

Penetration of dapsone into cerebrospinal fluid of patients with AIDS

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It has been proposed that dapsone in combination with pyrimethamine could be used for prophylaxis of both *Pneumocystis carinii* pneumonia and encephalitis due to *Toxoplasma gondii*. Ten patients with AIDS undergoing lumbar puncture for diagnostic purposes were studied in order to assess the penetration of dapsone into CSF. Blood and CSF samples were obtained between 3 and 72 h following administration. Six patients had received oral dapsone for at least 1 month at the dosage regimen of 100 mg twice of three times weekly and four patients had received a single oral 100 mg dose. Dapsone concentration in CSF ranged from 0.013 to 0.296 mg/L while concentrations in plasma ranged from 0.018 to 1.231 mg/L. The CSF:plasma concentration ratio ranged from 0.21 to 2.01. The MIC of dapsone in combination with pyrimethamine against *T. gondii* is unknown, and further data are required to confirm whether the CSF concentrations of dapsone found in our study are sufficient to inhibit *T. gondii* growth in patients infected with human immunodeficiency virus (HIV). The high interpatient variability of dapsone CSF concentrations warrants further studies in selected categories of patients with HIV infection.

Introduction

Dapsone has been proven to be a safe and effective alternative to cotrimoxazole or pentamidine as prophylaxis for *Pneumocystis carinii* pneumonia (PCP) in HIV-positive patients. Recently, it has been proposed that dapsone might be used in combination with pyrimethamine for prophylaxis of both PCP and cerebral toxoplasmosis.^{1–3}

Toxoplasmosis is a significant cause of morbidity and mortality among patients with HIV infection, especially in Western Europe where the incidence of HIV-positive patients with antibodies to *Toxoplasma gondii* may be as high as 96% and up to 50% may develop cerebral toxoplasmosis.⁴

Only three comparative clinical studies are available in the literature regarding the combination dapsone/pyrimethamine for prophylaxis of both PCP and cerebral toxoplasmosis. Opravil *et al.* showed that a dapsone/pyrimethamine combination, 200/75 mg weekly, was as effective as aerosolized pentamidine, 300 mg every 4 weeks,³ for PCP prophylaxis and significantly reduced the incidence of cerebral toxoplasmosis although tolerability was inferior to that of pentamidine. A previous study using dapsone at higher weekly dose (50 mg daily of dapsone combined with 50 mg weekly or pyrimethamine), essentially achieved the same results.² A study conducted in Italy comparing aerosolized pentamidine, co-trimoxazole and

dapsone/pyrimethamine found that a very low dose of dapsone, 100 mg/week combined with 25 mg pyrimethamine biweekly, was associated with a significant reduction in the risk of cerebral toxoplasmosis.¹

Since the achievement of an adequate concentration at the site of infection may be an important determination of drug efficacy, we sought to investigate dapsone penetration into CSF of HIV-positive patients.

Patients and methods

Ten patients with AIDS undergoing lumbar puncture for diagnostic purposes were enrolled into the study. Patient demographics are summarized in Table I.

All patients had normal renal function, and liver enzymes below three times the upper limit of the normal range. When the study began, six patients had been receiving oral dapsone 100 mg twice or three times weekly as PCP prophylaxis for at least 1 month. The remaining four patients volunteered to take a single 100 mg dose of dapsone before lumbar puncture. Dapsone doses for patients 4, 8 and 10 were prepared by the hospital pharmacy using the powder kindly provided by Roussel (Paris, France) while 100 mg tablets manufactured by Farmitalia-Carlo Erba (Milan, Italy) were used for the remaining patients.

A sample of blood was withdrawn at the same time as

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Table I. Demographics of patients

Patient no.	Age (years)	Sex	Body weight (kg)	CD4 ⁺ lymphocytes (cells/ μ L)	Protein (g/L)	CSF		WBC (cells/ μ L)
						protein (g/L)	glucose (mg/dL)	
1	47	M	65	70	7.5	1.07	30	20
2	42	M	55	55	7.9	0.39	80	0.2
3	39	M	66	63	8.1	5.10	20	88
4	40	M	75	8	6.7	0.70	43	1
5	39	M	54	127	8.7	0.46	52	3
6	30	F	51	4	6.0	0.48	20	1.6
7	33	M	74	6	7.4	0.31	30	2.4
8	40	M	81	28	7.1	0.55	3	8
9	35	F	50	153	8.3	0.14	45	3
10	40	M	84	50	7.4	0.51	22	70

CSF sampling in order to determine the ratio of dapsone concentration in CSF to that in plasma.

The HPLC assay used to determine plasma dapsone concentrations has been described elsewhere.⁵ The standard curve was linear in the range 0.0125–3 mg/L. Inter-day and intra-day variability determined at the concentrations of 0.0125, 0.0625, 0.250, 1 and 3 mg/L were <10%. The lower limit of detection was 0.0125 mg/L.

Standards and quality controls for determination of dapsone concentration in CSF were prepared by spiking specific amounts of dapsone in blank serum:saline solution (30:70). The assay parameters of linearity, precision and lower limit of detection using this matrix were comparable to the assay parameters reported above using plasma as a matrix.

Results

The concentrations of dapsone in plasma and CSF are given in Table II. Mean plasma concentrations of dapsone obtained between 3 and 72 h following administration were in the range of 0.018–1.231 mg/L. CSF concentrations of dapsone ranged from 0.013 to 0.302 mg/L. Patients 3 and 7 had culture-proven tuberculous meningitis; patients 2, 4, 8 and 10 had cryptococcal meningitis.

Discussion

Our study shows that dapsone penetrates into the CSF of HIV-positive patients. This observation was expected since dapsone is a highly lipid-soluble compound of low molecular weight. The CSF concentrations of dapsone found in

Table II. Dapsone concentrations in plasma and CSF following a single 100 mg dose or at steady-state following the administration of 100 mg twice or three times weekly

Patient no.	Dosage regimen	Time (h)	Concentration (mg/L)		
			plasma	CSF	CSF:plasma ratio
1	single	3	0.052	0.104	2.010
2	100 \times 3	3	1.180	0.294	0.249
3	single	3	1.231	0.302	0.245
4	100 \times 2	3	0.757	0.160	0.211
5	single	5	1.199	0.296	0.246
6	single	18	0.069	0.044	0.633
7	100 \times 3	20	0.129	0.158	1.227
8	100 \times 2	24	0.410	0.193	0.471
9	100 \times 3	48	0.018	0.013	0.726
10	100 \times 2	72	0.050	0.035	0.698

this study were less than those reported in a previous study⁶ in which CSF levels of six patients (five HIV-positive and one cardiac transplant patient) were found in the range of 0.26–2.78 mg/L. This difference may be due to the higher dosage (100 mg dapsone daily) used in some of the patients enrolled in the previous study, and the low levels of dapsone in CSF observed by us may be simply a reflection of the lower plasma levels. Some of our patients (1, 2, 3, 7 and 9) had been receiving rifampicin for at least 2 weeks at the time of the study. Rifampicin has been shown to increase the clearance of oral dapsone in HIV-infected patients by up to 70%,⁷ probably as a consequence of the induction of P450 microsomal enzymes. It is important to note that the CSF was abnormal in six of the patients enrolled in our study. It is unknown whether CSF penetration of dapsone is altered in patients with inflamed meninges, but our data would not support this.

It is not possible to establish whether the CSF concentrations of dapsone found in our study are sufficient to inhibit *T. gondii* in the CNS because of the paucity of data available in the literature; further investigation is required. The concentration of dapsone in brain tissue may also be relevant, although on the basis of the pharmacological properties of dapsone, CSF concentrations may represent a good approximation of the concentrations achieved by this compound in brain cells.

The MIC₅₀ of dapsone for *T. gondii*-infected fibroblast tissue culture has been estimated to be 0.55 mg/L.⁸ Dapsone administered alone failed to prevent dissemination in a murine model of acute toxoplasmosis; however, the study demonstrated synergy between dapsone and pyrimethamine, with 100% survival and prevention of relapse when the combination was administered from the day of the infection.⁸ Thus, even though the CSF dapsone concentrations observed in our study fall below the reported MIC₅₀, some degree of synergy with pyrimethamine would be anticipated. The CSF concentration of pyrimethamine has been described in five patients treated with 25 or 50 mg daily for at least 2 weeks.⁹ Concentrations were in the range 0.101–0.463 mg/L, with a CSF:plasma ratio in the range of 0.127–0.265; however, further synergy data are required to establish whether the CSF levels of dapsone found in our study would be sufficient to prevent reactivation or relapse of toxoplasmosis. In addition, any pharmacokinetic interaction between dapsone and pyrimethamine on the CNS penetration of both drugs and their clinical efficacy should be evaluated. It has been reported that pyrimethamine determines a 40% decrease in the volume of distribution and a 22.6% clearance of orally administered dapsone.¹⁰

Our study was a prospective, uncontrolled, exploratory study of the penetration of dapsone into the CSF of AIDS patients. Such an approach resulted in a very high inter-patient variability of plasma and CSF concentrations of dapsone, as a reflection of several factors which may have contributed to alter such concentrations; these include

underlying opportunistic infections of the CNS, stage of disease, gastrointestinal absorption and concomitant medications. The high variability of our results suggests that the penetration of dapsone into CSF of patients with AIDS should be studied further in selected categories of patients.

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