The Efficacy of Fluconazole 600 mg/day *versus* Itraconazole 600 mg/day as Consolidation Therapy of Cryptococcal Meningitis in AIDS Patients

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Abstract

Cryptococcal meningitis is one of the major complications affecting the central nervous system of patients suffering from AIDS. The results of treatment, when following current recommendation are still unsatisfactory.

Objective : This study aimed to evaluate the efficacy of a higher than recommended dose of oral fluconazole and itraconazole as consolidation therapy for cryptococcal meningitis in AIDS patients.

Design and Method : HIV infected patients with primary cryptococcal meningitis, who had been treated initially with amphotericin B for 2 weeks were included in this study. They were randomized into two groups, to receive either fluconazole 600 mg daily or itraconazole 600 mg daily for 10 weeks. The response towards the two different treatments was clinically defined to be successful, if after 10 weeks of treatment no clinical symptoms and signs of meningitis remained and the cerebrospinal fluid (CSF) fungal culture was negative.

Results : The trial was performed from April 1999 to April 2000 at Srinagarind Hospital, Khon Kaen, Thailand. At the beginning of the trial 44 cases were selected, but only 35 patients proved to be suitable for the final evaluation of the study. Out of those, 19 cases were assigned to the fluconazole and 16 cases to the itraconazole group. Ten weeks after treatment, all patients clinically recovered completely. The CSF sterilization rate for the fluconazole group and for the itraconazole group were 100 and 94 per cent respectively. The Fisher's exact test showed no significant difference in the CSF sterilization rate between both groups ($p = 0.26$).

Conclusion : The result of this study indicates that treatment with either 600 mg per day of fluconazole or itraconazole as consolidation treatment have the same efficacy for AIDS patients suffering from cryptococcal meningitis. The results of this study also suggest, comparing the result of

this trial with the results of similar trials published somewhere else, that treatment with the higher doses may be superior to treatment regimens using lower doses, as can be judged from the clinical outcome and the results of the mycological cultures.

Key word : Fluconazole, Itraconazole, Cryptococcal Meningitis, AIDS

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Cryptococcal infection is the most common fungal infection of the central nervous system in HIV-infected patients worldwide[1]. In Thailand, cryptococcal meningitis, as a complication of AIDS, occurs in 24 per cent of cases[2]. It aggravates the illness significantly and often is the ultimate cause of death for those suffering from AIDS. Up to now, the results of treatment of this infection is still unsatisfactory. Initially, amphotericin B with or without 5- flucytosine was given for a period of 4-6 weeks as the gold standard of treatment of cryptococcal meningitis in AIDS patients[3,4]. However, the relapse rate is very high, if no additional maintenance therapy is given. Moreover, because of the high toxicity of amphotericin B, attempts were made to shorten the time of giving amphotericin B in order to avoid exposing the patient to the toxic effects of the drug too long, and instead treatment was continued by giving oral triazole. Presently the treatment of AIDS patients suffering from cryptococcal meningitis consists of 3 phases [5]: Acute induction therapy with amphotericin B with or without 5- flucytosine; a consolidation phase with oral fluconazole or itraconazole 400 mg/day, and a maintenance phase with fluconazole 200 mg/day lifelong. According to the previous clinical study of Van Der Horst et al[6] amphotericin B (0.7 mg/kg/day) plus 5- flucytosine (150 mg/kg/day) for 2 weeks resulted in a CSF sterilization rate of only 50 per cent. After fluconazole 400 mg/day or itraconazole 400 mg/day was given for 10 weeks the CSF sterilization rate was 70 and 80 per cent respectively. It can be assumed that a high CSF sterilization rate may result in a low relapse rate, therefore higher doses of oral triazole may be beneficial. This study aimed to investigate, whether an increase in the dose of fluconazole and itraconazole to 600 mg/day would result in a higher CSF sterilization rate and decline of clinical symptoms and signs of meningitis. It also tested whether one treatments was superior to the other.

MATERIAL AND METHOD

Study population

This study was performed as an open randomized trial from April 1999 to April 2000 at Srinagarind Hospital, Khon Kaen, Thailand. The criteria used for enrollment in the study was to be an HIV-positive patient, aged 18 years or older with a primary episode of cryptococcal meningitis. All patients had a positive CSF culture of *Cryptococcus neoformans* and completed 14 days of amphotericin B 0.7 mg/kg/day treatment before entering the study. Patients were excluded, if they had been treated for cryptococcal infection before, could not tolerate oral triazole, received drugs which may interfere with triazole, such as rifampicin, phenylhydantoin, H2-blocker, or did not come for follow-up.

Treatment and evaluation

The medical history and basic data of patients were collected. The clinical symptoms and signs were

assessed and cerebrospinal fluid cultures for bacterial and fungal infections were performed as baseline data. Patients were randomized by blocks of four into two groups; one group received oral fluconazole 600 mg/day and the other itraconazole 600 mg/day. The duration of the consolidation treatment phase was 10 weeks. Clinical assessments and lumbar punctures were performed. Cerebrospinal fluid was obtained for the analysis of bacterial and fungal cultures. Each group was given fluconazole 200 mg/day or itraconazole 200 mg/day as maintenance therapy life long. The recommendation to give maintenance therapy life long is the standard procedure in order to prevent relapses. Because it is known that the toxicity of the drugs is low, laboratory tests were optional, and only done if it was suspected that adverse events occurred because of the drug used. The therapy was discontinued prematurely if the patients wished so, or the drug seemed to have a toxic effect.

Statistical analysis

This study aimed to demonstrate the efficacy of a higher dose of fluconazole and itraconazole in treatment of AIDS-associated cryptococcal meningitis compared to the published studies. As a secondary endpoint, this study also intended to test the hypothesis that 600 mg/day fluconazole are superior to itraconazole 600 mg/day in achieving CSF culture conversion. Assuming a CSF culture conversion rate of 100 per cent for fluconazole after 10 weeks of therapy *versus* 70 per cent for itraconazole with a dose of 600 mg/day, the sample size of 16 patients for each group should allow a statistically significant conclusion (two-sided $p = 0.05$, power = 80%). If 20 per cent of patients was expected to drop out, the patients enrolled in each arm should be 20 cases. Differences in proportions between groups were analyzed by using the Fisher's exact test. A p-value of ≤ 0.05 was considered to indicate a statistically significant difference between groups.

RESULTS

Forty-four patients with cryptococcal meningitis suffering from AIDS (31 males and 13 females), in the age range of 25-59 years (median: 32 years) were enrolled into the study. Twenty-two patients were assigned to receive oral fluconazole 600 mg/day and itraconazole 600 mg/day and the outcome of the study was measured after 10 weeks of treatment. At entry into the study, clinical parameters and CSF fungal culture results are shown in Table 1. The fluconazole group had a higher male sex and positive CSF fungal culture than the itraconazole group but was not statistically significant. CSF cultures, after 2 weeks of amphotericin B treatment, were done before the patients entered the study. Results of the CSF cultures could not be obtained for one case in the fluconazole group and for 3 cases in the itraconazole group. The remaining CSF cultures had positive results for 57.1 per cent of cases in the fluconazole group and for 31.5 per cent of cases in the itraconazole group. (Table 1).

During the 10 weeks of treatment, 9 cases were lost to follow-up, 3 cases in the fluconazole group and 6 cases in the itraconazole group. Clinical and mycological assessment were done in the remaining 19 cases of the fluconazole group and in the remaining 16 cases of the itraconazole group. All of the patients in both groups had no clinical symptoms and signs of active cryptococcal meningitis after 10 weeks of maintenance treatment. There were no adverse effects during the study period. The results of the CSF fungal cultures were 100 per cent negative for the fluconazole group, and 94 per cent negative for the itraconazole group. There was no statistically significant difference between both groups by applying the Fisher's exact test ($p = 0.26$) (Table 2).

DISCUSSION

Cryptococcal meningitis is a devastating complication in AIDS patients that requires long-term

Table 1. Demographic and CSF fungal culture data at the entry.

	Fluconazole	Itraconazole	P
Age (mean ± SD), years	32.1 ± 4.8	37.4 ± 4.8	0.44
Male (%)	81.8	59.0	0.09
Positive CSF fungal culture (%)	57.1	31.5	0.10

therapy with little hope of a final cure. The Infectious Disease Society of America recommends induction treatment with amphotericin B for an initial period of two weeks followed by 10 weeks of oral triazole, either fluconazole or itraconazole at doses of 400 mg/day, followed by maintenance therapy with fluconazole of 200 mg/day lifelong. The CSF sterilization rates after 10 weeks of oral fluconazole and oral itraconazole were 70 and 80 per cent respectively for this regimen. The clinical beneficial responses for both groups were comparable in that 80 and 90 per cent of patients were symptom free. If a positive fungal culture persists, this may result in a relapse during the maintenance therapy. Using the comparably low dose of oral triazole as recommended by the Infectious Disease Society of America, the positive CSF cultures are still quite high. This study aimed to test the efficacy of a higher dose of oral fluconazole and oral itraconazole therapy for treatment during the consolidation phase of cryptococcal meningitis in HIV-positive patients, in order to achieve a higher negative CSF culture outcome. Therefore, the mycological success was determined by negative fungal cultures of cerebrospinal fluid after the completion of the study.

All of the 35 cases had a beneficial clinical response. Treatment was successful that all 19 cases (100%) the fluconazole group and 15 of 16 cases (94%) of the itraconazole group had negative CSF cultures after 10 weeks. The difference between the groups was not statistically significant ($p = 0.26$).

The study of Van der Horst et al[6] compared the efficacy of oral fluconazole and oral itraconazole treatment at doses of 400 mg/day for 10 weeks in cryptococcal meningitis in AIDS patients. The cerebrospinal fluid culture had negative results in 72 per cent ($n = 151$) of the fluconazole and in 60 per cent ($n = 155$) of the itraconazole group. Clinical response was similar between fluconazole and itraconazole. When comparing the results of the study undertaken by Van der Horst et al[6] and Moskovitz et al [7] with the present study, using higher doses of fluconazole and itraconazole, the clinical outcome and CSF sterilization rate seemed to be better for the Thai patients (Table 3).

However, the present study involved a rather limited number of patients. The somehow more favorable result in terms of the clinical outcome and the CSF sterilization rate with higher doses of fluconazole may be explained by the dose dependent effect of oral triazoles. *In vitro* data suggest that an increase in the dose of fluconazole and itraconazole results in an increase of the plasma peak and the CSF concentration of the drug as well as an enlargement of the area under the curve[8]. Another clinical trial, using rather high doses of fluconazole up to 2,000

Table 2. CSF fungal culture after 10 weeks of fluconazole or itraconazole treatment.

Group	Fungal cultures			
	Number of positive cases	%	Number of negative cases	%
Fluconazole	0	0	19	100
Itraconazole	1	6	15	94

Table 3. Comparison of the efficacy of fluconazole and itraconazole as consolidation therapy.

Trial	Agent/dose	No. of patients	Mycologic response
Van Der Horst et al	Fluconazole 400 mg/day	151	72
	Itraconazole 400 mg/day	155	60
Moskovitz et al	Fluconazole 400 mg/day	40	41
	Itraconazole 400 mg/day	33	38
The present study	Fluconazole 600 mg/day	19	100
	Itraconazole 600 mg/day	16	94

mg/day in the treatment of cryptococcal meningitis in AIDS, with doses of 800 mg, 1,200 mg, 1,600 mg, and 2,000 mg/day had a beneficial response rate after 12 weeks of 11 per cent, 37 per cent, 62 per cent and 62 per cent[9]. The success rate increased between 65 to 87 per cent when each dosage of fluconazole was combined with 5-flucytosine. Dose dependent effect of itraconazole is less than for fluconazole and exceeding the highest recommended dose of 600 mg/day, the pharmacokinetics are non-linear.

In conclusion, both fluconazole and itraconazole, given as an oral dose of 600 mg/day are highly effective for the treatment of cryptococcal meningitis in AIDS patients. When the results of the present study are compared to studies undertaken with lower doses for treatment, it seems that the regime used in the present study is superior. The limitation of the present study is the low number of patients involved and that there was no direct comparison with groups of patients receiving 400 mg and 600 mg of triazole. Since cryptococcal meningitis is a major complication in AIDS, more clinical studies to evaluate the optimal dose of oral triazole as treatment should be undertaken.

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ประสิทธิผลของ ยาฟลูโคนาโซล 600 มก.ต่อวัน และ ยาไอทราโคนาโซล 600 มก. ต่อวัน ในการรักษาเยื่อหุ้มสมองอักเสบจากเชื้อรา*คริปโตคอคคัส* ในผู้ป่วยโรคเอดส์ ระยะที่ 2

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เยื่อหุ้มสมองอักเสบจากเชื้อรา*คริปโตคอคคัส* เป็นโรคติดเชื้อที่สำคัญของการติดเชื้อในสมองของผู้ป่วยโรคเอดส์ การรักษาที่แนะนำในปัจจุบันยังให้ผลไม่เป็นที่น่าพอใจ

วัตถุประสงค์ : การศึกษานี้มีจุดมุ่งหมายเพื่อประเมินประสิทธิผลของยาฟลูโคนาโซลและไอทราโคนาโซล ในขนาดที่สูงกว่าขนาดแนะนำในการรักษาระยะที่ 2 ของเยื่อหุ้มสมองอักเสบจากเชื้อรา*คริปโตคอคคัส*ในผู้ป่วยโรคเอดส์

วิธีการศึกษา : ผู้ป่วยติดเชื้อเอ็ชไอวีที่เป็นเยื่อหุ้มสมองอักเสบจากเชื้อรา*คริปโตคอคคัส*ครั้งแรก และได้รับยาแอมโฟเทอริซินบีมาแล้ว 2 สัปดาห์ได้เข้าร่วมในการศึกษา ผู้ป่วยถูกสุ่มโดยวิธีจับฉลากทีละสี่เป็น 2 กลุ่ม กลุ่มหนึ่งได้รับยาฟลูโคนาโซล 600 มก.ต่อวัน อีกกลุ่มหนึ่งได้รับยาไอทราโคนาโซล 600 มก.ต่อวัน ทั้งสองกลุ่มได้ยานาน 10 สัปดาห์ การตอบสนองทางคลินิกถือว่าสำเร็จ ถ้าผู้ป่วยไม่มีอาการและอาการแสดงของเยื่อหุ้มสมองอักเสบ การตอบสนองในแง่เชื้อราถือว่าสมบูรณ์ ถ้าได้ผลเพาะเชื้อราจากน้ำไขสันหลังให้ผลลบเมื่อสิ้นสุดการศึกษา

ผลการศึกษา : การศึกษานี้ทำที่โรงพยาบาลศรีนครินทร์ มหาวิทยาลัยขอนแก่น จังหวัดขอนแก่น ประเทศไทย ในระหว่างเดือนเมษายน 2542 ถึงเมษายน 2543 มีผู้เข้าร่วมการศึกษา 44 ราย แต่ประเมินผลได้ 35 ราย 19 รายได้รับยาฟลูโคนาโซล 16 ราย ได้รับยาไอทราโคนาโซล เมื่อให้ยาครบ 10 สัปดาห์ ผู้ป่วยทุกรายไม่มีอาการของเยื่อหุ้มสมองอักเสบ อัตราผลการเพาะเชื้อราจากน้ำไขสันหลังเป็นลบในกลุ่มที่ได้ยาฟลูโคนาโซลเท่ากับ 100 เปอร์เซ็นต์ และในกลุ่มที่ได้ยาไอทราโคนาโซลเท่ากับ 94 เปอร์เซ็นต์ การทดสอบฟิสเชอร์เอ็กแซค ไม่พบความแตกต่างของอัตราการเพาะเชื้อราจากน้ำไขสันหลังเป็นลบของทั้งสอง กลุ่ม ($p = 0.26$)

สรุป : การศึกษานี้แสดงให้เห็นว่ายาฟลูโคนาโซล และไอทราโคนาโซล ในขนาด 600 มก.ต่อวัน ในการรักษาระยะที่ 2 ของเยื่อหุ้มสมองอักเสบจากเชื้อรา*คริปโตคอคคัส*ในผู้ป่วยโรคเอดส์ให้ผลดี ผลการรักษาทั้งในด้านคลินิกและผลการเพาะเชื้อราเป็นลบ มีแนวโน้มดีกว่าการศึกษาอื่นที่ใช้ยาในขนาดต่ำกว่า

คำสำคัญ : ฟลูโคนาโซล, ไอทราโคนาโซล, เยื่อหุ้มสมองอักเสบจากเชื้อรา*คริปโตคอคคัส*, เอดส์

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