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TOPICAL HYDROXYUREA AND PSORIASIS*

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ABSTRACT

Hydroxyurea, as a 10% cream, produces a significant involutionary effect on psoriatic plaques when used under continuous plastic film occlusion. When used with only partial occlusion, however, the effect is only slightly better than that of the base alone. Further studies with the use of metabolically active derivatives of hydroxyurea and/or different vehicles are warranted.

Hydroxyurea has aroused considerable interest because it is a chemotherapeutic agent of a new class. It inhibits DNA synthesis but not RNA or protein synthesis in cultured mammalian cells (1), bacteria (2), and regenerating rat liver (3). It inhibits the conversion of cytidylic acid to deoxycytidylic acid, and it irreversibly inhibits enzyme protein B2 of the ribonucleotide reductase system. Recent studies indicate that hydroxyurea inhibits DNA synthesis and growth of mouse embryonic and kidney cells. It also inhibits polyoma virus synthesis in these cells (4). It is active against a variety of experimental and human neoplasms including chronic myeloid leukemia (5). Leavell and Yarbro (6) have reported effective results with oral hydroxyurea in the treatment of psoriasis.

In view of the ability of hydroxyurea to inhibit DNA synthesis without interfering with protein synthesis, the possibility suggested itself that the topical application of this agent might be effective in suppressing the epidermal hyperplasia of psoriasis without producing cutaneous atrophy such as is sometimes seen following the prolonged use of topical steroid creams under occlusion.

MATERIALS AND METHODS

Hydroxyurea (HU) is water soluble and makes a colorless, odorless solution. It was incorporated in a water-washable cream, either Acid Mantle Cream (R) (Dome) or Unibase (R) (Parke-Davis). Preparations of the cream base alone and those containing HU could not be distinguished. In all instances, paired comparisons were made between the base containing HU and the same base alone. The study was conducted as a double-blind.

Treatment was restricted to well-defined plaques in patients with relatively stable psoriasis. In most instances, comparisons were made between symmetrically located lesions, although in a few cases the plaques were on the same side of the body in the same general area. A total of 45 paired lesions were treated in 19 adult patients (10 men and 9 women). Judgment as to the clinical response was based on direct observation and color photographs taken with Kodachrome II 35 mm film under standard conditions.

The efficacy of the HU creams was graded (see Table) on the basis of the *comparative* degree of improvement of the HU treated plaque in contrast to that of the lesion treated with the base alone. Thus, if the HU-treated lesion showed +3 (marked) degree of improvement and the base-treated lesion showed a +1 (mild) improvement in favor of the HU-treated lesion. The improvement in favor of the HU treated lesion. The evaluations were made at the end of the treatment period.

RESULTS

Initial screening trials were made with 5%–25% HU creams. The 5% strength proved ineffective in 6 patients when applied b.i.d. for 2 weeks using Saran wrap occlusion at night, and in one patient using continuous Saran occlusion for 2 weeks. The 25% strength caused irritation and superficial erosion in 3 patients using it b.i.d. with continuous Saran. Encouraging initial results were obtained with the 10% and 15% creams and these series were expanded. The results are summarized in the Table.

In combining the results of treatment with 10% HU cream under continuous occlusion for 1 to 2 weeks, 13 of 14 paired lesions treated with 10% HU showed more improvement than the base alone. This favorable comparison was statistically significant as determined by the sign test ($P < 1\%$).

In one man with symmetrical plaques on the dorsa of the feet, the lesions treated with 10% HU cream applied b.i.d. with continuous occlusion for 2 weeks remained completely involuted with hyperpigmentation for an additional 6 weeks despite the appearance of new plaques on the other foot treated with base alone.

Three patients were treated b.i.d. for 2 to 3 weeks with 10% HU in Unibase with the addition of 10% and 25% dimethylacetamide in an effort to improve the penetration of the HU. Saran occlusion was not used. There was no improvement in lesions treated with the HU-dimethylacetamide combinations as compared to those treated with Unibase alone.

Biopsy specimens were removed from 6 lesions treated with a preparation of hydroxyurea from 7 to 14 days, and from 6 control sites treated only with the vehicle. Four of the lesions had received

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TABLE

Differential improvement of HU treated site vs. base alone

HU cream	Application	Period Rx	Paired lesions	Improvement*					Side effects
				−1	0	+1	+2	+3	
5%	b.i.d., occlus. h.s.	2 wks	6	0	6	0	0	0	
5%	", contin. occlus.	2 wks	1	0	1	0	0	0	
10%	", occlus. h.s.	2–9 wks	9	0	5	3	1†	0	† local irritation
10%	", contin. occlus.	1 wk	11	0	1	4	6	0	+1 to +2 erythema in 2
10%	", contin. occlus.	2 wks	3	0	0	1	2	0	
15%	", occlus, h.s.	1–4 wks	10	1	7	0	2	0	
15%	", contin. occlus.	1 wk	2	1‡	0	0	1	0	‡ oozing dermatitis
25%	", contin. occlus.	1 wk	3	—	—	—	—	—	Rx in all stopped due to dermatitis.

* −1 slightly worse; 0 no difference; +1 slightly better; +2 moderately better; +3 markedly better.

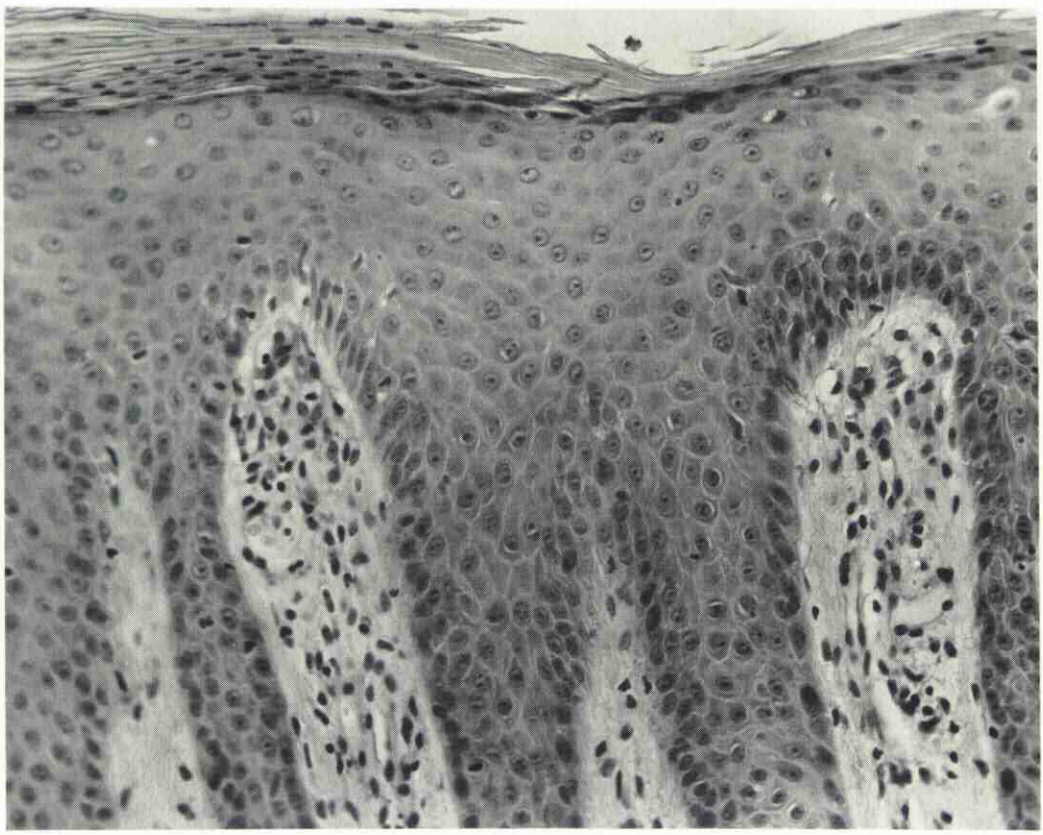

FIG. 1. Control lesion of psoriasis treated with Unibase (R) under continuous occlusion for 1 week, biopsied after 2 weeks. Parakeratosis is prominent and the stratum granulosum is practically absent. Hematoxylin-eosin; × 300.

10% HU under continuous occlusion. In two instances occlusion was maintained at night only; in one of these 15% HU was used. These lesions all showed some degree of clinical response. All were biopsied 2 weeks after the onset of treatment (Figs. 1, 2).

The histological changes were related more closely to the clinical response than to the character of the treatment.

The most pronounced change in a treated lesion was a reduction in epidermal thickness to less than half of that of the control, with complete return of a normal appearing granular layer and loss of parakeratosis, while the control still exhibited extensive parakeratosis and absence of keratohyalin granules. Other lesions showed only a mild reduction in epidermal thickness and incomplete return of normal keratinization.

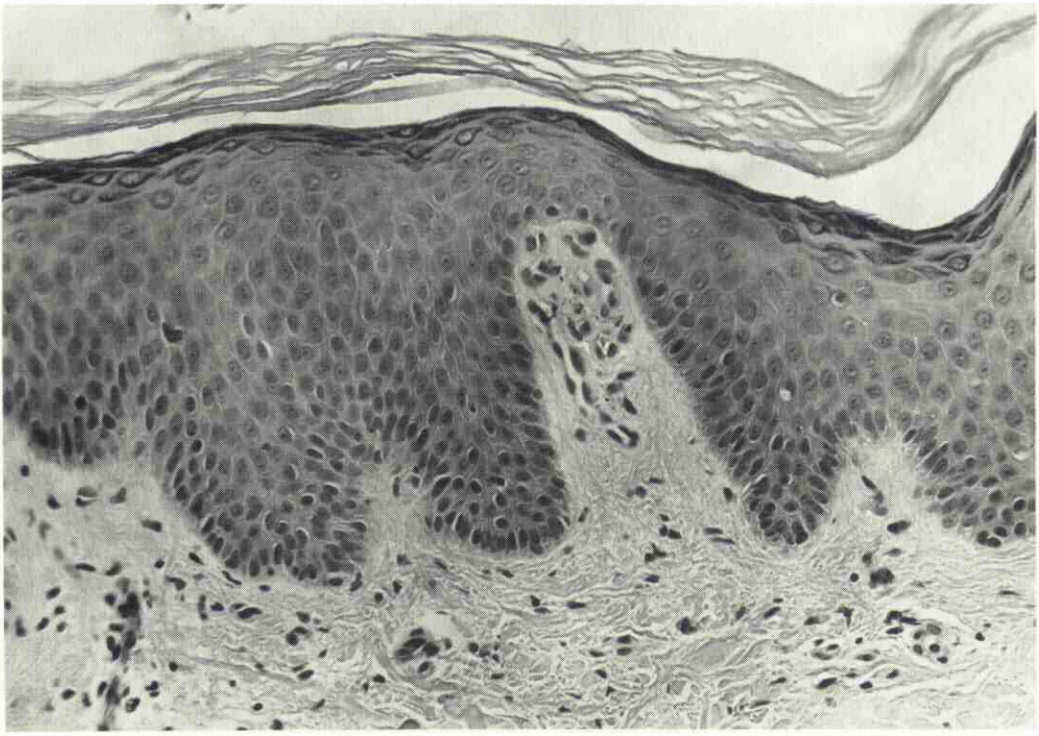

FIG. 2. Psoriatic plaque from the same case treated with 10% HU in Unibase (R) under continuous occlusion for 1 week, biopsied after 2 weeks. The epidermis is about half the thickness of the control, parakeratosis is absent and a stratum granulosum is well formed. Hematoxylin-eosin; × 300.

There was moderate to marked reduction in the number of epidermal mitotic figures as compared to the control specimens. There was mild basal epidermal edema in some instances, and an occasional epidermal cell in or near the basal layer was shrunken and contained a pyknotic nucleus. Otherwise the epidermis showed no distinct evidence of injury. Cellular infiltration in the dermis was comparable to that in the control specimens.

DISCUSSION

A good clinical response was obtained with the 10% HU cream, as compared to the base, when used under continuous occlusion. When used with occlusion at night only, however, the effect of the 10% and 15% HU creams was only slightly better than that of the base alone. Since continuous occlusion is impractical for most patients except those hospitalized, it appears that, at least with the present formulations, HU has limited value in the management of psoriasis. A favorable feature of the HU creams is that they are odorless, colorless, and do not stain.

This study evaluated the effect of HU preparations on isolated lesions only. An average of approximately 15 g of cream was used to treat one plaque for 2 weeks. Thus, with 10% HU, approximately 1.5 g of hydroxyurea, assuming complete absorption, would be absorbed over a 2-week period at a rate of approximately 100 mg daily. Leavell and Yarbro (6) found no depression of the white blood cell or platelet counts or of the hemoglobin level in patients taking 1.0 g of hydroxyurea daily for 4 weeks. We made no attempt to treat large surface areas. Since a 10% concentration was necessary to achieve a significant result, it is apparent that the treatment of large surface areas involves the hazard of absorption of considerable amounts of this drug.

An encouraging feature of this study is that only 2 of 11 patients using 10% HU cream under continuous occlusion for one week developed a local irritation.

Although the results with the HU formulations in this study are not sufficiently good to warrant the topical use of this substance in the practical management of most cases of psoriasis, they are nevertheless encouraging. It is possible that the use of metabolically active derivatives of HU and/or other vehicles may lead to a more striking effect.

The statistical evaluation was made by Byron Brown, Ph.D., Division of Biostatistics, Stanford University School of Medicine.

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