

THE TREATMENT OF PYOGENIC MENINGITIS — IS INTRATHECAL THERAPY NECESSARY?

SHEILA R. ESRACHOWITZ, M.B., CH.B., M.R.C.P., D.C.H.

Department of Child Health, University of Cape Town; Paediatric Registrar, Red Cross War Memorial Children's Hospital and Groote Schuur Hospital, Cape Town

Two studies^{1,2} of more than 300 cases of non-tuberculous pyogenic meningitis seen between 1956 and 1958 showed that there was a considerable divergence of opinion between the advocates of 2 therapeutic schemes which gave comparable results. The main point at issue was the lack of a clear indication regarding the need for intrathecal drug therapy. If this could be omitted without prejudice to the patient's recovery, there would be obvious benefits to all concerned. An attempt has therefore been made to obtain data which might decide the point, by comparing results in patients treated with and without intrathecal drugs.

For such a comparison to be of value, a judicious choice of the drugs to be used is imperative. They must have a high diffusion level from blood to cerebrospinal fluid (CSF); those used in my earlier study¹ — 'chloromycetin' and sulphadiazine, with penicillin and streptomycin in reserve — appear to meet that requirement.

The concentrations of various agents in the CSF, compared with blood levels, have been studied by a number of workers. Ross *et al.*³ found that the concentration of chloromycetin in the CSF was 30-50% of that in the blood stream. This was confirmed by Banks *et al.*⁴ who also studied other antibiotics and chemotherapeutic agents. Sulphadiazine reached a concentration in the CSF of 50-70% of the blood level, and streptomycin 10-20%, while 'aureomycin' and 'terramycin' were present in minute amounts only. Seeleman⁵ and his co-workers found that the level in the CSF of orally-administered tetracyclines was $\frac{1}{3}$ - $\frac{1}{2}$ of that in the blood, and that chloromycetin levels in the CSF and blood were approximately equal.

Eagle⁶ found, in studying the therapeutic significance of penicillin levels in the blood stream, that 0.03-0.1 units per ml. were bacteriostatic and 0.1-0.5 units per ml. bacteriocidal. It would be reasonable to assume that similar levels in the CSF would have the same therapeutic significance. Inflammation increases the diffusion rate of penicillin into the CSF.⁷ After 20,000 to 40,000 units, given intramuscularly, CSF concentrations of up to 0.35 units per ml. may be found and the same levels may be attained with doses of 10,000-20,000 units in infants. Cooke and Goldring⁸ found levels of 0.1-0.4 units per ml. with this dosage. Fortified procaine penicillin injection, i.e. procaine penicillin with benzylpenicillin, combines the advantage of soluble penicillin, reaching a maximum plasma concentration in 10-15 minutes, with the slower long-acting procaine penicillin, reaching maximum plasma concentrations within 1-2 hours and then decreasing slowly

over 24 hours. This should give reasonably high dosage in the CSF.

In an attempt to evaluate intrathecal chloromycetin therapy, 71 patients with pyogenic meningitis were studied at the Red Cross War Memorial Children's Hospital and Groote Schuur Hospital, Cape Town, over a 12-month period, September 1958 - August 1959.

PRESENT SERIES

Management

When the diagnosis of pyogenic meningitis was made, at lumbar puncture in the outpatient or casualty department, a loading dose of chloromycetin, 25 mg. per lb. body weight, was given intramuscularly and the first quarter of the daily sulphadiazine dosage of 2 gr. (120 mg.) per lb. was given orally. This was done to ensure immediate treatment, which was otherwise liable to be delayed for a few hours while the CSF was examined and the formalities of admission were completed. Intramuscular chloromycetin was continued in the ward at a dosage of 50 mg. per lb. per day for at least 24 hours or until vomiting had stopped; thereafter it was given orally. Sulphadiazine was continued orally at the above dosage, divided into 4 doses and given 6-hourly. Other antibiotics were added only if (a) organisms were present in the CSF after 48 hours of treatment; or (b) there was clinical deterioration. This included a rise in temperature, no improvement in the level of consciousness, development of central-nervous-system localizing signs, or the presence of subdural effusions. If these effusions were found, subdural taps were done daily until negative. In pneumococcal, streptococcal, and staphylococcal meningitis the additional antibiotic when required was fortified procaine penicillin in 1 daily dose of 10,000 units per lb. Similarly streptomycin was added for cases due to *H. influenzae*, *B. proteus*, or salmonella organisms in a dosage of 20 mg. per lb. divided into morning and evening injections. Systemic therapy was maintained for 1 week after the temperature had fallen to normal, or for a minimum period of 10 days from the time it began.

It was planned originally that alternate cases were to receive intrathecal therapy at the initial lumbar puncture in the outpatient department. This was to be 200 µg. of chloromycetin and it was to be repeated daily in the ward until the CSF had a normal sugar content and did not contain more than 40-50 cells per ml., mostly lymphocytes. Unfortunately this regime could not be adhered to strictly because of the difficulty in obtaining and preparing intrathecal chloromycetin. There was no

selection of cases, however, and alternate cases received intrathecal chloromycetin when this was available. Otherwise no intrathecal therapy was given at all. This accounts for the disproportionately greater number in all groups who did not receive intrathecal treatment. The allotment of cases was, therefore, much the same as if a random sample had been taken, since the clinicians had no control over the supplies of chloromycetin and the form of treatment was decided before the organism was known.

Patients Treated

Patients below the age of 1 month have been excluded from the series, since in neonatal meningitis the commonest causal organisms are of the enteric group, mainly *B. coli*. The prognosis is notoriously bad, and the duration of illness is likely to be too short for an enquiry such as this. Apart from neonatal cases, there were 71 cases of pyogenic meningitis at the Red Cross War Memorial Children's Hospital and Groote Schuur Hospital, Cape Town, during the period of this investigation (September 1958 - August 1959). Of these, 24 were due to *D. pneumoniae*; 26 to *H. influenzae* or *H. parainfluenzae*; 12 showed no organism on Gram's stain or on culture; and 9 were due to organisms unusual in these hospitals, of which 2 were *N. meningitidis*, 2 *Proteus mirabilis*, 3 salmonella, 1 *Klebsiella aerogenes*, and 1 a haemolytic streptococcus.

RESULTS AND DISCUSSION

Table I shows the race, sex, and age range in the different groups of infections. The preponderance of Coloured children is in keeping with past experience, but there is no obvious reason for the higher incidence in boys. The

TABLE I. RACE, SEX, AND AGE RANGE OF 71 PATIENTS WITH PYOGENIC MENINGITIS

Organisms	Race			Sex		Age range
	W	C	B	M	F	
Pneumococci	3	18	3	15	9	1 month - 5½ years
<i>H. influenzae</i>	5	21	0	16	10	3 months - 4¼ years
No organisms	0	10	2	8	4	3 months - 9 years
Various organisms	0	7	2	7	2	1 month - 11 months
Total	8	56	7	46	25	

W=White, C=Coloured, B=Bantu, M=male, F=female.

average age for the pneumococcal and influenzal groups was 1 year 7 months and 1 year 2 months respectively, fortuitously making these groups comparable in this respect. The average age for the abacterial group was 4

TABLE II. OVERALL RESULTS

Organisms	Cases	Deaths	Sequelae	Complete recoveries
Pneumococci	24	7 (29%)	3 (12%)	14 (58%)
			17 (71%)	
<i>H. influenzae</i>	26	4 (15%)	3 (11%)	19 (73%)
			22 (85%)	
No organisms	12	—	2 (17%)	10 (83%)
Various organisms	9	3 (33%)	1 (11%)	5 (55%)
			6 (66%)	

years 5 months and for the fourth (assorted) group, 5 months. Table II shows the overall results in respect of deaths, sequelae and apparently complete recovery. The survivors have been divided into those who showed some residual damage and those who made an apparently complete recovery.

Of 24 patients with pneumococcal meningitis (Table III), 11 received intrathecal (IT) therapy; 13 did not. Of the IT group, 6 (54%) recovered completely compared with 8 complete recoveries (61%) in the non-IT group. There were 3 deaths (27%) and 2 cases with sequelae (18%) in

TABLE III. COMPARISON OF RESULTS WITH AND WITHOUT INTRATHECAL TREATMENT

Organisms	Treatment	Deaths		Sequelae		Well		Total
		No.	%	No.	%	No.	%	
Pneumococci (24 cases)	IT	3	27	2	18	6	54	11
	No IT	4	30	1	7	8	61	13
<i>H. influenzae</i> (26 cases)	IT	2	18	2	18	7	64	11
	No IT	2	13	1	6.6	12	80	15
No organisms (12 cases)	IT	—	—	—	—	2	100	2
	No IT	—	—	2	20	8	80	10
Various organisms (9 cases)	IT	3	75	—	—	1	25	4
	No IT	—	—	1	20	4	80	5

IT=intrathecal treatment.

the IT group, compared with 4 (30%) and 1 (7%) respectively in the non-IT group. It would appear that omission of intrathecal therapy in pneumococcal meningitis did not handicap the prospects of recovery or increase the sequelae.

In the influenzal group the results of the analysis are similar, the bias being in favour of omitting IT treatment. If the pneumococcal and influenzal groups are combined (Table IVa), as might be done legitimately in view of the comparable age range and comparable prognosis in the earlier series which I reported,² the results are not strikingly different on comparing the two forms of therapy though, again, the simpler treatment gave a larger proportion of complete recoveries. If all the more dangerous types of pyogenic meningitis (Table IVb) are considered

TABLE IV. COMPARISON OF RESULTS IN VARIOUS GROUPS OF INFECTIONS

Infection	Treatment	No. of cases	Survivors	Well
(a) <i>D. pneumoniae</i> + <i>H. influenzae</i>	IT	22	17 (77%)	13 (59%)
	No IT	28	22 (78%)	20 (71%)
		50		
(b) <i>D. pneumoniae</i> + <i>H. influenzae</i> + various organisms	IT	26	18 (69%)	14 (54%)
	No IT	33	27 (81%)	24 (72%)
		59		
(c) All 4 groups	IT	28	20 (71%)	16 (57%)
	No IT	43	37 (86%)	32 (74%)
		71		

IT=intrathecal treatment.

together, i.e. excluding the more benign abacterial forms, the same result is obtained. When the results of the whole series are reviewed (Table IVc) the figures show quite

clearly that intrathecal therapy cannot be regarded as essential.

It remains to show whether there were other features influencing the outcome or other aspects of the treatment which may have to be taken into account in coming to a final decision. Those which can be reduced to tabular form are shown in Table V. Our knowledge of the

TABLE V. OTHER FACTORS INFLUENCING RESULTS

	IT group %	Others %
Had treatment before admission:		
Whole series	39	23
<i>D. pneumoniae</i> and <i>H. influenzae</i> groups	32	32
Had fits before admission	50	28
Depressed consciousness on admission	54	21
Localizing signs on admission	61	58
Duration of fever—survivors	6.6 days	6.8 days
Duration of systemic treatment—sur- vivors*	16.2 days	16 days
Duration of intrathecal treatment	9 days	—
Survivors	71	86
Complete recoveries	57	74

IT=intrathecal treatment.

duration of illness before admission is so unreliable, because of the vague and inaccurate histories given by some parents, that no attempt has been made to assess that very important point. The state of nutrition is not taken into account since the number of grossly malnourished children in each group (13 in all) is too small to be considered here. The standard for malnutrition, fixed at two-thirds of the expected weight, showed that 15% of the survivors, 18% of the whole series, and 28% of those who died, fell into this category.

Apart from a greater incidence of fits and depressed level of consciousness, the IT group were at no disadvantage and more of them had received treatment before admission, i.e. relatively early in the illness. After admission the parallel courses of the 2 groups is striking. Although not shown here, in the interests of brevity, the generally accepted criteria for assessing the prognosis during the acute phase of the illness were just as obvious in this series as in the previous one reported by me.² Coma and spasticity were bad prognostic signs, *irrespective of the type of treatment employed.*

CONCLUSION

It would appear, then, that when the treatment of pyogenic meningitis is surveyed little can be said in favour of intrathecal drug administration. Whether the choice of drugs used here is the best that can be achieved is another question and will be much more difficult to determine. However, if daily lumbar punctures can be omitted, the patient will be spared the ordeal, and the medical, nursing and laboratory staffs will be relieved of what seems to be unnecessary work. These are far from being insignificant and irrelevant points in deciding the issue. There is certainly no evidence in this study which would support IT medication as an essential or even advisable part of the procedure. Its omission would make things easier for everyone, and not least for the patient.

SUMMARY

1. Seventy-one cases of pyogenic meningitis were studied, consisting of 4 main groups caused by *D. pneumoniae*, *H. influenzae*, no demonstrable organism, and a mixed group of organisms.

2. The results of treatment with and without intrathecal (IT) chloromycetin are compared.

3. The overall survival rate with IT therapy was 71% and without it 86%. Complete recovery rates were 57% and 74% respectively.

4. The incidence of a number of features which might affect the choice of treatment is shown and their influence in this series is considered briefly.

5. The general conclusion is that any benefit derived from injection of drugs into the theca is very doubtful and that the benefit to the patient and his attendants from omission of this procedure would be considerable.

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