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Research paper

Pharmacokinetic analysis of the FDA guidance for industry – 'Topical dermatologic corticosteroids: in vivo bioequivalence'

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Dedicated to Prof. Dr. Dr.h.c. Bernd W. Müller on the occasion of his 60th birthday.

Abstract

The FDA (Food and Drug Administration) Guidance for Industry 'Topical Dermatologic Corticosteroids: In vivo Bioequivalence' describes two methods for evaluation of cutaneously applied corticosteroid formulations by measurement of the skin blanching response with a chromameter. The experimental options are: staggered application with synchronized removal or synchronized application with staggered removal. From the resulting response vs. time profiles, the areas under the effect curves (AUECs) are calculated and plotted as a function of the exposure time period to obtain dose/response-like relationships. If these experimental procedures are analyzed pharmacokinetically applying the Bateman equation and Fick's First Law of diffusion, several critical factors may be determined that need to be considered in order to avoid misinterpretation of the data. If solution-type preparations are investigated, the applied formulation volume should be the same on all application sites. In the case of suspension-type preparations, the applied drug dose is not critical. Moreover, it is essential to guarantee zero order kinetics during the application time periods, which may only be achieved with suspension-type preparations or a sufficiently high volume of solution-type preparations. If all these critical factors are taken care of, bioavailability factors (solutions) and enhancement factors (suspensions) may be calculated as the quotient of the AUECs of test and reference formulations.

Keywords: FDA; Corticosteroids; Skin blanching; Pharmacokinetics; Bioavailability; Bioequivalence

1. Introduction

With the exception of topical corticosteroids, the only means a US generic company has to demonstrate bioequivalence of a topical dermatologic product to an innovator's product is through comparative clinical trials with a bioequivalence endpoint [1]. In the case of topical corticosteroids however, the demonstration of bioequivalence of two physically alike formulations may be done using a vasoconstriction protocol, as outlined in the FDA Guidance for Industry 'Topical Dermatologic Corticosteroids: In vivo Bioequivalence' [2]. The use of the vasoconstriction response caused by cutaneously applied corticosteroid products as a measure of percutaneous absorption was first published by McKenzie and Stoughton [3]. Since 1962, many studies have been performed to verify and optimize this bioassay method [4–15]. Techniques that are reliable and reproducible have been developed either by taking advantage of reflectance spectrophotometers to measure the skin color or by simple visual assessment of the skin blanching response [5,14,16]. The FDA Guidance attempts to standardize the technique so that any assessment of bioequivalence of topical corticosteroids will be precise and accurate if the specified methodology is strictly adhered to [13]. Specifications in the FDA Guidance require a dose/vasoconstriction response estimation by the use of a Minolta chromameter in a preliminary pilot study to determine the parameters for use in a pivotal bioequivalence study [2]. In the preliminary pilot study two methods for the quantification of the skin blanching response are described. These methods are based on the application of the products for various time periods (dose durations) up to 6 h. After product removal the skin blanching response is measured with a chromameter over 24–28 h. From the resulting response vs. time profiles, the areas under the effect curves (AUECs) are calculated and plotted as a function of the exposure time period to obtain dose/response-like relationships. The dose is expressed in terms of the duration of

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exposure of the skin to the test formulation. From these dose/response-like relationships the maximum AUEC ($=E_{max}$) and the dose durations for the pivotal study (ED_{50}, $0.5ED_{50}$, $2ED_{50}$) are determined.

The manner in which the pilot study is performed and analyzed is critical since the protocol for the pivotal study depends entirely on the results of the pilot study. Therefore, the objective of this study was the pharmacokinetic analysis of the Guidance protocols to clarify the question whether drug penetration kinetics have a significant impact on the dose/response-like relationships obtained with the two pilot study protocols. The determination of the bioavailability with response parameters such as the latency time until onset of a pharmacodynamic response, the duration of the response, the maximum response and the slope of the response vs. time curve has been shown to depend on the type of formulation applied and thus drug penetration kinetics [17–20]. With solution-type formulations first order penetration kinetics and thus drug depletion may be observed while suspension-type formulations lead to the maximum drug flux and zero order penetration kinetics as long as there is undissolved drug present in the formulation, which acts as a reservoir [21–23].

2. Theoretical development

The experimental protocols recommended for the Guidance pilot study were analyzed pharmacokinetically based on a one-compartment model, the receptor compartment representing the central compartment. The two options for the cutaneous application of corticosteroid ointments according to the Guidance are: (1) staggered application with synchronized removal and (2) synchronized application with staggered removal (Fig. 1). In both cases the skin is exposed to the formulation for different time periods and the blanching response is measured at fixed time points after product removal [2].

Simulation of response vs. time and AUEC vs. exposure time curves was performed under the assumption that the pharmacodynamic response corresponds to the drug concentration in the receptor compartment. Therefore, the unit for the blanching response used in this study is μg/ml.

The first step of the pharmacokinetic analysis was the simulation of the drug concentration vs. time profiles in the receptor compartment after drug application. These profiles were simulated with the Bateman equation assuming a drug availability of 100%

$$C = \frac{D_0}{V_D}\frac{k_p}{k_p - k_e}\left(e^{-k_e t} - e^{-k_p t}\right), \quad (1)$$

C is the drug concentration at the receptor site, D_0 the drug dose, V_D the distribution volume at the receptor site, k_p the penetration rate constant, k_e the elimination rate constant, and t is the time.

The drug dose D_0, the distribution volume V_D and the elimination rate constant k_e were kept constant (10 mg, 10 ml and 0.2 h^{-1}, respectively). The first order penetration rate constant k_p derived from Fick's First Law of diffusion is defined as follows

$$k_p = D_B A PC_{B/V}/(d_B V_V), \quad (2)$$

D_B is the diffusion coefficient of the drug in the barrier stratum corneum, A the application area, $PC_{B/V}$ the stratum corneum/vehicle partition coefficient of the drug, d_B the thickness of the stratum corneum, and V_V is the volume of the applied preparation.

The ratio V_V/A represents the thickness h of the ointment layer.

Calculations were done with the two penetration rate constants 0.05 h^{-1} (reference formulation) and 0.5 h^{-1} (test formulation) and different penetration kinetics (first order,

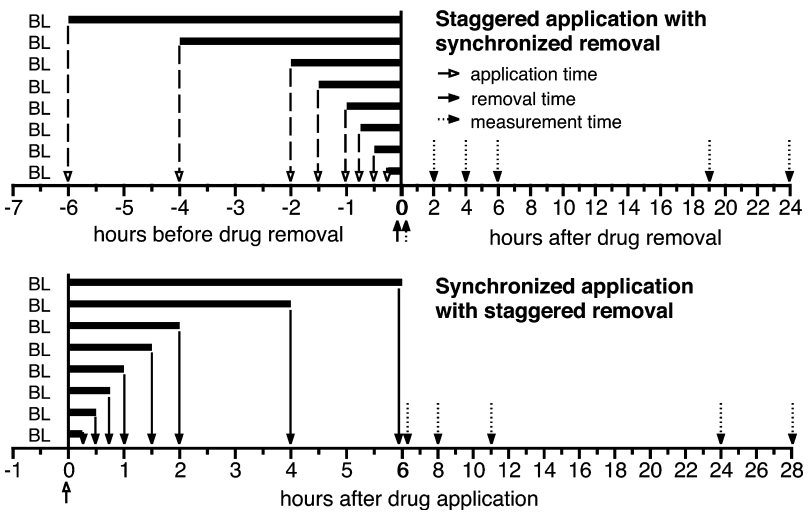

Fig. 1. Pilot study protocols according to the FDA Guidance (BL, baseline value).

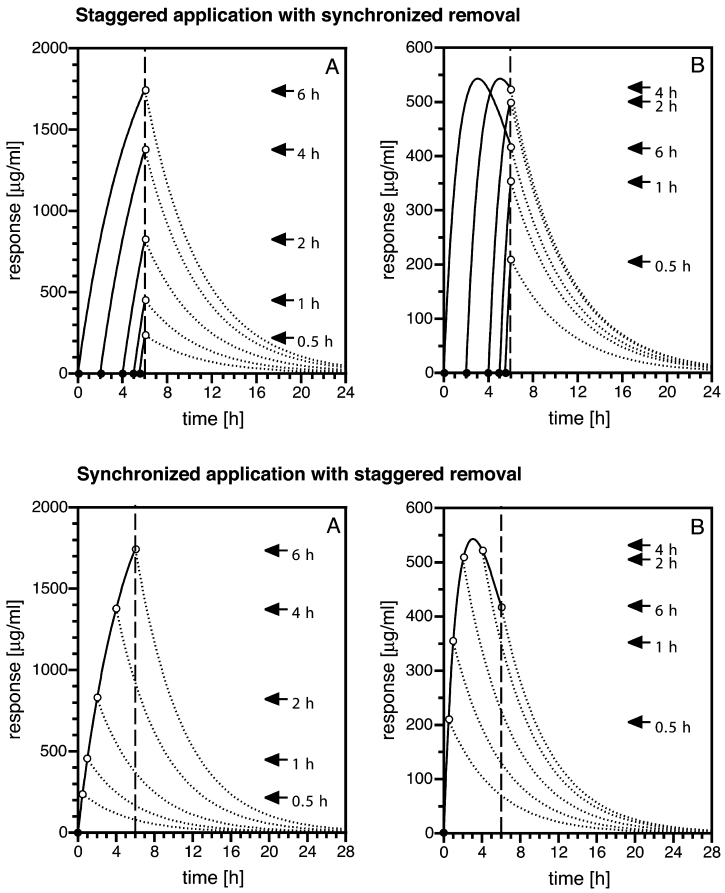

Fig. 2. Simulated response vs. time profiles with time points of drug application (•), drug removal (○) and the measurement time periods starting with the dashed vertical line; $k_p = 0.5\ h^{-1}$. Exposure time periods: 0.5, 1, 2, 4, 6 h; (A) zero order kinetics; (B) first order kinetics.

zero order). The two penetration rate constants were chosen to cover the wide range of constants observed during in vivo penetration studies in our lab (unpublished data). An overview of all pharmacokinetic parameters is given in Table 1.

In a second step, drug elimination vs. time curves after product removal were calculated assuming that the elimination step is a first order process. Integration of the curves starting with the first time point of measurement leads to the AUEC. AUECs may be determined for each investigated dose duration and then plotted as a function of the exposure time. The shape of the resulting curves is similar to that of dose/response curves if abscissa and ordinate are switched and the AUEC is plotted in logarithmic form. Therefore, the bioavailability factor f was determined graphically from the vertical distance between the log AUEC vs. exposure time curves of the test and the reference formulation in the same manner as this is done with parallel dose/response curves [17,21,24]. As this factor is defined as the quotient of the penetration rate constants of a test and a reference formulation, the theoretical value for f is 10 ($= 0.5/0.05\ h^{-1}$) in this study. The graphical determination of the relative bioavailability is not described in the Guidance, as the pilot study protocols are designed only for the reference product.

Table 1
Overview of the pharmacokinetic parameters used for the simulations according to Eq. (1).

Pharmacokinetic parameter	Abbreviation	Estimate used
Drug dose	D_0	10 mg
Distribution volume at the receptor site	V_D	10 ml
Elimination rate constant	k_e	$0.2\ h^{-1}$
Penetration rate constant	k_p	$0.05, 0.5\ h^{-1}$
Relative bioavailability factor	f	10 ($= 0.5/0.05\ h^{-1}$)

3. Results and discussion

Analyses of Agency Guidances by the FDA are part of an ongoing assessment of the usefulness of these Guidances with the aim of improving and updating them as required [25,26]. The presented analysis was done to investigate the influence of penetration kinetics on the outcome of the pilot study described in the FDA Guidance, 'Topical Dermatologic Corticosteroids: In vivo Bioequivalence'. This pilot

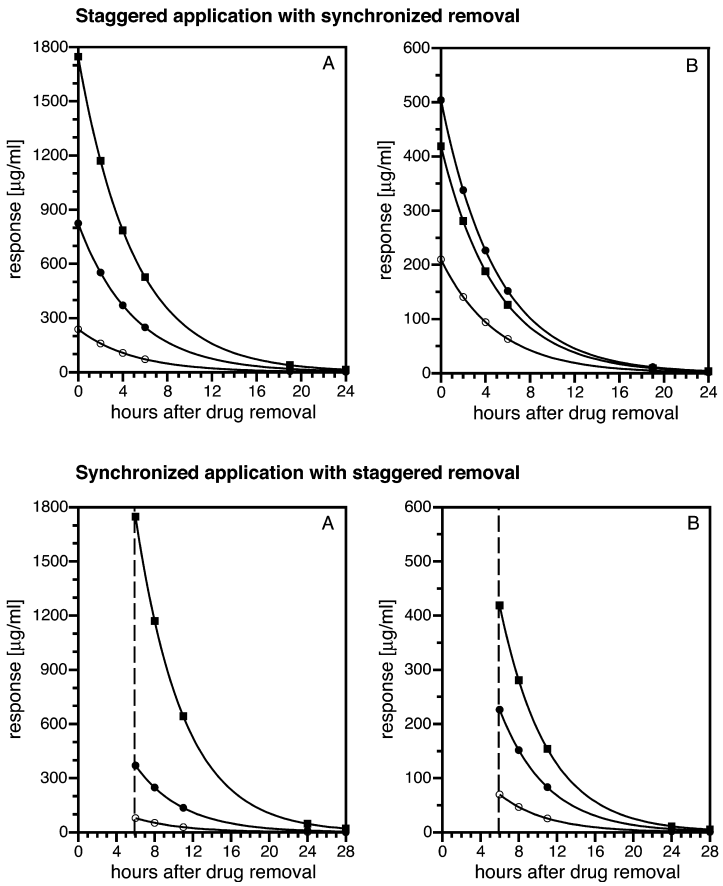

Fig. 3. Simulated time course of the blanching response after measurement start; $k_p = 0.5\ h^{-1}$; (A) zero order kinetics; (B) first order kinetics. Exposure time periods: ○, 0.5 h; •, 2 h; ■, 6 h.

study is based on the vasoconstrictor assay expressing the relationship between drug dose and effect by the E_{max} model [2].

It has been shown in the past that the estimation of the bioavailability and the documentation of in vivo bioequivalence of cutaneous drug formulations by pharmacodynamic measurements can strongly depend on drug penetration kinetics [17,18,20]. Various response parameters have led to incorrect estimations with regard to bioavailability data [21,22,27]. This includes the maximum response, which is the parameter usually used in the pharmacodynamic assessment of the percutaneous penetration of corticosteroids [18]. One of the reasons for these misestimations is drug depletion from solution-type drug formulations as a result of first order penetration kinetics [21,23,28]. In the Guidance pilot study the amount of drug product to be applied is unspecified. Thus, with solution-type formulations misestimations of the data for the pivotal study and false bioequivalence documentations could occur easily if experiments are done under finite dose conditions, i.e. first order penetration kinetics. Moreover, the fact that some formulations change with regard to their composition after cutaneous application is not taken into consideration in the Guidance. In particular hydrogels and emulsions, which contain water and other volatile compounds such as alcohol, may change over time as a result of evaporation. This evaporation process also affects the drug solubility and thus the drug escaping tendency in the vehicle. These formulations only lead to useful response data if applied under occlusion conditions.

The influence of penetration kinetics on simulated response vs. time profiles representing the Guidance methods is shown in Fig. 2. The dotted curves on the right hand side of the dashed vertical line represent the measurement time periods. According to the applied pharmacokinetic model these curves represent part of the elimination process from the receptor compartment. A significant difference with regard to the response can be observed between zero and first order penetration kinetics. Only with zero order penetration kinetics the expected order of the response profiles can be achieved. First order kinetics may lead to a reduced response as a result of drug depletion in the formulation. To gain a better impression of the curve profiles a selection of the curves from Fig. 2 is displayed in Fig. 3 as the time course of the blanching response after measurement start. Again, the differences between zero

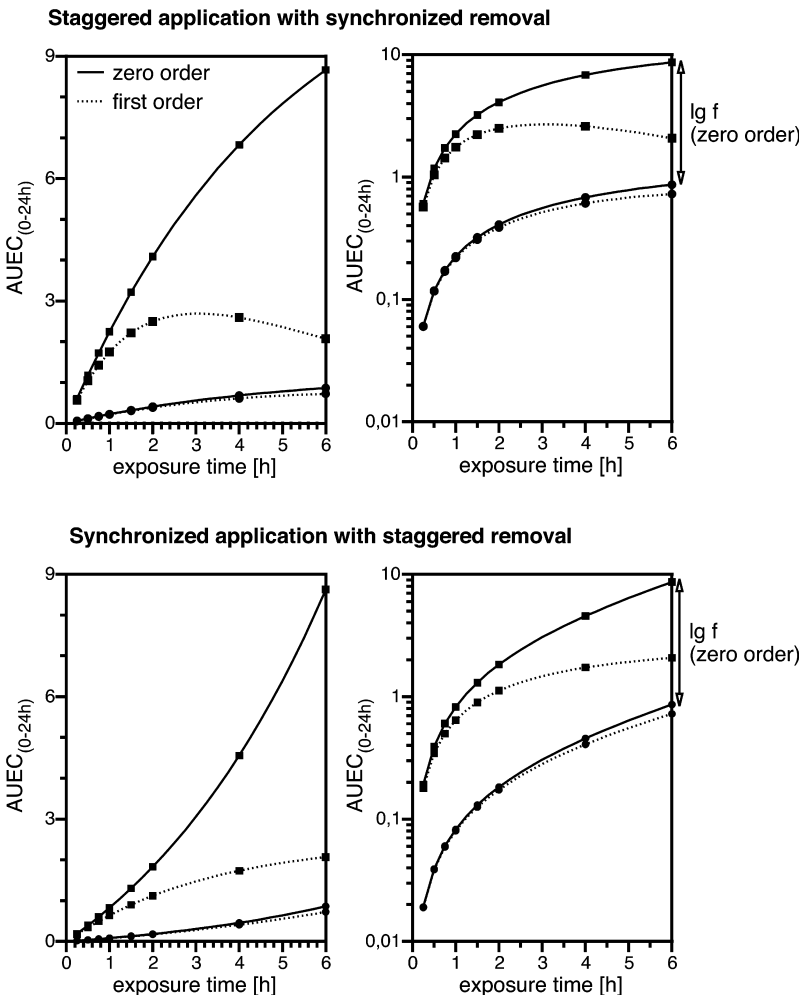

Fig. 4. AUEC data calculated for all exposure time periods (left panels: linear plot; right panels: semilogarithmic plot). •, Reference formulation ($k_p = 0.05\ h^{-1}$); ■, test formulation ($k_p = 0.5\ h^{-1}$) theoretical bioavailability factor $f = 0.5/0.05\ h^{-1} = 10$.

and first order kinetics are obvious. Preliminary in vivo experiments in our laboratory confirm the curve profiles in Fig. 3.

From each time course of the blanching response after measurement start the AUEC was calculated and plotted vs. the exposure time periods (Fig. 4). The higher the drug penetration rate, the more the simulated curves for zero and first order kinetics deviate from each other. First order kinetics lead to non-parallel log AUEC vs. exposure time curves resulting in a misestimation of the bioavailability factor *f*, which may be determined from the vertical distance between the test and the reference curve. The bioavailability factor *f* is defined as the AUEC ratio of the test and the reference formulation. Only with zero order kinetics accurate *f* values may be obtained (Fig. 4). This is also true if a two-compartment model with the stratum corneum representing the second compartment is applied.

This pharmacokinetic analysis of the two Guidance methods reveals that several critical factors not specified in the Guidance need to be considered to avoid misinterpretation of the data. First of all, it should be known whether the investigated products are solution-type or suspension-type preparations. If solution-type preparations are investigated, the applied formulation volume should be the same on all eight application sites. According to Eq. (2) the formulation volume is part of the penetration rate constant and can therefore affect the kinetics of drug penetration. A high formulation volume leads to infinite dose conditions and thus zero order kinetics. With solution-type formulations thermodynamic and penetration enhancing vehicle effects may be quantified [21,28]. In the case of suspension-type preparations, which lead to the maximum drug flux through the skin, the applied drug dose is uncritical as long as there is enough undissolved drug present in the applied formulation. With suspension-type formulations only true penetration enhancement resulting from structural changes of the stratum corneum by the vehicle or enhancer may be quantified [22]. The drug escaping tendency from these formulations is maximal because the maximum thermodynamic activity is reached as soon as the drug solubility in the

vehicle is exceeded. With regard to penetration kinetics it is essential to guarantee zero order kinetics during the exposure time periods to prevent drug depletion, which makes bioequivalence testing impossible. In contrast to suspension-type preparations, solution-type formulations have to be applied in an excess amount to guarantee infinite dose conditions and thus zero order kinetics. If all these critical factors are taken care of, both pilot study methods should lead to accurate and reproducible data. Moreover, bioavailability factors (solutions) and enhancement factors (suspensions) may be calculated from the vertical distance between the log AUEC vs. exposure time curves of the test and the reference product for any exposure time period (Fig. 4). Preliminary in vivo experiments confirm this pharmacokinetic analysis so far. However, more experiments have to be done to statistically support the data.

From the presented simulations it may be concluded that drug penetration kinetics have a significant impact on the results of the two FDA pilot study methods. Only with zero order penetration kinetics parallel AUEC vs. exposure time profiles and thus accurate bioavailability data can be expected. However, the data obtained with the two study methods are equivalent.

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