The use of ethambutol has lowered the 2-year mortality rate in patients with tuberculous meningitis

To the Editor—We have identified 38 bacteriologically confirmed cases of tuberculous meningitis in Hong Kong, which were diagnosed between 1993 and 1995 in eight regional general hospitals and chest clinics. The cerebrospinal fluid (CSF) of the 38 patients was either culture-positive for *Mycobacterium tuberculosis* or smear-positive for acid-fast bacilli. The patients were followed up until the end of 1997. Three patients were lost to follow-up. The treatment and clinical outcome of the remaining 35 were analysed retrospectively.

The mean duration of antituberculous treatment was 11 months (standard deviation, 8 months). There were 10 deaths due to tuberculous meningitis, all of which occurred within the first 2 months, and one of which was due to systemic lupus erythematosus. No patients had been infected with human immunodeficiency virus. Patients who had received ethambutol (15-25 $mg \cdot kg^{-1} \cdot d^{-1}$) had a significantly lower 2-year mortality rate than those who did not receive this drug (P=0.027; Table 1). Table 2 shows the outcome of patients according to whether they fully recovered, developed neurological sequelae, or died.

Logistic regression using the forward stepwise calculation method confirmed that the use of ethambutol was the only significant factor that influenced death from among the following: age, co-existing medical diseases, complications such as hydrocephalus and tuberculoma, CSF lymphocyte percentage, absolute CSF lymphocyte count, use of antituberculous drugs such as pyrazinamide or rifampicin, and steroid use. The adjusted odds ratio was 0.042 and the 95% confidence interval was 0.005 to 0.378.

Ethambutol targets the mycobacterial cell wall, which consists of an outer layer of mycolic acids that are bound covalently to peptidoglycan via arabinogalactan. The drug inhibits the formation of arabinogalactan, thereby blocking the synthesis of the mycobacterial cell wall.[1] Because of the reduced availability of arabinogalactan, newly synthesised mycolic acids are diverted to the synthesis of trehalose 6,6'-dimycolate.[2] The cell wall thus becomes weakened and the cells become more permeable to various metabolites, including antituberculous drugs.[2] Ethambutol treatment has also been shown to inhibit the synthesis of phospholipids, which are major constituents of the cell wall, and which are important for its permeability and the transport of metabolites across the cell membrane. Radiometric studies have demonstrated synergistic effects between ethambutol and each of the following drugs: rifampicin, streptomycin, and quinolones, but not between ethambutol and isoniazid.[3]

Ethambutol can penetrate the blood-brain barrier in patients with tuberculous meningitis to a greater

Table 1. Survival status of patients with tuberculous meningitis 2 years after the start of treatment

Characteristic/ treatment	2-year survival status		
	No. alive	No. died	P value*
Level of consciousness at admission			
fully conscious	9	2	0.447
drowsy or comatose	16	8	
Level of consciousness at start of treatment			
fully conscious	7	1	0.390
drowsy or comatose	18	9	
Presence of hydrocephalus			
yes	7	4	0.689
no	18	6	
Presence of tuberculoma			
yes	2	1	1.000
no	23	9	
Use of ethambutol (15-25 $mg \cdot kg^{-1} \cdot d^{-1}$)			
yes	22	5	0.027
no	3	5	
Use of isoniazid (5-10 $mg \cdot kg^{-1} \cdot d^{-1}$)			
yes	25	9	0.286
no	0	1	
Use of pyrazinamide (25-35 $mg \cdot kg^{-1} \cdot d^{-1}$)			
yes	25	8	0.076
no	0	2	
Use of rifampicin (10 $mg \cdot kg^{-1} \cdot d^{-1}$)			
yes	25	9	0.286
no	0	1	
Use of streptomycin (15-20 $mg \cdot kg^{-1} \cdot d^{-1}$)			
yes	14	6	1.000
no	11	4	
Use of steroid			
yes	21	6	0.186
no	4	4	

* Fisher's exact text

Table 2. Outcome of patients with tuberculous meningitis according to disease characteristics

Characteristic	Outcome at 2 years	No. of patients*	Mean (SD)	SE	P value†
Age (years)	Full recovery	19	37.8 (16.1)	3.7	0.012
	N/D§	16	53.9 (19.6)	4.9	
CSF‡ glucose (mmol/L)	Full recovery	17	2.71 (1.46)	0.35	0.762
	N/D	16	2.56 (1.47)	0.37	
CSF pressure (cm H_2O)	Full recovery	15	244.3 (113.4)	29.3	0.254
	N/D	14	194.3 (118.0)	31.5	
CSF protein (g/L)	Full recovery	17	1.73 (1.68)	0.41	0.289
	N/D	16	2.31 (1.38)	0.35	
CSF white blood cells (per mm^3)	Full recovery	17	173.1 (178.9)	43.4	0.586
	N/D	15	227.3 (358.7)	92.6	
CSF lymphocytes (per mm^3)	Full recovery	16	107.7 (143.7)	35.9	0.732
	N/D	14	90.83 (119.9)	32.1	
No. of days with symptoms before admission	Full recovery	18	11.4 (10.8)	2.6	0.823
	N/D	16	12.4 (14.6)	3.6	
No. of days after admission when treatment was started	Full recovery	19	12.7 (31.9)	7.3	0.442
	N/D	15	6.1 (8.2)	2.1	

* Data missing for some of the 35 patients
† Student's *t* test, 2-tailed to compare means for each outcome
‡ CSF cerebrospinal fluid
§ N/D neurological sequelae or death

extent than in healthy subjects.[4] The majority of these patients have CSF concentrations of the drug of up to 1 μg/mL after a dose of 25 mg/kg has been administered.[5] We suspect that the synergistic effects between ethambutol and other antituberculous drugs, and the high concentration of ethambutol in the CSF account for the significantly lower 2-year mortality rate in Hong Kong.

Drawbacks of this study include its retrospective design, the non-standardisation of drug dosage and treatment duration, and the fact that serum drug levels and drug compliance were not monitored closely. A prospectively designed, randomised controlled trial is needed to provide more clinical evidence to substantiate the importance of using ethambutol to treat tuberculous meningitis.

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