ยาขี้ผึ้ง Dithranol ในการรักษาโรคสะเก็ดเงิน Plaque Type : การเตรียมและการประเมิน
A Dithranol Ointment for Plaque – Type Psoriasis : Preparation and Evaluation

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บทคัดย่อ

ศึกษาการเตรียมยาขี้ผึ้ง dithranol (0.1-2%) ในยาพื้นชนิดล้างน้ำออกได้ ประเมินคุณภาพและความคงตัวของยาเตรียม และศึกษาผลเบื้องต้นทางคลินิกเทียบกับยาขี้ผึ้ง crude coal tar (3%) ในยาพื้นชนิดเดียวกันในผู้ป่วยโรคสะเก็ดเงินหรือเรื้อนกวางชนิด plaque type ผลการทดลองพบว่า ยาขี้ผึ้ง dithranol ที่พัฒนาขึ้นสามารถเตรียมได้ง่าย และคงตัว มีการแผ่กระจายน้อย ปรากฏคราบคงเหลือหลังจากล้างออกน้อย ผลการทดสอบโดย HPLC แสดงให้เห็นว่า salicylic acid ช่วยเพิ่มความคงตัวของยาขี้ผึ้ง dithranol และยังช่วยลดสะเก็ดที่ผิวของผู้ป่วยด้วย ยาขี้ผึ้งนี้ไม่ควรเก็บที่อุณหภูมิสูงกว่า 25°C ผลเบื้องต้นทางคลินิกในผู้ป่วยสะเก็ดเงินหรือเรื้อนกวางชนิด plaque type จำนวน 15 ราย แบ่งเป็น ได้รับยาขี้ผึ้ง dithranol แบบ short contact 9 ราย และได้รับยาขี้ผึ้ง crude cold tar โดยทาทิ้งไว้ 6 ราย พบว่าอัตราการหายซึ่งคำนวณจาก Psoriasis Area and Severity Index (PASI) ก่อนและหลังการรักษา ในผู้ป่วยที่ใช้ยาขี้ผึ้ง dithranol คิดเป็น 41.0% ในผู้ป่วยที่ใช้ยาขี้ผึ้ง crude coal tar 39.7% ในผู้ป่วยที่ได้รับยาขี้ผึ้ง dithranol พบอาการข้างเคียงที่ไม่อันตราย และความร่วมมือในการใช้ยาของผู้ป่วยอยู่ในเกณฑ์ดี

Abstract

Dithanol ointments (0.1-2%) in water washable base were prepared. The quality and stability were also evaluated. The good formulation was preliminary clinical studied in psoriasis patients (plaque type) compared with crude coal tar ointnent (3%). The preparation of dithranol ointment was simple and reasonable stable. The ointment was modified so as to reduce its spreading and residue after washing. The results by HPLC analysis indicated that the addition of salicylic acid was necessary for the stability of dithranol and might be able to improve plaque scaling. It also suggested the storage temperature not to exceed 25°C. The total number of patients completed the study was 15; 9 of these used dithranol ointment (short contact therapy) and 6 used crude coal tar ointment (long contact therapy). The average recovery estimated by the Psoriasis Area and Severity Index (PASI) scores assessed before and after the treatment of dithranol therapy was 41.0% whereas that of crude coal tar therapy was 39.7%. The effectiveness of dithranol ointment used was similar to the conventional therapy using crude coal tar ointment. The side effects were unharmful and did not cause non-compliance.

คำสำคัญ : ดิธทรานอล สะเก็ดเงิน (เรื้อนกวาง) ยาขี้ผึ้ง
Keywords : dithranol, psoriasis, ointment

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Introduction

Dithranol or anthralin has been used in the topical treatment of psoriasis since it was reported in 1878 (Ingram, 1953). It is a highly unstable substance that is oxidised in the presence of air, alkali, light and heat to danthrone, dianthrone and subsequently to dithranol brown (Fisher and Maibach, 1975). It was demonstrated that free radicals occurred during the oxidative degradation of dithranol are the cause of skin irritation when it is applied onto normal skin (Mustakallio et al., 1984). The free radicals play a vital role on the exertion of drug action (Martinmaa, Juselius and Mustskallio, 1981). Dithranol is effective and relatively non-toxic, although irritation or inflammation of normal skin and staining of clothes may substantially reduce patient compliance. Several regimens have been developed, including hospital-based ones such as those of Ingram (1953), and dithranol short contact therapy, which was proposed for out-patient use. The advantages of short contact therapy are, briefly, that it is as effective as traditional hospitalization modalities, less irritant and easier and more convenient for the patients, reducing resistance to the home use of dithranol. The short contact therapy of dithranol in psoriasis appears to be a promising and theoretically valid treatment since it was proposed (Naldi et al., 1992). A good preparation of dithranol could facilitate its therapeutic outcome as well as prevent its major side effects, irritation and staining. Various preparations of dithranol were investigated for use in short contact therapy, such as creams, pastes, ointments, and sticks. Ingram (1953) suggested the use of dithranol paste for short contact therapy so as to reduce irritation. The therapy requires a base that neither spreads to the normal skin adjacent to the treatment nor facilitate dithranol decomposition. A water washable base is thus preferential. Ponec-Walsch and Hulsebosch (1974) demonstrated an interaction between dithranol, salicylic acid and zinc oxide in pastes. The interaction resulted in a complex formation which affected the potency of dithranol. An ointment preparation could avoid such interaction yet required a modification to suit the short contact therapy. It was illustrated that a dithranol ointment could be stable up to 2 years if a good formulation was used (Lee, 1987).

This study was aimed at developing a dithranol ointment using a modified water-washable base for the use in a preliminary clinical trial by short contact therapy.

M.aterials and Methods

1. Chemicals

The chemicals used in this study were as follows: dithranol B.P. grade from S.Tong Chemical Co. Ltd., Bangkok; dithranol AR grade from Fluka Chemical Co.Ltd., Tokyo, Japan; danthrone AR grade from Fluka Chemical Co.Ltd., Tokyo, Japan; HPLC solvents, methanol, acetonitrile, chloroform, hexane, glacial acetic acid, from Famitalia Carlo Erba, Barcelona, Spain.

Ingredients for the ointment bases (cetomacrogol 1000, cetostearyl alcohol from S.Tong Chemical Co.Ltd., Bangkok); (salicylic acid, white soft paraffin, liquid paraffin from GPO, Bangkok); (ascorbic palmitate, propyl gallate from Fluka Chemical Co.Ltd., Tokyo, Japan).

2. Equipment

The equipment used consisted of UV spectrophotometer (Jasco 7800, Japan) and HPLC (Perkin Elmer pump series 410, UV detector series LC235 USA).

3. Preparation of Dithranol Ointment

The ointment base was modified from emulsifying ointment BPC (1979) as shown in Table 1.

The ingredients of the 'ointment base were melted, mixed, cooled and packed in collapsible tubes. The characteristics of the ointment bases tested were as follows:

Spreading test: An inch in length of each ointment base was taken from the collapsible tube onto a piece of clean surface glass. A movable bar, fixed gap between the glass and the bar, was used to move the ointment horizontally until the ointment was finished. The spreading of the ointment base, in comparison, was classified by the distance to which the base followed the bar.

Residue after washing: A known quantity of the ointment base was evenly spreaded onto a clean glass with a defined area. The glass was placed in shaken water bath (120 rpm, controlled temperature at 35°C). After 1 h, the area of the ointment residue was measured and weighed. The results were calculated as the percentage of average residue of the defined area.

Dithranol solution in chloroform was added and thoroughly mixed with the base, the strengths of dithranol ointment prepared were 0.1 - 3% w/w. Salicylic acid or ascorbyl palmitate was added as antioxidizing agent.

The quantitative analysis of dithranol was performed using high performance liquid chromatography (HPLC) developed and validated by Priprem (1991). The HPLC system was reverse phase, details being as follows: acetonitrile: glacial aceticacid: deionised water (12:1:7) as the mobile phase; flow rate of 1.5 ml/min ; UV detection at λ_{max} of 254 nm. Dithanol ointment was randomly sampled from the middle of the tube, dissolved and extracted for HPLC analysis.

4. Preliminary Clinical Trial of the Dithranol Ointment.

A randomized double-blinded clinical trial was carried out for the intervention of a conventional therapy using 3% crude coal tar ointment and short contact therapy by using the 0.1 - 1.5 % dithranol ointment. The base of the crude coal tar ointment was the same as that of the dithranol ointment. Dithranol therapy (Program D) started with 0.1% dithranol ointment for 7 days followed by stepping up to 0.5, 1, 1.5% every 7 days, while coal tar therapy (Program C) used the

same concentration throughout. The treatment program was 4 weeks.

Twenty-five psoriatic patients (plaque type), aged between 15-70, participated in this study. They were informed about the detail and the objectives of the experiment before signing the consent forms. The exclusion criteria included severe dithranol irritation, pregnancy, and using other therapy within 2 weeks prior to the study.

5. Evaluation

The clinical results, both before and after the treatment, were evaluated by the same person in order to minimize the personal variation. The outcome of the treatment was measured by using "Psoriasis Area and Severity Index" (P.A.S.I.) before and after the treatment program. The P.A.S.I. score was estimated as follows:

$$\text{P.A.S.I.} = 0.3A_{\text{trunk}}(E+P+S) + 0.2A_{\text{upper limb}}(E+P+S) + 0.4A_{\text{lower limb}}(E+P+S)$$

A = area of involvement

P = palpability (0-4 scale)

S = scaling (0-4 scale)

E = erythema (0-4 scale)

0.3, 0.2, 0.4 being the relative proportion of the body surface area on the trunk, upper limbs and lower limbs, respectively

The outcome of the result was evaluated in term of the percentage of recovery, monitored in each individual volunteer, using the calculation as follows:

% recovery = (P.A.S.I. at initial - P.A.S.I. at week 4) / P.A.S.I. at initial

The adverse side effects of dithranol and crude coal tar which were recorded consisted of irritation and staining using score ranging from 0, 1, 2, 3 to 4.

Each patient received counseling of the method of drug application and washing. The pharmacist provided other information such as the avoidance, recognition and management of adverse drug reactions at the time of counseling, patient compliance, etc. Patient compliance was evaluated by the weight of the ointment before and after use.

Results

The ointment bases, Formula A and B, were modified from emulsifying ointment BPC (1979) so as to improve the texture, such as viscosity and stiffness (Table 1). These were likely to affect the spreading and water washable properties of dithranol ointment. Table 2 demonstrates the physical evaluation of the ointment bases.

The results in Table 2 show that the ointment bases using formulae A and B spreaded less than that of BPC formula. Likewise, after washing with water, the residue of ointment base using formulae A and B were less than that of BPC formula. The desired ointment base should spread minimal and readily washed, therefore, formulae A and B were more appropriate for use in dithranol short contact therapy than that of BPC. After the incorporation of dithranol, the

spreading and the residue after washing were slightly altered. However, formulae A and B remained superior to that of BPC. It was then decided that the ointment base chosen for the study was formula A because of its less spreading and less percent residue after washing than formula B.

An antioxidant for use in the preparation of dithranol ointment was selected by HPLC analysis of the dithranol remaining in the ointment after storage, the results shown in Table 3. Addition of either salicylic acid or ascorbyl palmitate into dithranol ointment were studied in comparison with control (without an antioxidant). The ointments studied were duplicated from 2 different batches of production and stored at 25, 30, 40 and 50°C. The results demonstrated that the concentration of dithranol decreased with the increase in storage temperature. The addition of antioxidants could prevent dithranol degradation to some extent if the storage temperature was not exceeding 40°C. It suggests that antioxidant is needed for the dithranol ointment. From this study, salicylic acid and ascorbyl palmitate were not significantly different at 25-40°C. However, due to its keratolytic properties and effectiveness, salicylic acid was selected for use in the dithranol ointment.

The dithranol ointment was subjected to the physical tests as shown in Table 2. After dithranol and salicylic acid were introduced into the ointment, the preparations were less viscous than the corresponding bases. The pH of the ointment was approximately 4.

In the preliminary clinical study, the total number of volunteers participated was 25. As a result of the pre-determined system used to group the volunteers randomizedly, the volunteers in Program D or dithranol short contact therapy was 13 while those in Program C or crude coal tar therapy being 12. Among these, 21 completed the study programs and 4 drop-out cases, all of which involved Program C due to inconvenient traveling distance between the volunteers homes and the dermatological clinic.

Fig.1 shows the results of dithranol short contact therapy which was studied in 13 volunteers (male:female 9:4). The average age of the volunteers was 43.1 (± 14.5) years and the average time course of the disease was 8.5 (±7.3) years, the range of which being 1 to 28 years. Among the group of 13 volunteers participated in this study, volunteers who did not fully complete the 4-week program was no. 11, 12 and 13, who were assessed after 2, 2 and 1 week, respectively. The overall recovery rate of psoriasis in the group of 10 volunteers who completed the whole program of study was 41.04 (±15.62)%

Fig. 2 shows the results of crude coal tar therapy which was studied in 8 volunteers (male:female 6:2). The average age of the volunteers was 43.5 (±6.5) years and the average time course of the disease was 8.7 (±6.6) years, the range of which being 8 months to 20 years. Among these volunteers participated in this study, those who did not

fully complete the 4-week program was no. 7 and 8, both were assessed after 2 weeks. The overall recovery rate of psoriasis in the group of 6 volunteers who completed the whole program of study was 39.73 (± 23.56)%.

The results demonstrated that dithranol and crude coal tar were similarly effective for use in the treatment of plaque-type psoriasis. Dithranol short contact therapy was acceptable because the dithranol ointment did not give unpleasant odour as that found in crude coal tar products. The side effects of both therapy studied individually were reported in Table 4.

The major side effects of both therapy were irritation and staining which were observed after the volunteers completed the 4-week program of study, as shown in Table 4. The results showed an individual variations. One volunteer using dithranol short contact therapy and 3 of those using crude coal tar ointment did not experience the side effects. Most of the volunteers using dithranol therapy (8 in 9) suffered from staining. These side effects were temporary and unharmful. Thus, the use of both therapy was useful. The number of volunteers involved in the study might not be sufficient for statistical comparisons, however, this finding was useful. It could be an evidence which supported that the dithranol ointment did not cause irritation to all cases. Thus, the preparation developed is appropriate for use in dithranol short contact therapy.

Conclusion

A dithranol ointment was developed using a modified emulsifying ointment base. Salicylic acid was used as an antioxidant to improve dithranol stability. The dithranol ointment was used in a preliminary study in comparison with crude coal tar ointment. Both dithranol and crude coal tar used the same ointment base. Twenty-five volunteers participated in this study were plaque-type psoriatic patients who did not used any treatment before. Among these, 9 and 6 completed the 4-week program of study in dithranol short contact therapy (Program D) and crude coal tar therapy (Program C), respectively. The percent recovery rate of Program D was 41.04 and that of Program C being 39.73, suggesting a similar clinical outcome of dithranol and crude coal tar use in plaque-type psoriasis. With similar side effects found in both therapies, dithranol seemed to be more acceptable than crude coal tar because it did not cause unpleasant odour. It is concluded that the preparation of dithranol developed in this study was effective in the use of plaque-type psoriasis. The recovery and side effects were similar to crude coal tar therapy. Further investigation is required so as to prove statistically and also it is essential to demonstrate the recurrence of the disease with the use of dithranol and crude coal tar.

Acknowledgments

The authors would like to express our sincere gratitude to the Research Committee, Faculty of Medicine, Khon Kaen University, for the provision of financial support for the

study during 1993-1994. Dr. Wanchai Prakitritanon, Khon Kaen Hospital, was thanked for his clinical cooperation. Assoc. Prof. Sumitr Sutra's valuable comment and advice which enabled the research was also appreciated.

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ตารางที่ 1-3

Table 1. Compositions of ointment bases.

Ingredient	*Formula*		
	BPC	*A*	*B*
cetomacrogol 1000	60g	60g	60g
cetostearyl alcohol	240g	240g	240g
white soft paraffin	500g	600g	550g
liquid paraffin	200g	100g	150g

Table 2. Physical tests of ointment bases and 2% dithranol ointment

Physical test	*ointment bases*			*dithranol ointment*		
	BPC	*A*	*B*	*BPC*	*A*	*B*
spreading	+++	+	++	+++	+	++
% residue after washing	62	22	25	62	22	25

+,++,+++ indicating the degree of spreading, measuring in comparison from minimum, moderate to maximum spreading, respectively.

Table 3. Percentage of dithranol remaining in ointment after 21-day storage at 25,30,40 and 50°C

Dithranol strength (%w/w)	*Antioxidant* (%w/w)	*temperature*(°C)			
		25	30	40	50
0.1	none	100	100	72	65
	0.5% salicylic acid	100	100	100	100
	0.5% ascorbyl palmitate	100	100	94	78
0.5	none	100	84	82	81
	0.5% salicylic acid	100	97	94	90
	0.5% ascorbyl palmitate	100	93	88	81
1	none	100	86	82	72
	0.5% salicylic acid	100	98	86	NA
	0.5% ascorbyl palmitate	100	100	99	65
1.5	none	100	92	91	90
	0.5% salicylic acid	100	93	81	82
	0.5% ascorbyl palmitate	100	100	92	83

NA = not available

รูปที่ 1,2

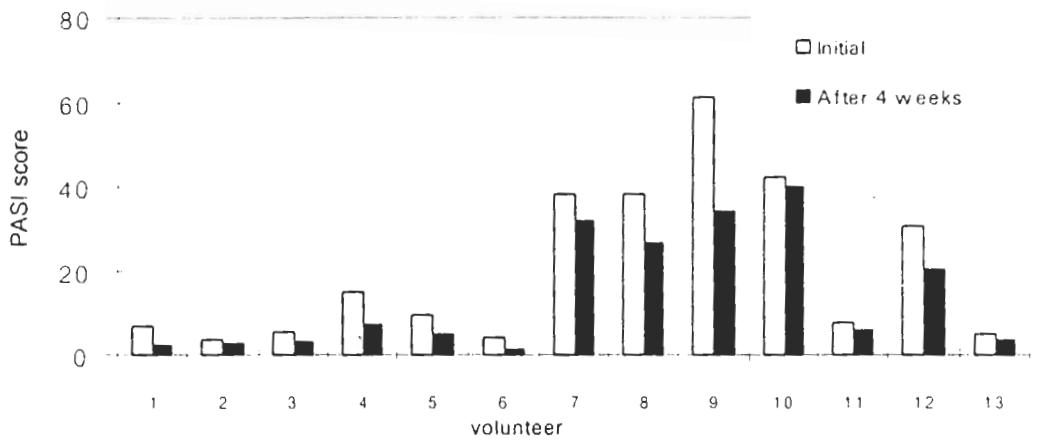

Figure 1. Dithranol short contact therapy

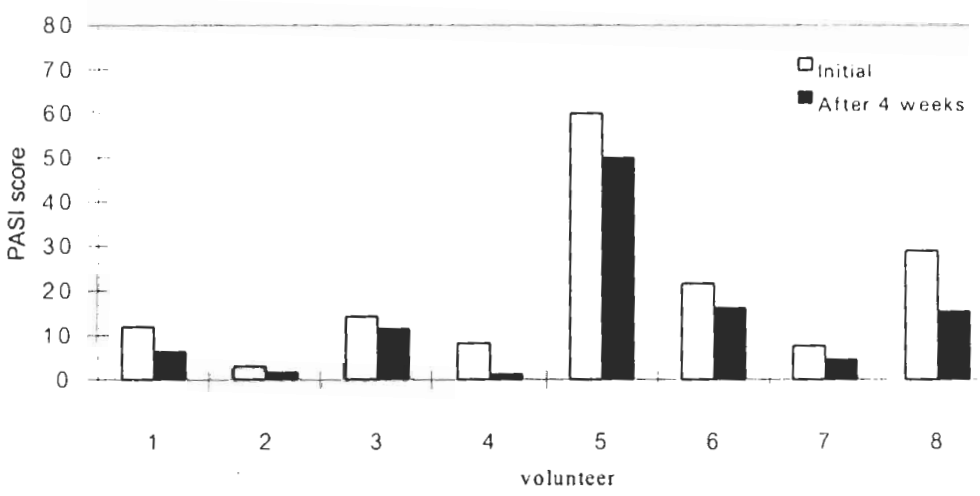

Figure 2. Crude coal tar therapy

Table 4 Adverse side effects of dithranol and crude coal tar therapy of volunteers after 4 weeks of study

volunteer	Dithranol		Crude coal tar	
no.	Irritation*	Staining*	Irritation *	Staining*
1	0	1	1	2
2	2	2	0	1
3	0	3	0	0
4	2	2	0	0
5	1	1	2	1
6	0	1	0	0
7	0	1	-	-
8	0	2	-	-
9	0	0	-	-

* 0,1,2,3,4 indicating the degree of irritation or staining, measuring in comparison from none, minimum, moderate to maximum, respectively.