INTRATHECAL AND INTRAMUSCULAR AMPICILLIN IN THE TREATMENT OF HAEMOPHILUS INFLUENZA MENINGITIS IN INFANTS

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THE DEVELOPMENT of ampicillin and its effectiveness against Gram-negative organisms has led to its use in the treatment of meningitis due to *Haemophilus influenzae* with encouraging results (Ivler, Thrupp, Leedom, Wehrle and Portnoy, 1963; Thrupp, Leedom, Ivler, Wehrle, Brown, Mathios and Portnoy, 1964; Pickup and Mathur, 1964).

Ampicillin for intrathecal injection is now available in this country and we report clinical details of four infants aged between eight and fifteen months, suffering from *Haemophilus influenzae* meningitis, who were treated with combined intrathecal and intramuscular ampicillin.

Materials and Methods

Four cases were admitted to this hospital during the winter of 1964-65. This investigation was planned to run *pari passu* with treatment, thus obviating the need for additional lumbar punctures. When lumbar puncture was performed some CSF was taken off before the intrathecal injection and stored in a deep freeze before being sent for ampicillin assay. The ampicillin concentrations given below represent the drug concentration in the CSF twenty-four hours after the intrathecal dose, unless otherwise stated.

Method of Assay

The ampicillin concentrations in the specimens of CSF were determined by microbiological assay using an agar diffusion method with *Sarcina lutea* as test organism (Knudsen, Rolinson and Stevens, 1961). The diluent used for the test specimens and for the standard solutions was M/20 phosphate buffer, pH 7.0.

Duration of Therapy

In all cases, the duration of therapy was determined by clinical and CSF findings. No rigid or pre-arranged criteria were used.

Case Reports

Case No. 1. Male, weighing 22 lbs., aged fifteen months. Admitted with a week's history of irritability, anorexia, loss of weight and constipation. Neck stiffness and one generalised convulsion on the day of admission. Therapy with oral penicillin had been given for three days prior to admission.

On examination, he was alert but fretful. He had signs of an upper respiratory infection and definite neck stiffness.

CSF:—5,500 cells/cu. mm., polys 90%; *Haemophilus influenzae* grown on culture.

Treatment: Intramuscular ampicillin 125 mg. six hourly for 21 days. Intrathecal ampicillin 5 mg. daily for 3 days and then after a lapse of 2 days for a further 8 days (see below).

CSF Ampicillin Assay

1. 12 hours after the commencement of intramuscular therapy—0.5 µg. ampicillin/ml.

2. 24 hours after the first intrathecal dose of 5 mg. of ampicillin—0.3 µg./ml.

3. 24 hours after the second intrathecal dose of 5 mg. ampicillin—0.25 µg./ml.

Progress: Improvement occurred until the fifth day when the clinical condition relapsed, with fever, vomiting and the recurrence of neck stiffness. Lumbar puncture: CSF cell count of 9,000 cu. mm., 99% polys. *Haemophilus influenzae* identified in CSF.

Intrathecal therapy was recommenced and two further CSF ampicillin assays were done, as follows:

24 hours after the fourth intrathecal dose of 5 mg. ampicillin—0.15 µg./ml.

24 hours after the fifth intrathecal dose of 5 mg. ampicillin—<0.1 µg./ml.

Uninterrupted clinical recovery then took place. Child apparently progressing well on out-patient follow up.

Case No. 2. Female, weighing 14 lbs., aged eight months. Had a week's history of rhinorrhoea, vomiting and fever. Oral penicillin administered for two days prior to admission—was not retained because of the vomiting.

On examination, a descending upper respiratory infection with neck stiffness was noted. CSF: 2,500 cells/cu. mm., 88% polys. *Haemophilus influenzae* identified.

Treatment: Intramuscular ampicillin 125 mg. six hourly for 14 days. Intrathecal ampicillin 5 mg. daily for 9 days.

CSF Ampicillin Assays

1. 12 hours after the commencement of intramuscular ampicillin—0.38 µg./ml.

2. 24 hours after the first intrathecal dose of 5 mg. ampicillin—0.88 µg./ml.

3. 24 hours after the second intrathecal dose of 5 mg. ampicillin—0.23 µg./ml.

4. 24 hours after the third intrathecal dose of 5 mg. ampicillin—0.34 µg./ml.

5. 24 hours after the fourth intrathecal dose of 5 mg. ampicillin—1.5 µg./ml.

Progress: This baby made a progressive, uneventful recovery and was thought to be normal on out-patient follow up. Two-and-a-half months after

discharge, however, she was re-admitted with acute bronchitis but there were no meningeal signs and the CSF was found to be normal.

Case No. 3. Female, weighing 22 lbs. aged one year. Admitted with a four day history of a mild upper respiratory infection. On the day of admission she was drowsy and had vomited twice.

On examination, there was a descending upper respiratory infection, neck stiffness and a Kernig's sign. CSF—6,500 cells/cu. mm., polys 90%. Initially this child was thought to be suffering from meningococcal meningitis and therapy was commenced with intramuscular penicillin G and oral sulphadimidine. Later on the day of admission, because of clinical deterioration, a further lumbar puncture was performed and *Haemophilus influenza* was cultured from the CSF.

Treatment: Treatment with ampicillin was as follows:

An immediate dose of 10 mg. was given intrathecally, and on each of the following four days 5 mg. intrathecally. The drug was given intramuscularly in a dosage of 125 mg. six hourly. Owing to the child's condition oral sulphadimidine was continued for nine days and intramuscular penicillin G was continued for six days.

CSF Assays

1. 12½ hours after the first dose of 10 mg. intrathecal ampicillin—0.75 µg. antibiotic/ml.

2. 24 hours after the second dose of 5 mg. intrathecal ampicillin—0.6 µg. antibiotic/ml.

3. 24 hours after the third dose of 5 mg. intrathecal ampicillin—0.9 µg. antibiotic/ml.

Sulphonamide activity was eliminated with para-aminobenzoic acid. It was not possible to differentiate between penicillin G and ampicillin so that the assay represents total antibiotic content.

Progress: The child made good progress and was developing normally at out-patient follow up.

Case No. 4. Male, weighing 20½ lbs. aged eleven months. Admitted with a seven-day history of nasal discharge and slight cough. Irritability, fever and vomiting were noted three days prior to admission. *On examination*, there were signs of an upper respiratory infection and slight neck stiffness. CSF: 11,500 cells/cu. mm., polys 90% *Haemophilus influenzae* noted in CSF.

Treatment: It was decided (see below) to treat this baby with larger doses of intrathecal and intramuscular ampicillin, i.e., Intrathecal ampicillin 10 mg. daily for four days. Intramuscular ampicillin 500 mg. stat and 250 mg. six hourly for fourteen days.

CSF Assays

1. 12 hours after 500 mg. ampicillin intramuscularly—2.8 µg./ml.

2. 24 hours after first dose of 10 mg. ampicillin intrathecally—13.8 µg./ml.

3. 24 hours after second dose of 10 mg. ampicillin intrathecally—1.4 µg./ml.

4. 24 hours after third dose of 10 mg. ampicillin intrathecally—0.4 µg./ml.

5. 24 hours after fourth dose of 10 mg. ampicillin intrathecally—5.2 µg./ml.

Progress: The child made good progress and was thought to be developing normally on follow up.

Discussion

The ampicillin levels in the CSF samples from our cases showed wide variation. Such variation was described by Ivler and Thrupp and their colleagues in their cases treated by ampicillin and they suggested that the minimum inhibitory concentration against *Haemophilus influenzae* is 0.4 µg./ml. This level was consistently maintained in only one of our cases (Case 4), using the higher intramuscular and intrathecal dosages of the drug.

In our opinion ampicillin doses of not less than 10 mg. intrathecally daily and 250 mg. six hourly intramuscularly are required for the treatment of this condition in infants.

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