Eyeing opthalmic products: Bioequivalence assessment and drug development - Strategic considerations

Sir,

The use of pharmacodyamic endpoints has been reported to assess the bioequivalence of two ophthalmic formulations of ketotifen.[1] The authors published a well designed and executed study, which, among other things,

included appropriate and *a priori* defined pharmacodynamic endpoints in the targeted patient population.[1] The applied bioequivalence strategy of using pharmacodynamic markers (but not pharmacokinetics) was adequately justified because of the lack of quantifiable levels of ketotifen in the systemic circulation after ocular administration.[1]

Typically, for other routes of drug administration such as oral, parentral, intranasal, etc., bioequivalence is established using universally well-accepted pharmacokinetic surrogates, where one would conclude bioequivalence of the two products if they exhibit an equivalent rate (i.e., peak concentration, Cmax parameter) and extent of absorption (i.e., area (please include: Area since it defines the pharmacokinetic variable) under the serum/plasma concentration time curve; AUC parameter). Such bioequivalence studies would be performed in healthy subjects, usually in a two-way randomized crossover study, ensuring that the study is powered adequately to address the inherent variability in the pharmacokinetics of the drug substance.[2]

It is important to clearly debate and establish the right strategy for bioequivalence assessment of ophthalmic dosage forms (traditional studies in healthy subjects using pharmacokinetic assessment versus pharmacodynamic markers and/or clinical endpoints in a relevant patient population). Some introspective thoughts are proposed for consideration: (a) does the systemic drug level correlate with the clinical effectiveness observed at the remote ocular site where the drug is applied to achieve local effects?; (b) does the local concentration at the ocular tissue be truly represented by the systemic exposure measurements?; (c) what is the influence of drug metabolism occurring in other organs/tissues (notably liver) - will this render a different disposition profile to the drug and, therefore, may not be reflective of the kinetics occurring at the ocular tissue; (d) product-specific issues of ophthalmic formulations such as drying effects and tear-film stability may, in turn, alter the kinetics of the drug at the local site where it is administered and, therefore, the tolerability profile of the ophthalmic drug products may play an indirect role.[3]

Interestingly, the utility of pharmacodynamic endpoints is further underscored, especially as it relates to switching of patients from one ophthalmic product to another one.[4] In this situation, the traditional pharmacokinetic approach would be of little use in establishing the switchability *per se* because different drugs with varied kinetics and disposition profiles are being considered. Using intraocular pressure as the pharmacodynamic marker, switchability from latanoprost to travoprost in a group of glaucoma patients was established.[4]

From the above considerations, although the practise of conducting a pharmacodynamic study for bioequivalence assessment in the patient population is an ideal approach for demonstrating clinical effectiveness of the two drug products, it carries a number of potential issues such as: (a) cost of the trials; (b) enrolment delays; (c) adequate washout time before first dose administration; (d) lack of drug-naïve patients; (e) influence of other comedications; (f) ethical constraints if reference formulation is ineffective. Additionally, from a drug development perspective, it would be extremely challenging because formulation switches/changes are part of any pharmaceutical development program. Oftentimes, formulation switches become necessary due to stability issues, avoidance of an excipient, manifestation of toxicity and/or tolerability episodes, need of larger dose size, etc. It may become impractical to address the changes in formulation strategy using both resource- and time-intensive clinical studies in patients. Therefore, the use of appropriate *in vitro* studies and/or animal models as possible tools to aid in the initial phases of clinical testing needs to be encouraged to guide ophthalmic product development. However, it is important that both *in vitro* and/or pre-clinical models are adequately validated to justify the important go/no go decisions that need to be made during drug development.

Overall, it appears that ophthalmic product development poses a significant challenge because the supportive evidence from pharmacokinetic surrogate markers are generally difficult to obtain. Also, underlying questions regarding the relevance of systemic kinetics for drug action at an intraocular site may also arise frequently. Nevertheless, pragmatic approaches, as put forward in this letter, need to be considered to overcome such hurdles. Additionally, regulatory feedback could also be sought to streamline the requirements for the development process regarding ophthalmic products.

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