Case Reports

HAEMOPHILUS INFLUENZAE MENINGITIS—TREATED WITH PARENTERAL AND INTRATHECAL PENBRITIN

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AMPICILLIN (Penbritin), a new synthetic penicillin was introduced in 1961 (Rolinson and Stevens, 1961; Brown and Acred, 1961; Knudsen, Rolinson and Stevens, 1961). We report two cases of *haemophilus influenzae* meningitis which failed to respond to the usual antibiotics and were ultimately treated with intramuscular and intrathecal Penbritin.

Case 1

A. K., aged 4½ months, was admitted on 13.1.63 with a three days' history of vomiting, pallor and fever.

On admission he had a temperature of 103°F, there was marked neck rigidity, Kernig's sign was positive and the fontanelle was bulging and tense. The throat was congested and the head circumference was 17½ in. There were no other neurological signs. Both plantar responses were flexor and the optic discs were normal.

Investigations. The CSF was turbid, not under pressure and contained macroscopic particles of pus. Proteins 200 mg., sugar 5 mg., chlorides 660 mg./100 ml., globulins not increased. Cell count 3,500/cu. mm. 95% polys., 5% Monos. Gram staining revealed gram negative coccobacilli and on culture there was a light growth of *haemophilus influenzae* sensitive to penicillin. Sensitivity against other antibiotics was not done. Hb. 65% (Haldane), wbc 13,500/cu. mm., polys. 35%: lymphs. 41%, Monos. 5%, eosinos. 1%. A throat swab grew scanty colonies of *staphylococcus albus*, coagulase negative, sensitive to penicillin, chloramphenicol, streptomycin and tetracycline. Urine examination and chest radiograph were normal.

Initially, intrathecal penicillin and streptomycin were given and the patient was put on penicillin 250,000 units im. six hourly, sulphadimidine 0.25 g. six hourly, streptomycin 0.25 g. twice daily and cortisone acetate 20 mg. daily, orally. After receiving the CSF report intrathecal streptomycin 40 mg. and hydrocortisone 5 mg. intrathecally, daily, were started. As the patient did not show any response, on 16.1.63 penicillin was replaced by chloramphenicol 75 mg. six-hourly orally. There was a clinical improvement but the temperature did not settle and the CSF flow was also noticed to be diminishing. On 18.1.63 the temperature rose to 103°F and he had generalized convulsions which were controlled with sedatives. By this time the CSF had become sterile and biochemically improved and the cell count diminished but slight xanthochromia was noticed at this stage. On 24.1.63 sulphadimidine and streptomycin were stopped and oral Penbritin 125 mg. six-hourly was added to the treatment. Unfortunately he started vomiting and Penbritin was stopped and chloramphenicol was changed to the intramuscular preparation.

CSF xanthochromia increased and became very thick with macroscopic pus particles. On 24.1.63 all other treatment was stopped and he was given intramuscular Penbritin 125 mg. six-hourly and from the next day Penbritin intrathecally 5 mg. daily and intrathecal hydrocortisone was added to the treatment. His condition once again deteriorated suddenly, he refused feeds, became unconscious; there was slight ptosis of the left eye and bilateral intermittent nystagmus appeared with left hemiplegia. Both the carotid arteries were palpable and the plantar responses were extensor and the optic discs were normal. Intrathecal Penbritin was given for ten days along with intramuscular Penbritin which was continued for three weeks. The temperature returned to normal after a week's treatment and remained normal. The CSF gradually improved and on 5.2.63 was clear; proteins 50 mg., sugar 30 mg./100 ml. and no cells were seen. Clinical improvement continued and gradually movement on the left side returned. At the time of discharge on 18.2.63 the CSF was normal he was moving the left leg and arm slightly. One week after discharge his general condition was excellent and he was kicking both legs equally. Two months after discharge there was little difference in the muscle tone and the reflexes on the two sides.

Case 2

C. S., aged 5 years, was admitted on 19.12.62 with a three days' history of being unwell, anorexia, headache, drowsiness and vomiting. On examination he was very drowsy and listless with marked neck rigidity and a positive Kernig's sign. The temperature was 100°F. There were no other neurological signs. The CSF was very turbid and under increased pressure. Proteins 400 mg., sugar 15 mg./100 ml., cells 18,410/cu. mm. Gram staining revealed gram-negative bacilli and on culture there was a moderate growth of *haemophilus influenzae* Pitman type B. sensitive to penicillin, chloramphenicol, streptomycin, erythromycin and tetracycline. After an initial dose of intrathecal penicillin and streptomycin treatment continued with chloramphenicol 125 mg. six-hourly im., streptomycin 40 mg., b.d. sulphadimidine 1 g. six-hourly. After receiving the CSF report, intrathecal streptomycin 40 mg. was given daily for three days. Twelve days later the temperature was normal but he remained fretful, irritable and complained of occasional headaches. The CSF on 29.12.62 showed 189 cells/cu. mm. and was sterile on culture. A repeat CSF on 3.1.63 showed 140 cells/cu. mm., proteins 50 mg., sugar 46 mg./100 ml. and culture revealed a moderate growth of *haemophilus influenzae* sensitive to penicillin, streptomycin, chloramphenicol and erythromycin. In view of the relapse, sulphadimi-

FIG. 1.—Case 1.

dine, chloramphenicol and streptomycin were recommenced on 3.1.63 for a week with daily intrathecal streptomycin for three days. The temperature remained normal and the general condition markedly improved. The CSF on 11.1.63 was clear; proteins 30 mg./100 ml., cells 66/cu. mm. Culture revealed a moderate growth of *hæmophilus influenzae* sensitive to chloramphenicol, streptomycin, sulphadimidine and penicillin. In view of the second relapse and failure to respond to the usual treatment, it was decided to try Penbritin which was given in doses of 250 mg. six-hourly orally which was continued until 17.1.63. On that day the CSF was still turbid and showed 73 cells/cu. mm., proteins 40 mg., sugar 86 mg./100 ml. and was sterile on culture. Another course of Penbritin was started on 19.1.63. The CSF on 25.1.63 was once again turbid with 213 cells/cu. mm., proteins 70 mg., sugar 63 mg./100 ml. and on culture gram-negative bacilli were grown which were later proved to be paracolon bacilli, probably contaminants. A third course of oral Penbritin was started on 26.1.63 and on 29.1.63 it was changed to intramuscular Penbritin 125 mg. six-hourly which was

given for five days. A single dose of intrathecal Penbritin 10 mg. was also given. The CSF at the end of the treatment was normal and sterile on culture. He was discharged on 6.2.63 and the CSF was normal. He has been well since his discharge home.

Discussion

Penbritin, a new broad spectrum antibiotic, is well known for its effectiveness against gram negative organisms. Activity of Penbritin *in vivo* against infections produced by gram negative organisms is considered to be greater than that of tetracycline and chloramphenicol (Brown and Acred, 1961). Against *hæmophilus influenzae* Penbritin showed a high level of activity; twice as high as penicillin G., and chloramphenicol and five times greater than tetracycline (Rolinson and Stevens, 1961). Peak serum concentration of the drug is obtained in about one to two hours and a significant serum concentration (0.2 µg/ml.) is still

FIG. 2.—Case 2.

present after six hours if the drug is given in doses of 100 mg./kg. per day orally, minimum inhibitory concentration for *haemophilus influenzae* being 0.1 to 0.5 µg/ml.

Only three cases have so far been reported where Penbritin has been used in meningitis. Two of them were adult cases with *E. Coli* meningitis following a serious head injury and CSF leak (Spittle and Phillips, 1961). After oral administration of Penbritin the CSF level in two to three hours was less than 0.2 µg/ml. and after six hours it rose to 2.42 µg/ml. A CSF level of 12.5 µg/ml. has been observed after 10 mg. of intrathecal Penbritin after six hours; doubling the dose virtually doubles the peak serum concentration which is not seen with tetracycline (Knudsen and others, 1961). Similarly, doubling

the intrathecal dose up to 40 mg. increases its concentration in the CSF without any sign of cerebral irritation (Spittle and Phillips, 1961).

Another case, that of a hydrocephalic child aged 9 months with urinary infection due to coliform bacilli and streptococci has been described, who developed meningitis in which the CSF yielded strains of streptococci (Stewart, Coles, Nixon and Holt, 1961). This child was treated with oral Penbritin and the CSF concentration was found to be 0.7 µg/ml. which was insufficient to inhibit the growth of the organisms. Intraventricular Penbritin, 2 to 4 mg. daily for four days, produced a CSF concentration of more than 20 µg/ml. which persisted at inhibitory levels (2 to 5 µg/ml.) for twenty-four hours or more.

Summary

Two cases of *hæmophilus influenzae* meningitis have been described who showed lack of response to the routine antibiotics. These two cases did not respond to the oral Penbritin because of vomiting and were treated with intramuscular and intrathecal Penbritin with successful results as shown by biochemical and clinical responses. It should be stressed that neither of these preparations of

Penbritin is yet available on the market; both were obtained by special arrangements. We consider that these routes of administration of Penbritin would be useful in the treatment of patients with *hæmophilus influenzae* meningitis.

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FIBRINOLYSIN THERAPY IN ARTERIAL THROMBO-EMBOLISM

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THE lysis of intravascular clot using thrombolytic substances has been achieved by various workers since Clifton, Grossi and Cannamela (1954) originally demonstrated the effect of fibrinolysin in venous thrombosis in 1954. A vast amount of literature has accumulated on the therapeutic uses of such drugs especially in the United States of America. In this country, thrombolytic therapy using streptokinase has recently been reported (Verastraete, Amery, and Verylan, 1963; and McNicol, Reid, Bail and Douglas, 1963). Our experience with fibrinolysin (Actase) therapy has been limited but favourable. The following cases are particularly significant:—

Case No. 1

A woman (A. H.) aged 64 years was admitted on 8.2.63 with colicky abdominal pain of twenty-four-hours' duration and constipation for two days. Her abdomen was moderately distended in the lower part and a straight X-ray showed some distention of the small intestine (Fig. 1).

A diagnosis of subacute intestinal obstruction was made and was treated on conservative lines with a satisfactory response.

She had had a sub-total thyroidectomy ten years ago. She had a blood pressure of 180/100 mm. Hg. and auricular fibrillation was noted. The chest X-ray and ECG were compatible with the diagnosis of mitral valve disease. She had no previous history of intermittent claudication.

FIG. 1.—Case 1.

On 12.2.63 she suddenly developed loss of sensation of her left foot and toes. On examination, the left foot and toes were extremely pale and cold. There was no