Pharm Res (2019) 36: 13
https://doi.org/10.1007/s11095-018-2537-8

RESEARCH PAPER

Bioequivalence Study Methods with Pharmacokinetic Endpoints for Topical Ophthalmic Corticosteroid Suspensions and Effects of Subject Demographics

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Received: 19 August 2018 / Accepted: 8 October 2018 / Published online: 15 November 2018

ABSTRACT

Purpose To establish bioequivalence for topical ophthalmic corticosteroid suspensions, some of U.S. product-specific guidances (PSGs) for generic drug products recommend evaluation of aqueous humor (AH) pharmacokinetics (PK). However, the AH PK study is complex because the relationships among AH PK, subject demographics, ocular anatomy, physiology and the compounds' physicochemical characteristics are not well understood. The objective of this research is to provide an overview of the *in vivo* human AH studies submitted to the U.S. Food and Drug Administration (FDA) for ophthalmic corticosteroid suspensions and to investigate the impact of subject demographics on the human AH PK.

Methods We summarized demographic data, sampling time points, sample size per time point and PK parameters to investigate correlations in the studies submitted to the FDA.

Results In the evaluation of subject-specific covariates, the area under the concentration-time curves (AUC) and maximum concentrations (C_{max}) were significantly different among ethnicities and age groups. Gender was not primarily associated with differences in AH PK.

Conclusions Our results suggest that the difference in ethnicity and age of the study population play an important role in the AH PK profiles of topical ophthalmic corticosteroid suspensions. Considering the subject-specific covariate effects in designing bioequivalence studies with AH PK endpoints could reduce bias from covariate imbalance and help identify true effects of formulation differences.

KEY WORDS Aqueous humor · bioequivalence · ocular pharmacokinetics · ophthalmic corticosteroid suspensions · subject demographics

INTRODUCTION

For topical ophthalmic products, following topical instillation, only a small percentage of the administered drug reaches the AH because of the rapid drainage in the precorneal area (1). The loss of drug from the precorneal area is a net effect of tear secretion, drainage, and noncorneal and corneal absorption rate processes (2). Generally, the hydrophilic and lipophilic properties dictate how products reach the AH through different routes. The thick cornea limits the absorption of the products that are hydrophilic products and contain large molecules (3) which are generally absorbed across the conjunctiva and sclera (4). The lipophilic molecules, like corticosteroids, penetrate the corneal epithelium, absorbed across the corneal stroma and into the anterior chamber, which are eliminated by aqueous flow and by diffusion into the blood circulation through the trabecular meshwork (5). Also, the uveoscleral outflow pathway, a passive flow and not a distinctive pathway like trabecular meshwork, consists largely of the ciliary muscle, iris root and sclera (6). The AH PK process of a drug will be affected by ocular anatomy, physiology and the compounds' physicochemical characteristics (3,7).

The *in vivo* PK bioequivalence study design for ophthalmic topical corticosteroid suspensions recommended by the FDA is a single-dose, *in vivo* AH sparse-sampling PK study in subjects undergoing cataract surgery collecting a single sample of AH from one eye at one assigned sampling time point. Either a crossover or parallel study design is recommended.

Guest Editors: Hovhannes J Gukasyan, Shumet Hailu, and Thomas Karami

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Although a true crossover, obtaining a pair of samples from a single eye, is not practical, a pseudo crossover study is possible by dosing and sampling from each eye contingent upon cataract surgery being required for both eyes of the subject. In general, *in vivo* PK bioequivalence determination of the ophthalmic topical corticosteroid suspensions relies on the observed AH drug concentration-time profile of an accumulation of individual measurement from each subject. However, the correlation between subject-specific covariates and the AH bioavailability of ophthalmic topical corticosteroid suspensions is not well understood. Hence, we investigated the impact of subject demographics on the human AH PK based on the *in vivo* human AH studies for ophthalmic corticosteroid suspensions submitted to the FDA. The influence of variability in physicochemical characteristics and possible physiological changes in the eye as a result of cataract on AH PK will not be discussed here.

The most common topical ophthalmic dosage forms are solution, suspension, emulsion, and ointment (8). For these topical ophthalmic products, as of June 10, 2018, a total of thirty-two U.S. PSGs are posted online (9). For topical ophthalmic corticosteroid suspensions indicated for subjects undergoing cataract surgery, FDA recommends a PK study in AH with and without an option of *in vitro* physicochemical characteristics and *in vitro* drug release testing to demonstrate bioequivalence when the test product is formulated qualitatively (Q1) and quantitatively (Q2) the same as the reference listed drug (RLD) (10). The generic ophthalmic products should meet the same physicochemical attributes as the RLD (Q3), since differences in the physicochemical values may alter the AH bioavailability. For any ophthalmic dosage form which is not Q1/Q2 equivalent in a permissible exception excipient (i.e., preservative, buffer, substance to adjust tonicity, or thickening agent), an *in vivo* bioequivalence study is requested. Concerning each drug product characteristics, the FDA intends to revise and update PSGs on a case-by-case base (11). For instance, a PK study in AH is not recommended for Loteprednol Etabonate 0.2%, as it is not indicated for subjects undergoing cataract surgery, and AH PK analysis may not be feasible. Measurement of drug concentrations in the AH provides rate and extent of bioavailability to investigate therapeutic equivalence for clinical safety and efficacy of products with the expected site of action in the anterior chamber.

For AH PK studies, instead of evaluating a full PK profile for each subject, multiple subjects are assigned to each of several prespecified sampling time because of limitations in collecting serial AH samples. The mean concentration at each sampling time is calculated by the average of these subjects' observed concentrations, and one profile of the mean concentration *vs.* time can be obtained for one product (12). One AUC value for one product can be calculated from the mean concentration–time profile using trapezoidal rules. PSGs recommend using a nonparametric bootstrap technique to calculate the variability of AUC from the variability of mean concentration at each time point along with the 90% confidence interval for the ratio of the true AUC of the test *vs.* the true AUC of the reference. The bootstrap procedures for parallel and crossover designs for AH PK studies are briefly presented in Table I.

The identification of influential subject-specific characteristics on AH PK will be pivotal in developing a reliable bioequivalence study design, as the AH PK process of a drug will be affected by ocular anatomy and physiology (13–15). The uncertain relationship among AH PK, subjects' specific ocular anatomy and physiology and the physicochemical properties of the drug will complicate the establishment of bioequivalence for topical ophthalmic corticosteroid suspensions and has never been fully evaluated due to limited *in vivo* human AH PK studies. The objective of this research is to provide an overview of the *in vivo* human AH studies submitted to the FDA for topical ophthalmic corticosteroid suspensions and to investigate the effect of subjects' specific ocular anatomy and physiology on the human AH PK for these corticosteroid suspensions. Our study will help improve the study design of AH PK for topical ophthalmic corticosteroid suspensions.

METHODS

A retrospective analysis of six bioequivalence studies containing human AH PK data submitted to the FDA for two different topical ophthalmic corticosteroid suspensions were conducted. Two topical ophthalmic corticosteroid suspension products, drugs I and II, with the same dose strength and inactive ingredients (Q1) and a difference of no more than 5% in the amount of any inactive ingredient (Q2) were used (9). In these single-dose, *in vivo* AH sparse-sampling PK studies in subjects undergoing cataract surgery, only one single sample of AH was collected from one eye, at one assigned sampling time point. Either a crossover or parallel study design was used. We summarized subject demographic data, sample size per time point, sampling time points, AUC and C_{max} to investigate correlations.

A single dose of the test or reference product was instilled into the inferior cul-de-sac of the eye prior to cataract extraction. Only a single sample of AH was collected from one eye at one assigned sampling time point. The average number of subjects at each PK sampling time point of drug I ranged between 14 and 79 subjects presented in Table II. For drug I, male and female subjects of per-protocol population (subjects who adhered the clinical study protocol), 18 years of age and older, of any race, who required cataract surgery were included for one of the nine post-dose time points per treatment and in the PK analysis. The per-protocol population includes all subjects who received study medication, satisfied pre-randomization protocol inclusion/exclusion criteria that were relevant to the assessment of PK parameters, and had an

Table I Summary of AH PK Study Designs for Topical Ophthalmic Corticosteroid Suspensions

	Parallel study	Crossover study
Sample	• One of two treatments, Test (T) or Reference (R), per subject	• A pair of T and R per subject (sequential bilateral surgery)
Sample Size	• Large (easier to recruit eligible subjects)	• Small
Duration	• Short (one period, T or R)	• Long (two periods, T-R or R-T, with washout period within 35 days)
Carryover	• No	• Possible without adequate washout period
Covariate Effect	• High (without appropriate randomizations)	• Low
T & R Arms	• Independent	• Related (same subjects are enrolled in each pair of sample time points)
90% CI of T/R ratio	• Nonparametric Bootstrap for Parallel Study	• Nonparametric Bootstrap for Crossover Study
	$h = T$ or R in the following bootstrap method.	$h = T$ and R in the following bootstrap method.
Bootstrap Methods	n: number of subjects (e.g., ni = subject treated at ith time point) k: number of sample time points j: number of bootstrap replicates (e.g., 10^5 times) • Calculate the mean concentration at each sampling time point $\overline{C}_{hi} = \sum_{j=n_{hi}} C_{hij}/n_{hi}$ • Calculate $AUC_{h,j}$ $AUC\ h, 0 \rightarrow t_i = t_1 * \overline{C}_{hi}/2 + \sum_{i=1}^{k_h-1} \left(\overline{C}_{hi} + \overline{C}_{h,i+1}\right) \cdot (t_{i+1} - t_i)\ /2$ • Calculate $C_{h,max,j}$ $C_{h,max} = \max_{i\in(1,\ldots,kh)} \left(\overline{C}_{hi}\right)$ • Calculate $AUC_{T,j}/AUC_{R,j}$ and $C_{T,max,j}/C_{R,max,j}$. • The 5th and 95th percentile of AUC_T/AUC_R and $C_{T,max}/C_{R,max}$ from all bootstrap replicates comprise the 90% CI for $\mu_T = \mu_R(AUC)$ and $\mu_T = \mu_R(C_{max})$.	

AH sample collected within the protocol-defined window for their assigned time and for whom adequate PK data were collected and available.

In the crossover study, subjects undergoing bilateral cataract surgery were randomly assigned to one of two treatment sequences (test-reference or reference-test) as presented in Table I. Each subject contributed two measurements of AH drug concentrations, a pair of test and reference per subject, at the same-time point in each study arm as follows: a single dose of test product or reference product was instilled in the respective operative eye at the assigned time point as per the randomized AH sampling time point prior to surgery. The actual time of AH sampling following test product or reference product instillation was recorded and used in the PK analyses. The wash-out period for the crossover study was not to exceed 35 days.

In the parallel studies, each subject was randomly assigned to one of two treatments and contributed one measurement as presented in Table I. A single dose of test product or reference product was instilled in the respective operative eye at the assigned time point as per the randomized AH sampling time point prior to surgery. The actual time of AH sampling following test product or reference product instillation was recorded and used in the PK analyses.

For the bioequivalence determination in each AH PK study, the bootstrap technique (iteration of 5000 times) was used to estimate the standard errors (SE) of the AUC and C_{max} of drugs I and II. In parallel studies, the AUC of the test product is independent of the AUC of the reference product. However, in crossover studies, the AUC of the test product is considered to be not independent of the AUC of the reference product because each subject contributes a pair of concentrations at one sampling time point (12).

The nonparametric bootstrap technique works well with crossover and parallel study designs for sparse sampling PK and is recommended in PSGs for AH PK studies for both study designs as summarized in the Table I. Briefly, a parallel study design for sparse sampling PK has one of two treatments, test or reference, assigned per subject in a single period. This study design will have a short duration of study without potential carryover effect and is easier to recruit eligible subjects. With independent test and reference arms, a parallel study design for sparse sampling PK has higher potential of having subject-specific covariate effects on AH bioavailability. On the other hand, a crossover study design for sparse sampling PK consists of two periods, sequence of test-reference or reference-test, with washout period within 35 days, which collects a pair of test and reference AH PK samples per subject undergoing sequential bilateral surgery. The crossover study design will have the same subjects in the same sampling time point in each arm. This study design for sparse sampling PK is beneficial to minimize the possible subject-specific covariate effects on AH bioavailability and reduce sample size.

Table II Result Summary

Drug I	Age Mean (Range)	Male %	Female %	Native American (%)	Asian (%)	African American (%)	Caucasian (%)	Other (%)
Subject Characteristics	62.1 (20–91)	43.80%	56.20%	8 (0.3)	1115 (40.3)	96 (3.5)	1533 (55.3)	18 (0.6)
Drug I Sample Time (hour)[a]	0.5	1	1.5	2	2.5	3	4	5
Total AH PK Samples	473	496	133	484	133	471	14	461
Average Samples per Study	78.8	70.9	66.5	69.1	66.5	78.5	14.0	76.8
Bootstrap (Drug I RLD only)		5000 iterations	$AUC_{0\text{-}1h}$	$AUC_{0\text{-}2h}$	$AUC_{0\text{-}3h}$	$AUC_{0\text{-}4h}$	$AUC_{0\text{-}5h}$	C_{max}
Asian		Mean	3.64	14.69	34.03	58.2	81.24	51.27
		%CV	14.22	8.53	6.29	5.53	4.97	7.74
Caucasian		Mean	0.85	4.63	22.81	48.48	72.84	26.76
		%CV	7.38	4.55	3.11	2.50	2.39	4.16
African American		Mean	0.87	3.4	12.98	29.49	49.18	22.68
		%CV	45.48	26.80	16.12	12.17	11.68	22.61
Caucasian Male		Mean	0.71	4.14	21.04	44.4	67.99	25.21
		%CV	10.54	6.92	4.83	4.02	3.99	7.31
Caucasian Female		Mean	0.99	5.11	24.46	52.09	77.29	29.16
		%CV	10.32	5.86	4.05	3.38	3.14	5.16
≤50 yo Caucasian		Mean	0.74	3.95	15.35	29.3	38.49	16.25
		%CV	42.87	19.43	13.19	13.77	20.37	22.67
>50 yo Caucasian		Mean	0.86	4.65	23.05	49.22	74	27.33
		%CV	7.58	4.66	3.17	2.60	2.47	4.29
Point Estimate (Drug I RLD only)		Acceptable Range	$AUC_{0\text{-}1h}$	$AUC_{0\text{-}2h}$	$AUC_{0\text{-}3h}$	$AUC_{0\text{-}4h}$	$AUC_{0\text{-}5h}$	C_{max}
Female / Male		0.8–1.25[b]	1.41 (Fail)[b]	1.24	1.17	1.18	1.14	1.16
≤50 yo / >50 yo Caucasian			0.87	0.85	0.67 (Fail)	0.60 (Fail)	0.52 (Fail)	0.60 (Fail)
Asian / Caucasian			4.32 (Fail)	3.18 (Fail)	1.49 (Fail)	1.2	1.12	1.92 (Fail)
African American / Caucasian			1.02	0.74 (Fail)	0.57 (Fail)	0.61 (Fail)	0.68 (Fail)	0.84
Asian / African American			5.20 (Fail)	4.63 (Fail)	2.69 (Fail)	2.00 (Fail)	1.67 (Fail)	2.35 (Fail)

[a] As only one study obtained AH sample after 5 h post-dose (i.e., 8 h post-dose), the pooled data was truncated at 5 h post-dose in this study

[b] To establish bioequivalence, the 90% confidence interval of the test and reference ratio of AUC and/or C_{max} should fall within the range 0.8–1.25. The current analysis includes only RLD and point estimate to evaluate any effect of subject specific characteristics on AH PK

Statistical Analysis

In the available demographic covariates, all significant covariates, such as specific age groups (≤ 50 years old and > 50 years old) and ethnicities (Caucasian, African American and Asian) with adequate number of subjects were evaluated. The difference in AH concentrations in each sampling time point was evaluated for each covariate. The differences between the AH concentrations of drug I of two age groups and three ethnicities at each timepoint, not normally distributed due to the limited number of samples, were analyzed using a Wilcoxon Rank Sum-test for the median values. To estimate the SEs of the AUC and C_{max} of each covariate, the bootstrap technique (5000 iterations) was utilized. A two-tailed unpaired t-test was used for comparing mean distributions of estimated PK parameters in the nonparametric bootstrap analysis. Also, point estimate of AUC and C_{max} subgroup ratio (e.g., subgroups of subject specific covariates such as Caucasian *versus* African American) in RLD of drug I was evaluated using the limit of 0.8–1.25.

Each covariate was analyzed in subgroups to reduce potential confounding factors. For instance, the age effect was evaluated in Caucasian and African American, separately. As no significant gender-related effect on AH PK was observed, each covariate analysis includes both genders.

RESULTS

Aqueous Humor Pharmacokinetics

In each *in vivo* bioequivalence PK study, AH concentrations of topical ophthalmic corticosteroid suspensions after administration of a single topical dose was evaluated. The

AH concentrations of drugs I and II were obtained at various intervals after topical ocular administration. Studies for drug II were used for validation studies in each subject-specific covariate analysis. The AH sampling time from each study for drug I is presented in Table II. AH PK samples were assayed from 2770 subjects receiving drug I. Basic demographic characteristics are summarized in Table II. Briefly, there was a near-equal distribution of male and female subjects, 44% *vs.* 56%. The subjects' age ranges between 20 and 91 years old, and approximately 55% of the subjects were Caucasian.

Ethnicity

The correlation between the AH bioavailability of ophthalmic topical corticosteroid suspensions and subject ethnicity was investigated. The differences between the AH concentrations of drug I were analyzed at each sample time point. The AUC and C_{max} of drug I in AH following administration of a single topical dose were estimated using a bootstrapping method ($n = 5000$) in Asian subjects and Caucasian subjects separately in pooled data. Only Asian and Caucasian subjects who completed per-protocol treatment were included in this analysis.

The distributions of mean $AUC_{0\text{-}5h}$ and C_{max} in Asian subjects were significantly higher than those in Caucasians (two-tailed unpaired t-test: $p < 0.001$), although the point estimate (PE) of Asian and Caucasian ratio of $AUC_{0\text{-}5h}$ fell with 0.8–1.25 (Table II). The predicted mean time to peak concentration in AH was approximately one hour earlier in Asians than in Caucasians. Table II summarizes the estimated mean (%CV) of AUCs and C_{max} in the pooled subjects who received RLD of drug I. Although most Asian subjects were younger than 50 years old [i.e., mean (SD) of 51.2 (5.9) years old] and most Caucasian subjects were older than 50 years old [i.e., mean (SD) of 70 (8.9) years old], the estimated AH exposures in Asian subjects were higher regardless of the tendency of lower bioavailability in younger subjects, which may indicate that the impact of subject ethnicity on AH PK.

The difference between African Americans and Caucasians were also evaluated in the pooled subjects who received RLD of drug I. A box-whisker plot in Fig. 1 shows the median and range (minimum and maximum) AH concentrations of drug I in African Americans and Caucasian groups at each sampling time point. Drug I AH concentration in Caucasians was significantly higher than in African Americans at each time point between 1 h and 3 h post-dose (Wilcoxon Rank Sum test: $p < 0.01$ at each time point) in the pooled data. Similar age distributions were observed in Caucasian and African American subjects (Fig. 1). There was a similar proportion of male and female African American (40.2 and 59.8%, respectively) and Caucasian (44.5 and 55.5%, respectively) subjects. The AH concentrations of drug I in African Americans and Caucasians were also evaluated in each study separately at each time point and displayed similar trends.

Our result shows that the subject ethnicity influences AH bioavailability of topical ophthalmic corticosteroid suspensions.

Age

The impact of subject age on AH PK of topical ophthalmic corticosteroid suspension was also evaluated. To minimize the ethnicity-dependent PK effect, the influence of age on the AH PK was evaluated in Caucasian subjects where we have adequate data for both younger ($n = 41$) and older ($n = 1492$) groups for this analysis. Asians, African-Americans, Native Americans and others (e.g., islanders) are excluded from the pooled data. The proportion of males and females in the younger subjects was 36.4 and 63.6%, respectively, and 45.7 and 54.3%, respectively, in older subjects.

A box-whisker plot in Fig. 1 shows the median and range (minimum and maximum) AH concentration of drug I in the younger and older groups at each sampling time point for the pooled Caucasian subjects. The median (range) of drug I in the older group is significantly higher than that in the younger group between 3 h and 5 h post-dose (Wilcoxon Rank Sum test: $p < 0.01$ at each time point) in the pooled data. To confirm the trend observed in the pooled data, the AH concentration of drug I in younger and older groups of Caucasians were also evaluated in each study separately at each time point, although the younger group does not have sufficient data in separate studies. As observed in the pooled data, in each study, the AH concentrations of drug I displayed higher AH bioavailability in the older group compared with the younger group at each sampling time point.

Drug II AH concentration in Caucasian subjects was also compared between older and younger groups, and the similar trend was observed in drug II, even though limited number of subjects were available at each sampling time point in the younger group. A similar strong correlation was observed between age and the AH bioavailability of topical ophthalmic corticosteroid suspension. The result suggests that the impact of subject age on bioavailability of topical ophthalmic corticosteroid suspension should be considered for the AH PK bioequivalence study design.

DISCUSSION

We investigated bioequivalence studies containing human AH PK data submitted to the FDA for two different ophthalmic topical corticosteroid suspensions and summarized demographic data, sampling time points, sample size per time point, AUC and C_{max} for the examination of correlations. Also, the

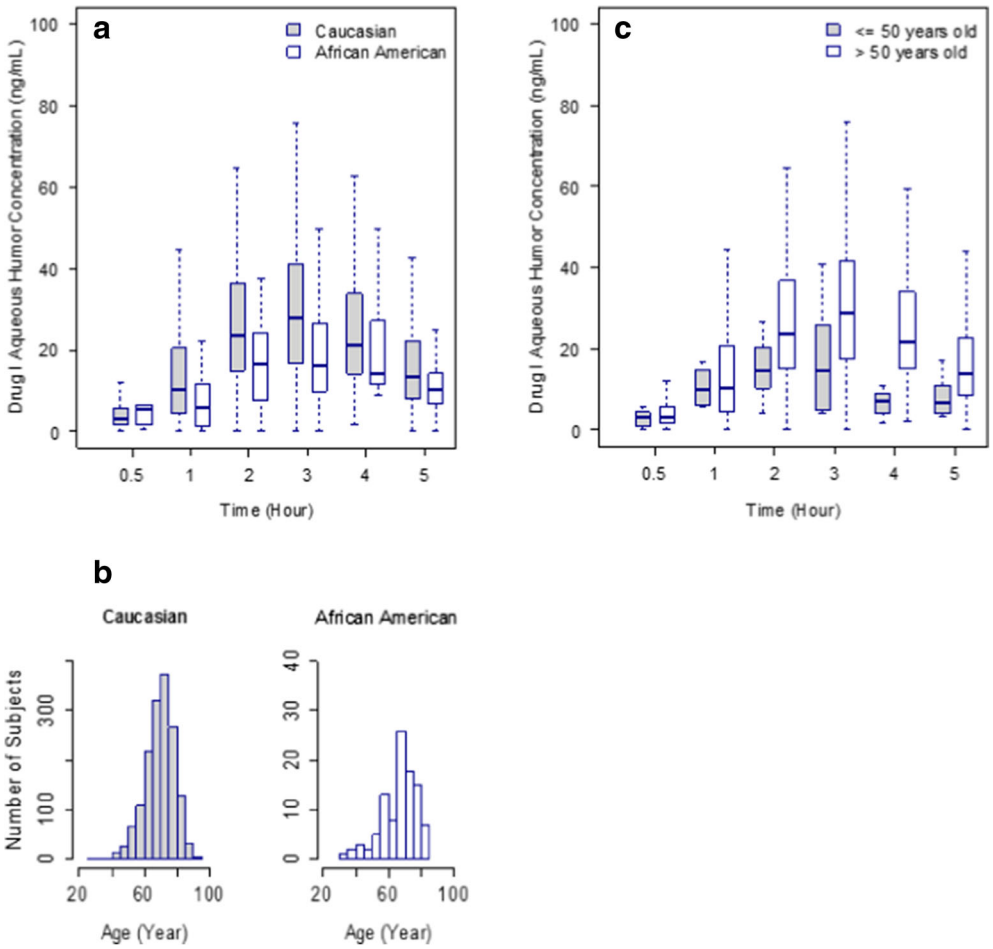

Fig. 1 Observed Aqueous Humor Concentration *versus* Time Curves of Drug I in Different Subject Specific Characteristics.(**a**) The median (range) of drug I AH concentration in Caucasians was significantly higher than in African Americans at each time point between 1 hour and 3 hours post-dose (Wilcoxon: $p<0.01$ at each time point) in the pooled data. (**b**) Similar age distributions were observed in Caucasian and African American subjects. (**c**) In Caucasian subjects, the median (range) of drug I in the older group is significantly higher than that in the younger group at each time point between 3 hours and 5 hours post-dose (Wilcoxon: $p<0.01$ at each time point) in the pooled data. In Caucasian subjects, the proportion of males and females in the younger group was 36.4% and 63.6%, respectively, and 45.7% and 54.3%, respectively, in the older group. The similar trend of age effect was observed between 3 hours and 5 hours post-dose in drug II.

evaluation of subject-specific covariate effects on AH bioavailability in subgroups including age (≤ 50 years old *vs.* > 50 years old), gender, and ethnicity was conducted.

As Fig. 1 displays, the correlations between subject-specific covariates and the AH bioavailability of ophthalmic topical corticosteroid suspensions are significant in drug I. In particular, age and ethnicity displayed a significant impact on AH PK. Also, a similar correlation was observed in subjects' age in drug II. The AH PK process of a drug will be affected by ocular anatomy and physiology (13–16). Our study indicates that the impact of covariate in the study design may be considered in AH PK studies for topical ophthalmic corticosteroid suspensions.

The difference in ocular anatomy among various ethnicities and ages (13,14) of the study population may be critical in the aqueous humor PK profiles of topical ophthalmic corticosteroid suspensions. Generally, Asians have the highest prevalence of primary angle-closure glaucoma, probably caused by the shallow anterior chamber (15). Our comparison of aqueous humor bioavailability of topical ophthalmic corticosteroid suspension using a bootstrapping resampling method in Asian and Caucasian populations displayed significantly higher corticosteroid aqueous humor concentrations in Asians than in Caucasians. The higher aqueous humor concentrations in Asians following a single application of topical ophthalmic corticosteroid suspensions could be attributed to the fact that Asians have a shallower anterior chamber than Caucasian subjects (15,17). The shallower anterior chamber may result in the lower volume of aqueous humor and higher AH concentrations in Asians. Of note, Asian population generally consists of East Asian, South Asian and Southeast Asian. As most Asian subjects in our study were enrolled in India, Asian subjects could be indicated as South Asian. In our study, due to a limited number of subjects available in East and Southeast Asian, Asian subjects are not clustered as East, South or Southeast, separately. Yet, the ocular anatomical and physiological differences among Asian population should not be ignored when evaluating the AH PK profiles of ophthalmic corticosteroid suspensions.

Trabecular meshwork is responsible for draining the aqueous humor from the eye and affects aqueous humor outflow. Shorter trabecular meshwork heights may trigger the higher prevalence of primary open-angle glaucoma. Trabecular meshwork size is also different among various ethnicities (18) and may play a role in ethnic differences in aqueous humor

corticosteroid bioavailability. The lower aqueous humor bioavailability in African Americans can perhaps be attributed to their relatively deep anterior chamber (15), as the deep anterior chamber may result in higher volume of aqueous humor, and the fact that their darker pigmented iris color's capacity to bind to certain compounds is known to be higher (2).

The age-related physiological ocular changes may increase the AH exposure to topical ophthalmic products for older subjects. For instance, the epithelial barrier function of cornea will be impaired with age and may increase the epithelial permeability of ophthalmic products (19). Also, with age, to maintain the stable intraocular pressure (IOP), the production of aqueous humor will be diminished as a result of reduction of its drainage through the uveoscleral outflow pathway (20) possibly due to age-related reduction of the ciliary muscle bundles (6).

The age-related increase in lens thickness and the age-related decrease in anterior chamber depth (17) may also contribute to the higher exposure in older subjects following a single topical instillation of ophthalmic corticosteroid suspensions. The shallowing of the anterior chamber and reduced aqueous humor flow rate with age can alter the aqueous humor PK profile in older subjects, with possible aggravation of a higher adverse event incidence rate (i.e., IOP elevation), which may create additional risk for the development of acute primary angle closure and primary angle closure glaucoma.

Topical corticosteroids are well known to be associated with IOP elevation (21). Some individuals are known to experience a high degree of IOP elevation with low doses or short durations of treatment with topical corticosteroids (21,22). Further study should be conducted to investigate the influence of subject-specific covariates on the PK and pharmacodynamics of topical ophthalmic corticosteroid suspensions to mitigate the risk of IOP elevation (21). For ophthalmic topical corticosteroids, dexamethasone and prednisone acetate and the newer corticosteroid difluprednate are more likely to result in clinically significant increases in IOP compared to fluorometholone, rimexolone, and loteprednol etabonate (21,23).

One of major limitations in the current study is locations of the clinical studies among pooled data. Differences in locations of clinical studies relate to differences in quality of primary care, surgical procedures, diagnoses, economic and environmental conditions in healthcare services, which will all influence clinical outcomes and study results (24). The subject population may need to be tested to better elucidate potential effects.

Well-developed study designs will reduce complexity of stipulating influential covariate effects. A parallel study design for sparse sampling PK is beneficial to avoid possible carryover effects and easier to recruit study subjects. A crossover study design for sparse sampling PK using sequential bilateral surgery is beneficial to minimize the possible covariate effects and to identify the true effects of formulation differences in AH PK studies in view of insignificant physiological differences between two eyes of a single subject compared to the differences between subject-specific characteristics. For a parallel study design for sparse sampling PK, applying stratified randomization with respect to subject-specific covariates to the same sampling time points in each arm (e.g., one hour post-dose for test and reference arm) will increase in statistical power (25). For crossover studies, the possible carryover effects will be negligible by adopting an adequate length of washout period (26).

CONCLUSION

Our results suggest that the differences in ethnicity and age of the study population play key roles in the AH PK profiles of topical ophthalmic corticosteroid suspensions. Considering the subject-specific covariate effects in designing bioequivalence studies with AH PK endpoints could reduce bias from covariate imbalance and help identify true effects of formulation differences. Major limitations evaluating the pooled data in the current study are differences in bioanalytical method and locations of the clinical studies among pooled data. To reduce the impact of limitations in the AH PK studies, analysis was also conducted in each PK study and each covariate subgroup, separately. Further investigation on the impact of covariates and physicochemical properties is desirable.

Disclaimer

This article reflects the views of the authors and should not be construed to represent the views or policies of the FDA.

REFERENCES

1. Ghate D, Edelhauser HF. Ocular drug delivery. Expert Opin Drug Deliv. 2006;3(2):275–87.
2. Edelhauser HF, Maren TH. Permeability of human cornea and sclera to sulfonamide carbonic anhydrase inhibitors. Arch Ophthalmol (Chicago, Ill : 1960). 1988;106(8):1110–5.
3. Durairaj C. Ocular Pharmacokinetics. Handb Exp Pharmacol. 2017;242:31–55.
4. Ahmed I, Patton TF. Importance of the noncorneal absorption route in topical ophthalmic drug delivery. Invest Ophthalmol Vis Sci. 1985;26(4):584–7.
5. Gaudana R, Ananthula HK, Parenky A, Mitra AK. Ocular drug delivery. AAPS J. 2010;12(3):348–60.
6. Alm A, Nilsson SF. Uveoscleral outflow–a review. Exp Eye Res. 2009;88(4):760–8.
7. Kang-Mieler JJ, Osswald CR, Mieler WF. Advances in ocular drug delivery: emphasis on the posterior segment. Expert Opin Drug Deliv. 2014;11(10):1647–60.

8. Baranowski P, Karolewicz B, Gajda M, Pluta J. Ophthalmic drug dosage forms: characterisation and research methods. Sci World J. 2014;2014:861904.
9. FDA. Product-Specific Guidances for Generic Drug Development 2017 [Available from: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm075207.htm.
10. Choi SH, Lionberger RA. Clinical, pharmacokinetic, and in vitro studies to support bioequivalence of ophthalmic drug products. AAPS J. 2016;18(4):1032–8.
11. Kozak D WY. OGD citizen petition consult response memorandum (DRAFT). 2016.
12. Shen M, Machado SG. Bioequivalence evaluation of sparse sampling pharmacokinetics data using bootstrap resampling method. J Biopharm Stat. 2017;27(2):257–64.
13. Blake CR, Lai WW, Edward DP. Racial and ethnic differences in ocular anatomy. Int Ophthalmol Clin. 2003;43(4):9–25.
14. Agrahari V, Mandal A, Agrahari V, Trinh HM, Joseph M, Ray A, et al. A comprehensive insight on ocular pharmacokinetics. Drug Deliv Transl Res. 2016;6(6):735–54.
15. Wang D, Amoozgar B, Porco T, Wang Z, Lin SC. Ethnic differences in lens parameters measured by ocular biometry in a cataract surgery population. PLoS One. 2017;12(6):e0179836.
16. Zore M, Harris A, Tobe LA, Siesky B, Januleviciene I, Behzadi J, et al. Generic medications in ophthalmology. Br J Ophthalmol. 2013;97(3):253–7.
17. Jonas JB, Iribarren R, Nangia V, Sinha A, Pardhi P, Shukla R, et al. Lens position and age: the Central India eye and medical study. Invest Ophthalmol Vis Sci. 2015;56(9):5309–14.
18. Chen RI, Barbosa DT, Hsu CH, Porco TC, Lin SC. Ethnic differences in trabecular meshwork height by optical coherence tomography. JAMA Ophthalmol. 2015;133(4):437–41.
19. Chang SW, Hu FR. Changes in corneal autofluorescence and corneal epithelial barrier function with aging. Cornea. 1993;12(6):493–9.
20. Goel M, Picciani RG, Lee RK, Bhattacharya SK. Aqueous humor dynamics: a review. Open Ophthalmol J. 2010;4:52–9.
21. Pleyer U, Ursell PG, Rama P. Intraocular pressure effects of common topical steroids for post-cataract inflammation: are they all the same? Ophthalmol Therapy. 2013;2(2):55–72.
22. Moss EB, Buys YM, Low SA, Yuen D, Jin YP, Chapman KR, et al. A randomized controlled trial to determine the effect of inhaled corticosteroid on intraocular pressure in open-angle Glaucoma and ocular hypertension: the ICOUGH study. J Glaucoma. 2017;26(2):182–6.
23. Sheppard JD, Comstock TL, Cavet ME. Impact of the topical ophthalmic corticosteroid Loteprednol Etabonate on intraocular pressure. Adv Ther. 2016;33(4):532–52.
24. Roy B, Riley C, Herrin J, Spatz ES, Arora A, Kell KP, et al. Identifying county characteristics associated with resident well-being: a population based study. PLoS One. 2018;13(5):e0196720.
25. Green SB, Byar DP. The effect of stratified randomization on size and power of statistical tests in clinical trials. J Chronic Dis. 1978;31(6–7):445–54.
26. Wellek S, Blettner M. On the proper use of the crossover design in clinical trials: part 18 of a series on evaluation of scientific publications. Dtsch Arztebl Int. 2012;109(15):276–81.