6 and 8 of therapy. Cultures of subdural fluid were sterile. Ventriculoperitoneal shunt drainage was performed in one patient.

The iodometric paper strip test for beta-lactamase was negative in all *H. influenzae* type b isolated from CSF and blood. Amoxicillin minimal inhibitory concentrations of bacteria isolated from CSF ranged from 0.3 μg/ml to less than 0.02 μg/ml, with 90% susceptible to less than 0.156 μg/ml. The minimal bactericidal concentrations varied from 1.25 μg/ml to less than 0.02 μg/ml and were equal to or no more than two concentrations greater than the minimal inhibitory concentration.

Clinical responses to treatment were comparable in the amoxicillin-only and the amoxicillin-probenecid groups. There were no deaths. The mean days of fever after the start of therapy was 3.2 days. Prolonged fever, defined as greater than 6 days, occurred in five children. Five patients had seizures and four had abnormal electroencephalograms. Two of these patients also had abnormal computerized axial tomograms. One patient was ataxic at discharge. Three patients had joint effusions in the elbow (2 patients) and the knee (1 patient). Needle aspirations of joint fluid done after 4 to 5 days of therapy yielded sterile fluid.

There were few drug reactions. One child had a small area of skin necrosis secondary to subcutaneous infiltration of the intravenous fluids. Mild elevations of serum glutamic oxaloacetic transaminase to 46 and 60 IU, respectively, occurred in two patients. Two children developed eosinophilia, with peak absolute eosinophil counts of 1,248 and 1,404/ mm^3. The hematocrit decreased from 31 to 18% in one child and from 28 to 22% in another. Serial blood urea nitrogen and creatinine values remained normal in all children.

DISCUSSION

The observations from this study have been compared with those of similar patients from this institution treated with ampicillin and reported by Wilson and Haltalin (26) in 1975 (Table 4). Mean peak serum concentrations were greater with ampicillin than with amoxicillin. This is probably due to the fact that each dose of ampicillin was infused during a 10-min period, whereas amoxicillin was given as a 20-min infusion. The calculated half-life of amoxicillin in serum was slightly longer than that of ampicillin. The computed area under the curve was similar with the two drugs but increased in patients who received probenecid.

Mean peak CSF concentrations were greater

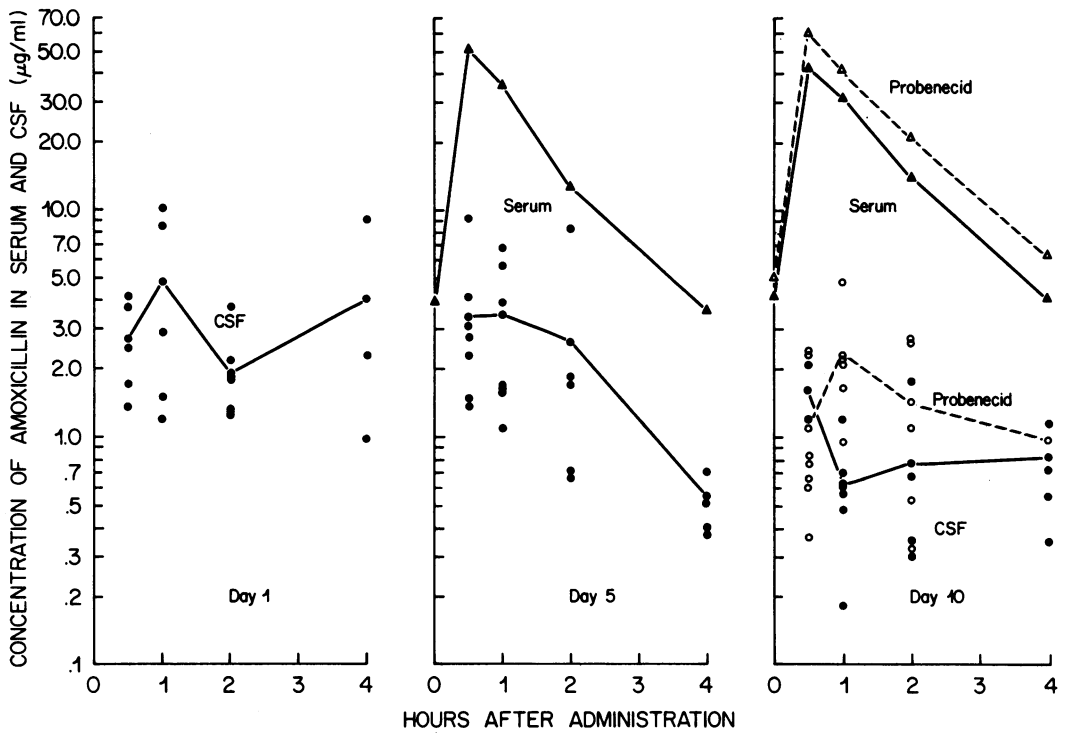

FIG. 1. *CSF and serum concentrations of amoxicillin after a dose of 50 mg/kg. Mean values are presented for serum concentrations. Individual and mean values are shown for CSF concentrations. Specimens from patients who received probenecid are represented by open circles and dashed lines.*

TABLE 3. *Amoxicillin concentration in CSF*

Treatment day	h after dose[a]			
	0.5	1	2	4
1	2.7 ± 0.54	4.8 ± 1.9	1.9 ± 0.32	4.1 ± 2.5
5	3.4 ± 1.0	3.5 ± 0.79	2.7 ± 1.43	0.6 ± 0.10
10				
Without probenecid	1.6 ± 0.44[b]	0.6 ± 0.13[c]	0.8 ± 0.34[c]	0.7 ± 0.18
With probenecid	1.1 ± 0.31	2.3 ± 0.66	1.5 ± 0.51	1.0 ± 0.0

[a] See Table 1, footnote *a*.
[b] $P > 0.10$.
[c] $P < 0.05$.

TABLE 4. *Mean concentration of ampicillin and amoxicillin in plasma*

Day after start of treatment	h after dose[a]				Mean half-life (h)	Area under curve (μg/ml·h)
	0.5	1	2	4		
Ampicillin, days 1, 5, and 10	73.8[b]	28.1	12.8	3.4	1.03	85.9
Amoxicillin, days 5 and 10	49.2	34.8	13.3	3.9	1.31	82.2
Amoxicillin-probenecid, day 10	61.4	42.5	20.6	6.4	1.48	112.5

[a] Time after a 10-min infusion of 50 mg of ampicillin per kg and after a 20-min infusion of 50 mg of amoxicillin per kg. Values are mean micrograms per milliter.

with ampicillin-treated patients than those found in amoxicillin-treated patients (Table 5). This may be due to the higher serum concentrations in patients who received ampicillin but could also be due in part to a greater penetration of ampicillin than amoxicillin, which has been reported in adults with uninflamed meninges (4). CSF concentrations from 1 to 4 h after a

dose were comparable with the two drugs, except for the augmented values observed in patients who received probenecid.

Patients in this study who had *H. influenzae* meningitis were compared with those treated with ampicillin in the earlier study by Wilson and Haltalin (26) (Table 6). There were no significant differences between patients treated with amoxicillin or those treated with ampicillin in regard to mean days of fever, CSF leukocyte count, glucose, and protein and number of relapses or deaths. Only 2 of 23 amoxicillin-treated patients had positive CSF cultures 24 h after the onset of therapy compared with 14 of 61 patients who received ampicillin, but the difference was not significant ($P < 0.20$). Repeat lumbar puncture was not done until approximately 48 h after start of therapy in the remaining 20 patients treated with amoxicillin. The difference between central nervous system sequellae present at the time of hospital discharge was significantly less ($P < 0.005$) in the amoxicillin-treated patients than in ampicillin-treated patients. In the ampicillin study of Wilson and Haltalin cultures were made with Levinthal medium (14). Chocolate agar, which is less sensitive in detecting *H. influenzae*, was used in this study. The patients in the ampicillin study received only ampicillin. Our patients received ampicillin and chloramphenicol initially and amoxicillin subsequently. Feldman (11) reported synergistic effects of ampicillin and chloramphenicol against many strains of *H. influenzae*, and it is possible that this in vitro observation has an in vivo corollary in the trend toward fewer positive cultures after 24 h of therapy.

TABLE 5. *Mean concentration of ampicillin and amoxicillin in CSF*

Day after start of treatment	h after dose[a]			
	0.5	1	2	4
1				
Ampicillin	9.9	2.0	3.0	2.1
Amoxicillin	2.7	4.8	1.9	4.1
5				
Ampicillin	14.7	2.1	1.6	1.2
Amoxicillin	3.4	3.5	2.7	0.6
10				
Ampicillin	6.7	1.1	1.0	0.9
Amoxicillin	1.6	0.6	0.8	0.7
Amoxicillin-probenecid	1.1	2.3	1.5	1.0

[a] Time after a 10-min infusion of 50 mg of ampicillin per kg and after a 20-min infusion of 50 mg of amoxicillin per kg. Values are mean micrograms per milliliter.

In this study with amoxicillin, in the Wilson and Haltalin study with ampicillin (26) and in the Hieber and Nelson study with penicillin G (15), CSF concentrations of antibiotic on day 1 showed a similar pattern (Fig. 2). The initial high CSF concentration was followed by a drop in concentration and a secondary rise during 2 to 4 h after administration of the antibiotics. The fact that the pharmacokinetics in CSF are consistent with the three penicillin derivatives indicates a reproducible characteristic of penicillins which may represent a redistribution between blood, CSF, and brain, but we have no explanation for the observation.

The observed probenecid effect is consistent with that in other studies in animals and humans (8, 9, 12). The elevated amoxicillin serum concentrations, the increased area under the curve, and the diminished plasma clearance value with probenecid are consistent with the hypothesis that probenecid blocks the excretion of penicillins by the kidney. The concentration of amoxicillin in CSF of patients treated with probenecid showed a delayed rise and a mean peak level significantly higher than that observed in patients who did not receive probenecid. The elevated levels persisted throughout the test period, suggesting that probenecid has an effect on elim-

TABLE 6. *Comparison of clinical responses to amoxicillin and ampicillin in patients with H. influenzae meningitis*

Characteristic	Amoxicillin (43 patients)	Ampicillin (61 patients)
Time after start of therapy until afebrile	3.6 days	4.4 days
Culture positive 24 h after start of therapy	2 patients	14 patients
CSF day 5		
Leukocytes (mean)	246 per mm^3	224 per mm^3
Glucose (mean)	46 mg/dl	49 mg/dl
Protein (mean)	61 mg/dl	101 mg/dl
CSF day 10		
Leukocytes (mean)	74 per mm^3	113 per mm^3
Glucose (mean)	50 mg/dl	47 mg/dl
Protein (mean)	39 mg/dl	48 mg/dl
Relapses	0	0
Neurological residua	6 patients	19 patients
Death	0	1 patient

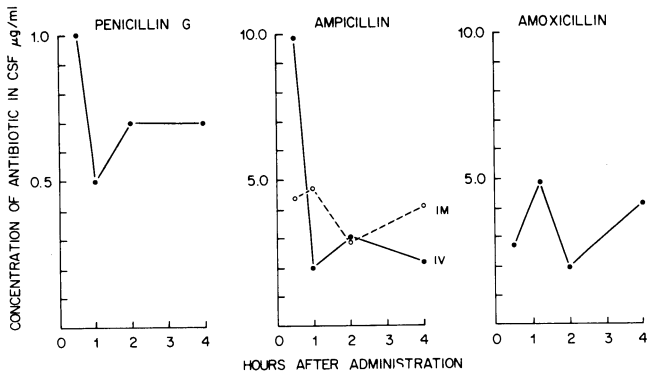

FIG. 2. *Comparative mean CSF concentrations of penicillin G, ampicillin, and amoxicillin during the first 24 h of therapy. IM and IV refer to intramuscular and intravenous administration routes.*

ination of amoxicillin from the CSF. The ratio of CSF to serum concentration remained relatively low, indicating no significant effect on penetration.

We concluded from this study that probenecid is an effective means of increasing the concentration of amoxicillin in the CSF of children with meningitis late in the course of therapy when CSF concentrations of antibiotic are generally at their lowest due to minimal inflammation of the meninges. This conclusion may have no clinical relevance and may be merely an interesting pharmacological observation. In unusual situations of low-grade infection, doubling of the CSF concentrations of amoxicillin or other penicillins by probenecid could possibly have clinical importance.

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