Comparative Study of 2% Ketoconazole Cream and 1% Hydrocortisone Cream in the Treatment of Infantile Seborrheic Dermatitis

Siriwan Wannanukul MD*,
Jutamas Chiabunkana MD*

** Department of Pediatrics, Faculty of Medicine, Chulalongkorn University*

Objective *: To compare efficacy of 2% ketoconazole cream with 1% hydrocortisone cream in the treatment of infantile seborrheic dermatitis (ISD). This study recruited infants of 2 weeks to 2 years old with a clinical diagnosis of infantile seborrheic at the Department of Pediatrics, King Chulalongkorn Memorial Hospital from December 2001 to November 2003.*
Method : *The severity of the rash of the patients was examined in terms of erythema, scale and crust before treatment based on a scoring system comparing two sides (left and right) of the lesion with numeral representation for it a severity, namely: 0 for no lesion; 1, mild; 2, moderate; and 3, severe. They were treated with 2% ketoconazole cream on the left side of the lesion and 1% hydrocortisone cream on the right side of the lesion, twice a day.*
Results *: The responses of treatment of 2% ketoconazole cream compared with 1% hydrocortisone cream in 48 patients had no statistical significant difference at 2-3 days of treatment and 4-7 days of treatment. By one week, both 2% ketoconazole cream and 1% hydrocortisone cream have significant clinical improvement of the lesion. The skin lesions were cleared in 31% of the ketoconazole group and 35% of the hydrocortisone group. All skin lesions were cleared by the end of the second week.*
Conclusion : *The efficacy of 2% ketoconazole cream and 1% hydrocortisone cream in the treatment of ISD was not significantly different. Ketoconazole is another option for the treatment of ISD, to avoid the side effects of topical corticosteroid in long-term use and on large surface areaa of treatment.*

Keywords : *Ketoconazole, Hydrocortisone, Seborrheic Dermatitis, Infantile*

J Med Assoc Thai 2004; 87 (Suppl 2): S68-71
e-Journal: *http://www.medassocthai.org/journal*

Infantile seborrheic dermatitis (ISD) is a common skin lesion found in the first months of life. The skin lesion consists of yellowish or whitish greasy, thick adherent, often confluent scales, mostly occurring on the vertex, frontal area, eyebrows, retroauricular areas and the flexural areas [1,2]. It often begins around the second or third week of age coinciding with sebaceous gland hyperplasia of the newborn and colonization of *Malassezia* [4]. There is still no evidence that it is analogous to seborrheic dermatitis in adults [3].

The etiology of ISD is still unclear [3]. *Malassezia furfur* (or *Pityrosporon ovale*) has been found in lesion of ISD (73%)[5,6] but also found in other skin conditions such as atopic dermatits (33%) and in healthy infants (33%) [7].

Treatment of ISD includes emollients, mild topical steroids[3] topical ketoconazole cream [8] ketoconazole shampoo [9]. Miconazole [10] and ketoconazole [10-12] are also effective in seborrheic dermatitis in adults, which suggests a pathogenic role of *M. furfur* in seborrheic dermatitis.

Both topical corticosteroid and ketoconazole have been recommended for the treatment of ISD [1,3]. The clinical course and severity of ISD vary from patients to patients. The aim of this study was to compare the efficacy of 2% ketoconazole cream and 1% hydrocortisone cream in the treatment of ISD in the same patient.

Method

All infants with the diagnosis of ISD without prior treatment, aged 2 weeks to 24 months, from December 2002 to November 2003 were recruited for the present study. Consent for participation in the study was signed by the parents of all children. On the initial evaluation, the severity of the rash of the patients was examined in terms of erythema, scale and crust before treatment based on a scoring system

Correspondence to : Wananukul S. Division of Pediatric Dermatology, Department of Pediatrics, Faculty of Medicine, Chulalongkorn University, Rama IV Road, Bangkok 10330, Thailand. Phone:0-2256-4951, Fax: 0-2256-4911, E-mail: wananusw@hotmail.com

comparing two sides (left and right) of the lesion with numeral representation for it severity, namely: 0 for no lesion; 1, mild; 2, moderate; and 3, severe.The patients were treated with 2% ketoconazole cream on the left side of the lesion and 1% hydrocortisone on the right side of the lesion, twice a day.

The patients were evaluated 2-3 days and 4-7 days after starting the treatment. If the skin lesions had not improved, or had side effects from the topical medication, they were treated by authors topical medication. Statistic differences between group comparisons were calculated by using dependent samples t-test in SPSS for Window, with statistical significance at $p < .05$.

Results

A total of 48 infants (26 boys, 22 girls) with the diagnosis of ISD, aged 2 weeks to 15 months, with a mean age of 2.5 months, were recruited. None had prior medication. Table 1 shows the number of sites of the skin lesions. The scalp was the most common site (Table 2). The efficacy of 2% ketoconazole cream was not significantly different from 1% hydrocortisone cream on D 2-3 (p = 0.749, Table 3) and D 4-7 (p = 0.268, Table 4). By one week, both 2% ketoconazole cream and 1% hydrocortisone cream had improved the skin lesion significantly (p < 0.05, Table 5, 6). The skin lesions were cleared in 31% in the ketoconazole group and 35% in the hydrocortisone group. All skin lesions were cleared by the end of the second week.

Table 1. Number of sites of skin lesions in infantile seborrheic dermatitis

Number of sites	Number of patients (%)
1	4 (8.33)
2	14 (29.17)
3	12 (25.00)
4	10 (20.83)
5	5 (10.42)
6	3 (6.25)
Total	48 (100)

Table 2. Site of involvement in infantile seborrheic dermatitis

Site	Number of patients (%)
scalp	41 (29.08)
ear	30 (21.27)
eyebrow	26 (18.44)
cheek	23 (16.31)
forehead	11 (7.81)
upper trunk	10 (7.09)
Total	141 (100)

Table 3. Efficacy of 1% hydrocortisone (HC) compare with 2% ketoconazole (KC) in the treatment of infantile seborrheic dermatitis in day 2-3

	n = 48					
	1% HC		2% KC		*t*	*p*
	$\bar{X}$	SD	$\bar{X}$	SD		
Erythema	0.83	0.83	0.88	1.00	-0.405	.688
Crust	1.15	0.80	1.10	0.81	0.628	.533
Scale	0.92	0.74	0.98	0.79	-0.724	.473
Total	0.97	0.52	0.99	0.59	-0.322	.749

*$p < .05$

Table 4. Efficacy of 1% hydrocortisone (HC) compare with 2% ketoconazole (KC) in the treatment of infantile seborrheic dermatitis in day 4-7

	n = 48					
	1% HC		2% KC		*t*	*p*
	$\bar{X}$	SD	$\bar{X}$	SD		
Erythema	0.10	0.37	0.13	0.33	-0.375	.710
Crust	0.52	0.68	0.58	0.65	-0.724	.473
Scale	0.44	0.58	0.56	0.71	-1.288	.204
Total	0.35	0.37	0.42	0.38	-1.121	.268

p < .05

Table 5. Scoring of pre and post treatment at (4-7 day) with 1% hydrocortisone (HC) in infantile seborrheic dermatitis

	n = 48					
	Day 0		Day 4-7		*t*	*p*
	$\bar{X}$	SD	$\bar{X}$	SD		
Erythema	2.02	0.86	0.10	0.37	13.777*	<.001
Crust	1.94	0.84	0.52	0.68	12.793*	<.001
Scale	1.85	0.82	0.44	0.58	11.957*	<.001
Total	1.94	0.53	0.35	0.37	20.020*	<.001

*$p < .05$

Table 6. Scoring of pre and post treatment at (4-7 day) with 2% ketoconazole cream in infantile seborrheic dermatitis

	n = 48					
	Day 0		Day 4-7		*t*	*p*
	$\bar{X}$	SD	$\bar{X}$	SD		
Erythema	2.06	0.86	0.13	0.33	15.597*	<.001
Crust	1.69	0.82	0.58	0.65	12.511*	<.001
Scale	1.83	0.81	0.56	0.71	9.860*	<.001
Total	1.95	0.53	0.42	0.38	17.795*	<.001

*$p < .05$

Side effects of topical medication were found in 2 patients. One patient had marked xerosis with desquamation on the side that applied 2% ketoconazole cream on day 5. 2% Ketocanazole cream was discontinued and 1% hydrocortisone cream was used. Another patient had multiple folliculitis on the side that applied 1% hydrocortisone cream on day 3. Hydrocortisone was discontinued and treated with ketoconazole on both sides.

Discussion

Both topical corticosteriod and ketoconazole have been used to treat ISD [1,3,8]. There have been many studies about the role of *Malassezia furfur* and seborrheic dermatitis in infants [5-7] and adults [4]. Beside seborrheric dermatitis, *Malassezia* is found in many skin diseases such as psoriasis, atopic dermatitis, tinea versicolor and pityrosporum folliculitis [7,9]. Both oral [8, 12, 14-15] and topical antifungal [9, 11-13,16-18] agents have been used with clinical benefit in seborrheic dermatitis. Another drug that has been used to treat seborrheic dermatitis in adults is isotretinoin, which reduced the sebum production rate and, also benefited seborrheic dermatitis [19].

Topical ketoconazole not only has an antifungal activity but also has an anti-inflammatory effect [20, 21]. Blood level was undetectable even when used in large body surface area [8,16]. Faegermann studied the efficacy of 2% miconazole-1% hydrocortisone, 2% miconazole and 1% hydrocortisone is 91%, 68% and 70%, respectively. The number of cultured *Pityrosporon orbiculare* was significantly lower in all groups after treatment, but in the hydrocortisone group was still significantly higher than in the two other groups. In this study, the present used 2% ketoconazole cream on the left side and 1% hydrocortisone cream on the right side to avoid variation of clinical severity among the patients. The efficacy of ketoconazole and hydrocortisone were not significantly different in the treatment of ISD in the present study. If *Malassezia furfur* is the causative agent of ISD, hydrocortisone alone should not benefit ISD and isotretinoin, which has a reduced sebum production rate and should not benefit seborrheic dermatitis in adults. The genus *Malassezia* can now be divided into seven species [22]. Cell-mediated immunity to *Malassezia furfur* has been shown to be different in patients with seborrheic dermatitis and pityriasis versicolor [23]. *Malassezia* can induce cytokines production by keratinocytes [24,25]. Further studies are needed for more information about the role of *Malazzesia furfur* on ISD.

In conclusion, the efficacy of 2% ketoconazole cream and 1% hydrocortisone cream in the treatment of ISD were not significantly different. Ketoconazole is safe and effective in the treatment of ISD. It is another option for the treatment of ISD, to avoid the side effects of topical corticosteroid in long-term use on large surface areas of treatment.

References

1. Faergemann J, Jones TC, Hettler O, Loria Y. *Pityrosporum ovale* (*Malassezia furfur*) as the causative agents of seborrhoeic dermatitis: new treatment options. Br J Dermatol 1996; 134: S12-5.
2. Janniger CK. Infantile seborrheic dermatitis: An approach to cradle cap. Cutis 1993; 51: 233-5.
3. Rajka G. Infantile seborrheic dermatitis. In: Harper J, Orange A, Prose N, editor. Textbook of pediatric dermatology. Oxford. Black well Science 2000: 255-9.
4. Ljubojevic S, Skerlev M, Lipozencic J, Basta - Juzbasic A. The role of *Malassezia furfur* in dermatology. Clin Dermatol 2002; 20: 179-82.
5. Tollesson A, Frithz A, Stenlund K. *Malassezia furfur* in infantile seborrheic dermatitis. Pediatr Dermatol 1997; 14: 423-5.
6. Broberg A, Faergemann J. Infantile seborrheic dermatitis and *Pityrosporum ovale*. J Dermatol 1994; 21: 334-40.
7. Ruiz-Maldonado R, Lopez-Matinez R, Pezez Chavarria EP, Rocic Castanon LR, Tamayo L. Pityrosporum ovale in infantile seborrheic dermatitis. Pediatr Dermatol 1989; 6: 16-20.
8. Taieb A, Legrain V, Palmier C, Lejeans, Six M, Maleville J. Topical ketoconazole for infantile seborrhoeic dermatitis. Dermatologica 1990; 181: 26-32.
9. Brodell RT, Patel S, Venglarcik JS, Moses D, Gemmel D. The safety of ketoconazole shampoo for infantile seborrheic dermatitis. Pediatr Dermatol 1998; 15: 406-7.
10. Faergemann J. Seborrheic dermatitis and *Pityrosporum orbiculare*: treatment of the seborrheic dermatitis of the scalp with miconazone-hydrocortisone (Daktacort), miconazole and hydrocortisone. Br J Dermatol 1986; 114: 695-700.
11. Skinner RB, Noah PW, Taylor RM, Zanolli MD, West S, Guin JP, et al. Double-blind treatment of seborrheic dermatitis with 2% ketoconazole cream. J Am Acad Dermatol 1985; 2: 852-6.
12. Ford GP, Farr PM, Ive FA, Shuster S. The response of seborrheic dermatitis to ketoconazole. Br J Dermatol 1984; 111: 603-7.
13. Stratigos JD, Antoniou C, Katsambas A, Bohler K, Fritsch P, Schmolz A, et al. Ketoconazole 2% cream versus hydrocortisone 1% cream in the treatment of seborrheic dermatitis: a double-blind comparative study. J Am Acad Dermatol 1988; 19: 850-3.
14. Baysal V, Yildirim M, Ozcanli C, Ceyhan AM. Itraconazole in the treatment of seborrheic dermatitis:a new treatment modality. Int J Dermatol 2004; 43: 63-6.
15. Sei Y, Hamaguchi T, Ninomiya J, Nakabayashi A, Takiuchi I. Seborrheic dermatitis: Treatment with antimycotic agent. Br J Dermatol 1989; 120: 359-62.
16. Pierard-Franchimont C, Pierard GE, Arrese JE, De Doncker P. Effect of ketoconazole 1% and 2% shampoos on severe dandruff and seborrhoeic dermatitis: clinical, squamometric and mycological assessments. Dermatology 2001; 202: 171-6.

17. Ortonne JP, Lacour JP, Vitetta A, Le Fichoux Y. Comparative study of ketoconazole 2% foaming gel and betamethasone dipropionate 0.05 % lotion in the treatment of seborrhoeic dermatitis in adults. Dermatology 1992; 184: 275-80.
18. Pierard-Franchimont C, Pierard GE. A double-blind placebo-controlled study of ketoconazole and desonide gel combination in the treatment of facial seborrheic dermatitis. Dermatology 2002; 204: 344-7.
19. Orfanos CE, Zouboulis CC. Oral retinoids in the treatment of seborrhoea and acne. Dermatology 1998; 116: 140-7.
20. Van Cutsem J, Van Gerven F, Cauwenbergh G, Odds F, Janssen PA. The anti-inflammatory effect of ketoconazole: A comparative study with hydrocortisone acetate in a model using living and killed *Staphylococcus aureus* on the skin of guinea-pigs. J Am Acad Dermatol 1991; 25: 257-6.
21. Beetens JR, Loots W, Somers Y, Conene MC, De Clerck F. Ketoconazole inhibits the biosynthesis of leukotriens *in vitro* and *in vivo*. Biochem Pharmacol 1986; 35: 883-91.
22. Gupta AK, Kohli Y, Li A, Faergemann J, Summerbell RC. In vitro susceptibility of the seven *Malassezia* species to ketoconazole, voriconazole, itraconazole and terbinafine. Br J Dermatol 2000; 142: 758-65.
23. Bergbrant IM, Andersson B, Faergemann J. Cell-mediated immunity to *Malassezia furfur* in patients with seborrhoeic dermatitis and pityriasis versicolor. Clin Expl Dermatol 1999; 24: 402-06.
24. Faergemann J, Bergbrant IM, Dohse M, Scott A, Westgate G. Seborrhoeic dermatitis and *Pityrosporum (Malassezia)* folliculitis: characterization of inflammatory cells and mediators in the skin by immunohistochemistry. Br J Dermatol 2001; 144: 549-56.
25. Watanabe S, Kano R, Sato H, Nakammura Y, Hasegawa A. The effects of Malassezia yeasts on cytokine production by human keratinocytes. J Invest Dermatol 2001; 116: 769-73.

การศึกษาเปรียบเทียบการใช้คีโตโคนาโซลความเข้มข้นร้อยละ 2 กับไฮโดรคอร์ติโซลความเข้มข้นร้อยละ 1 ในทารกที่เป็น ซีบอริอิกเดอร์มาไตติส

ศิริวรรณ วนานุกูล, จุฑามาศ เชี้ยบุญคณา

วัตถุประสงค์ *: เพื่อเปรียบเทียบประสิทธิภาพของยา ketoconazole ครีมความเข้มข้นร้อยละ 2 กับยา hydrocortisone ครีมความเข้มข้นร้อยละ 1 ในการรักษา infantile seborrheic dermatitis (ISD) ในผู้ป่วยเด็กทารกอายุ 2 สัปดาห์ถึง 2 ปี ที่มารับการรักษาที่ฝ่ายกุมารเวชศาสตร์ โรงพยาบาลจุฬาลงกรณ์ ในช่วงเดือนธันวาคม 2544 ถึง พฤศจิกายน 2546*

วิธีการศึกษา *: ผู้ป่วยเด็กที่เป็น ISD จะได้รับการประเมินความรุนแรงของผื่น โดยดูจาก erythema, scale และ crust ตั้งแต่ก่อนการรักษา ในวันที่ 2-3 วัน ของการรักษาและ 4-7 วัน ของการรักษา เปรียบเทียบกันทั้ง 2 ข้าง โดยให้คะแนนความรุนแรงเป็นค่าตัวเลขในการเปรียบเทียบ คือ 0 หมายถึงไม่มีรอยโรค 1 หมายถึงรุนแรงน้อย 2 หมายถึงรุนแรงปานกลาง และ 3 หมายถึงรุนแรงมาก จากนั้นจะได้รับการรักษาด้วยการยาทา ketoconazole ครีมความเข้มข้นร้อยละ 2 ที่รอยโรคด้านซ้าย และยาทา hydrocortisone ครีมความเข้มข้นร้อยละ 1 ที่รอยโรคด้านขวา*

ผลการศึกษา *: พบว่าผลของการรักษา ISD ด้วยยา ketoconazole ครีมความเข้มข้นร้อยละ 2 กับยา hydrocortisone ครีมความเข้มข้นร้อยละ 1 ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติในวันที่ 2-3 และวันที่ 4-7 ของการรักษาและเมื่อรักษาครบ 1 สัปดาห์ พบว่ายาทาทั้ง 2 ชนิดทำให้รอยโรคดีขึ้นอย่างมีนัยสำคัญทางสถิติ โดยในข้างที่ทายา ketoconazole ดีขึ้นร้อยละ 31 และข้างที่ทายาhydrocortisone ดีขึ้นร้อยละ 35 และผื่นทั้งหมดหายภายใน 2 สัปดาห์*

สรุป *: ประสิทธิภาพของยาทา ketoconazole ครีมความเข้มข้นร้อยละ 2 และยาทา hydrocortisone ครีมความเข้มข้นร้อยละ 1 ไม่แตกต่างกันอย่างมีนัยสำคัญทางสถิติ ยาทา ketoconazole ซึ่งเป็นยาที่ปลอดภัยจึงเป็นอีกทางเลือกหนึ่งในการรักษา ISD แทนการทายา corticosteroid ซึ่งการทาในระยะยาวและพื้นที่บริเวณกว้างอาจมีผลข้างเคียง*