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Rapid Assay of the Anti-inflammatory Activity of Topical Corticosteroids by Inhibition of a UVA-induced Neutrophil Infiltration in Hairless Mouse Skin

II. Assessment of Name Brand versus Generic Potency

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The hairless mouse model of a UVA-induced dermal neutrophilic infiltrate was used to compare the efficacy of equal concentrations of name brand versus generic corticosteroids. The generic brand was significantly less effective in suppressing the inflammatory response.

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Within the last decade there has been over a five-fold increase in the United States in the number of generic products reaching the market (1). With regard to corticosteroids, serious questions have been posed about the equivalence of generic products in comparison to the name brand (1–3). A number of studies have put the question to test using the human vasoconstriction assay (4–6). In two studies (5, 6) the generic betamethasone dipropionate was found to be less potent than the name brand. A similar discrepancy was found with betamethasone valerate preparations (6). Interestingly, Stoughton (4) found no difference between three concentrations (0.025, 0.1, 0.5) of Kenalog® cream (triamcinolone acetonide), but the lowest concentration was still more potent than the generic cream at 0.1%.

After we developed the UVA-neutrophil assay for the anti-inflammatory efficacy of corticosteroids (7), we were interested in using the model to address the generic question. We included, within a series of different potency corticosteroids, two concentrations of desoximetasone (Topicort®, 0.05 and 0.25% emollient cream) and a generic brand (Taro, 0.05 and 0.25%). As in other published reports, we found a significant reduction in potency in the generic product.

MATERIALS AND METHODS

The UVA source, irradiation parameters and quantification of neutrophils are described in the accompanying paper (7). In this study there were some differences in methodology. Briefly, the Skh-hairless-1 (albino) mice were obtained from Charles River Laboratories (Wilmington, MA, USA) and there were 5 animals per treatment group.

To prevent undue discomfort to the mice, irradiation was confined to a 2×2 cm square of the dorsal trunk which was outlined with opaque tape. The remainder of the dorsal surface was treated with a broad spectrum (sun protection factor 15) sunscreen. Because exposure time was 200 min, mice were anesthetized with an intraperitoneal injection of 100 µl of a 1:9 dilution of γ-hydroxybutyric acid lactone (Sigma Chemical Co., St. Louis, MO).

In order to better approximate human use of corticosteroids, treatment schedule in this study was longer than that used in the development of the assay (7). Steroid treatment was once daily for 7 days. Irradiation was on the 8th day. The results of neutrophil quantification were analysed by a paired *t*-test at the 95% confidence level.

RESULTS

All steroid-treated animals had significantly less neutrophil infiltration than the UVA controls (Figs. 1 and 2). Additionally, the higher potency steroids reduced the neutrophil count to a significantly greater degree than those of lower potency (Fig. 1).

A comparison of the higher concentration (0.25%) generic desoximetasone to the name brand (Fig. 2) showed the latter to be significantly more potent in reducing the neutrophil count ($p = 0.004$). The difference between the two brands at 0.05% was not significant, but there was a trend for the name brand to be more potent than the generic. However, the lower concentration name brand steroid (0.05%) was marginally significantly more potent than the high concentration (0.25%) generic ($p < 0.05$). The name brand, at the two concentra-

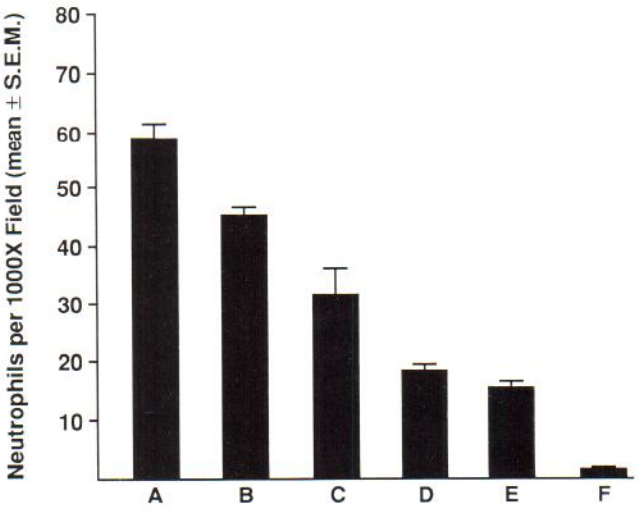

Fig. 1. Comparative potency of various steroids: average number of neutrophils per 1000X field ± S.E.M.
Key *A*: UVA only. *B*. hydrocortisone (Hytone 1% cream). *C*. triamcinolone acetonide (Aristocort A 0.1% cream). *D*. fluocinonide acetonide (Lidex 0.05% cream). *E*. clobetasol-17-propionate (Termovate 0.05% cream). *F*. unirradiated control.
Statistical analysis: paired *t*-test at 95% confidence level.
All steroids significantly different from UVA only: $p < 0.01$ to 0.0001. *B* vs *C*: $p = 0.03$. *B* vs *D*: $p = 0.0003$. *B* vs *E*: $p = 0.0001$. *C* vs *D*: $p = 0.04$. *C* vs *E*: $p = 0.02$. *D* vs *E*: N.S. *E* vs *F*: $p < 0.0001$.

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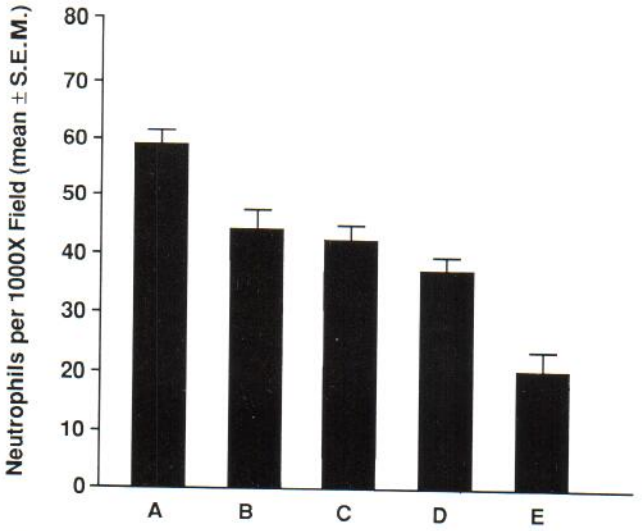

Fig. 2. Comparison of name brand and generic steroids: average number of neutrophils per 1000X field ± S.E.M. *A*. UVA only. *B*. generic desoximetasone (0.05%). *C*. generic desoximetasone (0.25%). *D*. name brand desoximetasone (0.05%). *E*. name brand desoximetasone (0.25%).
Statistical analysis: paired *t*-test at 95% confidence level.
All steroids significantly different from UVA only: $p < 0.04$–0.001.
B vs *C*: NS. *B* vs *D*: NS. *B* vs *E*: $p = 0.008$. *C* vs *D*: $p = 0.05$. *C* vs *E*: $p = 0.004$. *D* vs *E*: $p = 0.002$.

tions, showed a clear-cut dose response ($p = 0.0017$), whereas the two concentrations of the generic were not different from each other.

DISCUSSION

Despite some methodologic changes from the original assay (7), the two approaches produced comparable results, supporting the validity of the model. As an example, in the original assay, hydrocortisone cream was tested at 0.5% and 2.5%, yielding neutrophil counts of 68 and 33, respectively. In this assay, hydrocortisone cream tested at 1% resulted in an intermediate count of 45.

The UVA-induced dermal neutrophil infiltration assay for corticosteroid potency has added to the evidence that generic brands can be less efficacious in suppressing inflammation than equal concentrations of name brand corticosteroids. The clinical implications with regard to the two brands tested in this study are identical to those expressed by others (4, 6, 8, 9). It is agreed that generic substitutions for name brand corticosteroids are not acceptable unless proof is provided for their equivalence in potency assays as well as in clinical applications.

REFERENCES

1. Stoughton RB. Are generic topical glucocorticosteroids equivalent to the brand name? J Am Acad Dermatol 1988: 18: 138–139.
2. Jackson DB, Thompson C; McCormack JR, Guin JD. Bioequivalence (bioavailability) of generic topical corticosteroids. J Am Acad Dermatol 1989; 20: 791–796.
3. Shah VP, Peck CC, Skelly JP. Vasoconstriction – skin blanching-assay for glucocorticoids-a critique. Arch Dermatol 1989; 125: 1558–1561.
4. Stoughton RB. Are generic formulations equivalent to trade name topical glucocorticoids? Arch Dermatol 1987; 123: 1312–1314.
5. Sequira J, Berardi M, Chan T-M, Letarte J, Malchow R, Pramanick B, et al. Assessing equivalence of innovator and generic formulations of betamethasone dipropionate cream and ointment. Clin Therapeut 1991; 13: 687–694.
6. Olsen EA. A double-blind controlled comparison of generic and trade-name topical steroids using the vasoconstriction assay. Arch Dermatol 1991; 127: 197–201.
7. Woodbury RA, Kligman LH, Woodbury MJ, Kligman AM. Rapid assay of the anti-inflammatory activity of topical corticosteroids by inhibition of a UVA-induced neutrophil infiltration in hairless mouse skin. I. The assay and its sensitivity. Acta Derm Venereol (Stockh) 1994; 74: 15–17.
8. Burdick KH. Extemporaneous vs commercial formulations of steroids for topical usage. J Am Med Assoc 1970; 211: 462–466.
9. Lamy PP. Generic equivalents: issues and concerns. J Clin Pharmacol 1986; 26: 309–316.