Inhaled steroids: new concepts on therapeutic index and dose equivalence

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Background – It is well known that for systemically administered drugs, such as corticosteroids, the therapeutic index cannot be improved by increasing their potency, since efficacy and safety are both attributable to circulating drug concentrations, and common receptor interactions. However, the validity of this assumption has not yet been investigated for inhaled corticosteroids, which are used in the treatment of asthmatic patients.
Objective - The objective of this study is to analyse evidence exploring the relationship betweeninhaled corticosteroidspotency and therapeutic index.
Methods - Analysis of recent literature on factors influencing the therapeutic index of inhaled corticosteroids.
Results – The most recent evidence on this topic was the paper by Daley-Yates, thatinvestigated the relationship between inhaled corticosteroids potency and therapeutic index, and applied a physiologically based PK/PD modelling to estimate inhaled corticosteroids safety (as impact on the hypothalamic–pituitary-adrenal axis) (Daley-Yates, 2015). The data show an approximately exponential relationship between potency and therapeutic index for inhaled corticosteroids (fig. 1). The inhaled corticosteroid molecules with highest potency, longer lung retention, low oral bioavailability and high systemic clearance (fluticasone furoate, fluticasone propionate, mometasone, ciclesonide) are reported to have the highest therapeutic index (>1) as compared to beclomethasone, budesonide and triamcinolone (<1). The highest value of 5.8 is observed for the 100 μg/day dose of fluticasone furoate. To put these values into context, 5 mg/day and 20 mg/day dose regimens of oral prednisolone have corresponding therapeutic index values of 0.32 and 0.08 respectively. Thus the molecular structural features that increase glucocorticoid receptor binding affinity and selectivity not only drive topical anti-inflammatory activity, but also result in enhanced targeting to the airways and reduced systemic exposure.
Conclusions – The data by Daley-Yates support the concept that desired local effects and systemic adverse events of inhaled corticosteroids can be separated, and that higher potency can improve the therapeutic index. However, these considerations are not reflected in asthma treatment guidelines, that classify inhaled corticosteroid formulations as low, mid and high doses solely on the basis of potency and efficacy, without consideration of the systemic exposure and relative risk of side effects. This historical approach is not appropriate for the wider range of molecules, potencies and device/formulations now available, and a more robust method is needed which includes both efficacy and safety when classifying inhaled corticosteroid regimens in terms of dose equivalence.