Letter to the Editors

Guidelines to establish relative potency are not in touch with reality

Brian Lipworth & Karine Clearie

Asthma and Allergy Research Group, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK

García-Arieta [1] interprets our data [2] purely from a regulatory perspective with regard to demonstrating equivalence. In this regard, we demonstrated a significant overall dose–response relation from regression analysis of the common slope for shift in methacholine PC₂₀, indicating assay sensitivity for this outcome. However, when one inspects the difference in PC₂₀ shift between the 200 and 800 µg doses, while there was significant dose separation it has to be taken in the context of the biological variability which is of the order of ± 1 doubling dilution (i.e. ± 2 -fold shift). Thus, one needs to distinguish between a statistically significant difference from what may be clinically irrelevant. Pointedly, our patients were selected *a priori* for being methacholine responsive, with a mean PC₂₀ of 0.66 mg/ml⁻¹, i.e. they had plenty of room for improvement in response to inhaled corticosteroid. When comparing the formulations at each dose level, the confidence limits for the mean difference in PC₂₀ was contained within accepted limits of variability of ± 1 doubling dilution, indicating therapeutic equivalence. Our study shows that even using $n = 89$ patients, while the point estimate for relative potency was close to unity, the 95% confidence interval was well outside of accepted pharmacodynamic equivalence limits. Given that this was performed within a single centre with considerable experience of challenge studies, we are of the firm opinion that it is not feasible to assess relative potency using Finney, and as such this should no longer be recommended in current guidelines for establishing equivalence. Although we also showed significant dose separation for suppression of exhaled nitric oxide, the mean difference between 200 and 800 µg was rather small, amounting to 14% with HFA and 11% with CFC, in comparison to 29 and 20% differences, respectively, for methacholine PC₂₀ shift.

We evaluated pharmacokinetic outcomes at steady state to mirror what happens in real-life clinical practice, where patients take their inhaled steroid twice daily and not as single doses, i.e. also to reflect the chronic dosing

protocol for our challenge study. In fact, our data for area under the curve showed that the two formulations were equivalent within conventional limits of $\pm 20\%$, in keeping with the challenge data when comparing the methacholine PC₂₀ shift at each dose. Finally, subtle differences in pharmacokinetic and pharmacodynamic outcomes pointed out by García-Arieta [1] need to be put in their true perspective, because variations in real-life inhaler technique will result in at least 50% differences in dose delivered to the lungs, even within the same individual from day to day. Thus, from a clinical perspective, a 10% difference in delivered dose is rather meaningless for the patient. In the light of our study, we believe that the guidelines are no longer in touch with the reality of performing clinical trials using surrogate inflammatory end-points with inhaled steroids and especially the need to calculate relative potency ratios using Finney.

Competing Interests

BJL has received funding from AstraZeneca for consulting, expert witness and performing a clinical trial on Budesonide HFA.

REFERENCES

- 1 García-Arieta A. Sensitive studies with a significant dose–response curve for inhaled corticosteroids to investigate equivalent relative potency are feasible. *Br J Clin Pharmacol* 2011; 72: 832–3.
- 2 Clearie KL, Williamson PA, Meldrum K, Gillen M, Carlsson LG, Carlholm M, Ekelund J, Lipworth BJ. Pharmacokinetic and pharmacodynamic comparison of hydrofluoroalkane and chlorofluorocarbon formulations of budesonide. *Br J Clin Pharmacol* 2011; 71: 504–13.

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CORRESPONDENCE

Dr Brian Lipworth MD, Asthma and Allergy Research Group,
Ninewells Hospital and Medical School, Dundee DD1 9SY, UK.
E-mail: brianlipworth@googlemail.com