Ampicillin Dosage in Bacterial Meningitis with Special Reference to *Haemophilus influenzae*

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Ampicillin remains the preferred drug for most cases of bacterial meningitis, including those due to *Haemophilus influenzae* type b. A prospective study was performed comparing high (400 mg/kg per day)- and low (150 mg/kg per day)-dosage regimens of ampicillin in the treatment of 172 patients with bacterial meningitis. Response to both regimens was equivalent in terms of average hospital stay, duration of ampicillin therapy, microbiological response, and death and residua. Patients with *H. influenzae* infections treated with low-dosage regimens had slightly prolonged febrile courses. This study suggests that high-dosage regimens of ampicillin offer no benefit over low-dosage regimens in the treatment of bacterial meningitis.

Ampicillin resistance in strains of *Haemophilus influenzae* type b (HIB) was first recognized in 1974 (3, 12), although resistant strains may have existed earlier (6). This has resulted in the addition of chloramphenicol to the initial therapy of suspected HIB meningitis (1). However, if the causative strain is found to be susceptible to ampicillin, ampicillin remains the preferred drug (5). A recent nationwide survey of pediatric hospitals has demonstrated ampicillin resistance in approximately 4.5% of isolates of HIB from blood and cerebrospinal fluid (CSF) (13). In this survey, West Coast hospitals had a higher average rate (9%). The authors point out that hospitals using only disk susceptibility testing may report false-positive resistance. Therefore, as many as 90% of patients with meningitis due to HIB can still be successfully treated with ampicillin. Furthermore, there does not seem to be a population of HIB with intermediate resistance to ampicillin (10).

The appropriate dose of ampicillin in meningitis due to susceptible bacteria remains unresolved. Recommendations vary from 150 to 400 mg/kg per day (6, 8). There has not been a prospective evaluation of "low"- versus "high"-dosage regimens. Since increased dosage may be associated with greater toxicity and cost, on the one hand, or more rapid resolution and enhanced survival, on the other, we prospectively studied the response of patients with bacterial meningitis to a low-dose (150 mg/kg per day) or a high-dose (400 mg/kg per day) ampicillin regimen prior to the recognition of generalized ampicillin resistance in HIB. The focus of this report will be those patients in the study with HIB meningitis.

**MATERIALS AND METHODS**

Patients over 3 months of age admitted to the Los Angeles County-University of Southern California Medical Center with bacterial meningitis were eligible for the study. The study period was from 20 March 1972 to 20 December 1973. Patients were excluded if initial evaluation suggested a causative organism which would likely be resistant to ampicillin or if there was a history of penicillin allergy. Eligible patients with even file numbers were begun on 400 mg of ampicillin/kg per day ("400") and those with odd file numbers received 150 mg/kg per day ("150"); both groups received an initial 50-mg/kg intravenous push dose. Ampicillin in both regimens was administered intravenously at 4-h intervals. Therapy was continued until the following clinical and laboratory criteria were met: (i) afebrile for at least 5 days; (ii) CSF with <30 cells or <80 if therapy was longer than 18 days; (iii) CSF glucose, >50 mg/dl, or >66% of the serum glucose; (iv) CSF protein, <100 mg/dl (7). Lumbar puncture was performed on admission and at the following intervals postadmission: 24 to 48 h, 72 to 96 h, 7 days, 10 days, 14 days, and, if necessary, 12, 21, 24, and 28 days. Patients were observed for at least 36 h in the hospital after cessation of ampicillin before being discharged. There were no relapses. The severity of the meningitis on admission was assessed by a grading system previously described (6, 7): 4+, coma or shock; 3+, convulsions without shock or coma; 2+, temperature ≥ 104°F (40°C), 5 or more days of illness, or marked lethargy; 1+, none of these.

During the study period 202 patients with purulent meningitis were admitted. Of these, 89 cases were due to HIB, 45 were due to *Streptococcus pneumoniae*, and 18 were due to *Neisseria meningitidis*; in 21 cases no organism was identified. In one instance the hospital record could not be found. The remaining 28 cases were caused by a variety of other bacteria. Identification of HIB was confirmed by quellung reaction to specific antiserum. All the patients with HIB
meningitis were children ranging in age from 3 months to 7.5 years, with the exception of one adult in the "150" group. All of the isolates from these patients were susceptible to ampicillin and were negative on subsequent testing for beta-lactamase activity (10). After appropriate exclusions had been made, chi-square analysis was used to compare the low- and high-dose groups. Yeates correction was included for two-by-two tables.

RESULTS

HIB meningitis. Seven cases of HIB meningitis were excluded. Five had been assigned to the wrong dose regimen (three with odd and two with even file numbers). Two children with odd file numbers had been given a second antibiotic. After the exclusions, 37 patients receiving the "150" regimen were compared with 45 who got the "400." There were no significant differences between these groups with respect to age, sex, or race (Table 1). The "150" group had a higher percentage of females and was older on the average, with a broader age range. There were also no significant differences when the groups were compared as to symptomatic days before admission, prior history of antibiotic use, and severity on admission (Table 2). The patients in the "150" group were more likely to have received antibiotics before admission and to be more severely ill at presentation.

Table 3 compares the outcomes of the two dosage regimens. Calculations of length of hospital stay, ampicillin therapy, and febrile days, as well as those dealing with meeting CSF criteria, exclude the patients who died. Patients on

TABLE 1. Comparison of clinical status of patients with HIB meningitis assigned to low-dose ("150") and high-dose ("400") ampicillin therapy regimens

| Criteria                  | No. of patients | Level of significance |
|---------------------------|-----------------|-----------------------|
|                           | Low-dose regimen | High-dose regimen     |
| Sex                       |                 |                       |
| Male                      | 15              | 26                    | 0.2 > P > 0.1 |
| Female                    | 22              | 19                    |               |
| Race                      |                 |                       |
| White                     | 15              | 13                    |               |
| Black                     | 5               | 7                     |               |
| Latin surname             | 17              | 23                    | 0.5 > P > 0.4 |
| Other                     | 0               | 2                     |               |
| Age                       |                 |                       |
| <6 mo                     | 9               | 5                     |               |
| 6-11 mo                   | 11              | 19                    |               |
| 12-23 mo                  | 6               | 12                    |               |
| 24 mo-4 yr                | 7               | 9                     | 0.1 > P > 0.05|
| >5 yr                     | 4               | 0                     |               |

a Total number assigned regimen, 37.
b Total number assigned regimen, 45.

TABLE 2. Comparison of factors possibly influencing disease outcome of patients with HIB meningitis treated with low-dose ("150") and high-dose ("400") ampicillin therapy regimens

| Criteria                  | No. of patients | Level of significance |
|---------------------------|-----------------|-----------------------|
|                           | Low-dose regimen | High-dose regimen     |
| Days symptomatic before treatment |                 |                       |
| ≤23 h                     | 8               | 5                     | P = 0.4 |
| 24-71 h                   | 8               | 15                    |       |
| 3-5 days                  | 12              | 17                    |       |
| ≥6 days                   | 9               | 8                     |       |
| Antibiotics administered before admission |         |
| No                        | 14              | 26                    | 0.3 > P > 0.2 |
| Yes                       | 23              | 19                    |       |
| Severity on admission     |                 |                       |
| 1+                        | 7               | 5                     | 0.2 > P > 0.1 |
| 2+                        | 17              | 22                    |       |
| 3+                        | 5               | 13                    |       |
| 4+                        | 8               | 5                     |       |

a Total number assigned regimen, 37.
b Total number assigned regimen, 45.
TABLE 3. Comparison of hospital outcome, morbidity, and mortality of patients with HIB meningitis treated with low-dose ("150") and high-dose ("400") ampicillin therapy regimens

| Ampicillin regimen | Avg hospital stay (days)* | Avg duration of ampicillin therapy (days) | Avg duration of fever ≥100°F (37.8°C) (days)* | % of patients with fever for ≥7 days* | No. of positive CSF cultures for HIB at 24 h* | % Lived Without residua | With residua | % Died |
|--------------------|--------------------------|------------------------------------------|-----------------------------------------------|--------------------------------------|-----------------------------------------------|----------------------|-------------|--------|
| Low dose b         | 20.8                     | 17.4                                     | 4.7                                           | 23.5                                 | 1*                                            | 81.1                 | 10.8        | 8.1    |
| High dose c        | 23.7                     | 17.0                                     | 3.4                                           | 11.6                                 | 1*                                            | 76.7                 | 18.9        | 4.4    |

Level of significance

0.6 > P > 0.5

0.3 > P > 0.2

0.9 > P > 0.8

* Excludes patients who died.

b Total number assigned regimen, 37.

c One culture positive at 27 h post-initiation of therapy.

d Total number assigned regimen, 45.

e One culture positive at 42 h post-initiation of therapy.

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group. This is not a significant difference (0.5 > P > 0.4).

Other bacterial meningitis. Eleven and 22 of 45 patients with pneumococcal meningitis qualified for the “150” and “400” groups, respectively. These groups were not comparable, as the “400” group had a significantly higher percentage of men and individuals over 40 years of age. There were four deaths and two patients with significant residua in the “400” pneumococcal group and one death and two patients with residua in the “150” group, which does not represent a significant difference in outcome since the “400” group was skewed towards higher-risk individuals. One of the seven “150” group patients with meningococcal meningitis died; this patient was moribund on admission. There were no deaths among eight “400” group patients with meningococcal meningitis. One of five “150” group patients with meningitis of unknown etiology died, whereas all eight “400” group patients with meningitis of unknown etiology survived.

DISCUSSION

This study does not support recommendations for high doses of ampicillin for treatment of meningitis due to susceptible strains of HIB when cessation of therapy is dependent upon clinical and CSF criteria. Although the numbers are small, we feel this study also suggests that doses of ampicillin over 150 mg/kg per day are not necessary to treat meningitis due to S. pneumoniae and N. meningitidis or patients who are culture negative.

Ampicillin levels in CSF increase with increasing parenteral dosage. In prior studies, mean CSF levels of ampicillin measured 1 to 1.5 h postintravenous administration increased from 0.45 to 1.60 μg/ml when the intravenous dosage was raised from 200 to 400 mg/kg per day (9). Somewhat higher CSF concentrations (2.0 to 3.0 μg/ml) were found by Wilson and Haltalin 1 to 2 h after the parenteral administration of ampicillin at 200 mg/kg per day (15).

Despite lower CSF concentrations of ampicillin after smaller parenteral doses, a regimen of 150 mg/kg per day has proven successful in large numbers of patients (6, 7). This may be because 94 to 100% of ampicillin-susceptible HIB strains are killed at concentrations of ≤0.8 μg of ampicillin per ml (2, 8, 14). Concentrations of antibiotic in CSF have been assumed to reflect the concentration in meningeal tissue, but this assumption is not confirmed and the exact relationship between CSF and tissue levels is unknown. Regimens of ampicillin in low dosage have been questioned based on reports of relapse or poor outcome (16). However, reports of failure or poor outcome while on high-dose regimens suggest that multiple undefined factors, other than dosage per se, contribute to therapeutic failures (11).

This institution has traditionally utilized CSF changes as well as clinical criteria to determine length of therapy; therefore, on the average our patients may be treated longer. In this study, cellular criteria proved least useful. Among HIB patients, 32% of the “150” group and 37% of the “400” group had not met cellular criteria at the time ampicillin was discontinued. It may be that the duration of therapy is more critical than the daily or total dose of ampicillin in determining outcome, but this study was not designed to evaluate different preset lengths of treatment, dosage intervals, or routes of administration.

Increased ampicillin toxicity with the higher-dose regimen was not clearly demonstrated. The “400” group tended to experience more episodes of eosinophilia or rash, but this was not a significant difference. In a previous study comparing ampicillin and carbenicillin, toxicity could not be related to increasing dose; a greater percentage of patients in this study who received 400 mg of carbenicillin/kg per day had eosinophilia than those receiving 200 mg/kg per day.

Chloramphenicol should continue to be used initially in the therapy of suspected HIB meningitis, and if the organism proves to be resistant to ampicillin, it should be continued. At least

| Protein (≤100 mg/dl) | Cumulative % | Low-dose regimen | High-dose regimen |
|----------------------|-------------|------------------|------------------|
| 96 h                 | 23.3        | 30               |
| 7 days               | 53.3        | 60               |
| 10–11 days           | 76.7        | 72.5             |
| 14 days              | 83.3        | 85.0             |
| 23 days              | 96.7        | 97.5             |
| Cellular criteria    |             |                  |
| 7–8 days             | 11.8        | 25.6             |
| 10–11 days           | 20.6        | 34.7             |
| 14 days              | 29.4        | 41.9             |
| 20 days              | 61.7        | 55.8             |

* Excludes patients who died.
two chloramphenicol-resistant strains of HIB have been reported, both of which were susceptible to ampicillin (4,5). At present, ampicillin resistance in HIB varies considerably geographically, but there is no information to suggest that an increase in frequency of resistant strains beyond current levels is likely to occur. Therefore, for the present, ampicillin continues to be the preferred drug in the vast majority of cases of HIB meningitis, since it is less toxic than chloramphenicol. This study suggests that dosages of ampicillin over 150 mg/kg per day for bacterial meningitis caused by susceptible organisms offers little advantage, but does not seem to incur increased toxicity. Further prospective studies of treatment should be designed to evaluate length of therapy, dosage interval, and route of administration, as well as total daily dose.

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