CASE STUDY

TREATMENT OF CRYPTOCOCCAL MENINGITIS WITH SHORT-COURSE AMPHOTERICIN B AND FLUCYTOSINE, FOLLOWED BY ITRACONAZOLE

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Itraconazole is an orally active triazole antifungal drug which has demonstrated a broad spectrum of activity. It is a potent inhibitor of most human fungal pathogens including *Cryptococcus neoformans* (Grant and Clissold, 1989). A recent study by Denning *et al* (1989) revealed the usefulness of itraconazole therapy for cryptococcosis. We also experienced the good result of itraconazole in the treatment of cryptococcal meningitis (Chotmongkol and Jitpimolmard, 1992).

In this paper we report our results of an open study concerning treatment of cryptococcal meningitis with a 2 week course of amphotericin B and flucytosine, followed by itraconazole.

Ten patients fulfilled the following entry criteria: (1) proven cryptococcal meningitis based on two of the following : a) cerebrospinal fluid (CSF) Indian ink stain positive; b) culture of CSF, blood, urine, biopsy or sputum positive for *C. neoformans;* c) serum or CSF cryptococcal latex antigen test positive; (2) life expectancy of at least one week after initiation of treatment; (3) ability to respond to verbal stimuli; (4) age of more than 16 years.

Clinical response was assessed by a combination of symptoms, fever and physical findings. Culture response was assessed by repeated fungal cultures of previously positive site. Serologic response was assessed by repeated measurements of CSF and serum cryptococcal antigen titers.

All patients recieved intravenous amphotericin B (0.3 mg/kg/day) plus oral flucytosine (150 mg/kg/day) for 2 weeks, then switched to itraconazole 200 mg orally twice daily for 2 weeks and scaled down to 100 mg orally twice daily for 6 weeks.

The following definitions of clinical efficacy were used: (1) Cure, defined as disappearance of all pre-treatment signs and symptoms of cryptococcal meningitis; (2) Improvement, defined as improvement or partial disappearance of pretreatment symptoms and signs; (3) Failure, defined as no change in or worsening of pre-treatment and symptoms; (4) Relapse, defined as clinically cure and complete eradication of pre-treatment pathogen followed by its reappearance.

From June 1991 to March 1992, ten cases were included in the study. There were five males and five females. Age incidence ranged from 26-69 years with a mean of 51 years. All of them had positive CSF Indian ink staining, culture and cryptococcal antigen for *C. neoformans,* except patient no. 9 had negative Indian ink staining and patients no. 6, 7 had negative CSF culture (Table 2). The clinical manifestations and clinical outcome are shown in Table 1. Nine patients had high initial opening CSF pressure (>300 mm H_2O). Associated condition were found in two cases (malnutrition of patient no. 9 and lymphoma in patient no. 10). Clinical assessment demonstrated cure in six cases and improvement in four cases. Of the four improving patients, visual impairment remained persistent while other clinical manifestations disappeared. Five patients had persistent high CSF pressure which required theco-peritoneal shunt in 4 cases and ventriculo-peritoneal shunt in 1 case.

Table 2 demonstrates the CSF results before and during treatment. Two of the six patients who were cured (patient no. 4 and no. 10), failed to respond amphotericin B and flucytosine, but were cured with itraconazole therapy. Side effects and toxicity of itraconazole were not observed.

The patients were observed for 5 to 16 months (mean 11 months) after completion of treatment. There was only one patient who had a relapse (patient no. 10). The symptoms and signs, including CSF abnormalities, occurred ten days after

Table 1

Patient characteristic and clinical outcome.

Patient no.	Age/sex	History	Physical examination	Other foci of infection	Outcome
1	62/F	headache, mild drowsiness, decreased vision 15 days	stiffneck, VA : CF 2', 4/60	-	improvement
2	58/F	headache, mild drowsiness, decreased vision 1 month	stiffneck, bilat 6th N palsy, papilledema, VA : 4/36, 6/24	-	improvement
3	61/M	fever, headache mild drowsiness, decreased vision 1 month	T 38.3°C, stiffneck papilledema, VA : 2/60, CF 2'	lung	improvement
4	45/M	headache 1 month, mild drowsiness 2 weeks	stiffneck, papilledema	-	cure
5	39/F	headache, mild drowsiness, decreased vision 1 month	stiffneck, bilat 6th N palsy, VA : 6/60, 6/60	-	improvement
6	47/F	fever, headache, mild drowsiness, convulsion 10 days	T 38.0°C, stiffneck, cerebellar sign, papilledema	-	cure
7	68/M	fever and headache 5 months, stuporous 1 week	T 38.0°C, stiffneck, papilledema	lung	cure
8	42/M	fever and headache 3 months, confusion and decreased hearing 1 week	T 38.8°C, stiffneck, papilledema, bilat sensori-neural hearing loss	-	cure
9	69/F	fever and headache 1 month, stuporous 1 week	T 39.0°C, stiffneck, malnutrition	lung	cure
10	26/M	fever and headache 3 days	T 38.5°C, stiffneck	-	cure

Table 2

CSF results before and during therapy.

Patient no.	Indian ink stain			Culture			Cryptococcal Ag		
		Itraconazole			Itraconazole			Itraconazole	
	initial	before	after	initial	before	after	initial	before	after
1	+	+	-	+	-	-	128 (2)	32 (-)	4 (-)
2	+	+	-	+	-	-	64 (64)	16 (-)	- (-)
3	+	+	ND	+	-	ND	128 (32)	32 (-)	ND (-)
* 4	+	+	ND	+	+	ND	2,048 (4,096)	4,096 (8,192)	ND (-)
5	+	+	ND	+	-	ND	512 (-)	128 (-)	ND (-)
6	+	-	-	-	-	-	32 (-)	2 (-)	- (-)
7	+	-	-	-	-	-	8 (-)	2 (-)	- (-)
8	+	-	-	+	-	-	32 (32)	16 (4)	16 (1)
9	-	-	-	+	+	-	128 (64)	32 (128)	8 (-)
10	+	+	-	+	+	-	128 (64)	128 (64)	- (-)

+ = positive, - = negative, ND = not done because of lumbar puncture yielded no CSF.
* cryptococcal antigen titer was 1 : 512 and 1 : 256 at the 1st week and 4th week respectively after itraconazole treatment.
( ) = serum cryptococcal antigen.

completion of treatment. Retreatment with the same dosage of itraconazole and maintenance with itraconazole 200 mg per day was successful.

The present study has documented the efficacy of itraconazole after 2-week course of amphotericin B and flucytosine in patients with cryptococcal meningitis. The advantage of this regimen is to reduce both the serious side effects of amphotericin B in combination with flycytosine and to reduce the hospital-days. Interestingly itraconazole could cure the patients who failed to respond to amphotericin B and flucytosine. From these clinical data and our previous experience we suggest that itraconazole can be used as initial or maintenance therapy in cryptococcal meningitis.

REFERENCES

Chotmongkol V, Jitpimolmard S. Itraconazole in the treatment of cryptococcal meningitis. *J Med Assoc Thai* 1992; 75 : 85-8.

Denning DW, Tucker RB, Hanson LH, *et al.* Itraconazole therapy for cryptococcal meningitis and cryptococcosis. *Arch Intern Med* 1989; 149 : 2031-8.

Grant SM, Clissold SP. Itraconazole. A review of its pharmacodynamic and pharmacokinetic properties, and therapeutic use in superficial and systemic mycoses. *Drugs* 1989; 37 : 310-44.