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Release of Betamethasone 17-Valerate from Extemporaneous Dilutions of a Proprietary Topical Cream

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Abstract. Six different vehicles for topical use were used to prepare 50% dilutions of Betnovate® (betamethasone 17-valerate, 0.1%) cream. Blanching assessment was undertaken immediately after preparing the various dilutions and at 1 and 3 months thereafter. Few statistically significant differences were noted between any of the preparations tested indicating that the rate of release of betamethasone 17-valerate is relatively unaffected by dilution. All preparations were assayed by a stability indicating high pressure liquid chromatographic technique for corticosteroid content. A diminution in the content of betamethasone 17-valerate in the E45 dilution was found 14 months after preparation. All other formulations tested were found to comply with label claim specifications.

The effect of vehicle composition on the release of corticosteroids from various topical formulations has been well documented [4, 8–10]. These observations have resulted in the expenditure of considerable time, effort and money by pharmaceutical manufacturers in an attempt to produce suitable bases for optimum release characteristics.

Depending upon the physico-chemical properties of a particular corticosteroid molecule, bases are thus tailored to produce a formulation displaying the desired release characteristics for that specific steroid. The sophisticated nature of these bases imply that any changes in concentration or components of the base may affect the rate of release of the corticosteroid from the final preparation. It would therefore appear that extemporaneous dilution of proprietary topical corticosteroid formulations could result in a disturbance of the equilibrium of base components necessary for optimum release of active ingredient. In addition it has recently been reported [11] that betamethasone

17-valerate in extemporaneously diluted semi-solid bases decomposes to the 21-valerate when subjected to accelerated storage testing. For these reasons, manufacturers contend that interference with well researched products by dilution may result in a reduction in clinical efficacy [2, 7]. In addition to possible effects of dilution on the release of corticosteroids from topical preparations, bacteria may be introduced into the formulation during preparation. This factor may result in instability of the final product.

The present study was undertaken to evaluate the effect of dilution on the release of betamethasone 17-valerate from a diluted proprietary cream formulation. Several different diluting media were utilized and the release of betamethasone 17-valerate was monitored using the human blanching assay. Since this assay was first described [6], it has undergone many modifications resulting in a precise, reproducible and quantitative method for the *in vivo* evaluation of topical corticosteroid formulations [1].

Materials and Methods

A commercially available brand of betamethasone 17-valerate (0.1%) cream (Betnovate®) was purchased from a local pharmacy. A survey of local prescribing habits was conducted to establish the most commonly diluted corticosteroid preparations, the various diluting media used and the degree of dilution occurring with the highest incidence.

The various bases used to dilute the corticosteroid cream were: aqueous cream BP, buffered cream BPC, Emulsifying ointment BP, E45 cream (Boots), Ultrabase (Schering) and the base used in the manufacture of Betnovate cream. All these diluents were obtained from local distributors with the exception of buffered cream BPC which was freshly prepared prior to use. All dilutions contained 50% Betnovate cream.

Each dilution was assessed 1 day after preparation and then after 1 month and again 3 months later. Finally, since the E45 dilution was found to contain approximately 50% less betamethasone 17-valerate than expected on re-assay 14 months after preparation, a further *in vivo* assessment was performed. All bases used as diluents were also assessed for blanching activity. Negligible responses were observed.

All the preparations were assayed by a high pressure liquid chromatographic technique [5] 6 months after the initial trials and then re-assayed 8 months later.

Several trials were mounted in order to evaluate the effects of the various bases on the blanching activity of betamethasone 17-valerate. The preparations were arbitrarily divided into two separate batches. Each batch was tested during a single 28-hour period on a trial group consisting of 10 healthy male and female caucasian volunteers, none of whom had received topical or systemic corticosteroid therapy for at least 4 weeks prior to each trial. Where possible, the same volunteers used for a particular dilution were used again to evaluate the same preparation at the various intervals described above.

The blanching assay and mode of application, evaluation and statistical analysis of results were carried out as previously described [3]. Both forearms of each volunteer were

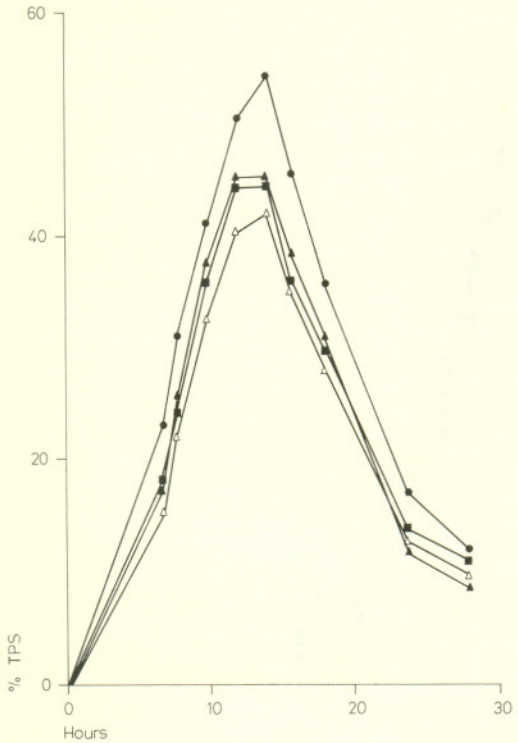

Fig. 1. Percentage of the total possible score (% TPS) as a function of time for various freshly prepared 50% dilutions – occluded test. ● = Betnovate cream; ▲ = Betnovate/Betnovate base; ■ = Betnovate/aqueous cream; △ = Betnovate/ultrabase.

occluded using a non-porous plastic film (Blenderm) for 6 h. The blanching responses were evaluated at 7, 8, 10, 12, 14, 16, 18, 24 and 28 h after application. No readings were taken after 28 h since after this time it becomes difficult to differentiate between actual blanching and variation in skin condition and colour. Consequently all area under the curve (AUC) values do not reflect total blanching to infinite time; i.e., zero response.

Results and Discussion

The results obtained on the freshly prepared dilutions and Betnovate (0.1%) cream are shown in figures 1 and 2. Results of χ^2 analysis on the blanching profiles depicted in figure 1 show statistically significant differences between all the 50% preparations and Betnovate cream in favour of the latter.

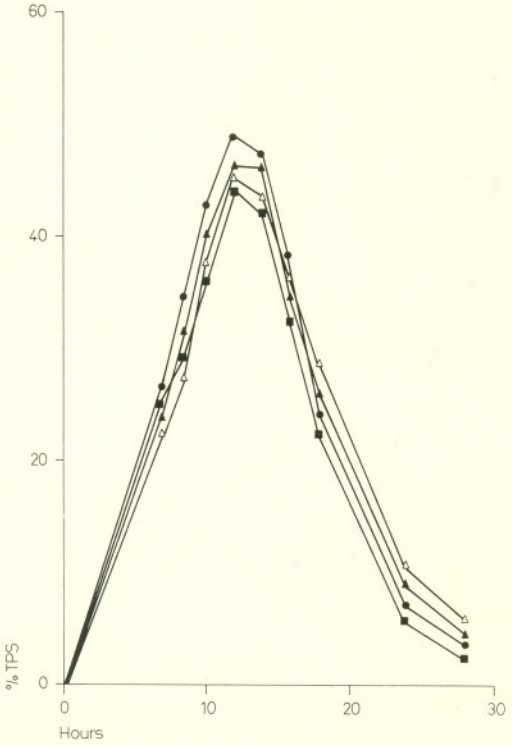

Fig. 2. Percentage of the total possible score (% TPS) as a function of time for various freshly prepared 50% dilutions – occluded test. ● = Betnovate cream; ▲ = Betnovate/buffered cream; △ = Betnovate/emulsifying ointment; ■ = Betnovate/E45 cream.

Similar analysis of the results depicted in figure 2 show no statistically significant differences between any of these formulations.

The results of all the trials are shown in table Ia, b. In order to make intercomparisons between the results of each trial, Betnovate cream (0.1%) was included as a control in all trials. The mean value of the areas under the blanching curves of all the Betnovate controls was 692.5 (range 763.8–639.5) with a standard deviation of 36.8 (5.3% of mean value). These data are in agreement with those of *Barry and Woodford* [1] who have shown that under controlled conditions the vasoconstrictor test is sensitive, accurate and reproducible.

Table I. The blanching response expressed as area under the curve (AUC) values

Preparation		Time, months			
		0	1	3	14
a	B	763.8	686.6	680.4	
	B/A	628.9	708.6	685.9	
	B/Bb	621.8	619.1	594.2	
	B/U	585.2	672.2	688.1	
b	B	639.5	686.5	694.2	696.3
	B/E45	594.1	630.2	657.4	584.1
	B/Bc	625.2	582.9	723.4	
	B/E	623.4	587.8	570.4	

B = Betnovate; A = aqueous cream; Bb = Betnovate base; U = ultrabase; E45 = E45 cream; Bc = buffered cream; E = emulsifying ointment.

The results indicate that, from the biopharmaceutical point of view, dilution of the proprietary cream is not as detrimental as has been emphasized [2, 7]. In spite of the 50% reduction in corticosteroid concentration which theoretically should result in a relative reduction in the degree of blanching observed, the blanching responses produced by the various dilutions remained similar to the undiluted control. Profiles of all the remaining trials were essentially similar to those depicted in figures 1 and 2. Only the AUC values have therefore been reported.

After a storage period of 1 month, all the preparations were re-assessed. χ^2 analysis of these data showed very few statistically significant differences between the various dilutions and Betnovate cream. Similar results were observed after a 3-months storage period (table I).

High pressure liquid chromatographic analysis of all the formulations 6 months after the initial trial showed that the amount of betamethasone 17-valerate present conformed to label claim specifications. However, when the formulations were re-assayed 14 months after the initial trial, all were once again within specifications except for the dilution with E45 cream. This dilution was found to contain approximately 50% less betamethasone 17-valerate than expected. The HPLC method of analysis used is stability indicating and the betamethasone 21-valerate component found was also

quantitated (theoretical: betamethasone 17-valerate, 0.05%; found: betamethasone 17-valerate 0.026%, betamethasone 21-valerate 0.024%) [5]. Consequently, a further trial was undertaken to compare the blanching profile of Betnovate cream with the E45 dilution 14 months after preparation. The AUC value of 584.1 is surprisingly high considering that the E45 dilution contains approximately only a quarter of the amount of betamethasone 17-valerate present in Betnovate cream. It would thus appear that the relatively high AUC result obtained may reflect the blanching contribution from the 21-isomer.

In a recent publication, *Yip and Po* [11] have described the instability of several different extemporaneous dilutions of betamethasone 17-valerate ointment at elevated temperatures. In most of the dilutions it was found that there was an extremely rapid decomposition of the active ingredient; e.g., when betamethasone 17-valerate ointment (0.1%) was mixed 1:1 with emulsifying ointment, the time for 50% decomposition of the 17-valerate was 40 min at 22.5 °C. This is in marked contrast to the results obtained during our investigations performed under ambient temperature conditions (approximately 25 °C).

Conclusion

The above results show that should dilutions of Betnovate cream (0.1%) be indicated, any of the several diluting bases utilized in this study may be employed without a significant reduction in the degree of release of betamethasone 17-valerate from the particular dilution for a minimum of 6 months. This is very different from the results of *Yip and Po* [11] who investigated the stability of betamethasone 17-valerate dilutions in ointment bases. However, whilst the diluted preparations studied appeared relatively stable, the possibility of microbial contamination of extemporaneously prepared dilutions and the subsequent deleterious effects on long-term stability should not be discounted.

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