การศึกษาประสิทธิผลของฟลูโคนาโซลขนาด 400 มิลลิกรัม ทางปาก โดยการให้ซ้ำ 2 ครั้งในการรักษาโรคเกลื้อน โดยใช้รูปแบบการวิจัยชนิดการทดลองแบบสุ่มตัวอย่าง และมีตัวควบคุม

นายกฤษฎา มโหทาน

วิทยานิพนธ์นี้เป็นส่วนหนึ่งของการศึกษาตามหลักสูตรปริญญาวิทยาศาสตรมหาบัณฑิต
สาขาวิชาการพัฒนาสุขภาพ หลักสูตรการพัฒนาสุขภาพ
คณะแพทยศาสตร์ จุฬาลงกรณ์มหาวิทยาลัย
ปีการศึกษา 2545

ISBN 974-17-1564-1

THE EFFECTIVENESS OF REPEATED DOSES OF ORALLY 400 mg FLUCONAZOLE IN THE TREATMENT OF PITYRIASIS VERSICOLOR, A RANDOMIZED CONTROLLED TRIAL

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A Thesis Submitted in Partial Fulfillment of the Requirements
for the Degree of Master of Science in Health Development
Faculty of Medicine
Chulalongkorn University
Academic year 2002

ISBN 974-17-1564-1

Thesis Title	The Effectiveness of Repeated Doses of Orally 400 mg Fluconazole in the Treatment of Pityriasis Versicolor, a Randomized Controlled Trial
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กฤษฎา มโหทาน: การศึกษาประสิทธิผลของฟลูโคนาโซลขนาด 400 มิลลิกรัม ทางปากโดยการให้ซ้ำ 2 ครั้งในการรักษาโรคเกลื้อนโดยใช้รูปแบบการวิจัยชนิดการทดลองแบบสุ่มตัวอย่างและมีตัวควบคุม (THE EFFECTIVENESS OF REPEATED DOSES OF ORALLY 400 mg FLUCONAZOLE IN THE TREATMENT OF PITYRIASIS VERSICOLOR, A RANDOMIZED CONTROLLED TRIAL) อาจารย์ที่ปรึกษา: ผศ. นพ. มนต์ชัย ชาลาประวรรตน์, อาจารย์ที่ปรึกษาร่วม: รศ. นพ. สุมิตร สุตรา, รศ. พญ. เจศฎา ถิ่นคำรพ 71 หน้า ISBN 974-17-1564-1

วัตถุประสงค์: เพื่อเปรียบเทียบประสิทธิผลในการรักษาโรคเกลื้อนโดยการใช้ฟลูโคนาโซล 400 มิลลิกรัม ทางปาก โดยการให้ซ้ำสองครั้งเปรียบเทียบกับการใช้ 20% โซเดียมไธโอซัลเฟต

รูปแบบการวิจัย: การทดลองทางคลินิกแบบสุ่มตัวอย่างและมีตัวควบคุม

สถานที่ทำการวิจัย: สถานบำบัดโรคผิวหนังกรุงเทพ

กลุ่มตัวอย่าง: ผู้ป่วยโรคเกลื้อนที่เข้าได้กับเกณฑ์การศึกษาจำนวน 97 คน ในจำนวนนี้ผู้ป่วยอยู่จนครบการศึกษา 93 คน

วิธีการศึกษา: ผู้ป่วยโรคเกลื้อนที่เข้าได้กับเกณฑ์การศึกษาจะได้รับการสุ่มเป็นสองกลุ่ม กลุ่มแรกได้รับประทานยาฟลูโคนาโซล ในวันแรกและวันที่ 7 พร้อมกับได้รับยาหลอก (น้ำเกลือ) ไปทาเป็นเวลา 2 สัปดาห์ กลุ่มที่สองได้รับ 20% โซเดียมไธโอซัลเฟต ไปทาเป็นเวลา 2 สัปดาห์ พร้อมกับรับประทานยาหลอกในวันแรกและวันที่ 7

การวัดผล: อัตราการหายในแต่ละกลุ่มโดยประเมินจากลักษณะทางคลินิกและผลทางห้องปฏิบัติการ เมื่อครบ 4 สัปดาห์ หลังจากเริ่มต้นได้รับยา

ผลการวิจัย: หลังจากควบคุมด้วยขนาดของบริเวณที่เกิดโรคบนร่างกาย ความแตกต่างระหว่างอัตราการหายในกลุ่มที่ได้รับยาฟลูโคนาโซลกับอัตราการหายในกลุ่มที่ได้รับยา โซเดียมไธโอซัลเฟต เท่ากับ 26.9 % (99% CI -18.0, 71.9)

สรุป: มีหลักฐานไม่เพียงพอที่จะสรุปว่า การใช้ยาฟลูโคนาโซลขนาด 400 มิลลิกรัม ทางปากโดยการให้ซ้ำ 2 ครั้งมีประสิทธิผลสูงกว่า การทายา 20% โซเดียมไธโอซัลเฟต ในการรักษาโรคเกลื้อน

ภาควิชา	การพัฒนาสุขภาพ	ลายมือชื่อนิสิต……...…….
สาขาวิชา	การพัฒนาสุขภาพ	ลายมือชื่ออาจารย์ที่ปรึกษา……...……...
ปีการศึกษา	2545	ลายมือชื่ออาจารย์ที่ปรึกษาร่วม……...…….
		ลายมือชื่ออาจารย์ที่ปรึกษาร่วม……..……..

42753767530 : MAJOR HEALTH DEVELOPMENT

KEY WORD: RANDOMIZED CONTROLLED TRIAL/ FLUCONAZOLE/ TREATMENT/PITYRIASIS VERSICOLOR

KRISADA MAHOTARN: THE EFFECTIVENESS OF REPEATED DOSES OF ORALLY 400 mg FLUCONAZOLE IN TREATMENTS OF PITYRIASIS VERSICOLOR, A RANDOMIZED CONTROLLED TRIAL: THESIS ADVISOR ASST. PROF. MONTCHAI CHALAPRAWAT, M.D., M.Sc., THESIS CO-ADVISOR ASSOC. PROF. SUMITR SUTRA, M.D., M.Sc., ASSOC. PROF. JADSADA THINKHAMROP, M.D., M.Sc. 71 pp. ISBN 974-17-1564-1

Objectives: To compare the effectiveness between repeated doses of 400 mg Fluconazole and 20% Sodium thiosulfate in patients with Pityriasis versicolor

Design: Double blinded**,** randomized controlled trial

Setting: Bangkok skin clinic

Subjects: Ninety-seven patients with Pityriasis versicolor, enrolled in the study, while 93 patients complete the study.

Intervention: The eligible patients were allocated into two groups by stratified randomization according to body area of involvement. One group received Fluconazole at day 0, 7 plus placebo solution (normal saline) for two weeks. The other group received Sodium thiosulfate for two weeks plus placebo capsulse at day 0, 7.

Main outcome measurement: Cure rate in each group was assessed by both clinical and mycological cure.

Results: The difference of cure rates between Fluconazole and Sodium thiosulfate groups was 26.9% (99%CI -18.0, 71.9) after adjusted for the body area of involvement.

Conclusion: There is insufficient evidence to make conclusion that repeated doses of orally 400 mg Fluconazole is more effective in treating Pityriasis versicolor than 20% Sodium thiosulfate .

Program ……... Health Development…… Student's signature…….....

Field of study…. Health Development……... Advisor' s signature……..

Academic year……..2002……... Co-advisor's signature……...

Co-advisor's signature…….

ACKNOWLEDGEMENT

I would like to express my sincere thank to Assistant Professor Montchai Chalaprawat for his guidance and invaluable comments on my thesis. I wish to express my deep gratitude to my co-advisor Associate Professor Sumitr Sutra, Associate Professor Jadsada Thinkhamrop and Associate Professor Malinee Laopaiboon for their advice and comments, especially Associate Professor Sumitr Sutra for his kind patience.

I would like to thank my colleague: Dr. Thaverit Sittiwakin, Dr. Venus Vana-anandacho, Ms. Puongkaew Niramansakul , Ms. Marayat Srikanok and the staff at Bangkok skin clinic for their contribution in the study.

I would like to thank Mr. Koragot Sangkate for his kind assistance during developing the thesis.

Last but not least, I wish to thank all personnel in the clinical epidemiology unit both in Chulalongkorn University and Khon Kaen University for their help in processing this thesis.

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CHAPTER 1

BACKGROUND AND RATIONALE

Pityriasis versicolor (Tinea versicolor) is a common superficial fungal infection caused by the lipophylic yeast Malassezia furfur (also known as Pityrosporum ovale, Pityrosporum orbiculare), which is a part of the normal flora of the human skin.[1-4] The organism is found in 90 – 100 % of subjects as normal flora.[5] Pityriasis versicolor occurs when the yeast converts to its mycelial form due to certain predisposing factors including high temperature and humidity, a probable reason why the disease is more prevalent in the tropic,[1,6] such as in Thailand.

Because pityriasis versicolor is of fungal origin, it was once thought to be contagious. From the current knowledge, it is not contagious nor is it due to poor hygiene.[2,7] In fact, it is now known to be affected by the predisposing endogenous and exogenous factors. The difficult cases of pityriasis versicolor encountered in patients with AIDS and in some other patients with immunosuppression, would support the important role that cell-mediated system plays in control of this infection. Therefore, abnormalities in the immune system may be an important endogenous factor. Other endogenous factors include

excessively oily or greasy skin and hyperhidrosis. These conditions also provide heat, moisture, and essential oils for proliferation of the organism.[8] The high prevalence in postpuberty and mature ages when the sebaceous glands are most active[8]would emphasis these factors. Other possible endogenous factors include Cushing's syndrome, immunosuppressive treatment, and malnutrition.[10,11]

In term of exogenous factors. The significant ones are temperature and humidity,[8] which also lead to excessive sweating. An another important exogenous factor is occlusive condition, such as occlusive clothing of soldiers with uniform. When the occlusion takes place, both pH and microflora are altered and there is an increase carbon dioxide concentration.[12] The significant role of heat, humidity, and occlusive conditions were supported by the fact that in Thailand, high prevalence of Pityriasis versicolor could be found among soldiers or policemen who wear occlusive uniforms and work routinely in the condition of high temperature and humidity.[13]

Pityriasis versicolor is common in temperate climate and is prevalent in tropical climate. In the U.S. National Health Survey, Pityriasis versicolor was found in 0.8 percent of population.[1] In Sweden, national survey revealed 1.1% cases with pityriasis versicolor. In Thailand, the prevalence of Pityriasis versicolor is not available but expected to be much higher than those of the U.S. and Sweden. It is

the most common fungal infection in Thailand. In Siriraj hospital, there were approximately 1639 patients/year or 28.5 percents of total fungal infection.[13] In Bangkok skin clinic, the patients with Pityriasis versicolor account for 1.7 percent of the total out patients, most of them are government service , labour, merchants and students.

Though, not a life threatening disease, it produces multiple lesions at chest, neck, trunk or face that are disfiguring and embarrassing to the patients.[14] It is extremely chronic and can produce cosmetic changes, which is emotionally disturbing to many patients. Expenditure of treatment would be substantial amount as compare to the total health care expenditure.

According to guidelines of care for superficial mycoses infections of the skin, topical treatment alone may be indicated for most patients.[15] Topical treatment with 20% sodium thiosulfate is conventional treatment for pityriasis versicolor and has been widely used for years.[8,16] It is listed in the national essential drug list and available in most of the hospitals in Thailand. Compliance, however, is sometimes low due to a variety of reasons, including odour and difficulty in applying the solution on the whole back and the long period of treatment resulting in unsuccessful treatment.

Systemic treatment with oral ketoconazole is very effective, but the potential of idiosyncratic in hepatotoxicity with incidence of 1:10,000 may reduce its usefulness. In addition, ketoconazole exhibits high affinity to mammalian cytochrome P-450 enzyme, resulting in alteration of testosterone and cortical syntheses.[17] Therefore, most physicians, both general practitioners and dermatologists are reluctant to use systemic ketoconazole for the treatment of pityriasis versicolor, even in extensive or recalcitrant cases.

Fluconazole, a bis – triazole antifungal agent indicated for the treatment of systemic candidiasis and cryptococcal meningitis may ultimately prove a superior therapeutic alternative in the treatment of superficial fungal infections. Fluconazole exhibits a high specificity for the fungal cytochrome P-450 enzyme, but a very weak affinity for mammalian P-450 enzyme, at effective antifungal doses fluconazole is unlikely to result in the endocrine side effect seen with ketoconazole. Compared to ketoconazole, fluconazole give safer profile in term of hepatotoxicity. Pharmacokinetics studies indicated excellent oral absorption, independent of food or pH and minimal protein binding.[20, 21] The pharmacokinetics of fluconazole in skin may permit weekly dosing.

In a noncomparative studies in Sweden, 24 patients with Pityriasis versicolor were treated with a single oral dose of 400 mg. of fluconazole and 74% of them were free of lesions at 3 weeks after treatment.[22] However, cutaneous pharmacokinetic studies indicated that 2 doses given 1 week apart may be even more effective.[9] The safety, efficacy and convenience of once – weekly oral fluconazole recommend its more widespread use.

In a randomized double-blind, clinical trial comparing the effectiveness of fluconazole and ketoconazole, a total of 128 patients with pityriasis versicolor were randomly divided into two groups, group 1 received two 150 mg capsules of fluconazole in a single dose repeated weekly for 2 weeks; and group 2 received two 200 mg tablets of ketoconazole in a single dose repeated weekly for 2 weeks. Of 128 patients, 100 completed the study and no major side-effect was noted between the two treatment regimens. Results of the study showed no significant difference in effectiveness, safety and tolerability between the two treatment regimens.[23]

Currently there is no study of the effectiveness of any regimen of fluconazole in the treatment of Pityriasis versicolor in Thailand. Therefore, the study of effectiveness of repeated doses of fluconazole would be extremely helpful in term of operational aspect. It would be essential information for the doctors, both dermatologists and general

practitioners for selecting the appropriate regimen for the patients. This new regimen would yield better compliance with more convenient dosage, rapidly relieve suffering from emotional disturbance and reduce period of patients' social embarrassment. In term of cost, the new regimen of fluconazole might be more cost – effective.

CHAPTER 2

REVIEW OF RELATED LITERATURES

Pityriasis versicolor is a mild disease but its chronic relapsing nature warrants its need for safe and effective treatment. Topical treatment with 20% sodium thiosulfate is one of the conventional treatment which has been and widely used for years.[8,16] The poor compliance of 20% sodium thiosulfate, due to strong odour, difficulty in applying and occasionally irritation result in premature discontinuation of treatment.

Systemic treatment may eliminate the poor compliance of topical treatment and provide higher cure rate.[24] Ketoconazole is the first systemic antifungal for treatment of pityriasis versicolor. In 1984, Saven R.E. showed that ketoconazole is effective in treatment of pityriasis versicolor[25]but high potential hepatotoxicity limits its use.

Fluconazole, the new antifungal, accumulates in eccrine sweat and diffuse rapidly and extensively into stratum corneum, and once weekly doses of 150 mg. lead to a high stratum corneum level.[26] In 400 patients receiving fluconazole for various indications and for a duration of 7 days or more, the incidence of side effects was 16%.[27] They were most frequently related to the gastrointestinal system:

nausea 3.7%, abdominal pain 1.7%, vomiting 1.7%, headache 1.9% and rash 1.8%. Approximately 1.5% of patients discontinued the drug because of clinical side effects. These suggest that fluconazole should be safe for treating Pityriasis versicolor.

There are limited information on the use of fluconazole in treating pityriasis versicolor. From the extensive review, there were as follow.

In Sweden, a single oral dose of 400mg of fluconazole has been shown to be effective for the treatment of pityriasis versicolor in 24 patients with extensive recurrent pityriasis versicolor. Of 23 evaluated patients, 74% were free of lesions 3 weeks after treatment, with no relapse in this cohort 6 weeks after therapy. [22] However, there is no control group in the study.

In Egypt, Amer A.M., et al demonstrated that fluconazole in weekly or forthnightly pulse doses was effective in Pityriasis versicolor in all three dosage regimens evaluated, namely 150mg/week, 300mg/week, and 300mg single dose repeated when needed after 2 weeks. Clinical and mycological efficacy results indicated that the most effective regimens are those of group II (300mg for 4 weeks) with eradication rate of 93%, and group III (300 mg as an initial dose to be repeated after 2 weeks) with eradication rate of 87%. Considering the small difference between over-all effectiveness in

group II and III, they considered the group III regimen to constitute a pragmatic alternative.[28]

In the comparative study of fluconazole versus itraconazole in the treatment of pityriasis versicolor, it was reported that there are no difference in term of efficacy between the two antifungal agents. However only limited subjects were recruited in the study which made the conclusion difficult. [29]

The advantages of fluconazole in term of favourable pharmacokinetics include extensive excretion through eccrine sweat and, also direct, diffusion to stratum cornium.[30] In addition, therapeutic level could be detected in stratum corneum even 10 days after discontinuation of treatment.[20,21,26,31] These advantage made it possible for once weekly doses for pityriasis versicolor, which the causative agent confined only stratum corneum. With appropriate pharmacokinetics, administration of fluconazole less frequent and shorter periods of time may be an effective alternative[20] Since 400 mg fluconazole, single dose, gives only 74% cure rate, more frequent doses should yield higher cure rate. From Egyptian study, repeated dose of 300 mg in 2 weeks apart give 87% cure rate. However, shorter duration of treatment is still possible by increasing the pulse doses. Therefore, 400mg. fluconazole repeated in 1week apart would be more effective and shorter duration of treatment than the Egyptian regimen.

In Thailand, Fluconazole is available in 50mg, 100mg and 200mg capsules, thus the cost of repeated dose 400mg would be more cost effective than the regimen of repeated dose 300mg.

All of the previous studies of fluconazole in the treatment of pityriasis versicolor were descriptive, and small trials effectiveness studies in the different countries such as Sweden, Egypt, where the climates and humidity are totally different from Thailand. We would like to test the effectiveness of repeated doses of 400mg fluconazole in the treatment of Pityriasis versicolor, compared to 20% sodium thiosulfate by using double blind randomized controlled trial, in the setting of the humidity and climate of Thailand.

CHAPTER 3

RESEARCH QUESTIONS AND OPERATION DEFINITIONS

3.1 Research Questions and Objectives

3.1.1 Research Questions

3.1.1.1 Primary Research Question

Does repeated dose of orally 400mg of fluconazole increase cure rate by 25% relative difference when compare to topical treatment with 20% sodium thiosulfate in the treatment of Pityriasis versicolor at 4 weeks ?

3.1.1.2 Secondary Research Question

What are the side effects of repeated dose of orally 400 mg fluconazole ?

Rationale

- We considered 25% difference as the critical value for the magnitude of difference, since we asked two dermatologists and two general practitioners for their critical value for making decision to change from topical treatment to the new systemic treatment regarding effectiveness and side effect of the new medication.

- We measure the effectiveness by cure rate at 4 weeks because generally the turnover rate of stratum corneum in normal subject is 2 weeks.[32] The first two weeks are allowed for therapeutic action of the tested regimens and another two weeks are allowed for disappearance of clinical and negative KOH preparation. If treatment is effective which means that the fungus is not viable, it will be eliminated by physiologic turnover of the stratum corneum. If at four weeks, the clinical is still persist and KOH preparation is still positive, it means that the fungus is still viable and persist in the new stratum corneum. It means that the treatment is not effective.

3.1.2 Research Objectives

3.1.2.1 To compare the effectiveness between repeated dose of 400 mg fluconazole and 20% sodium thiosulfate in patients with Pityriasis versicolor at Bangkok skin clinic

3.1.2.2 To identify the side-effects of repeated dose of 400 mg fluconazole in patients with Pityriasis versicolor at Bangkok skin clinic skin clinic.

3.2 Research hypothesis

There is a 25% relative difference between the cure rate of orally 400 mg of fluconazole and 20% sodium thiosulfate in the treatment of pityriasis versicolor at 4 weeks.

3.3 Key words

randomized controlled trial, fluconazole, treatment, pityriasis versicolor, effectiveness

3.4 Operational Definitions

1) Pityriasis versicolor was defined as the case of scaly hypo or hyperpigmented macules in any part of the body with positive KOH preparation, diagnosed by dermatologists.

2) Cure Rate was defined as the proportion between number of patients with **complete cure** and total number of patients who received the treatment in each group.

2.1 Complete cure was defined as the patient who was **both** clinical cure and mycological cure.

2.2 Clinical cure was defined as the complete disappearance of scale over all lesions.

2.3 Mycological cure was defined as complete absence of spore and hyphae from the original lesions, by KOH preparation, performed on two separate lesions on two separate slides, confirmed by two technicians.

3) Treatment failure was defined as presence of scale and positive KOH preparation.

4) **Partial response** was defined as either presence of scale or positive KOH preparation.

5) **Side effects** were defined as all expected and unexpected undesirable signs and symptoms that occurred with relevant to the studied medications including placebo. Unexplained signs and symptoms that occurred during treatment and within one month after discontinuation of particular treatment were counted as side effects of that regimen. Expected side effects were as follows.

- CNS : headache, dizziness
- gastrointestinal: nausea , abdominal pain
- dermatological:skin rash, pruritus.

6) Extensive involvement was defined as lesion of pityriasis versicolor with equal or greater than 10% of body area involvement.

7) Non-extensive involvement was defined as lesion of pityriasis versicolor with less than 10% of body surface area involvement.

CHAPTER 4

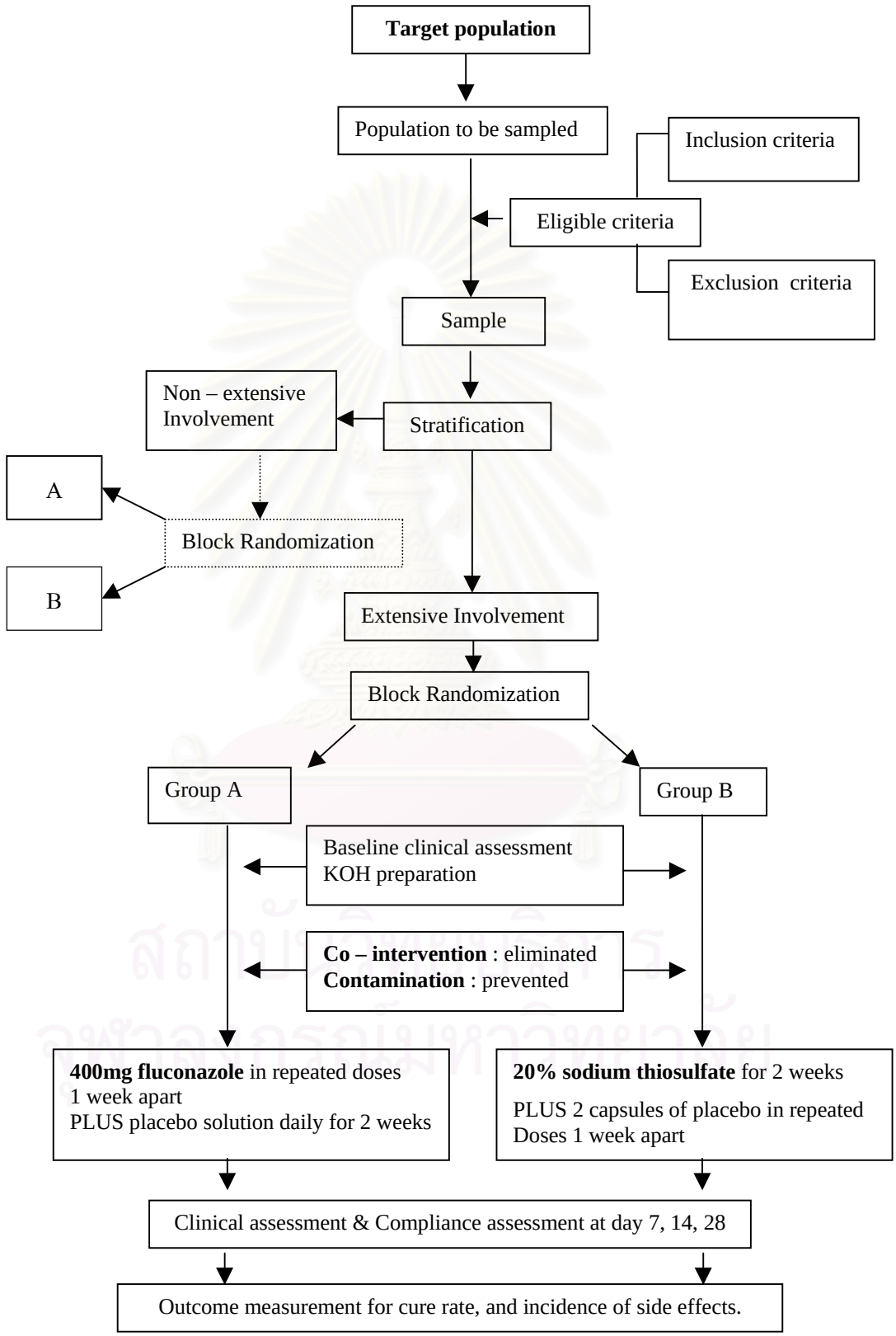
RESEARCH METHODOLOGY

4.1 Research Design : This was a double blind randomized control trial.

Over view of the study design:

This was double blind randomized control trial to investigate of the effectiveness of repeated doses of orally 400 mg fluconazole as compared to 20% sodium thiosulfate in the treatment of Pityriasis versicolor. The total of 196 samples who met the eligible criteria were recruited from the consecutive patients who had been diagnosed as Pityriasis versicolor at Bangkok skin clinic during October 2001 to December 2002. All the samples were randomly allocated to receive either fluconazole or sodium thiosulfate and followed up for 28 days. The outcome measures were cure rate and the incidence of side effects of the treatment medication.

Figure 1 Overview of the study design



Assessment was repeated on the schedule below.

Table 1 Schedule of assessment

	Day of Visit			
	0	7	14	28
Clinical Examination	☐	☐	☐	☐
KOH Examination	☐	-	☐	☐

4.2 The Population

4.2.1 Target population Patients with Pityriasis versicolor in Bangkok

4.2.2 Population to be sampled Patients with pityriasis versicolor who attended the Bangkok skin clinic during October 2001-December 2002

4.2.3 Sample The sample was recruited from the consecutive cases of patients with Pityriasis versicolor who attended the Bangkok skin clinic during October 2001 – December 2002, and met the eligible criteria.

4.2.4 Eligible criteria

4.2.4.1 Inclusion Criteria

1) Patients with pityriasis versicolor diagnosed by dermatologist with mycological confirmed based on a positive KOH

2) Patients who agreed to participate in the study and signed the consent form

4.2.4.2 Exclusion Criteria

1) Patients with serious concurrent medical condition, diabetes, chronic liver disease, Cushing's disease, malnutrition, patients during treatment with immunosuppressive agents.

2) Patients with other fungal infection.

3).Patients with known hypersensitivity to fluconazole

4) Patients who had been treated with systemic antifungal agents or corticosteroids within 30 days before entry.

5) Patients who had been treated with topical antifungal agents or corticosteroids , selenium sulfide, or zinc Pyrithione within 30 days before entry.

6) Pregnant or lactating women

7) Children below 12 years old

Statistical Hypothesis

Ho: $P_2 = P_1$

Ha: $P_2 =/= P_1$

P_1 = Cure rate of 20% sodium thiosulfate

P_2 = Cure rate of repeated doses of 400 mg fluconazole

4.3 Sample Size Calculation

Since repeated doses of 400 mg fluconazole is a new treatment for pityriasis versicolor, we do not know the treatment will be better or worse than the conventional 20% sodium thiosulfate. Therefore, the study here is two-tailed.

$$\text{n/group} = \frac{\left\{ Z_{\alpha/2}\sqrt{2P(1-P)} + Z_{\beta}\sqrt{P_1(1-P_1)+P_2(1-P_2)} \right\}^2}{\{P_1 - P_2\}^2}$$

To use α equal to 0.05 (two tailed) and power of study is 80%

α = Type 1 error = 0.05

$Z_{\alpha/2}$ = 1.96 (two-tailed)

β = Type 2 error

Z_{β} = 0.84 for 80% power

P_1 = Cure rate of 20% sodium thiosulfate = 0.70 (from the pilot study with same eligible criteria)

P_2 = Expected cure rate of repeated doses of 400 mg fluconazole (25%increase relatively to P_1 which will be clinical importance)

P_2 = 0.70 + (0.70 x 0.25) = 0.88

P = $(P_1 + P_2) / 2$

$$\text{n/group} = \frac{\left\{ 1.96\sqrt{2 \text{ x } 0.79\text{x } 0.21} + 0.84\sqrt{0.70 \text{ x } 0.30 + 0.88\text{x } 0.22} \right\}^2}{\{0.70 - 0.88\}^2}$$

Estimate sample size from the above formula = 79

- Expected drop out rate = 20%
- Sample size = 79 / (1 – 0.20) = 98 cases/group

4.4 Maneuver

4.4.1 Randomization method

Stratification

Since extension of lesion is one of the major confounding factors which might affect the outcome, all the eligible patients were be stratified into two categories namely, extensive involvement and non extensive involvement according to extension of lesion as described in the operational definitions.

Sampling Technique

After stratification, the patients were **randomly allocated** to group A, treated with repeated dose of 400 mg fluconazole and group B, treated with 20% sodium thiosulfate, according to concealed pre code order run by block randomization using the size block of four.

Due to the advantage of blocking there was a balance between the number of subjects in each group during the course of randomization. The number in each group never differed by more than 4 /2 when we used 4 as the size of the block.

4.4.2 Blinding Method

In this study we used double blind technique design. To blind **the patients**, we used double dummy technique. On the first visit both treatment group and control group received 2 capsules and 2 bottles of solution (with could be **either** 2 capsules of 200 mg fluconazole and 2 bottles of 0.9% normal saline solution **or** 2 capsules of placebo and 2 bottles of 20% sodium thiosulfate).

To blind the dermatologist and technician who assess the clinical outcome and mycological outcome respectively. We kept the code confidentially, only research assistants who gave the medication but did not participate in any process of assessment, knew the code.

4.4.3 Intervention

Day 0 (The first visit)

Patients were clinically evaluated, KOH preparation was performed at the baseline visit. Double dummy technique was applied as follows.

Group A patients were given 400 mg fluconazole orally (2 capsules of 200 mg) after breakfast and 2 bottles of 0.9 normal saline as the placebo in appropriate amount, estimated for applied on all affected area twice daily for 7 days.

Group B patients were given 2 capsules of placebo (identical looking like fluconazole) after breakfast and 2 bottles of 20% sodium thiosulfate solution in appropriate amount for application, the patients was instructed to apply the solution on the affected area twice a day for 7 days.

Day 7 (The second visit)

a. The patient were assessed for side effects occurred in the previous 7 days , by interviewing the undesirable signs and symptoms according to the data record form (appendix A) .
b. Dermatologist recorded the clinical assessment but no KOH preparation performed.
c. The same treatment was repeated exactly as day 0.
d. Assessment of the solution in term of determining whether any solution had been used, was performed on day 7 to check the compliance.

Day 14 (The third visit)

a. The patient were assessed for side effects occurred in the previous 7 days , by interviewing the undesirable signs and symptoms according to the data record form.

b. Dermatologist recorded the clinical assessment, and technician performed KOH preparation.
c. Assessment of the solution in term of determining whether any solution had been used, was performed on day 14 to check the compliance.

Day 28 (the fourth visit).

After assessment of side effects by interviewing the undesirable signs and symptoms in the previous 14 days, according to the data record form , clinical assessment and KOH preparation were performed, to assess the primary outcome which was complete cure at 4 week.

Co-intervention During the study, patients were asked to avoid using medicated bathing soap or shampoo which may have antifungal activity in order to avoid the co-intervention. List of these soap or shampoo in the market were given to the patients.

To promote good compliance: The dosage and method of drug application were explained to every patient. The detail and importance of patient cooperation were emphasized at the beginning of the study and at every visit.

To minimize drop out rate, clear appointment dates were recorded on patient cards , confirmation for appointment was done by phone call 2 days before appointment date. If the patients did not come to the clinic, tracing was done by another phone call.

4.5 Measurement

Variables to be measured

1. Administrative Variables

Name, address, identification number

2. Baseline Variables

Age, sex, weight,

Occupation (military service, student, labour, government service, merchant, others) site of the lesion (head & neck, back, chest wall & abdomen, upper extremities, lower extremities) body area of involvement (extensive and non-extensive involvement)

3. Outcome Variables

Primary outcome variable: Cure rate at 28 days after the first treatment

Secondary outcome variables: Incidence of side effect was assessed by patients interviewed together with physical examination for the following signs and symptoms.

I. Dermatological : skin rash, pruritus

II. CNS :dizziness, headache

III. Gastrointestinal: nausea, abdominal pain

IV. Other unexplained signs and symptoms that occurred during particular period of treatment.

The primary outcome variable was cure rate, which was determined by clinical cure and mycological cure

- The instrument to measure the clinical cure was clinical judgement of the physician.
- The instrument to measure the mycological cure was technician interpretation for KOH preparation.

Assessment of Instrument's validity & reliability

1. Instrument for clinical cure

Content validity, Four experts' opinions agreed to use "absence of scales" as instrument for clinical cure.

Criterion validity , physicians had been validated by testing on one group of subjects compared with the expert. Kappa statistic was applied.

Interrater reliability between two dermatologists was assessed by Kappa statistics. The Kappa was equal to 0.93.

2. Instrument for Mycological cure

- Assessment of Reliability, Kappa statistics was used for intrarater reliability & interrater reliability among technician
- Pre-test of the instrument & statistical test of the reliability was performed before starting the study
- Before conducting the study, the meeting was held, together with standardized training.

All Kappa statistics was accepted at 0.9

4.6 Data Collection

Data was collected at Bangkok Skin Clinic, recorded in the special design data record form. (Appendix 1) All of the variables were recorded according to the operational definition specified. The author regularly checked for completeness and correctness every 2 months. One research assistant was assigned to keep the code. Another research assistant was assigned to keep the data files confidentially until the time of data analysis. Each assessment both clinical and laboratory were assessed independently to minimized bias that might occurred. Data entry was done by the author.

4.7 Data Analysis :

4.7.1 Demographic data and baseline variables;

Table 2 Demographic data and baseline variables

Variables	Type of variables	Statistics
1.age (years)	continuous	mean, range, S.D.
2.sex	categorical	percentage
3.weight (kg)	continuous	mean, range, S.D.
4.occupation	categorical	percentage
5.site of lesion	categorical	percentage

4.7.2. Outcome variables

Table 3 Outcome variables

Variables	Type of data	Statistics
Cure rate	Categorical (nominal) Proportion Two independent groups	Two sample Z test 99% CI of $P_2 - P_1$

- Side effects from both regimen were summarized by descriptive statistics : percentage
- Analysis was performed by using “intention-to-treat” principle.
- Statistical tests were two-tailed with significant level at 0.01.
- Data analysis was performed by using STATA program version 6
- Confidence intervals were calculated by using confident interval analysis program.

4.8 Ethical Consideration :

1. Risk

I. All of the medication are safe and had been widely used in other diseases for many years.

II. If there was any side effect that might occurred during the study period, the research team would take all responsibility for the treatment and all the supportive care without any charge.

2. Benefit :

The researcher teams consisted of dermatologists, nurses and technicians who are competent in this field. The patients were taken care by competent staffs. The medication were free of charge and no expenditure on laboratory test.

3. Protection of the patients

I. All of the record was kept confidentially.

II. The patients can withdraw from the study whenever they want, without interference with regular care.

III. The details of the study protocol were explained to the patient verbally and patient information sheet (appendix 2) was provided. Written informed consent (appendix 3) were obtained in all cases.

4.9 Expected benefit and application :

If repeated dose of 400mg of fluconazole is efficacious in treatment of the Pityriasis versicolor. It could be generalized to be used in the target population, the patients with Pityriasis versicolor in Bangkok. The regimen would have been accepted by the dermatologists and the general practitioners. They do not have to concern the risk of systemic treatment. The regimen will eventually be listed as one of alternative regimen to the conventional regimen and will be included in the treatment guideline for superficial fungal infection.

4.10 Obstacles

Sample size may not be reached in time frame, the staffs involved in the study may be transferred to somewhere else. New staffs may not be the same in term of validity and reliability. Another standardized training should solve this problem.

4.11 Time Schedule : August 2001 – April 2003

Preparation	August 2001
Training of personnel	September 2001
Data collection	October 2001-December 2002
Data analysis	January 2003
Thesis writing	February 2003-March 2003
Presentation	April 2003

4.12 Budget

Personnel

Research assistants

2000 Baht / months x 2persons x 10 months	40,000 Baht

Laboratory technicians

1000 Baht / months x 2persons x 10 months	20,000 Baht

Drugs	
20% Sodium thiosulfate	
30 Baht / treatment x 98 patients	2,940 Baht
Fluconazole	
25 Baht / capsule	
100 Baht / treatment x 98 patients	9,800 Baht
Placebo	1,000 Baht
Lab costs	
KOH Preparation	
30 Baht / slides x 3 visits x 196 patients	17,640 Baht
Data processing	2,000 Baht
Communications	
Fax, phone, E-mail and postage	5,000 Baht
Total	98,380 Baht

CHAPTER 5

RESULTS

This study was conducted in Bangkok Skin Clinic from October 2001 – December 2002. Because of time limitation, the interim analysis was performed when a total of 97 patients were enrolled in the study.

5.1 Demographic Characteristics of Patients

Of the 97 patients enrolled in the study, 49 patients were allocated in the study group (Fluconazole) and 48 patients in the control group (Sodium thiosulfate). The demographic data of the patients were shown in table 4. The baseline characteristics of two group were comparable with respect to age, sex, weight, occupation, site of lesion and body area of involvement.

Of the 97 patients recruited, 93 patients completed the study. All of 4 patients who withdrew from the study were the patients who were assigned to receive regimen B (Sodium thiosulfate). The reason for withdrawal was the same in all of 4 patients, e.g. strong odour of Sodium thiosulfate.

Table 4 Demographic Characteristics of the Patients

Characteristics	Fluconazole group (n=49)	Sodium Thiosulfate group (n=48)
Sex: number (%)		
Male	30 (61.2)	31 (64.6)
Female	19 (38.8)	17 (35.4)
Age (year)		
Mean (SD)	31.3 (13.87)	35.1 (15.84)
Range	14-73	12-79
Age > 45 years: number (%)	8(16.3)	13(27.1)
Weight (kg)		
Mean (SD)	58.7 (11.57)	60.8 (11.28)
Range	32-85	41-92
Occupation		
Military service	2	4
Student	14	11
Labour	20	16
Government service	6	11
Merchant	5	1
Others	2	5
Site of lesion: number (%)		
Head and neck	6 (12.3)	3 (6.3)
Upper extremities	4 (8.2)	1 (2.0)
Lower extremities	1 (2.0)	1 (2.1)
Chest wall and abdomen	14 (28.6)	9 (18.8)
Back	24 (48.9)	34 (70.8)
Body area of involvement: number (%)		
Extensive involvement	19 (38.8)	20 (41.7)
Non-extensive involvement	30 (61.2)	28 (58.3)

5.2 Primary outcome analysis

We expected to see the difference of the cure rates, therefore the interim analysis was performed because of the following reasons.

1. Time limitation
2. The trial had been conducted for quite a long period (15 months) and the patients had already been recruited up to nearly 50% of expected sample size.
3. The dosage (400 mg) and frequency (2 repeated doses, one week apart) of Fluconazole regimen were higher than the regimens of previous studies.

Because this was the interim analysis, the sample size was not reached the expected number that was previously planned in the proposal of this study. In the proposal of this study, the sample size was calculated on the condition which set significant level of the statistical tests at 0.05. But in the interim analysis, we need more confidence in drawing the conclusion. To minimize the probability of a type I error, we set α equal to 0.01. Therefore, in this study we set the significant level at 0.01, instead of 0.05 and 99% confidence intervals were provided.

Analysis was performed by using “intention-to-treat” principle. In order to demonstrate the best scenario of Sodium thiosulfate group , 4 patients who lost follow up in this group, were counted as the successful treatment.

The primary outcome analysis was summarized in table 5.

Table 5 Summary of Primary Outcome Analysis

Regimen	Initial enrollment (case)	Complete cure (case)	Cure rate (percentage)	Difference (percentage)
Fluconazole	49	48	98.0	25.1 (99% CI, 7.7-42.4%)
Sodium thiosulfate	48	35	72.9	

P value = 0.0005

At the 4th week, the cure rate was higher in Fluconazole group (98.0 %,) than Sodium thiosulfate group (72.9%). Analysis by the two sample test of proportion (two sample Z test) gave P value equal to 0.0005. The result was consider statistically significant with mean difference of cure rate equal to 25.1 % (99 % CI, 7.7, 42.4%).

Table 6 Summary of Outcome Analysis at Day 14

Regimen	Initial enrollment (case)	Complete cure (case)	Cure rate (percentage)	Difference (percentage)
Fluconazole	49	49	100.0	57.8 (99% CI, 38.8-76.8)
Sodium thiosulfate	45	19	42.2	

P value = 0.000000

At Day 14 , the cure rate was higher in Fluconazole group (100.0 %,) than Sodium thiosulfate group (42.2%). Analysis by the two sample test of proportion (two sample Z test) gave P value equal to 0.000000. The result was consider statistically significant with mean difference of cure rate equal to 57.8 % (99 % CI, 38.8,76.8).

Table 7 Stratified analysis of primary outcome at the 4 th week

Body area of involvement	Fluconazole		Sodium Thiosulfate		Cure rate difference (99%CI)
	Complete cure	Treatment failure	Complete cure	Treatment failure	
Non-extensive involvement	29	1	24	4	11.0 (-8.1, 30.0)
Extensive involvement	19	0	11	9	45.0 (15.6, 74.4)
Overall	48	1	35	13	26.9 (-18.0, 71.9)

Tau-squared = 0.0519 (variance between groups)

After stratified analysis which account for body area of involvement, Fluconazole was more effective than Sodium thiosulfate only in the extensive group. However 99%CI of the cure rate difference was very wide. When combining the two group via DerSimonian & Laird method, the overall cure rate difference was 26.9% but it was inconclusive evidence.

5.3 Secondary outcome analysis

Side effects of repeated doses of orally 400 mg Fluconazole were as follow :

- nausea 1 case (2 %)
- dry mouth 1 case (2 %)
- pruritus 1 case (2 %)
- skin exfoliation 1 case (2 %)

Side effects of 20% Sodium thiosulfate were as follow :

- nausea 1 case (2 %)
- pruritus 3 case (6 %)
- skin exfoliation 5 case (10.4 %)

Side effects at day 7, 14 and 28 were summarized in table 8.

Table 8 Side effects at day 7, 14 and 28

	Fluconazole group			Sodium thiosulfate group		
	Day 7	Day 14	Day 28	Day 7	Day 14	Day 28
	n=49	n=49	n=49	n=44	n=45	N=44
Nausea	1	0	0	1	0	1
Dry mouth	1	0	0	0	0	0
Pruritus	1	1	1	4	3	0
Skin exfoliation	0	1	0	1	1	3

CHAPTER 6

DISCUSSION, CONCLUSION AND RECOMMENDATION

6.1 Discussion

Without stratified analysis according to body area of involvement. The cure rate was higher in Fluconazole group, 98.0%, than in Sodium thiosulfate group, 72.9% . The difference of cure rate between the two regimens was 25.1% (99 %CI , 7.7 ,42.4).

However , after adjusted for the body area of involvement, Fluconazol was more effective than Sodium thiosulfate only in the extensive group but 99%CI (15.6, 74.4) of the cure rate difference was very wide. When combining the two groups via DerSimonian & Laird method, the overall cure rate difference was 26.9% (99%CI, -18.0, 71.9) which was an inconclusive evidence.

The significant difference between the cure rate of the two regimen groups only in extensive body area group could be explained by the difficulty in applying Sodium thiosulphate solution in large area.

The results of the previous studies in term of cure rate of various doses of Fluconazole were shown in table 9.

Table 9 Cure rate from various regimens of oral Fluconazole

Authors	dosage	timing when cure rate was measured	Cure rate (%)	n
Faergemann J.[22]	400 mg single dose	3 weeks	74	24
Bhogal C.S. et al[33]	400 mg single dose	4 weeks	82	45
	150 mg weekly, x 4 pulses	4 weeks	64	45
Amer A.M. et al [28]	150 mg weekly, x 4 pulses	8 weeks	78	207
	300 mg weekly, x 4 pulses	8 weeks	93	190
	300 mg weekly, x 2 pulses	6 weeks	87	206
Silva H. et al [35]	300 mg weekly, x 2 pulses	30 days	91	194
Farshchian M. et al[23]	300 mg weekly, x 2 pulses	4 weeks	82	60
This study	400 mg weekly, x 2 pulses	4 weeks	98	49

Compared to previous studies the cure rate of Fluconazole in this study, was quite high (98%). The study by Faergerman J.[22] in 24 patients showed that 400 mg single dose of Fluconazole yielded 74% of cure rate at the 3rd week. Similarly, the study by Bhogal C.S.et al[33] in 45 patients showed that 400 mg single dose of Fluconazole yielded 82% cure rate at the 4th week. After oral administration, Fluconazole accumulates in eccrine sweat and diffuses rapidly and extensively into the stratum corneum thereby achieving a much higher concentration than in serum or plasma and is eliminated about 2-3 times more slowly.[34] The cure rate was increased up to 98% in our study because weekly pulse dosing could maintain high stratum corneum

concentration of the drug after treatment.[26] Consequently , the fungi were eliminated and clinical improvement could be assessed at two weeks after the last dose.

The study by Amer A.M. et al[28] showed that pulse treatment of weekly 300 mg Fluconazole, whether 2 pulses or 4 pulses, gave comparable cure rates 87%, 93%, respectively. But lower cure rate (78%) was found in 4 pulses treatment of weekly 150 mg Fluconazole. Their study showed that dosage of pulse treatment could give more contribution to effectiveness than number of pulse. The effect of dosage of pulse treatment was confirmed by Bhogal C.S. et al.[33] They showed that 4 pulses treatment of weekly 150 mg Fluconazole yielded 64% cure rate, outcome evaluation was performed at the 4th week. The study of Silva H. et al[35] showed that 2 pulses treatment of weekly 300mg Fluconazole yielded 91% cure rate. In our study, randomized control trial was designed, 2 pulses treatment of weekly 400 mg Fluconazole gave superior cure rate to the previous studies, which confirmed the idea that dosage of pulse treatment could give more contribution to effectiveness than number of pulse.

Recently, the study of Farshchian M. et al ,[23] supported the important of adequate dosage that contributed to effectiveness. In their study they also used weekly doses for 2 weeks similar to our study but

lower weekly dosage might contribute to lower cure rate compared to our study.

The results from previous studies and our study confirmed that Fluconazole was effective in treating pityriasis versicolor when pulse dosage was administered. The higher pulse dosage might contribute to higher cure rate. Pulse dosages between 300-400 mg were effective and well tolerated. At least two pulse treatment might be required, more than two pulse treatment might not contribute to higher cure rate . Further study is required to identify the appropriate number of pulse.

This study showed that repeated doses of orally 400 mg Fluconazole was well tolerated and there was no serious side effect. The side effects included nausea (2%), dry mouth (2%), pruritus (2%), skin exfoliation (2%). Because in blinding method we used double dummy technique, in Fluconazole group , and gave normal saline as the placebo. Fluconazole was unlikely to cause dermatological side effects biologically . Therefore, the side effects of pruritus and skin exfoliation had to be interpreted with care. In our study, the small percentage of GI side effects such as nausea and vomiting were not different from previous studies.[26]

The price of 4 capsules of Fluconazole (200 mg) in this regimen is now reduced to only 16 baht compared to 1,000 baht, 5 years previously. Fluconazole is a good alternative in treating Pityriasis

versicolor not only because of their effectiveness but also reasonable price and convenience .

When treated with Sodium thiosulfate, at four weeks assessment, the mycological cure rate (75%) was higher than clinical cure rate (70%). There were 2 cases defined as partial response because of the presence of scale but negative KOH preparation . However, there was no case that was defined as partial response because of positive KOH preparation but the absence of scale. Since sodium thiosulfate is mild keratolytic agent, it can cause fine scale that are consequently misinterpreted as presence of scale from Pityriasis versicolor. In Fluconazole group there was 1 out of 49 patients whose KOH preparation showed only yeast cells but no short hyphae . According to our definition of mycological cure, this case was defined as partial response. Pure yeast form is not usually seen in clinical phase of [1] *Malassezia furfur* and only experienced technicians can differentiate yeast form from artefact. Mycological cure is more objective assessment than clinical cure, but required specialized technicians. The above findings from our study suggested that the combination of clinical cure and mycological cure was appropriated as the instrument for assessment of effectiveness of the tested regimens.

6.2 Limitations of the study

6.2.1 The topical sodium thiosulfate had the specific odour, we do try to produce the same odour in placebo solution but it was not possible. To minimize this problem, the assessors were blinded to the treatment arm. However, some subjects may probably recognise the odour, therefore they may not be blinded. It is possible that in the sodium thiosulfate group, some subjects may aware that they were received the inferior regimen and may seek for another treatment. Anyhow, this co-intervention may probably result in higher cure rate in this group. These higher cure rate may diminish the difference between the two regimens.

6.2.2 Since we excluded the suspected subjects of diabetes and chronic liver disease , only by history taking and clinical finding. These diseases are confounding factors in the study and commonly occurred in the elderly. If there is any imbalance of these factors in both arms may effect the result of the outcomes.

6.2.3 Since the target population are the patients only in Bangkok which may have daily activities and life style different from the patients in other part of the country, the reader should be

careful when try to generalize the result of this study to their patients.

6.3 Conclusion

1. There is insufficient evidence to make conclusion that repeated doses of orally 400 mg Fluconazole is more effective in treating Pityriasis versicolor than 20% Sodium thiosulfate.
2. This regimen was well tolerated and had no serious side effect.

6.4 Recommendation

6.4.1 Recommendation for extrapolation of the results

I. Repeated doses of orally 400 mg Fluconazole yield quite high cure rate . This regimen was well tolerated and had no serious side effect. This regimen should be used as an alternative treatment of Pityriasis versicolor in the target population (patients in Bangkok).

II. Since we did not study the long term outcomes such as recurrence and relapse rate. This regimen is intended to use only in each episode of the disease. Since the causative organism is a part of normal flora, the predisposing factors could play important roles in recurrence and relapse. General measures such as avoiding sweating and occlusive condition, in order to

eliminate the predisposing factors would be benefit for prevention of recurrence and relapse. Therefore, we recommend to use this regimen in combination with those general measures.

6.4.2 Recommendation for the further study

I. Sample size should be re-calculated for stratified analysis.

II. In exclusion criteria, there should be laboratory tests for confirming the diseases that are major confounders.

III. Further study should be conducted to identify effectiveness of this regimen in population in different parts of Thailand where different precipitating factors may not be the same as patients in Bangkok .

REFERENCES

1. Borelli, D., Jacobs, P.H., and Nall, L. Tinea versicolor: Epidemiological, clinical, and therapeutic aspects. Journal of the American Academy of Dermatology 25 (1991): 300-305.
2. Faergermann, J., and Fredrikson, T. Tinea versicolor : Some new aspect on etiology, pathogenesis, and treatment. International Journal of Dermatology 21 (1982): 8 –11.
3. Rippon, J. W. Superficial infections. In: Medical mycology : The pathogenic fungi and the pathogenic actinomycetes, pp. 154-168. Philadelphia : WB Saunders, 1988.
4. Imwidthaya, S., and Thianprasit, M. Malassezia furfur in dermatological patients and clinically normal persons. Journal of Thai Medical Association 71(3) (1988): 145-149.
5. Ashbee, H.R., Ingham, E., Holland, K.T. and Cunliffe, W.J. The carriage of Malassezia furfur Serovars A,B, and C in patients with pityriasis versicolor, seborrhoeic dermatitis and control. British Journal of Dermatology 129 (1993): 533 – 540.

6. Sunenshine, P.J., Schwartz, R.A., and Janniger, C.K. Tinea versicolor. International Journal of Dermatology 37 (1998): 648-655.

7. Sunenshine, P.J., Schwartz, R.A., and Janniger, C.K. Tinea versicolor : An update, Cutis 61 (1998): 65 – 72.

8. Shrum, J.P., Millkan, L.E., and Bataineh, O. Superficial fungal infection in the tropics. Dermatologic Clinics 12(4) (1994): 687-693.

9. Faergemann, J. Pityriasis versicolor. Seminar in Dermatology 12 (1993): 276-279.

10. Robert, S.B. Pityriasis versicolor : A clinical and mycological investigation. British Journal of Dermatology 81 (1969): 315-326.

11. Burke, R.C. Tinea versicolor. Susceptibility factors and experimental infection in human beings. Journal of Investigative Dermatology 36 (1961): 389 – 302.

12. King, R.D., Cunico, R.L., Maibach, H.I., Greenberg, J.H., West, M.L., and Jeppsen, J.C. The effect of occlusion on carbon dioxide emission from human skin. Acta Dermatologica and Venerologica 58 (1978): 135-138.

13. Thianprasit, M. Pityriasis versicolor. Journal of Thai Dermatology Association 7 (1) (1988): 31-44.

14. Assaf, R.R., and Weil, M.L. The superficial mycosis. Dermatologic Clinics 14 (1) (1992): 57-67.

15. Drake, L.A., et al. Guideline of care for superficial mycotic infections of the skin : Pityriasis (tinea) versicolor. Journal of American Academy of Dermatology 34 (1996): 287-289.

16. Gupta, A.K., Sauder, D.N., and Shear, N.H. Antifungal agents Journal of American Academy of Dermatology 30 (1994): 677-698.

17. Elewski, B.E. Mechanisms of action of systemic antifungal agents. Journal of American Academy of Dermatology 28 (1993): 528-5 34.

18. Faergemann, J. Use of Fluconazole in the treatment of human fungal infections of the skin. International Journal of Dermatology 31 (1992): 1-2.

19. Eckat, H. Pharmacokinetic evaluation of Fluconazole in plasma, epidermis and blister fluid. International Journal of Dermatology 31 (1992): 3-5.

20. Suchil, P., Gel, F.M., Robles, M., Perera, R.A., Welsh, O., and Male, O. Once – weekly oral doses of Fluconazole 150 mg in the treatment of tinea corporis / cruris and cutaneous candidiasis. Clinical Experimental of Dermatology 17 (1992): 397 – 401.

21. Gupta, A.K., Sauder, D.N., and Shear, N.H. Antifungal agents : An Overview part II. Journal of American Academy of Dermatology 30 (1994): 911 – 933.

22. Faergemann, J. Treatment of pityriasis versicolor with a single dose of fluconazole. Acta Dermatologica and Venerologica (Stockh) 72 (1992): 74-75.

23. Farshchian, M., Yaghoobi . R., and Samadi. Fluconazole versus ketoconazole in the treatment of tinea versicolor. Journal of Dermatological Treatment. 13 (2002): 73-36.

24. Rausch, L.J. and Jacobs, P.H. Tinea versicolor. Treatment and prophylaxis with monthly administration of ketoconazole. Cutis 34 (1984) : 470-471.

25. Savin, R.C. Systemic ketoconazole in tinea versicolor. A double – blind evaluation and 1 year follow up. Journal of American Academy of Dermatology 10 (1984): 824-830.

26. Faergemann, J., and Laufen, H. Levels of fluconazole in serum, stratum corneum, epidermis – dermis (without stratum corneum) and eccrine sweat. Clinical Experimental of Dermatology 18 (1993): 102-106.

27. Lizama, E.S. E. Tinea versicolor. International Journal of Dermatology 34 (1993): 611-617.

28. Amer, A.M., et al. Fluconazole in the treatment of tinea versicolor. International Journal of Dermatology 36 (1997): 940-942.

29. Kose, O. Fluconazole versus itraconazole in the treatment of tinea versicolor. International Journal of Dermatology 34 (1995): 498-499.

30. Faergemann, J. Pharmacokinetics of fluconazole in the skin and nails. Journal of American Academy of Dermatology 40 (1999): 14-20.

31. Grant, M.S., and Clissold, P.S. Fluconazole : A Review of its Pharmacodynamic and Pharmacokinetic Properties, and Therapeutic Potential in Superficial and Systemic Mycoses. Drugs 39(6) (1990): 877-910.

32. Dover, R., and Wright, N.A. Epidermal cell kinetics. In T.B. Fitzpatrick, A.Z. Eisen, K. Wolff , I.M. Freedberg, and K.F. Austen (eds.), Dermatology in General Medicine, pp. 165-167. New York: McGraw-Hill, 1993.

33. Bhogal, C.S., Singal, A., and Baruah, M.C. Comparative Efficacy of Ketoconazole in the Treatment of Pityriasis versicolor: A One Year Follow-up Study. The Journal of Dermatology 28 (2001): 535-539.

34. Wildfeuer, A., Faergemann, J., Laufer H, et al: Bioavailability of fluconazole in the skin after oral medication, Mycoses, 37 (1994): 127-130.

35. Silva, H., Gibbs, D., and Arguedas, J. A comparison of Fluconazole with Ketoconazole, Itraconazole, and Clotrimazole in the Treatment of Pityriasis versicolor. Current Therapeutic Research Clinical and Experimental 59 (4) (1998): 203-214.

APPENDICES

APPENDIX A

Data Record Form

Identification Number…….

Hospital Number…….

Date of Recruitment……

Bangkok Skin Clinic

Name……Age..…….……

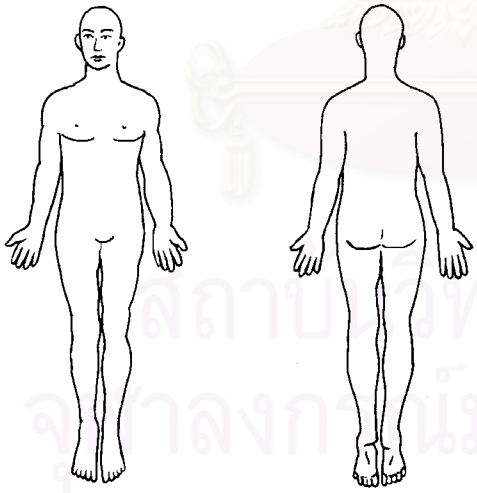
Occupation……..……..Weight……..….kg

Address……

……

Telephone Number…….……

Sign and symptom at DAY O



Date..……..……

Short description of lesion…….…..……

……..……...……

……..

Number of lesion…….……...

Body area involvement……

Size……palm.

Site……..

KOH preparation……

Name of recorder……..…….……..

Next follow up date…….

Sign and symptom at; DAY 7

Date……..……

Clinical ☐ Cure ☐ Not cure

SIDE EFFECT ☐ Headache ☐ Dizziness ☐ Others…….

☐ Nausea ☐ Abdominal pain ……..

☐ Skin rash ☐ Pruritus

Amount of topical solution used…….ml

Patient's comment……

……..

Name of recorder……

Next follow up date ……..

Sign and symptom at; DAY 14

Date……..……

Clinical ☐ Cure ☐ Not cure

KOH preparation ☐ Negative ☐ Positive

SIDE EFFECT ☐ Headache ☐ Dizziness ☐ Others…….

☐ Nausea ☐ Abdominal pain ……..

☐ Skin rash ☐ Pruritus

Amount of topical solution used…….ml

Patient's comment……

……..

Name of recorder……

Next follow up date ……..

Sign and symptom at; DAY 28

Date……..……

Clinical	☐ Cure	☐ Not cure	
KOH preparation	☐ Negative	☐ Positive	
SIDE EFFECT	☐ Headache	☐ Dizziness	☐ Others…….
	☐ Nausea	☐ Abdominal pain	……..
	☐ Skin rash	☐ Pruritus	

Patient's comment……

……..

Name of recorder……

****

APPENDIX B

ข้อมูลสำหรับผู้ป่วย

การศึกษาทางคลินิก ประสิทธิผลของยาฟลูโคนาโซล (Fluconazole) ในการรักษาโรคเกลื้อน

เรียน ผู้ป่วยทุกท่าน

ท่านเป็นผู้ได้รับเชิญจากแพทย์ให้เข้าร่วมการศึกษาทางคลินิกเพื่อศึกษาประสิทธิผลของยาฟลูโคนาโซล ก่อนที่ท่านจะตกลงเข้าร่วมการศึกษาดังกล่าว ขอเรียนให้ท่านทราบเหตุผล และรายละเอียดของการศึกษาวิจัยในครั้งนี้

- โรคเกลื้อนเป็นโรคที่เกิดจากเชื้อราที่พบบ่อยในประเทศไทย การรักษาโรคเกลื้อน แต่เดิมรักษาด้วยยาทา ซึ่งมีกลิ่นเหม็น อีกทั้งไม่สามารถป้องกันการกลับเป็นโรคใหม่ได้ ขณะนี้มียารักษาโรคเกลื้อนชนิดกิน ซึ่งมีประสิทธิผลในการรักษาเพิ่มมากขึ้น มีความปลอดภัยอย่างเพียงพอ โดยมีการวิจัยในต่างประเทศรองรับ แต่ในประเทศไทยซึ่งมีอุณหภูมิร้อนชื้น ยังไม่เคยมีการศึกษาประสิทธิผลของยาฟลูโคนาโซลในคนไข้ไทยมาก่อน

เมื่อท่านตกลงเข้าร่วมโครงการศึกษาในครั้งนี้ ท่านอาจจะได้รับยาในสูตรที่ 1 หรือสูตรที่ 2 โดยยาทั้ง 2 สูตรนี้ สามารถรักษาโรคเกลื้อนได้เช่นเดียวกัน และมีความปลอดภัยทั้งสองสูตร

- ยาสูตรที่1 และสูตรที่ 2 ประกอบด้วยยาเม็ดซึ่งจะให้ท่านรับประทาน 1 เม็ดในวันแรกที่ท่านมารับการรักษา และท่านจะได้ยาทาชนิดน้ำกลับไปทาบริเวณรอยโรคที่บ้าน เช้า – เย็น (2 ครั้ง) เมื่อครบ 7 วัน แล้วขอความร่วมมือจากท่านให้กลับมาพบแพทย์เพื่อประเมินผลการรักษา และรับยาเม็ดเพิ่มอีก2 เม็ด พร้อมกับยาทาชนิดน้ำ ทาเช้า-เย็นติดต่ออีก 7 วัน

- หากท่านตกลงที่จะเข้าร่วมการศึกษาวิจัยครั้งนี้ จะมีข้อปฏิบัติดังต่อไปนี้

  ท่านไม่ต้องเสียค่าใช้จ่ายในการรักษาใด ๆ ทั้งสิ้น

  ก่อนจะเริ่มต้นการศึกษาและการพบแพทย์แต่ละครั้ง แพทย์จะตรวจร่างกายเพื่อบันทึกความเปลี่ยนแปลง และผลการรักษา พร้อมกับการเก็บสะเก็ดผิวหนัง เพื่อส่งตรวจเชื้อราด้วยเครื่องมือที่สะอาดปลอดภัยไม่เกิดความเจ็บปวดใด ๆ

  ขอความร่วมมือจากท่านให้กลับมาพบแพทย์ใน วันที่ 7, 14 และ 28 หลังจากเริ่มต้นการรักษา เพื่อบันทึกผลการรักษาดังกล่าว

- อาการข้างเคียงที่เกิดระหว่างรับประทานยาดังกล่าว จะเกิดเพียงเล็กน้อย ซึ่งแพทย์จะเป็นผู้อธิบายรายละเอียดต่าง ๆ ของผลข้างเคียง แพทย์จะแจ้งให้ท่านทราบ และยินดีตอบคำถามต่างๆ ที่ท่านสงสัยโดยละเอียด

- การเข้าร่วมการศึกษานี้ เป็นโดยสมัครใจ ท่านอาจจะปฏิเสธที่จะเข้าร่วม หรือถอนตัวจากการศึกษานี้ได้ทุกเมื่อ โดยไม่มีผลกระทบต่อการดูแลรักษาที่ท่านจะได้รับจากแพทย์

ประการสำคัญที่ท่านควรทราบ คือ

- ผลการศึกษานี้จะใช้สำหรับวัตถุประสงค์ทางวิชาการเท่านั้น โดยข้อมูลต่าง ๆ จะถูกเก็บไว้ในคอมพิวเตอร์ และไม่มีการแพร่งพรายสู่สาธารณชน ขอรับรองว่าจะไม่มีการเปิดเผยชื่อของท่าน

- หากท่านมีปัญหา หรือข้อสงสัยประการใด กรุณาติดต่อ นายแพทย์กฤษฎา มโหทาน สถานบำบัดโรคผิวหนังวัดมกุฎกษัตริยาราม โทรศัพท์ 0 2282 3554-6 ในเวลาราชการ ซึ่งยินดีให้คำตอบแก่ท่าน

ขอขอบคุณในความร่วมมือของท่านมา ณ ที่นี้

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APPENDIX C

ใบยินยอมให้ทำวิจัยในมนุษย์ (Consent Form)

โครงการวิจัยเรื่อง ประสิทธิผลของยาฟลูโคนาโซลในการรักษาโรคเกลื้อน

วันให้คำยินยอม วันที่.....เดือน.....พ.ศ. .....

ก่อนที่จะลงนามในใบยินยอมให้ทำการวิจัยนี้ ข้าพเจ้าได้รับการอธิบายจากผู้วิจัยถึงวัตถุประสงค์ของการวิจัย วิธีการวิจัย อันตรายหรืออาการที่อาจเกิดขึ้นจากการวิจัยหรือจากยาที่ใช้ รวมทั้งประโยชน์ที่จะเกิดขึ้นจากการวิจัยอย่างละเอียด

ผู้วิจัยรับรองว่าจะตอบคำถามต่าง ๆ ที่ข้าพเจ้าสงสัยด้วยความเต็มใจ ไม่ปิดบัง ซ่อนเร้น จนข้าพเจ้าพอใจ

ข้าพเจ้ามีสิทธิ์ที่จะบอกเลิกการเข้าร่วมโครงการวิจัยนี้เมื่อไรก็ได้ และเข้าร่วมโครงการนี้โดยสมัครใจและการบอกเลิกการเข้าร่วมการวิจัยนี้ จะไม่มีผลต่อการรักษาโรคที่ข้าพเจ้าจะพึงได้รับต่อไป

ผู้วิจัยรับรองว่าจะเก็บข้อมูลเฉพาะเกี่ยวกับตัวข้าพเจ้าเป็นความลับและจะเปิดเผยได้เฉพาะในรูปที่เป็นสรุปลการวิจัย การเปิดเผยข้อมูลเกี่ยวกับตัวข้าพเจ้าต่อหน่วยงานต่าง ๆ ที่เกี่ยวข้องกระทำได้เฉพาะกรณีจำเป็นด้วยเหตุผลทางวิชาการเท่านั้น

ข้าพเจ้าได้อ่านข้อความข้างต้นและมีความเข้าใจดีทุกประการ และได้ลงนามในใบยินยอมนี้ด้วยความเต็มใจ

ลงชื่อ.....ผู้ยินยอม

( )

ลงชื่อ.....พยาน

( )

ลงชื่อ.....พยาน

( )

VITAE

Dr. Krisada Mahotarn was born on December 9, 1959, in Bangkok, Thailand. He graduated from Faculty of Medicine, Chiangmai University, in 1984. He finished his residency training program from Ramathibodi Hospital, Mahidol University and obtained the Certification of Proficiency Board of Dermatology in 1991. He started his carrier as dermatologist at Khon Kaen skin clinic in 1991. Then he became the director of Leprosy Centre Zonal 5, in Nakorn Ratchasima since 1992. During his working there, he received national award as the best public health officer in 1996. Then in 2001, he was appointed as the director of Leprosy Division. Currently, he is the chief of Leprosy Control Task Force Group in Rajprachasamasai Institute, Department of Disease Control, Ministry of Public Health.