Assessing Penetration Enhancers for Topical Corticosteroids

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I. INTRODUCTION

Topical corticosteroids have been used for a wide range of dermatological conditions for the last 4 decades. For many years the topical delivery system was a relatively simple cream or ointment base, with little thought given to improving the formulation as far as drug delivery was concerned. The main emphasis in the initial stages of development was on the alteration of the corticosteroid molecule, in an attempt to produce moieties with a higher intrinsic topical effect with lower mineralocorticoid side effects. Once this avenue of research was exhausted, attention was placed on the lipophilicity of the molecule with the production of various types of esters in an attempt to produce molecules which would pass through the stratum corneum (SC) with reasonable ease.

In recent years the nature of the semisolid drug delivery base has received considerable attention. The nature of the vehicle has a profound effect on the rate of release of the topical corticosteroid from the formulation and its passage through the SC. One of the most important aspects of the formulation of the base is the inclusion of substances which aid this trans-SC diffusion, the so-called penetration enhancers. The modes of action of the various different types of penetration enhancers are reviewed elsewhere in this book.

The best method for the assessment of the release of corticosteroids from topical formulations is obviously the clinical trial. Clinical trials, however, are laborious, costly, and difficult to mount. Patients suffering from dermatological complaints are not ideal subjects for the testing of topical corticosteroid formulations as it is difficult to obtain standardized lesions which are necessary for the comparison of results between formulations. Alternatively, a number of in vitro models exist for this type of assessment, but it is often problematic to obtain correlation with the in vivo situation.

Of all the in vivo methods available for the assessment of topical corticosteroid formulations, the human skin blanching assay is one of the most reliable. The production of blanching in human skin is a side effect of topical corticosteroid
application and was first observed in 1950. In 1962 it was postulated that this blanching might be utilized as a measure of the percutaneous absorption of corticosteroids from topical formulations. The test has been improved considerably over the years and it now provides a reliable and precise method for the assessment of the release of topical corticosteroids from their delivery formulations. For many years this test was (and sometimes still is) referred to as the vasoconstriction test. The exact mechanism of induced blanching has not been fully elucidated, and because the measurement performed during the test is the estimation of the degree of blanching produced, we believe that the best terminology for this test is the human skin blanching assay.

A number of publications questioned the validity of the human skin blanching assay. While it must be appreciated that this assay procedure is highly subjective, this problem can be minimized by utilizing large numbers of application sites for the same formulation, a group of volunteers numbering no less than 12, and visual assessments of blanching made by at least two, and preferably three, observers. However, we do not believe that this is the reason for recent criticism of this technique. Some researchers have made their comments based on the apparent nonequivalence of some generic products. This seems to us to be nonsense. It is hardly scientific to question the technique because it produces unexpected results! In our opinion one of the main problems with regard to the use of the human skin blanching assay is that many researchers still attempt to make comparisons between formulations based on a single reading of topical corticosteroid-induced blanching. For several years we have advocated the use of multiple readings over a period of time (normally on the order of 36 h) after application of the steroid. In this way time-response curves can be generated which produce much more meaningful results.

A number of instrumental (mainly reflectance) methods for the objective determination of corticosteroid-induced blanching have been available for many years. Several years ago we advanced the opinion that these were cumbersome, expensive, and time consuming, and that no real advantages over the visual method of determination had been demonstrated by their use. These methods have been the subject of debate in the recent literature, many researchers again insisting that the instrumental methods are superior even though they have themselves demonstrated that the instrumental results obtained agree closely with those obtained by visual determinations. The superiority was defined on the basis of producing absolute numbers by the instrumental method and numerical gradings by visual assessments. It is of interest to us that antagonists of the use of visually scored data in the human skin blanching assay reported recently that the human observer method is unlikely to be replaced by a spectrophotometric assessment method in the near future. We previously mentioned that instrumental techniques that measure one aspect of the blanching phenomenon do not seem to have the same reproducibility and discriminating potential as that of the human eye, which assimilates the global appearance of the skin at the application site and surrounding tissue. We have documented exceptional reproducibility using visual data which, to our knowledge, has not been paralleled using instrumental techniques.

Because the human skin blanching assay can be used to assess the release of topical corticosteroids from semisolid bases, it stands to reason that it can also be
useful in the assessment of the efficacy of penetration enhancers. A number of publications give details of the optimized methodology for this assay procedure.\textsuperscript{11,12} Provided the protocol of this method is strictly adhered to by experienced workers, the assay has been shown to be sensitive, accurate, and reproducible.\textsuperscript{10} Some of the advantages of using this assay procedure are that healthy normal skin is used, it is not painful to the volunteers and several preparations can be compared simultaneously. Another great advantage of the use of the human skin blanching assay is that it has been conclusively proven that the degree of observed corticosteroid-induced blanching in normal human skin is directly proportional to the clinical efficacy of the formulation.\textsuperscript{20}

II. \textit{IN VIVO ASSESSMENT OF TOPICAL CORTICOSTEROID FORMULATIONS}

We were involved recently in the efficacy assessment of the excipients urea, resorcinol, oleic acid, and propylene glycol in an extemporaneous oil-in-water cream delivery system containing 0.12% betamethasone 17-valerate, in order to ascertain whether, in this particular delivery system, they act as penetration enhancers. All four of the compounds mentioned above were investigated previously and found to act as penetration enhancers for various topical corticosteroids in a number of different semisolid formulations, but their effects on the release of betamethasone 17-valerate from an oil-in-water cream base were not previously reported. The corticosteroid-induced blanching produced by the formulations was measured over 32 h using the human skin blanching assay and the scores were plotted as a function of the percentage of the total possible score (%TPS) vs. time. The blanching assessment experiments were all conducted in the unoccluded mode only. Occlusion causes hydration of the SC, thus aiding the passage of the corticosteroid through the SC (discussed elsewhere in this book). The occluded mode would therefore tend to mask any effects that the other compounds may have on the rate and extent of the release of betamethasone 17-valerate from the formulation. The unoccluded mode is also the most commonly utilized therapeutic application procedure. All the formulations were assayed by high-performance liquid chromatography\textsuperscript{21} and found to contain the equivalent concentrations of betamethasone 17-valerate.

As can be seen from Figures 1 and 2, it is quite clear that only propylene glycol acts as a penetration enhancer for betamethasone 17-valerate from this particular formulation. Oleic acid, resorcinol and urea all reduce the amount of betamethasone 17-valerate penetrating the SC. Therefore, the formulations containing these excipients would be expected to be less efficacious than the formulations containing propylene glycol or that containing no penetration enhancer. The three excipients that do not act as penetration enhancers for betamethasone 17-valerate in this particular formulation clearly cause a reduction in the partitioning potential of the steroid from the semisolid base. Thus, less drug will be released from the delivery system to the SC. Propylene glycol, which does act as a penetration enhancer in this particular system is thought to act by perturbing the multilamellar bilayers of the SC intracellular lipids which consist mainly of cholesterol, ceramides, and free fatty acids.
III. CONCLUSIONS

Of interest is the fact that some compounds act as penetration enhancers in certain systems with particular corticosteroids and not in others. We have preliminary results showing that resorcinol acts as a penetration enhancer with betamethasone 17-valerate in a different semisolid cream base. It is obvious, therefore, that generalizations cannot be made with respect to which enhancer will be the most useful for a particular steroid in a particular formulation. Each individual system is required to be assessed for topical availability, preferably utilizing a reliable in vivo method.

From the above results it can be seen that the human skin blanching assay is a particularly useful method for assessing the effects of possible penetration enhancers in identical topical formulations containing the same concentration of a particular corticosteroid. While the foregoing discussion is concerned primarily with the assessment of the effect of penetration enhancers on the topical availability of corticosteroids from semisolid formulations it is clear that the arguments will apply to any molecule designed for release from a topical formulation to the SC.
REFERENCES


