การศึกษามิวพิโรซินในโรคติดเชื้อผิวหนังในผู้ป่วยชาวไทย

ปิติ พลังวชิรา พบ.*
ปราณี พลังวชิรา พบ.**

Abstract **An open study of mupirocin in Thai patients with skin infections**

Piti Palungwachira, M.D.*
Pranee Palungwachira, M.D.**

In an open study in Thai 49 patients suffering from skin infections, usually caused by staphylococci and streptococci, were treated with a new topical antibiotic, mupirocin, applied three times daily for 7 days. By day 7 of treatment 93.5% of patients were asymptomatic and were considered cured, and 100% were consideres cured 1 week later. In total, 48 bacterial strains were isolated, of which, 88% were staphylococci and 16% were streptococci. Neither adverse events nor cutaneous reactions were reported. Mupirocin 2% ointment proved to be effective and safe in the treatment of primary and secondary skin infections.

Keywords : Mupirocin; topical Antibiotic; skin infections; staphylococci; streptococi; Thai

บทคัดย่อ ได้ศึกษาผู้ป่วย 49 ราย ที่ได้รับการติดเชื้อทางผิวหนัง เชื้อส่วนใหญ่มีสาเหตุมาจากสแตฟฟิโลคอคไค และสเตร็ปโตคอคไค ผู้ป่วยทั้งหมดได้รับการรักษาโดยใช้ยาปฏิชีวนะชนิดทาโดยทามิวฟิโรซิน วันละ 3 ครั้ง ทุกวันเป็นเวลา 7 วัน พบว่าหลังจากได้รับการรักษา 7 วัน 93.5% ของผู้ป่วย อาการดีขึ้นจนหายขาด และพบว่าถ้าได้รับการรักษาซ้ำอีก 1 อาทิตย์ต่อมา จะมีโอกาสหาย 100% จากการเพาะเชื้อพบว่า เชื้อส่วนใหญ่ 88% เป็นสแตฟฟิโลคอคไค และ 16% เป็นสเตร็ปโตคอคไค ไม่พบผลข้างเคียงหรือปฏิกิริยาภูมิแพ้ทางผิวหนังจากการใช้ยา จึงสามารถสรุปได้ว่า 2% มิวฟิโรซินชนิดทาได้ผลดีและมีความปลอดภัยในการรักษาโรคผิวหนังติดเชื้อทั้งชนิดปฐมภูมิและทุติยภูมิ *(MJS 2000 ; 1 : 20 – 27)*

* ศูนย์ผิวหนัง มหาวิทยาลัยศรีนครินทรวิโรฒ ประสานมิตร กรุงเทพมหานคร
* Srinakharinwirot University Skin Center, Srinakharinwirot University
** ภาควิชาเวชศาสตร์ครอบครัว โรงพยาบาลรามาธิบดี กรุงเทพมหานคร
** Family Medicine Department, Ramathibodi hospital, Mahidol University

Introduction

The incidence of bacterial infections is usually higher in Thai than in Europe; this is well established for skin and soft-tissue infections which have a variety of causes. The excessive use of antibiotics and self-medication have contributed to the relatively high incidence of resistant staphylococci, which, together with B-haemolytic streptococci are the main causes of common primary and secondary skin infections. This high incidence of resistant bacterial strains complicates the treatment of such infections. Both the efficacy of a treatment and its cost are important, especially in Thailand.

Mupirocin (Bactroban; pseudomonic acid A) is a new topical antibiotics with a unique chemical structure unrelated to that of any other group of antibiotics.[1] This naturally occurring antibiotic is produced by the anaerobic metabolism of a particular strain of Pseudomonas fluorescens.[2] Mupirocin covers a broad spectrum of Gram-positive and Gram-negative bacteria and is particularly active against staphylococci (including methicillin and multiply resistant strains)[3] and streptococci (minimum inhibitory concentrations, 0.14-.048 mg/l).[4]

The mode of action by which this antibiotic inhibits bacterial growth is by inhibiting isoleucyl transfer-RNA synthetase which results in the inhibition of bacterial proteins.[5,6] Because of its unique mode of action, mupirocin shows neither cross-reaction with, nor cross-resistance to, any other commonly used and clinically important antibiotic.[7] The opportunity for the emergence of strains of Staphylococcus aureus that are less sensitive, and are resistant to antibiotics, exists in patients who receive long-term or frequent courses of antibiotic therapy, particularly patients with chronic inflammatory conditions such as atopic dermatitis.[8] When applied as ointment, systemic absorption of mupirocin is minimal.[9] The small amount that enters the blood is rapidly converted to an inactive metabolite, 90% of which is excreted in the urine.[10]

This open study was set up in Thai to confirm the safety and efficacy of mupirocin in the treatment of primary and secondary skin infections.[11-14]

Patients and Methods

Patients

Adults and children aged at least 4 weeks, of either sex, with skin infections suitable for topical antibiotic treatment who gave oral witnessed or written consent to participate were eligible for entry into the study.

The following patients were excluded from the study: those with infected eczema, infected burns or scalds, systemic lupus erythematosus or severe skin disease requiring the use of a systemic antibiotic; those who had received topical or systemic antibiotics within the preceding 48 h; those receiving steroids; those with an associated disease that might interfere with the study (e.g.diabetes); those with renal insufficiency; those with suspected pregnancy or lactation; and those who were hypersensitive to mupirocin or preparations containing polyethylene glycols.

Investigators had to explain to the patient, orally and in writing, the nature, duration and purpose of the study, and the possible side-effects. Patients were informed that they might withdraw from the study at any time, without this affecting their future status.

Study Desing

An open, non-comparative study was set up in the Srinakharinwirot University Skin center, Bangpai general Hospital Bangkok, Thailand. The study included three visits on days 0, 7 and 14 if appropriate; on day 0, corresponding with the inclusion visit, the investigator had to record on the case-report from, demographic data such as the patient's age and sex, the nature of the infection, the duration and severity of symptoms, the site of infection, the presence or absence of systemic complications (e.g.lymphadenopathy and pyrexia), and all previous and/or concomitant treatments. A swab was also taken from each appropriate site for bacteriological evaluation; isolated organisms were cultured and their sensitivities to mupirocin, penicillin G, tetracycline, chloramphenicol and fusidic acid were assessed using the disk diffusion susceptibility test.

On entry to the study each patient received two tubes of 2% mupirocin ointment. The patients were instructed to apply this three timse a day for at least 6 days; no other antibiotics were to be taken by the patient during the study period and only symptomatic treatments were allowed and recorded on the patient's case report form.

The clinical response to treatment was evaluated by the investigator by comparing the patient's general health on day 7 and/or day 14 to that on the previous visit and was judged as cured if all the signs and symptoms of infection were eliminated, as improved if the clinical findings were significantly reduced but not completely resolved, as failed if there was no response to treatment or as non-evaluable in the case of patients with any of the exclusion criteria and those who did not attend at least one of the follow-up visits. All patients who had improved by day 7 were allowed to continue with their treatment. Compliance with treatment was evaluated by the investigator at each study visit.

Adverse Events

Any adverse events observed by the investigator or reported spontaneously by the patient were recorded on the patient's casereport from. The date of onset, duration, intensity, course, action taken, outcome and relation to the study drug were recorded. The relationship of the adverse event to the study drug was categorized as: unassessable, unrelated, probably unrelated, probably related or related. For each adverse event, the decision of whether to withdraw the patient from the study and initiate appropriate treatment or to continue the study medication was made by the investigator.

Statistical Analysis

Study results were analysed, through statix software (statmatic co.).

Results

A total of 49 patients were enrolled in the study comprising 23 women (aged 3 months-51 years; mean, 12.8 years) and 26 men (aged 4 months-65 years; mean, 21 years). There was no statistically significant difference between the ages of the women and men enrolled in the study (Student's t test $P>0.05$).

The clinical features observed before study drug administration are summarized in Tables 1 and 2. Impetigo was observed in 22 (44.9%) and sycosis barbae in 11 (22.4%) of the patients; the infected skin lesions included an infected vesicle,

Table 1 clinical characteristics of patients with skin infections before study drug administration

Clinical features	No. of patients affected		
	Women (n=23)	men (n=26)	Total (n=49)
present infection			
Impetigo	9	13	22
Furunculosis	4	2	6
Sycosis barbae	0	11	11
Folliculitis	3	1	4
Ecthyma	3	1	4
Infected skin lesions	3	1	4
Symptoms			
Itching	3	5	8 (16.7%)
Pain	3	8	11 (22.9%)
Itching+pain	7	8	15 (29.1%)
No symptoms	11	8	19 (35.5%)
Mean duration of symptoms (days)	14	12	13
Severity			
Mild	9	8	17 (35.4%)
Moderate	12	18	30 (62.5%)
Severe	1	0	1 (2.1%)
Systemic complications			
Lymphadenopathy	3	3	6
Pyrexia	0	0	0
Site of intection			
Head/neck	14	25	39 (79.5%)
Trunk	2	2	4 (8.3%)
Limbs/hands	4	4	8 (16.7%)
Legs	6	2	8 (16.7%)
Genitals	0	1	1 (2.1%)

an infected wound and an infected bite in three women and infected scabies in a young man. Neither pain nor itching were reported for 35.5% of the patients, mainly those with a diagnosis of impetigo, while 29% of the patients complained of both itching and pain; only six of the 49 patients presented with a symptom of systemic complications, such as lymphadenopathy, and all of the patients were apyretic at the inclusion visit on day 0.

The mean duration of symptoms was 13 days (range: 3–110 days) and 30 patients out of 49 (61.2%) presented with a skin infection judged as moderate by the investigator; one 48–year–old women with infected vesicles on the face and lips presented with a severe skin infection.

The site of the infection was mainly the head and neck (79.5), especially for patients with impetigo, furunculosis or a sycosis barbae' infection; a young boy aged 8 years old had multiple locations of infected scabies, including the genital area.

Seventeen patients had received treatments before administration of the study drug, and these included local and systemic antibiotics, such as erythromycin, ampicillin, flucloxacillin, fusidic acid or radiotherapy for 1 week in three cases: an ecthyma and a sycosis barbae infection. Four patients took medication concomitantly: one took an antihistaminic drug (anti-HI) for an infected scabies infection, one took a systemic steroid (prednisolone) for an infected vesicle and another two, cloxacillin for sycosis barbae. These last three patients were not included in the efficacy analysis according to the study exclusion criteria.

A positive culture was obtained from all patients: a total of 48 bacterial strains were isolated from the lesions, predominantly staphylococci (88%) and streptococci (16%). Only one strain of coagulase negative staphylococci was isolated (Table 2).

Table 2 Clinical and bacteriologocal findings of patients with skin infections, grouped according to clinical diagnosis before study drug administration

Persent infection/ clinical and bacteriological findings	No. of patients affected						
	Impetigo (n=20)	Sycosis barbae (n=10)	Furuncu losis (n=6)	Folliculi tis (n=4)	Ecthyma (n=4)	infected skin lesions (n=5)	Total (n=49)
Symptoms							
Itching	2	2	1	–	1	2	8
Pain	4	3	3	–	1	–	11
Itching+pain	4	5	1	1	1	3	15
No symptoms	12	–	1	2	1	–	16
Severity							
Mild	13	–	2	2	–	–	17
Moderate	7	10	4	2	4	4	31
Severe	–	–	–	–	–	1	1
Sytemic complications							
Lymphadenopathy	1	1	1	–	1	1	5
pyrexia	–	–	–	–	–	–	–
Site of infection							
Head/neck	18	10	3	2	1	3	37
Trunk	2	–	–	1	–	1	4
Limbs/hands	2	–	–	1	3	2	8
Legs	3	–	3	–	1	1	8
Genitals	–	–	–	–	–	1	1
Bacteriological findings							
Staphylococcus aureus	17	10	5	1	3	4	40
Other Staphylococcus spp.	–	–	–	1	–	–	1
Streptococci	3	–	–	1	1	–	5
Staphylococcus+Streptococcus	–	–	1	1	–	–	2

At the inclusion visit resistance of staphylococci to penicillin was high (71.1%) for overall primary and secondary infections. Tetracycline resistance occurred in 48.5%, chloramphenicol resistance was found in 18.8% and fusidic acid in 48.8%. No strains were resistant to mupirocin (Table 3). On the same study visit, the tetracycline resistance of the streptococci was high (72.4%). Penicillin resistance was found in 19% and fusidic acid resistance in 58%; no strains were resistant to chloramphenicol or mupirocin. (see Table 4). Mupirocin ointment was applied three times a day for a mean duration of treatment of 7 days (range: 4–10 days) for all patients enrolled.

On day 7, 42 out of 46 evaluable patients (91.3%) remained or become asymptomatic and were judged as cured by the investigator. Three patients who had a sycosis barbae infection did

Table 3 Sensitivities of staphylococci to various antibiotics, in patients with skin infections grouped according to clinical diagnosis

	% response																				
	Impetigo			Sycosis barbae			Furunculosis			Folliculitis			Ecthyma			Infected skin lesions			Total		
ANTIBIOTIC	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Mupirocin	100	–	–	100	–	–	100	–	–	100	–	–	100	–	–	100	–	–	100	–	–
Tetracycline	44	–	54	67	–	32	20	–	78	67	–	32	67	–	31	25	–	73	8	–	48.5
Penicillin G	47	6	48	0	13	88	40	–	61	–	–	100	–	–	100	–	–	100	26	5	71.1
Chloramphenicol	66	7	25	86	–	12	67	–	31	67	33	–	100	–	–	67	–	32	73	5	18.8
Fusidic acid	29	21	47	50	–	47	33	–	64	67	–	28	67	–	31	67	–	31	38	11	48.8

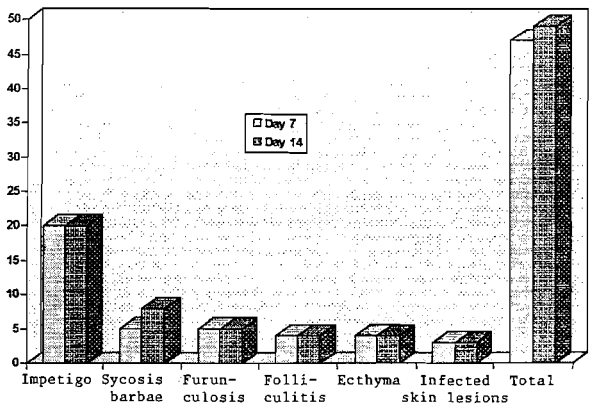
S, susceptible; I, intermediate; R, resistamt.

Table 4 Sensitivities of streptococci to various antibiotics, in patients with skin infections grouped according to clinical diagnosis

	% response														
	Impetigo			furunculosis			Folliculitis			Ecthyma			Total		
Antibiotic	S	I	R	S	I	R	S	I	R	S	I	R	S	I	R
Mupirocin	100	–	–	–	–	–	100	–	–	100	–	–	100	–	–
Tetracycline	–	33	69	–	–	100	–	–	100	100	–	–	14	14	72.4
Penicillin G	50	–	48	100	–	–	100	–	–	100	–	–	80	–	19
Chloramphenicol	100	–	–	100	–	–	100	–	–	100	–	–	100	–	–
Fusidic acid	–	50	48	–	–	100	–	100	–	–	–	100	–	40	58

S. susceptible; I, intermediate; R. resistant.

not respond to the treatment but were considered improved by the investigator and continued their treatment with mupirocin ointment, twice or three times daily, for a further week. These three patients were considered cured by the investigator on the final study visit on day 14 (Fig. 1).



Number of patients cured after 7 or 14 days' treatment with mupirocin, grouped according to clinical diagnosis.

No bacteriological samples were taken from the patients on days 7 or 14. Compliance with treatment was judged good, for all patients, by the investigator. Neither adverse events nor cutaneous reactions were recorded in the case report forms. The tolerance and safety of mupirocin was judged as very good in the 49 patients enrolled.

Discussion

The topical use of antibiotics should be encouraged. These agents, however, must be properly selected and used only for appropiate cases. The incidence of drug resistance has been greatly increased by the topical use of antibiotics. As a result many topical drugs are not effective. Topical antibiotics should, where possible, meet the following requirements: the development of bacterial resistance during therapy should be slow, they should either have no or have only slow patient sensitization potential and it should not be necessary to apply antibacterial agents that are also used systemically (because of the risk of resistance development). The use of topical antibiotics is appropriate in superficial skin infections since the agents are directly active at the infection site. Common diseases in this catetory are pyoderma. (e.g. impetigo, folliculitis), ecthyma and infected skin lesion Mupirocin meets all these requirements. Owing to its unique mode of action and the fact that it is designed for topical use only, the risk of resistance development is minimal compared with that of other topical antibiotics. In vitro–experiments with susceptible strains of strains of Staphylococcus aureus revealed that in the presence of mupirocin spontaneous resistant mutants developed only at a frequency of 10^{-8} to $10.^{-9}$[15] The potential for sensitization and the development of allergy to 2% mupirocin ointment. In studies with healthy volunteers, no evidence of phototoxic or photoallergic was observed.[16]

At the end of treatment 93.5% of the patients evaluable in the present study, including all those suffering from the most common disease, impetigo, were cured. The remaining patients (6.5%) showed an improvement in symptoms and after a further period of treatment the clinical success rate reached 100%. These results are consistent with those of other open or comparative studies.[11] In addition, the safety and tolerance were particularly good: no adverse events were reported among the 49 patients treated with mupirocin ointment.

This study highlighted the importance of staphylococci and streptococci in bacterial skin

infections and the emergence of resistance to common drugs although some of the results must be interpreted with care because of the small number of strains isolated. Mupirocin ointment 2% is a highly effective topical agent agaist both streptococci and staphylococci, including methicillin resistant strains. Reports indicate that mupirocin may be comparable to systemic erythromycin and cloxacillin. The results of this open study confirm the safety and efficacy of mupirocin ointment in the treatment of superficial skin infections.

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