Letter to the Editors

Sensitive studies with a significant dose–response curve for inhaled corticosteroids to investigate equivalent relative potency are feasible

Alfredo García-Arieta*

Division of Pharmacology and Clinical Evaluation, Human Use Medicines, Spanish Agency for Medicines and Health Care Products, C/ Campezo 1, Edificio 8, Planta 2, 28022 Madrid, Spain.

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I read with interest the paper by Clearie *et al.* [1] because the development of inhaled corticosteroid products is currently hindered by the lack of valid methodology to investigate therapeutic equivalence. Importantly, this paper illustrates that both methacholine provocative concentration of methacholine needed to produce a 20% fall in FEV₁ (PD₂₀) and exhaled nitric oxide (NO_e) exhibit a significant dose–response curve, which is the first step towards calculating the relative potency (RP) between products. This can be anticipated from the plots in the paper by Kelly *et al.* [2]. In addition, if the placebo response is not taken into account in these plots, sputum eosinophilia dose–response is non-existent.

In the USA, RP estimation is essential for the comparison of inhalation products owing to their flat dose–response curve. In contrast, in Europe, the traditional and insensitive comparison of the response (at two different dose levels now) is better understood by regulatory clinicians. Fortunately, both analyses are required at present in the European Union [3].

This type of evidence is necessary to develop guidelines on how to compare inhalation products pharmacodynamically. In fact, the US Food and Drug Administration (FDA) has not issued any guidance on this topic because of this limitation. Interestingly, this paper confirms that NO_e, the pharmacodynamic end-point suggested by the FDA, shows a significant dose–response curve. It would be valuable if the authors could compare both end-points to identify the most sensitive and less variable one, and discuss whether they provide the same information or if each provides information on a different aspect of the therapeutic effect, in which case both should be equivalent.

Unfortunately, in the presented study, the selection of patients was not limited to those able to respond differ-

ently to the two doses of budesonide. This inclusion criterion would have hampered the recruitment of subjects but would have increased the slope of the dose–response curve and perhaps even reduced the intrasubject variability, which in turn would have allowed the conclusion of equivalence within the 0.5–2.0 or even 0.67–1.5 acceptance range with a reasonable sample size ($n = 50$ – 100). A response from the authors on the sample size required would be welcome.

Despite some concerns related to the absence of washout between the two dose levels of each treatment, it would be beneficial, although others may prefer simpler studies without RP estimation, if this study was taken as a model in future inhaled corticosteroid comparisons. If this were the case, it is necessary to clarify some misconceptions that can be found in the paper, as follows

The $\pm 33\%$ (0.67–1.50) acceptance range of the Committee for Human Medicinal Products guideline refers only to RP, because it is a comparison in the dose axis (x -axis), and RP confidence interval can be calculated at a 90% confidence level as in pharmacokinetic bioequivalence studies. The comparison of the responses at each dose level has to be based on a predefined and clinically justified acceptance range.

In vitro data comparison is essential before any *in vivo* study and should be compared based on the whole distribution, not simply on the fine particle dose. The acceptance range of $\pm 15\%$ (0.85–1.18) is used for each individual stage of the impactor, and it is a requirement only if a biowaiver is applied, which is not possible in this case due to the differences in formulation composition.

Pharmacokinetic comparisons should be performed in a single-dose study because they are considered most sensitive to detect differences between products, and the

sampling times should be taken as early as 2 and 5 min after inhalation to characterize properly time of maximum concentration ($t_{\max}$) and maximum concentration ($C_{\max}$), because it is not adequate to detect the $C_{\max}$ in the first sampling time.

Moreover, this study shows that the CHMP guideline [3], which was an important advance, requiring assay sensitivity and the investigation of two doses to avoid approval based on insensitive studies and describes bio-waivers based on *in vitro* data or pharmacokinetic safety and lung deposition studies, needs to be updated. The study design should be cross-over in order to reduce variability and sample size, and this study shows that spirometric variables are less sensitive than PD_{20} or NO_e . Fortunately, the cross-over design and alternative endpoints, such as PD_{20} or NO_e , are considered in the CHMP guideline if justified, which is now evident.

Finally, I would like to highlight that as $C_{\max}$ is not influenced by the later absorption from the gut, it is indicative of the extent and pattern of distribution within the lung, because the deeper the deposition within the lungs the higher $C_{\max}$. Then, the point estimate of $C_{\max}$ (0.89) in the pharmacokinetic study suggests a more central deposition of the new hydrofluoroalkane (HFA) formulation and a slightly lower efficacy, which is in complete agreement with an RP estimation for PD_{20} of 1.10. This means that 10% more of the new HFA formulation is required to obtain the same effect as a given dose of the chlorofluorocarbon (CFC) formulation. Therefore, it is confirmed that pharmacokinetic information is a surrogate for efficacy and safety.

Competing Interests

Alfredo García Arieta is a bioequivalence assessor of the Spanish Agency for Medicines and Health Care Products and was involved in the assessment and authorization of the variation from CFC to HFA formulation of the budesonide product described in the paper and the drafting of the CHMP Guideline.

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CORRESPONDENCE

Dr Alfredo García-Arieta, Division of Pharmacology and Clinical Evaluation, Human Use Medicines, Spanish Agency for Medicines and Health Care Products, C/ Campezo 1, Edificio 8, Planta 2, 28022 Madrid, Spain.
Tel.: +34 918225167
Fax: +34 918225171
E-mail: agarciaa@agamed.es