



# Comparative bioavailability of some locally manufactured betamethasone valerate containing preparations

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**Abstract.** *The bioavailabilities of three locally manufactured proprietary betamethasone-17-valerate containing creams and ointments were compared by measuring their abilities to cause blanching of human skin after topical application. The preparations studied were Betnovate Cream and Ointment, Celestoderm-V Cream and Ointment and Persivate Cream and Ointment. Celestoderm-V cream displayed a significantly superior blanching activity over both Betnovate and Persivate creams in the occluded mode, whereas Persivate cream displayed a significantly superior blanching activity over both Betnovate and Celestoderm-V creams in the unoccluded mode.*

*Persivate ointment was found to produce a significantly superior blanching activity over Betnovate and Celestoderm-V ointments in both the occluded and unoccluded modes of application.*

The McKenzie and Stoughton blanching assay has been extensively used as a reliable method of assessing the rate of release of corticosteroids from topically applied formulations (1). It is a well documented and generally accepted fact that there is a direct relationship between the blanching activity of a topically applied corticosteroid and its clinical efficacy (2).

Several variables have been found to affect the blanching response of a topically applied corticosteroid preparation. Occlusion of the sites of application by a plastic covering has been found to cause a marked increase in blanching due to an increased ease of percutaneous penetration of the corticosteroid after hydration of the stratum corneum (3). This simple method of increasing percutaneous absorption is used successfully in therapy today for unresponsive dermatoses (4).

The different types of pharmaceutical vehicles have also been found to affect the degree of blanching caused by corticosteroids after topical application (5). When ointments and creams containing the same steroid in equal concentrations were compared by means of a modified McKenzie and Stoughton blanching assay, the ointment was found to give a significantly greater blanching response than the cream, especially in the unoccluded mode (6). This increase in the intensity of blanching is presumably due to the occlusive nature of the vehicle. A further observation has been that the release of a steroid from the same type of vehicle can differ, depending on the formulation (7). Two locally manufactured proprietary fluocinolone acetonide containing creams were found to produce significantly different blanching responses (8). This is most likely due to the solubility of the steroid in the base, a factor that would alter the partition coefficient of the steroid be-

tween the vehicle and the skin (9). The base effects of lotions have been found to be less significant than those of creams and ointments (10).

In this study, two trials were mounted, the first to compare the release of betamethasone-17-valerate from three locally manufactured proprietary creams and the second to compare the release of betamethasone-17-valerate from three locally manufactured proprietary ointments. All the preparations contained 0,1 % of the steroid. The preparations used were Betnovate cream and ointment (Glaxo (Pty) Ltd), Celestoderm-V cream and ointment (Scherag (Pty) Ltd) and Persivate cream and ointment (Lennon Ltd).

## Materials and methods

The creams and ointments were purchased shortly before the trials from a local pharmacy.

The method of experimentation was similar for both trials. Twelve healthy Caucasian volunteers were selected for each trial from a panel known to show a response to topically applied corticosteroids. No reference was made to steroid sensitivity or sex. The volunteers had not received topical or systemic corticosteroids for at least six weeks prior to the investigation.

The preparations were applied to the flexor aspect of the forearm in four different arrangements, each application pattern being chosen randomly to avoid any bias during application and observation. Four stripes of the preparations (equivalent to approximately 3,2 mg (11)) were applied to twelve 7 mm square sites on each forearm of the volunteers in a double-blind fashion by means of 1 ml syringes, the needles of which had been cut to about 5 mm in order to facilitate extrusion of the preparations. The first gram of cream or ointment of each tube was discarded and the syringes were filled immediately prior to use so as to minimize any possible interaction between the corticosteroid and the plastic

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matrix of the syringe barrel. The preparations were evenly spread over the application sites by means of a glass rod.

Both trials were performed in both the occluded and unoccluded modes. In the occluded mode the sites were covered with a non-porous plastic covering (Blenderm surgical tape) and the unoccluded sites were protected by cardboard coverings cut in such a way so as to allow a free flow of air and held in place by Micropore surgical tape.

The measurement of the degree of blanching and the statistical analyses were performed as previously reported (10) with the addition of a reading at 32 hours after application in both trials and an additional reading at 52 hours after application in the trial on ointments. The blanching response of topical corticosteroid ointments is generally observable for a longer time due to the increased intensity of blanching.

All the preparations were assayed by means of an HPLC technique similar to that described by Coleman (12).

## Results and discussion

The HPLC analyses performed indicated that the concentration of corticosteroid in all the preparations studied were within the limits as specified in the U.S.P. (13).

Figures 1 - 4 are the blanching profiles obtained using the percentage of the total possible score (% TPS) and the time in hours after application.

Celestoderm-V cream in the occluded mode was found to have a larger area under the curve (AUC) than Persivate cream which in turn had a larger AUC than Betnovate cream. In the comparison of adjacent sites Celestoderm-V cream showed a significantly higher

degree of blanching than both Persivate and Betnovate creams, with Persivate cream showing a significantly higher degree of blanching than Betnovate cream. The graded response analyses indicated that the degree of blanching elicited by Celestoderm-V cream was significantly superior to that of Betnovate cream. Similar blanching responses were found in this analysis for Celestoderm-V and Persivate creams. Celestoderm-V cream, however, exhibited a superior blanching response over Persivate cream at the peak times of 14, 16 and 18 hours after application. No significant difference was found between Betnovate and Persivate creams. In the unoccluded mode Persivate cream exhibited a significantly superior blanching response in all the methods of analyses than both Betnovate and Celestoderm-V creams. There were no significant differences found between Betnovate and Celestoderm-V creams in this mode.

Persivate ointment exhibited a larger AUC and was found to elicit a statistically significant superior blanching response than both Betnovate and Celestoderm-V ointments in all the methods of statistical analysis in both the occluded and unoccluded modes of application. No significant differences were observed between the blanching abilities of Betnovate and Celestoderm-V ointments.

## Conclusion

The main conclusions that can be drawn from this study are that:

1. Betamethasone-17-valerate is released more effectively from Persivate cream and ointment than from Betnovate cream and ointment in both modes of application.

Figure 1 Blanching profiles of creams in the occluded mode.

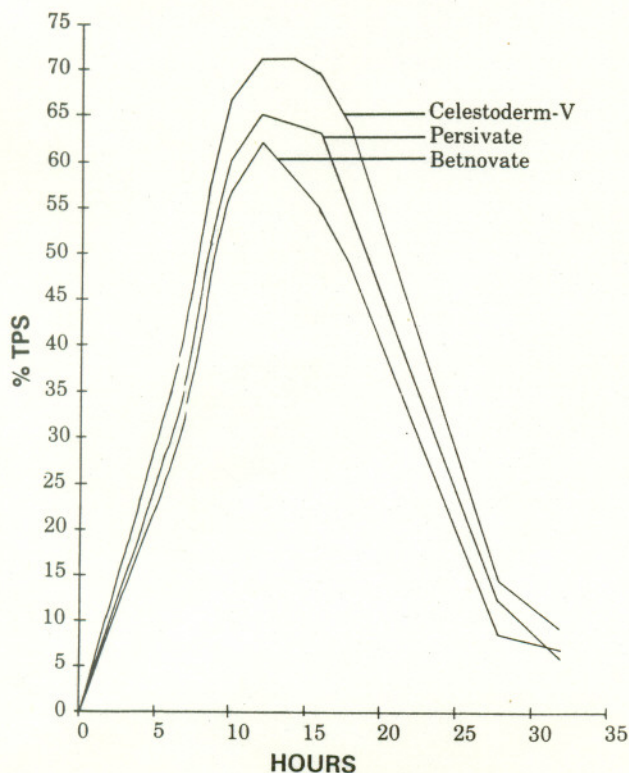


Figure 2 Blanching profiles of creams in the unoccluded mode.

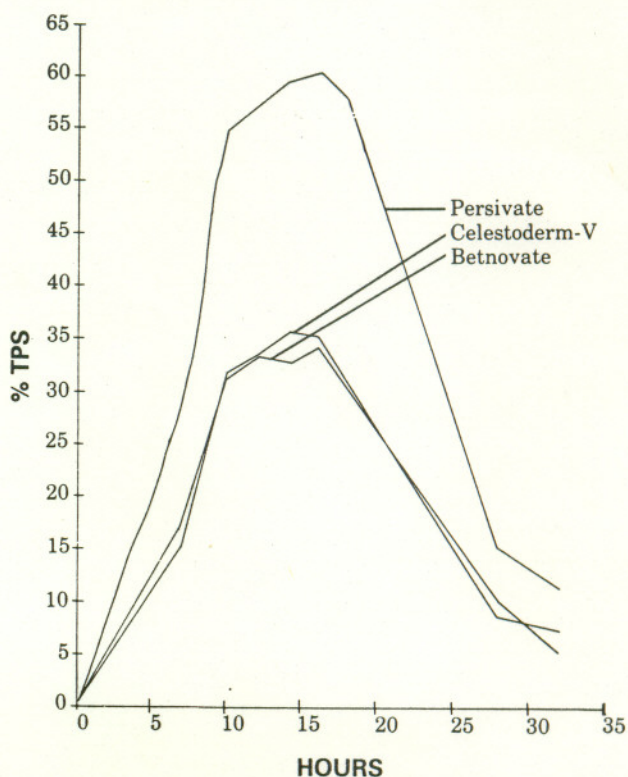


Figure 3 Blanching profiles of ointments in the occluded mode.

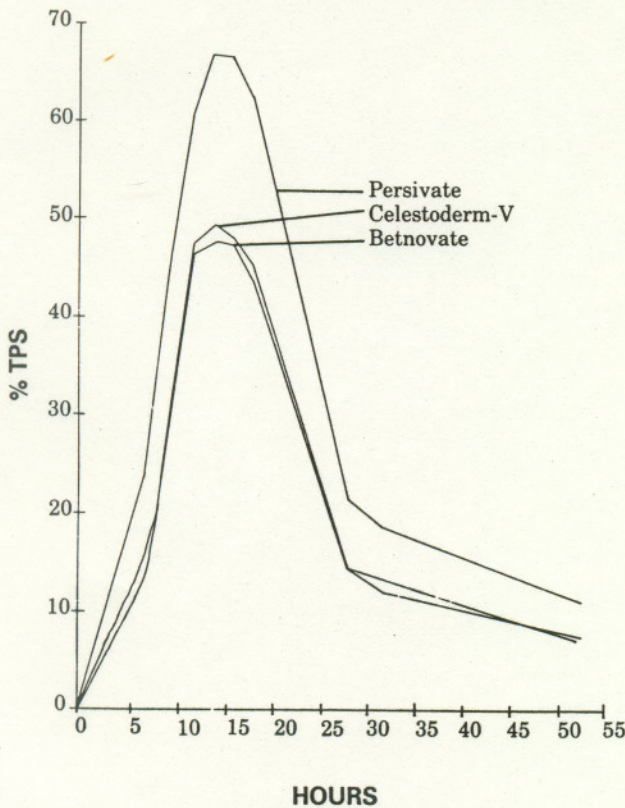
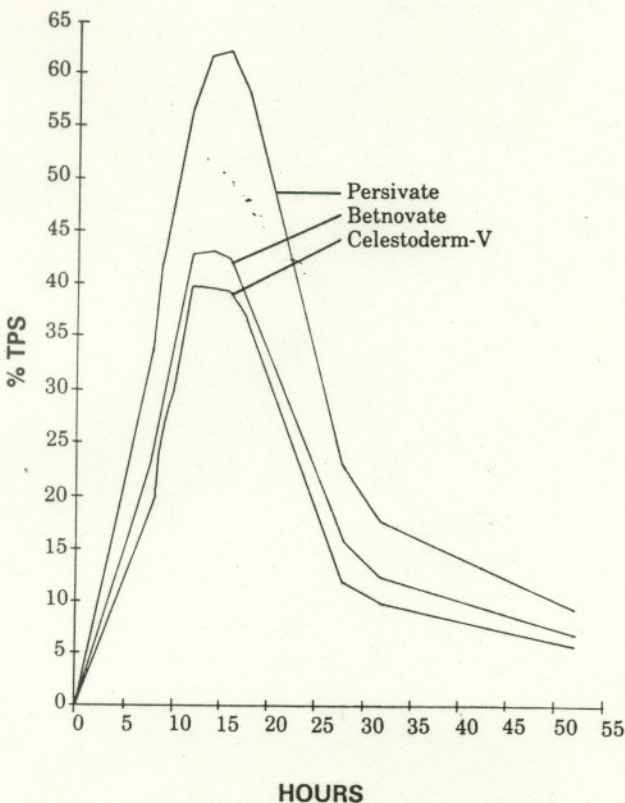


Figure 4 Blanching profiles of ointments in the unoccluded mode.



- The bioavailability of the steroid from Celestoderm-V cream is superior to both Betnovate and Persivate creams in the occluded mode, but equivalent to Betnovate cream in the unoccluded mode.
- There is no statistically significant difference in the release of the steroid from Betnovate ointment and Celestoderm-V ointment in either mode of application.

The trials therefore served to reinforce the findings that the formulation of a topical vehicle can have a significant effect on the bioavailability of corticosteroids, which could influence the clinical efficacy of the product.

It was further observed that the mode of application (occluded or unoccluded) can alter the comparative bioavailability of a steroid from topical formulations.

### Acknowledgements

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