Application of E_{max} model to assess the potency of topical corticosteroid products

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Abstract

Various potency classification listings for topical corticosteroid products (TCPs) have been based on clinical data and/or data using the US FDA's vasoconstrictor assay (VCA). However, studies that used VCA data mainly used a single visual measurement and often the doses and dose durations were not determined in accordance with the VCA requirements. The objective was to compare the potencies of two TCPs using the Emax model to fit the blanching responses obtained from the VCA as described in a previous publication and to illustrate the influence of formulation on potency. The potencies of two marketed creams, Dermovate® containing clobetasol propionate (CP) and Elocon® containing mometasone furoate (MF) were assessed using healthy human subjects. In order to investigate the influence of formulation and associated vehicle properties, the TCPs were compared to their respective TCs from a previously published study wherein the inherent potencies of those TCs were assessed using a validated VCA method. Whereas the inherent potency of MF (Emax = -94.45 ± 0.21) was found to be greater than CP (Emax = -58.80 ± 15.65), when formulated as creams, the TCP containing CP had a higher potency (Emax = -86.15 ± 0.17) than that containing MF (Emax = -42.61 ± 26.04). This reversal of potency may be attributed to the effect of formulation factors. The comparison of the potencies of TCPs with inherent potencies of their corresponding TCs confirmed the influence of formulation parameters on the potency of those products.

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Abstract

Various potency classification listings for topical corticosteroid products (TCPs) have been based on clinical data and/or data using the US FDA's vasoconstrictor assay (VCA). However, studies that used VCA data mainly used a single visual measurement and often the doses and dose durations were not determined in accordance with the VCA requirements. The objective was to compare the potencies of two TCPs using the E_{max} model to fit the blanching responses obtained from the VCA as described in a previous publication and to illustrate the influence of formulation on potency. The potencies of two marketed creams, Dermovate® containing clobetasol propionate (CP) and Elocon® containing mometasone furoate (MF) were assessed using healthy human subjects. In order to investigate the influence of formulation and associated vehicle properties, the TCPs were compared to their respective TCs from a previously published study wherein the inherent potencies of those TCs were assessed using a validated VCA method. Whereas the inherent potency of MF (E_{max} = -94.45 ± 0.21) was found to be greater than CP (E_{max} = -58.80 ± 15.65), when formulated as creams, the TCP containing CP had a higher potency (E_{max} = -86.15 ± 0.17) than that containing MF (E_{max} = -42.61 ± 26.04). This reversal of potency may be attributed to the effect of formulation factors. The comparison of the potencies of TCPs with inherent potencies of their corresponding TCs confirmed the influence of formulation parameters on the potency of those products.

Introduction

Topical products containing a wide range of corticosteroids and presented in different strengths are available for the treatment of various skin disorders (1). However, the efficacy of a specific topical corticosteroid (TC) is related to its potency and ability to be absorbed into target cells within the viable epidermis and dermis (2). The clinical choice of a particular topical corticosteroid product (TCP) is governed by the type and severity of inflammatory skin condition/lesions, location of the lesion, and age of the patient, amongst others. For example, dermatologists recommend lower potency TCPs for infants and the elderly owing to an increased surface-to-weight ratio and skin fragility, respectively resulting in the absorption of proportionally large amounts of TC. Agents belonging to the lower potency classes are used to treat acute inflammatory lesions of the face and other body parts with thinner skin, whereas highly potent agents are preferred in the treatment of chronic, keratotic, or lichenified lesions found on surfaces with thicker skin,*e.g.* , palms, soles. Additionally, the type of lesion to be treated influences the choice of vehicle, *e.g.* , ointment bases are recommended for lichenified lesions as they improve drug penetration due to an occlusive effect and subsequent hydration (3). A consideration of possible side effects is important when prescribing TCPs since unwanted cutaneous (atrophy, striae, telangiectasia, hypo-pigmentation, acne, rosacea, perioral dermatitis, and hypertrichosis) and also several systemic effects including cataracts, hyperglycemia, and hypothalamic-pituitary-adrenal suppression can occur (3).

The standard methods to evaluate the potencies of TCPs have largely been based on results of their clinical use and/or randomised clinical comparative studies using the vasoconstrictor assay (VCA) (4). The VCA evaluates corticosteroid potency based on the contribution of several factors: ability to penetrate the skin barrier after release from the vehicle, intrinsic activity at the receptor, and rate of clearance from the site of application (5,6). Vasoconstrictor rankings based on validated and appropriately conducted VCA studies are generally good predictors of the efficacy of TCs (7).

Various factors such as drug lipophilicity and solubility, drug concentration, anatomical site, age of the patient, presence of skin disease, and use of occlusive dressings may influence percutaneous absorption TC. These factors, amongst others, impact the degree to which TCs achieve their intended therapeutic outcome (8). The therapeutic benefit of a topically applied corticosteroid is derived from a combination of its pharmacokinetic and pharmacodynamic effects. Furthermore, the intrinsic activity of a TC at the cellular level is also dependent on the release and delivery of drugs from the vehicle to the site of action. Overall,

the VCA tells us a lot about corticosteroid potency, which is a complex function of both the chemical and physical properties of the drug and its vehicle (2). It indicates the ability of the vehicle to deliver the TC molecule into the skin and its ability to activate the receptor (7). Current classification systems rank the relative potencies of specific proprietary preparations assuming potency and side effects are directly related (9).

Potency ranking of TCPs in the USA involves seven classes from superpotent to least potent whereas a four-category system is used in Northern Europe, the United Kingdom (UK), France, Germany, The Netherlands and New Zealand (3,10–15). However, in New Zealand, class I is the most potent and class IV the least potent, whilst in Germany, class I is considered mildly potent and class IV very highly potent (11,13,14). Furthermore, various formulation factors such as vehicle and excipients can affect potency including the presence or absence of penetration enhancers, lipophilicity of the drug and additives used, chemical modifications, and substitutions which have not been taken into consideration (16,17).

Various discrepancies relating to the current classification systems have been observed, which are probably due to the use of non-standardised approaches to assess potency. Furthermore, in some cases, clinical data have been used, whereas in other instances, vasoconstrictor responses have been used as the basis of potency assessment. Also, several publications do not even include information on how the potency was assessed. The use of non-standardised VCA method to assess potency is also a cause for concern since it can result in erratic and erroneous data. For example, some generic formulations have been shown to be less or more potent than their brand-name equivalent, indicating a discrepancy between clinical assessment and VCA (18). Creams containing 0.25 and 0.05% desoximetasone were found to be equipotent by Stoughton *et al* (19). However, the USA classification list ranks the 0.25% cream as a class II (high potency) TCP (20), whereas the 0.05% cream is classified as a class IV/V (medium potency) agent. A further example showing inconsistency using a single point visual assessment lists creams containing 0.05% diflorasone diacetate as a group II (high potency) (21) whereas the USA classification list ranks it as a class I (ultra-high potency) (20). However, the data generated did not comply with the requirements of the VCA guidance (22) since a simple single-point assessment was used, making such results questionable. On the other hand, using a validated VCA method in compliance with related requirements assures consistency relating to precision, reproducibility, and associated validation parameters. Additional discrepancies in the published literature relate to differences in the ranking procedures used in different classification systems. In the UK, products containing 0.1% mometasone furoate (Elocon$^{(r)}$), irrespective of the formulation, are ranked as potent (method of assessment not provided) (23) compared to the USA classification, which classifies products containing 0.1% mometasone furoate depending on the formulation (3). Hence, Elocon$^{(r)}$ ointment has been classified as superpotent, and Elocon$^{(r)}$ cream is ranked under midstrength potency (3). Furthermore, the Monthly Prescribing Reference (MPR) lists Elocon$^{(r)}$ cream, ointment, and lotion as being of intermediate potency (24). In the classification list published by the British National Formulary, none of the items indicate the type of formulation, and most do not state the percentage of the active pharmaceutical ingredient (API) incorporated in the dosage form (23). Similarly, in New Zealand's classification list, apart from betamethasone dipropionate products, no mention is made of the formulation or corticosteroid concentration (11). The method of potency classification is based on a comparison with hydrocortisone, creating a further discrepancy. In some instances, classifications have been based on skin pathology, *e.g.* , in a study comparing Eumovate$^{(r)}$ (0.05% clobetasone 17-butyrate) *vs*Locoid$^{(r)}$ (0.1% hydrocortisone 17-butyrate) ointments, the potency was based on the various responses between effects on eczema and psoriasis (25). In the former condition, the products were shown to be equipotent, whereas, in the latter, Eumovate$^{(r)}$ was superior to Locoid$^{(r)}$, which is classified as a potent preparation (25). The general assumption that the higher concentrations are more potent than the lower concentrations irrespective of the particular corticosteroid may not always be true (19). Furthermore, different dosage forms containing the same TC may have different potencies. For instance, 0.1% halcinonide cream is ranked as a class II agent that is more potent than 0.1% halcinonide ointment which is ranked as a class III TCP (3). Stoughton and Cornell conducted a series of experiments to compare the ability of VCA with clinical data to establish the potencies of specific TCPs. In 20 of the 23 (˜ 87%) comparisons involving 30 TCPs, VCA was in agreement with the clinical studies, whereas data for the other 7 TCPs were inconclusive (4) although a non-validated

VCA was used. The author stressed the need to develop a system for evaluating the potency of these compounds without having to rely on clinical data (4).

The relatively vague bases of the potency determinations raise concerns about the reliability of the current potency classification systems. Some do not provide any indication of how the classification was done. In most cases, there is no clarity on how the TCPs were ranked in terms of their potency, and tables with the different potency classes and classification are simply provided without explanation. Whereas the application of VCA usually requires the use of a chromameter, most rankings and classifications using the VCA were based solely on visual assessment. These were usually based on a single visual reading, where the dose or dose duration used were not standardised, and the method used was not appropriately validated. Therefore, there is an urgent need to revisit and reassess the existing classification systems using newer, reliable, and innovative technology using chromametric measurements of the skin blanching response (3,22).

Hence, the objective of this study was to compare the potencies of two marketed TCPs using the Food and Drug Administration's (FDA's) VCA as described in a previous publication (26) used to rank TC APIs and also to illustrate the influence of formulation and associated vehicle properties on potency.

Materials and Methods

Materials

Two TC creams, Dermovate(r) containing 0.05% clobetasol propionate (CP) and Elocon(r) containing 0.1% mometasone furoate (MF) were investigated in this study. The TCPs were chosen based on their widespread use and availability and were purchased from a local pharmacy. The TCPs were kept away from direct sunlight and at ambient room temperature, not exceeding 25 degC. The results were compared with the outcomes published by Zvidzayi *et al* (26) wherein 0.0025 M (˜ 0.1%) solutions each of CP and MF in propylene glycol were assessed for their inherent potencies.

Experimental Design

Ethical approval (Ref No: 160614243, 01 July 2016) was obtained from Pharma-Ethics (Pty) Ltd. research ethics committee (Lyttelton Manor, South Africa), in compliance with the 1964 Declaration of Helsinki and its subsequent amendments. The study was conducted in accordance with the FDA's VCA guidance (22) as described in a previously published study by Zvidzayi *et al* (26). A 10µL dose of the relevant creams were applied to demarcated sites on the ventral surface of the arms of each subject and left on for the relevant dose durations (*i.e.* , at 5, 10, 20, 40, 60, 90, and 150 min). The products were removed from the application sites after the relevant dose durations using cotton swabs, 3 wet wipes (warm water) followed by 2 dry wipes. Chromameter (Model CR 400, Minolta®, Osaka, Japan) readings at all sites were taken over 24 h by a single chromameter operator. Only the a-scale data were used in the statistical analysis in accordance with the FDA guidance (17,26–28).

Statistical Analysis

P-Pharm (Simed) software was used to analyse the data and determine theE_{max} and ED_{50} values using the no-intercept E_{max} model (22,26). The data sets for each of the TCs and TCPs were analysed with the log-normal distribution assumption for ED_{50} to fit theE_{max} model (22) according to Equation 1 that describes the elicited effect (E) in terms a maximal effect (E_{max}), dose (D) and the dose at which the effect is half-maximal (ED_{50}).

$$E = (E_{\max} \times D)/(\mathrm{ED}_{50} + D), \quad (1)$$

where

E = Pharmacodynamic effect metric *i.e.* , $AUEC$;

D = Duration of exposure (min) to the TC;

E_{max} = Maximum possible value for E ;

ED_{50} = Dose duration necessary to achieve 50% of the E_{max} response.

Although the FDA's VCA guidance recommends the use of naive pooling or Non-Linear Mixed Effect modelling (NLME) to fit the pharmacodynamic response data (22,27,29,30), naive pooling does not take into consideration the inter-individual variability, which may not accurately represent the study population (29,30). Therefore, P-Pharm software which uses NLME modelling with the likelihood estimation (30,31) is a more appropriate method for the determination of population parameters such as ED_{50} and E_{max} (30).

Plots of individual a-scale readings *vs* the assessment time points over a period of 24 h were constructed and the areas under the effect curve ($AUEC_{0\text{-}24}$) values for each subject at each dose duration for the respective TCPs were determined using the linear trapezoidal method from the baseline adjusted and untreated site corrected a-scale values (26,32). $AUEC_{0\text{-}24}$ values*vs* the respective dose durations were used to estimate theE_{max} model that best described the data based on the minimum Akaike Information Criterion (AIC).

A Student's t -test was used to compare theE_{max} values of TC API solutions and TCPs. The TC API solutions and the TCPs were compared amongst themselves using a paired t -test.

The TC APIs were compared with the TCPs containing the corresponding corticosteroids using a one-way analysis of variance (ANOVA) to determine the presence/absence of significant differences in theE_{max} parameters between the TCPs and their corresponding TCs.

Results

Potency assessment of Dermovate® and Elocon® creams

Ten Caucasian subjects (2 females and 8 males) were enrolled and all completed the study without any adverse drug reactions or other clinical events. The dose duration-response data of the subjects were obtained for the two TCPs, Dermovate® and Elocon® creams. Figure 1a illustrates a typical blanching response of one of the subjects after application of Dermovate® and Elocon®. Figure 1b shows a typical blanching response of one of the subjects after application of 0.0025 M (˜0.1%) solutions of CP and MF from a previous study conducted by Zvidzayi *et al* (26). Details of the dose durations and treatments received by subjects in Figures 1a-b are provided under supplementary material in Tables S1-2.

After the different times of exposure (*i.e.* , at 5, 10, 20, 40, 60, 90, and 150 min dose durations), the blanching effects for both Dermovate® and Elocon® peaked at 12 h after product removal, decreasing thereafter. The mean baseline corrected and untreated site corrected a-scale values for Dermovate® and Elocon® were plotted against the time after product removal, illustrating the blanching response of the 10 subjects as shown in Figures 2a-b, respectively. The negative values of the means (*i.e.* , mean multiplied by -1) were plotted since the actual means were < 0. The plots show that as the dose durations increase, there is a corresponding increase in the skin blanching response.

The data sets for the products were analysed using population modelling to fit the E_{max} model according to Equation 1. The $AUEC$ values (< 0 indicates blanching) were calculated to yield a fitted dose-duration versus $AUEC$ profile of all the subjects to illustrate the response at the various dose durations for Dermovate® and Elocon® as shown in Figures 3a-b, respectively. The results obtained from data fitting analyses using P-Pharm software are summarised in Table 1.

Comparisons of TC API solutions and TCPs

The E_{max} values of the 10 subjects for Dermovate® and Elocon® creams along with the E_{max} data from Zvidzayi *et al* (26) (10 subjects for CP and MF) were statistically evaluated as previously described. The paired$t$- test results indicated statistically significant differences amongst the TCs ($t = 7.29$; $p < 0.0001$) as well as the TCPs ($t = 5.32$; $p = 0.0005$). Furthermore, the one-way ANOVA revealed significant differences between the TCPs and their corresponding TCs as follows: Dermovate® and CP ($F = 30.55$;$p < 0.0001$); Elocon® and MF ($F = 39.63$; $p< 0.0001$). Hence, the null hypothesis that theE_{max} values for any of these

comparisons were equal, was rejected ($p < 0.05$) and the alternative hypothesis that the E_{max} values of these treatments differed from each other was accepted. The results of these comparisons are summarised in Table 2.

Statistical analysis of the paired comparison of theE_{max} values of Dermovate® and Elocon® indicated significant differences in theE_{max} values, where Dermovate®had a greater mean E_{max} value than Elocon®, indicating a higher potency for that TCP.

The mean E_{max} value for CP was statistically different from those of MF.

CP had a lower mean E_{max} value than Dermovate®. MF exhibited a higherE_{max} value and differed statistically from Elocon®.

Figures 4a-c show composite plots for fitted $E_{ma\ x}$ model for Dermovate®*vs* Elocon® creams, Dermovate®cream *vs* CP, and Elocon® cream *vs* MF, respectively.

Discussion

Although Dermovate® contains 0.05% CP and Zvidzayi*et al* (26) used ˜0.1% solution of CP, the TCP was found to be more potent than the API solution. This may be attributed to the influence of formulation and associated vehicle properties. The presence of excipients such as permeation enhancers result in better permeation subsequently increasing the potency of the TCP.

MF had a significantly higher$E_{ma\ x}$ value than Elocon® cream which contains the same strength of MF*i.e.* , 0.1% as the solution used by Zvidzayi *et al* (26). This too is presumably the result of the influence of formulation and associated vehicle properties. Certain excipients may impede the release of APIs from the formulation, leading to slower permeation and the resultant lower potency.

It is interesting to note that Dermovate® which contains CP was found to be more potent than Elocon®which contains MF whereas the potencies of the corresponding APIs were reversed in the study reported by Zvidzayi *et al* (26), further implicating formulation effects. However, the potency ranking of the TCPs is in line with the existing classification systems worldwide. The US classification system ranks a 0.05% CP cream as a class I (superpotent) agent and 0.1% MF cream as a class IV (midstrength) agent. The British National Formulary classifies 0.05% clobestasol propionate as class I (very potent) and 0.1% MF as class II (potent) without specifying the type of formulation. New Zealand classifies CP as very potent/ superpotent and MF as potent but does not provide the details about the strength of the TC or the type of formulation. The presence of such discrepancies reiterates the need for the development of a more reliable classification system for TCPs using standardised procedures and validated methods such as the FDA's VCA (22) which will ensure consistency relating to precision, reproducibility and associated validation parameters. Furthermore, the determination ofE_{max} values for specific products is a further advantage, whereby a specific metric can be used as a standard potency determinant.

Conclusions

An improved potency classification system with the necessary clinical relevance to facilitate the choice of an appropriate potency for a specific indication is proposed. The TCP containing CP (Dermovate®) was found to be more potent than that containing MF (Elocon®) where the rank order was in line with existing classification systems. However, the inherent potency assessments of the TCs, CP and MF, showed opposite results. The potencies of the TCPs under investigation were then compared to the inherent potencies of their corresponding TCs. It was observed that the potency of the TCP containing 0.05% CP (Dermovate®) was higher than its corresponding TC, even though the concentration of the drug in the TCP was 50% lower than the TC solution (0.1%). Furthermore, Elocon®, despite containing the same strength of MF (0.1%) exhibited a reduced potency compared to the TC API itself. Although the inherent potency of MF was shown to be higher than that of CP, when the TCs are formulated into products, the potencies were altered. Hence, potency of a TC may be increased or decreased based on the type of formulation and vehicle components. These data clearly indicate the effects and importance of formulation on TCs. Furthermore,

inconsistencies seen in the existing TCP classification systems, stresses the need for the development of an improved potency classification system that consistently ranks the potencies of TCPs by using standardised and validated methods.

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Figure Legends

Figure 1 Typical blanching responses after randomised application of (a) Dermovate® and Elocon® creams; (b) 0.0025 M (˜0.1%) solutions of clobetasol propionate and mometasone furoate

Figure 2 Blanching profiles for (a) Dermovate® cream; (b) Elocon® cream; (c) clobetasol propionate (26); (d) mometasone furoate (26)

Figure 3 Fitted E_{max} model of $AUEC$ data derived from the chromameter a-scale values for (a) Dermovate® cream; (b) Elocon® cream; (c) clobetasol propionate (26); (d) mometasone furoate (26)

Figure 4 Composite plots showing fitted E_{max} models for (a) Dermovate® and Elocon® creams; (b) Dermovate® cream and clobetasol propionate; (c) Elocon® cream and mometasone furoate

Table captions

Table 1 E_{max} and ED_{50} values obtained for TCPs and their corresponding TCs (26)

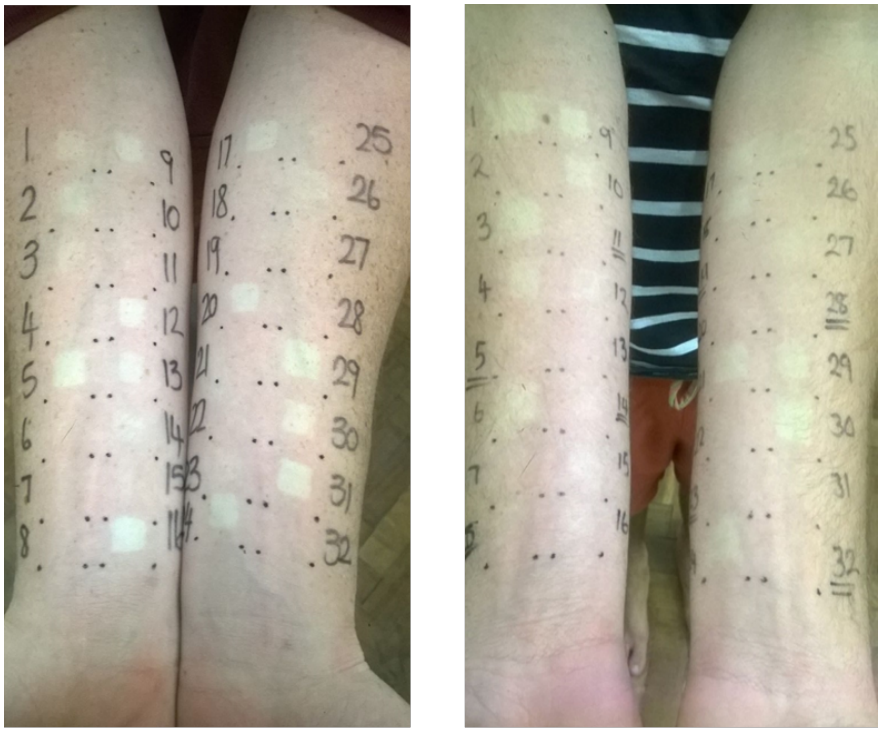
Table 2 Pairwise E_{max} comparisons

Supplementary table captions

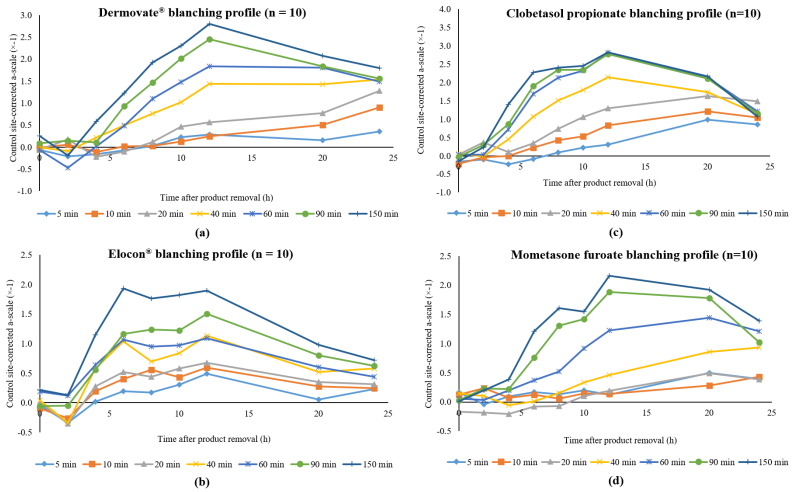
Table S1 Application template showing details of the TCP (Dermovate® and Elocon®) responses obtained

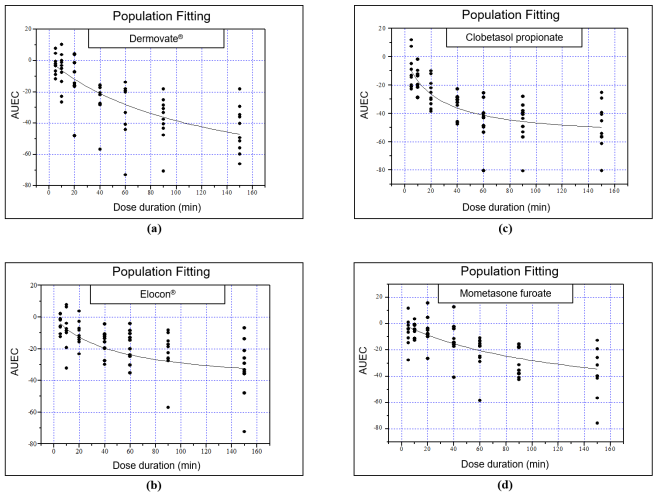
at various dose durations in Figure 1a.

Table S2 Application template showing details of the TC (clobetasol propionate and mometasone furoate) responses obtained at various dose durations in Figure 1b.



(a) (b)





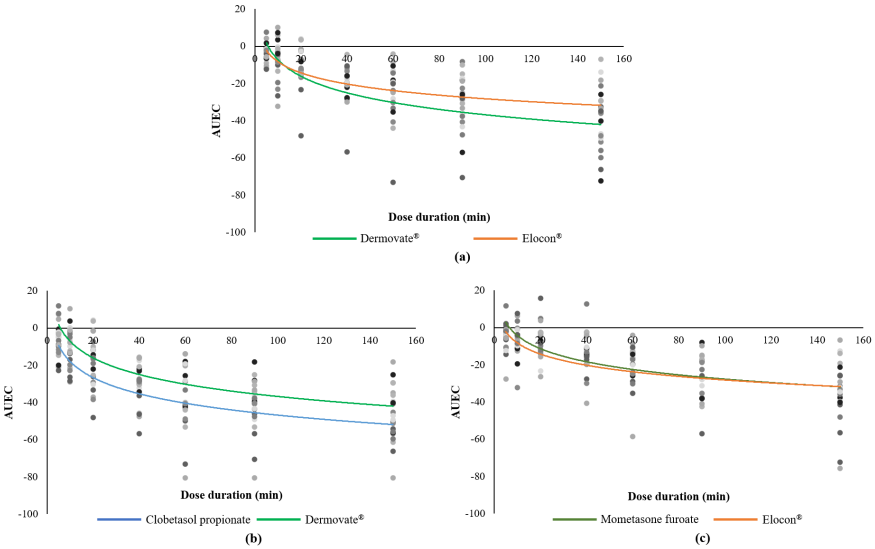


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Table_1_Emax_and_ED50_values_obtained_for_TCPs_and_their_corresponding_TCs.docx available at https://authorea.com/users/472466/articles/563278-application-of-emax-model-to-assess-the-potency-of-topical-corticosteroid-products

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Table_2_Pairwise_Emax_comparisons.docx available at https://authorea.com/users/472466/articles/563278-application-of-emax-model-to-assess-the-potency-of-topical-corticosteroid-products