BIOEQUIVALENCE TESTING OF TOPICAL DERMATOLOGICAL FORMULATIONS, THE GAP BETWEEN SCIENCE AND LEGISLATION

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Introduction

Bioavailability concerns for topical dermatological products are complex and it is especially difficult to determine the bioequivalence of similar topical formulations. Since only small amounts of drug dispersed in an appropriate vehicle are applied to the skin, the amount of drug that actually reaches the systemic circulation is often too small to be easily quantified. Additionally, it can be argued that the relevance of any serum/plasma concentration-time curve of a topical agent is questionable, since the curve reflects the amount of drug after the active moiety has left the site of action. For some topical drugs e.g., topical corticosteroids, it is possible to perform a pharmacodynamic bioassay to obtain acceptable bioequivalence data. In this case, the intensity of the side effect of blanching (vasoconstriction) in the skin caused by topical corticosteroids can be measured. The response is directly proportional to the clinical efficacy [3, 7] and the skin blanching assay has proved to be a reliable procedure for the determination of topical corticosteroid bioavailability.

Recently, we had sight of the results of a topical bioequivalence study, which was conducted for the registration of a new generic corticosteroid cream formulation. In this trial the new formulation was compared to two equivalent products from the local market and bioequivalence was demonstrated by the investigators for all three products. These results were examined with interest as the respective reference products have been used repeatedly as standard formulations in our laboratory. However, one of these reference formulations has consistently shown superior bioavailability in our trials, but was not demonstrated to be superior in the study results examined. In the present publication an overview of topical bioequivalence testing in general is given and the difficulties occurring in practice, for topical corticosteroid formulations in particular, are demonstrated.

Methods

(1) A bioequivalence study with the new corticosteroid generic formulation and the same two references (innovator and one other generic cream formulation) was repeated according to our standard protocol [5, 6]. The application was performed in the unoccluded mode and the induced skin blanching was estimated at 7, 8, 9, 10, 12, 13, 14, 15, 16, 18, 26, 28 and 32 hours after product application. The blanching results were scored visually by three independent observers and the results were calculated as a percentage of the total possible score (%TPS) at each observation time.

(2) The legislation of different countries was studied to find sections concerning the determination of bioequivalence of topical dermatologic generic products on which the results of this study could be assessed.

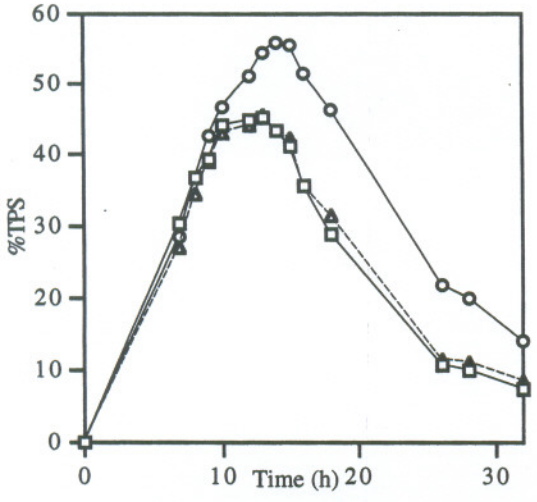
Results

(1) Figure 1 depicts the blanching profiles for the new generic, registered generic and the innovator cream formulations. Whereas in the examined trial for registration purpose identical blanching profile-curves were obtained for all three products, in this investigation the reference generic product showed a superior blanching response and therefore an increased bioavailability. This would suggest that our standardised methodology is more discriminatory in demonstrating the subtle pharmacodynamic differences between similar formulations than that of the registration study. Hence it follows that in this particular case, the pharmacodynamic responses were determined by the protocol of the registration study and are not a true reflection of the performance of the formulations.

(2) *European Union:* According to a specific guideline [8], either for generic and reformulated products equivalence has to be shown with regard to efficay and safety. In order to demonstrate therapeutic equivalence clinical trials are in principle necessary, but other validated models (e.g. skin blanching assay) may be used if their relevance is justified. Moreover, safety and local tolerance have to be addressed appropriately. *South Africa*: South Africa does not have any form of legislation regarding topical bioequivalence assessment. Registration requirements are based on the judgement of the

evaluators of the Medicines Control Council at the time of submission. *Switzerland*: There are no regulations specifically for topicals. A bioavailability study (in vivo or in vitro) *and* investigation of clinical efficacy/therapeutic equivalence are required [1]. *USA*: In the absence of measurable concentrations of drug/metabolite in an accessible biological fluid, the FDA may rely on in vivo and in vitro methods to assess bioequivalence which are pharmacodynamic effect studies, clinical trials, in vivo animal studies and in vitro studies (descending order of preference). Historically, only in vivo pharmacodynamic or clinical studies have been relied on. In 1995, a guidance document providing recommendations on methods to document in vivo bioequivalence of topical dermatologic corticosteroids in particular was released [2].

Fig. 1: %TPS vs time for the new generic formulation (triangle), and the reference products: innovator (square) and registered generic (circles) formulations.



Discussion

Since there are no standard procedures for bioequivalence assessment outside the USA, the outcome of a clinical trial is likely to be influenced to a large extent by the study protocol and by the interpretation of the results on the part of the investigators and regulators. In the case of topical corticosteroid bioavailability determination, factors such as time, amount and manner of application (occluded vs. non-occluded), number of assessment times and method of response estimation will influence the outcome of clinical studies. These variables can easily be used to manipulate the outcome of a bioequivalence study to some extent. While the methodology of the Human Skin Blanching Assay has been optimised, there is still insufficient knowledge of the clinical relevance of the results obtained from the assay [4]. It is therefore difficult to rationally assess the therapeutic significance of trials that may demonstrate a 20-30% difference (for example) in the pharmacodynamic blanching effect of similar formulations. Therefore, in the European Union [8] said limits have to be set individually in respect of the therapeutic compound and the investigated parameters.

The availability of in vivo or in vitro bioequivalence studies *and* investigations of clinical efficacy/ therapeutic equivalency in general are useful means of determining the bioequivalence of topical products. Recently, the US-FDA released a guidance document [2] providing recommendations on methods to determine the in vivo bioequivalence of topical corticosteroids. The proposed advantage of this guidance is that it provides a standard procedure to assess bioavailability so that comparable results are obtained from all clinical trials. The drawbacks of the recommended procedure are the laborious experimental design and the fact that differences in bioavailability detected by the assay are not a priori related to relevant clinical differences [4]. Furthermore, without the establishment of internationally-accepted regulations for assigning topical bioequivalence, the latter will remain in the subjective assessment realm of the regulator once presented with a dossier of trial data.

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