ORIGINAL RESEARCH ARTICLE

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Pharmacokinetics of Dapsone Gel, 5% for the Treatment of Acne Vulgaris

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Abstract

Background: Oral dapsone has been available for over 60 years and has been used to treat severe acne vulgaris; however, the oral formulation is known to cause dose-dependent haematological reactions and is currently indicated only for diseases such as dermatitis herpetiformis and Hansen's disease. A gel formulation of dapsone was recently developed to treat acne vulgaris. As dapsone is administered topically, it was expected that systemic absorption would be considerably lower than that observed with oral dapsone therapy, thereby avoiding any adverse haematological effects.

Objective: To report the pharmacokinetic profile of topically applied dapsone gel, 5% in the treatment of acne vulgaris.

Study participants and methods: Three prospective, open-label studies enrolled a total of 548 subjects with acne vulgaris: two phase I pharmacokinetic studies (crossover and drug interaction) and one phase III long-term safety study. In the crossover study (n = 18), topical dapsone gel applied twice daily for a total of 14 days to 22.5% of the body surface area was compared with a single dose of oral dapsone 100mg (the typical clinical dose). In the drug-interaction study (n = 24), oral trimethoprim/sulfamethoxazole monotherapy, topical dapsone gel monotherapy and the two in combination were used twice daily for 7, 21 and 7 days, respectively. In the long-term safety study (n = 506), topical dapsone gel was applied twice daily to acne-affected areas for up to 12 months. Blood samples were drawn at various timepoints in each study to assess drug and metabolite concentrations. Systemic concentrations of dapsone, *N*-acetyl dapsone, dapsone hydroxylamine, trimethoprim and sulfamethoxazole were determined, according to the study design.

Results: In the crossover study, the mean area under the plasma concentration-time curve (AUC) from 0 to 24 hours for dapsone was 417.5 ng • h/mL after 2 weeks of dapsone gel therapy (n = 10), compared with an AUC from time zero to

infinity of 52 641 ng • h/mL after a single dose of oral dapsone; this represents a 126-fold lower systemic exposure for dapsone gel at typical therapeutic doses. In the drug-interaction study, the AUC from 0 to 12 hours for dapsone was 221.52 ng • h/mL after 3 weeks of dapsone gel monotherapy compared with 320.3 ng • h/mL after 1 week of coadministration with trimethoprim/sulfamethoxazole. In the long-term safety study, the mean plasma dapsone concentrations ranged from 7.5 to 11 ng/mL over 12 months. Overall, total systemic exposures to dapsone and its metabolites were approximately 100-fold less for dapsone gel than for oral dapsone, even in the presence of trimethoprim/sulfamethoxazole. There were no reports of any haematological adverse events.
Conclusions: Topical application of dapsone gel in various settings ranging from 2 weeks to 12 months resulted in systemic exposures to dapsone and its metabolites that were approximately 100-fold less than those after oral dapsone at a therapeutic dose level. The concentrations of dapsone and its metabolites reached steady state and did not increase during prolonged treatment.

Background

Acne vulgaris is the most common reason individuals visit a dermatology office[1] and, increasingly, more patients are seeking treatment for acne from non-dermatologists.[1,2] Acne has both inflammatory and bacterial components[2,3] but, until recently, the inflammatory events were considered secondary occurrences in the sequence of lesion development.[4] Newer data now suggest that inflammatory events occur before, and possibly initiate, the hyperproliferation observed in acne lesions.[5] These findings support the classification of acne vulgaris as an inflammatory skin disease as opposed to a keratinocyte/hyperproliferative disorder.[5] Proinflammatory cytokines play a role in the formation of acne lesions, and it has recently been suggested that the bacterium *Propionibacterium acnes*, one of the key pathogenic factors linked to the development of acne, releases proinflammatory cytokines.[6,7]

Dapsone (4,4′-diaminodiphenyl sulfone) is a synthetic sulfone with both anti-inflammatory and antibacterial actions.[8,9] Its primary metabolites are *N*-acetyl dapsone and dapsone hydroxylamine. Oral dapsone has been available for over 60 years and is currently indicated only for the treatment of dermatitis herpetiformis and Hansen's disease in doses ranging from 100 to 300mg,[10] but historically, oral dapsone was also used for the treatment of severe acne in doses ranging from 25 mg/day to 300 mg/week.[11-13] The most notable adverse effects of oral dapsone are haematological reactions, including dose-dependent haemolysis and methaemoglobinaemia, which result from the increased oxidative stress produced by the hydroxylamine metabolite.[8,9,13] Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency are sensitive to these effects, since the absence of functional G6PD can lead to haemolysis and denaturation of haemoglobin.

Oral dapsone was usually most effective for patients with severe acne; however, some improvement was also noted in patients with mild acne.[13] It was hypothesised that topical application of dapsone in a gel formulation for the treatment of acne vulgaris would greatly minimise the systemic exposure to dapsone, while delivering an effective clinical dose of dapsone to the affected area and avoiding the adverse haematological effects observed with oral dapsone therapy.

Dapsone gel, 5% (Aczone™, QLT USA, Inc., Fort Collins, CO, USA)[1] was approved in the US for the treatment of acne vulgaris, based on two randomised controlled studies that demonstrated statistically and clinically significant improvements in both acne lesion counts and treatment success over 12 weeks.[14] This article reports the pharmacokinetic results of three additional studies that investigated the systemic absorption and safety of dapsone gel in the treatment of acne vulgaris.

Study Participants and Methods

Two phase I pharmacokinetic studies and a phase III long-term safety study were conducted between 24 January 2002 and 14 April 2004. The crossover study compared 15-day administration of dapsone gel with a single dose of oral dapsone 100mg to evaluate the relative systemic concentrations of oral and topical administration. The drug-interaction study of dapsone gel and oral trimethoprim/sulfamethoxazole was conducted to explore possible interactions between dapsone gel and trimethoprim/sulfamethoxazole; coadministration of oral dapsone and oral trimethoprim/sulfamethoxazole is known to increase the plasma concentrations of both drugs by approximately 1.5 times compared with monotherapy.[10] The long-term safety study of dapsone gel examined the safety and efficacy of dapsone gel over 12 months in a setting more closely aligned to clinical practice;[15] the dapsone plasma concentration results from that study are reported here.

All three studies were open-label trials conducted in subjects with a clear diagnosis of acne vulgaris, defined as at least 20 inflammatory lesions at baseline (ten or more inflammatory lesions on the face, with the remaining lesions on the back, shoulders and chest). Dapsone gel was applied twice daily (once in the morning and once in the evening at least 1 hour before bedtime) to the face, upper back, shoulders and/or upper chest, representing up to approximately 22.5% of the total body surface area. Following application of dapsone gel in all studies, swimming and bathing were prohibited for 2 hours; the use of moisturisers, sunscreens and cosmetics on the treatment areas was prohibited for 1 hour. In the pharmacokinetic studies, to represent maximum exposure, dapsone gel was applied to all of these body areas regardless of whether acne was present at the particular site. In the long-term safety study, it was applied only to acne-involved parts of these body areas and could be discontinued where the acne had cleared; likewise, it was to be restarted if acne lesions reappeared in these parts.

The studies were conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with the US FDA Good Clinical Practice Guidelines, and the protocol for each study was reviewed and approved by an institutional review board or ethics committee. All subjects and their parents or guardians, as appropriate, gave written informed consent before the start of study procedures.

Crossover Study of Dapsone Gel, 5% Followed by Oral Dapsone

Study Design and Subjects

The crossover study was a single-centre, open-label, two-period, pharmacokinetic and safety study (figure 1). The primary objective was to evaluate the pharmacokinetic profile of dapsone gel and the relative systemic drug concentrations following oral and topical dapsone administration at typical therapeutic doses. Subjects applied dapsone gel for 15 days to the maximum expected skin area (approximately 22.5% of body surface area). A subset of subjects then underwent a 14-day washout period and returned to the clinic for administration of a single dose of oral dapsone, given at the recommended

1 The use of trade names is for product identification purposes only and does not imply endorsement.

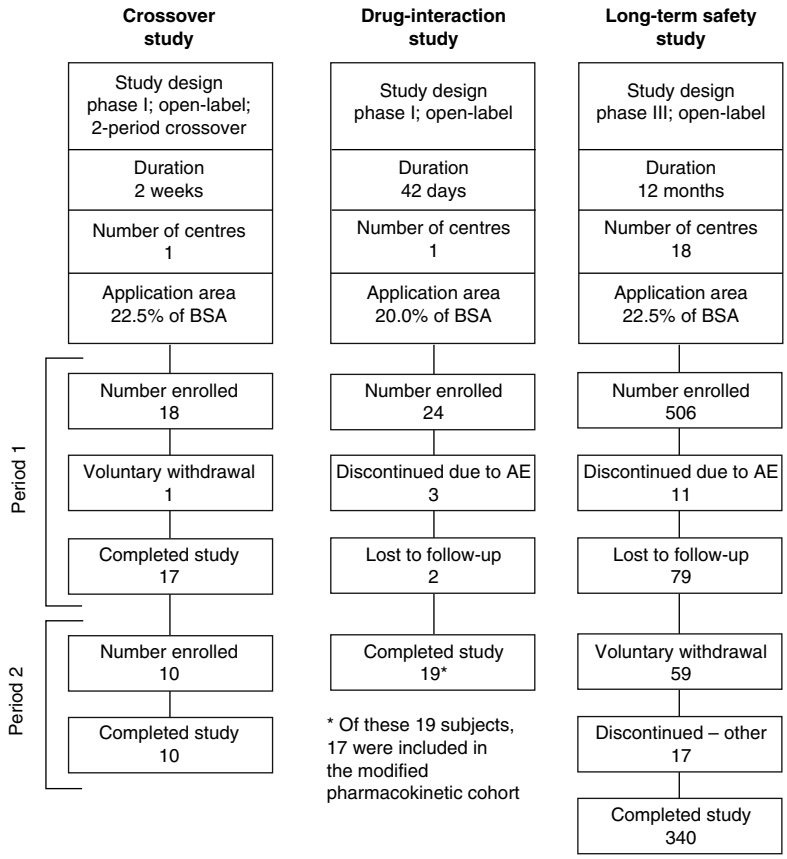

Fig. 1. Summary of trials. **AE** = adverse event; **BSA** = body surface area.

therapeutic dose of 100mg. Pharmacokinetic evaluations of plasma dapsone and *N*-acetyl dapsone concentrations were performed in both periods of the study. Eligible subjects were men or women between the ages of 18 and 40 years with acne vulgaris. Subjects with G6PD deficiency were not eligible for participation in the oral dapsone period of the trial.

Treatment

Dapsone gel was applied twice daily to all of the face, upper back, shoulders and upper chest. However, on the first and last topical treatment days (days 0 and 14, respectively), dapsone was applied only in the morning. After the 14-day washout period, a subset of ten subjects returned to the clinic for administration of a single dose of oral dapsone 100mg (Jacobus Pharmaceutical, Princeton, NJ, USA).

Blood Sampling

Dapsone Gel, 5%

On all treatment days that coincided with pharmacokinetic sampling (days 0, 1, 2, 3, 5, 7 and 14), the first blood sample was drawn prior to the morning application of topical dapsone to yield trough samples. On days 0 and 14, blood samples for the topical dapsone pharmacokinetic analysis were collected before dapsone application (hour 0), and at 1, 2, 3, 4, 6, 8, 10 and 12 hours following the morning application (which was the only application on those days). Trough blood samples were also

obtained on days 1, 2 and 3 (hours 24, 48 and 72) and on days 5 and 7. In addition, blood samples were drawn 24, 48 and 72 hours after the last application of topical dapsone. A total of 26 blood samples were collected from each subject in this period of the study.

Single-Dose Oral Dapsone 100mg

Baseline blood samples for the oral dapsone pharmacokinetic analysis were obtained on day 28 after the 14-day washout period. After administration of oral dapsone 100mg, blood samples were drawn over 3 days at hours 1, 2, 3, 4, 6, 8, 10, 12, 24, 48 and 72. A total of 12 blood samples were collected from each subject in this period of the study.

Bioanalytical Methods

Plasma concentrations of dapsone and *N*-acetyl dapsone were assayed in a central laboratory (MDS Pharma Services, Saint-Laurent, QC, Canada) using a validated high-performance liquid chromatography-tandem mass spectrometry (HPLC-MS/MS) method. The lower limit of quantitation (LLQ) for dapsone and *N*-acetyl dapsone was 0.05 ng/mL.

Pharmacokinetic Analyses

The following pharmacokinetic parameters were assessed: the area under the plasma concentration-time curve (AUC), maximum plasma concentration (C_{max}), time to reach C_{max} (t_{max}) and elimination half-life ($t_{1/2}$). For oral dapsone, the terminal elimination half-life was determined. For dapsone gel, the apparent elimination half-life of dapsone after the last treatment was determined. Non-compartmental methods were used to calculate the pharmacokinetic parameters using WinNonlin® version 4.0.1 (Pharsight Corporation, Mountain View, CA, USA). The linear trapezoidal rule was used in conjunction with the extravascular input model 200. Both the C_{max} and the t_{max} were determined directly from the plasma concentration data without interpolation. The AUC from 0 to 24 hours (AUC_{24}) was calculated by numerical integration using the trapezoidal rule. For oral dapsone, the AUC from 0 to infinity (AUC_∞) was estimated as $AUC_{0-t} + C_t/k_e$, where C_t is the last measurable concentration (at time t) and k_e is the elimination rate constant calculated by linear regression of the terminal phase data. The $t_{1/2}$ was calculated as $\ln(2)/k_e$. Concentrations below the LLQ were assigned a value of zero for all pharmacokinetic calculations. Relative exposures were estimated by comparing the AUC_{24} for dapsone gel with the AUC_∞ for oral dapsone.

Statistical Methods

The sample size was based on having a reasonable number of subjects for computing descriptive statistics. Twenty subjects were planned and it was estimated that ten subjects would cross over to the oral dapsone subset. A total of 18 subjects were enrolled in the study (the all-subjects dataset). The pharmacokinetic evaluable dataset also included all 18 subjects, except for determination of the k_e, which included 17 subjects (one subject had voluntarily discontinued after day 15). Descriptive statistics for the pharmacokinetic analysis (mean, median, standard deviation, minimum, maximum) were determined using data from all subjects who completed the sampling sequence (the pharmacokinetic evaluable set). Laboratory data were summarised by timepoints at screening and on days 5 and 14 and, for the subset of ten subjects only, on days 28 and 31. Shift tables were constructed for change from baseline. The pharmacokinetic parameters of basic interest were the C_{max} and AUC_{24}.

Drug-Interaction Study of Dapsone Gel, 5% with Trimethoprim/Sulfamethoxazole

Study Design and Subjects

The drug-interaction study was an open-label, single-centre study to evaluate the steady-state pharmacokinetics of trimethoprim/sulfamethoxazole alone, dapsone gel alone and the two agents in combination (figure 1). Oral trimethoprim/sul-

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