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Letter to the Editor

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A Good and Reliable Bronchodilator Dose-Response Relationship

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Dear Editor,

The article by Li et al. [1] is the first to describe the dose-response relationship in the delivered dose by nasal therapy. The authors have tested the effect of delivered bronchodilator through nasal cannula on forced expiratory volume in 1 s (FEV_1) and compared the results to a metered-dose inhaler with the valved holding chamber. The study by Li et al. [1] was the first to show dose ranging with aerosol delivery via transnasal pulmonary delivery in chronic obstructive pulmonary disease and asthma patients who were known responders, as identified by pre- and postbronchodilator administration in the pulmonary function tests as recommended by the American Thoracic Society and European Respiratory Society. They reported equivalent changes in FEV_1 with a nominal dose of 1.5 mg of albuterol, which is less than a standard unit dose of the drug, suggesting that the standard label dose would be sufficient for bronchodilator therapy via nasal therapy. I have some comments related to the technique.

The bioequivalence of inhaled medications is complex since the therapeutic effect is a response to the medication deposited in the lungs, and safety is an effect of systemic absorption of the orally ingested part. The FDA has recommended that the therapeutic equivalence between innovator and generic inhaled medications has to be evaluated by a human study that measures the degree of protection to bronchoprovocation [2]. This method measures the amount of the inhaled bronchoprovocation agent that is needed to decrease the FEV_1 by 20% after the inhalation of placebo and then active medication from the innovator and generic inhaled bronchodilators. Any method used in bioequivalence studies should be reproducible and have a dose-response relationship. Though a dose-response relationship has been previously shown [3], a bronchoprovocation study including two doses from an innovator and a generic inhaled medication suggested that therapeutic equivalence may have been due to the plateau of the dose-response curve [4]. This hypothesis was made because the two inhaled medications had a different fine-particle dose determined by in vitro studies.

The use of pharmacokinetic and imaging methods to determine the bioequivalence of inhaled products has been proven effective with the dose-response relationship [5]. These methods have been used to compare generic and innovation metered-dose inhalers with large volume spacer and dry powder inhalers and even salbutamol delivered through nasal cannula [6, 7]. So, in my humble opinion, to better understand the clinical dose-response

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relationship, additional testing would be appropriated based on the delivered dose using pharmacokinetic or imaging methods not only therapeutic response that has a plateau [4].

Disclosure Statement

The author declares that he has no conflicts of interest to disclose.

References

1 Li J, Zhao M, Hadeer M, Luo J, Fink JB. Dose Response to Transnasal Pulmonary Administration of Bronchodilator Aerosols via Nasal High-Flow Therapy in Adults with Stable Chronic Obstructive Pulmonary Disease and Asthma. Respiration. 2019;98(5):401–9.

2 Adams WP, Poochikian G, Taylor AS, Patel RM, Burke GP, Williams RL. Regulatory aspects of modifications to innovator bronchodilator metered dose inhalers and development of generic substitutes. J Aerosol Med. 1994;7(2):119–34.

3 Creticos PS, Adams WP, Petty BG, Lewis LD, Singh GJ, Khattignavong AP, et al. A methacholine challenge dose-response study for development of pharmacodynamic bioequivalence methodology for albuterol metered-dose inhalers. J Allergy Clin Immunol. 2002 Nov;110(5):713–20.

4 Mallol J, Aguirre V, Rhem R, Rodriguez J, Dolovich M. Therapeutic equivalence of three metered-dose inhalers containing salbutamol (Albuterol) in protecting against methacholine-induced bronchoconstriction in children with asthma. Pediatr Pulmonol. 2001 Dec;32(6):447–52.

5 Tomlinson HS, Corlett SA, Chrystyn H. Dose-response relationship and reproducibility of urinary salbutamol excretion during the first 30 min after an inhalation. Br J Clin Pharmacol. 2003 Aug;56(2):225–7.

6 Madney YM, Fathy M, Elberry AA, Rabea H, Abdelrahim ME. Aerosol delivery through an adult high-flow nasal cannula circuit using low-flow oxygen. Respir Care. 2019 Apr;64(4):453–61.

7 Madney YM, Laz NI, Elberry AA, Rabea H, Abdelrahim ME. The influence of changing interfaces on aerosol delivery within high flow oxygen setting in adults: an in-vitro study. J Drug Deliv Sci Technol. 2020;55:101365.