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Systemic availability of Rhinocort Aqua (budesonide) nasal spray: Importance of formulation and definition of delivered dose

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To the Editor:

In a recent review, Dr Stanley Szefer¹ discussed the pharmacokinetics/pharmacodynamics, metabolism/elimination, and distribution of intranasal corticosteroids. He clarified the importance of the improved therapeutic index of second-generation intranasal corticosteroids, compared with oral and parentally administered corticosteroids, in limiting systemic exposure and potential systemic side effects. However, he presented the systemic availability of budesonide as being 102% after 100 µg budesonide administered intranasally, a value not relevant for this parameter because the study cited² used an experimental, nonmarketed formulation. The correct labeled values for the systemic availability of the 2 formulations of intranasal budesonide suspension marketed in the United States are 21% for the pMDI formulation and 34% for the aqueous nasal spray.

The study referenced² was designed to determine the rate of absorption and local metabolism of budesonide after instillation (with a micropipette) of an experimental, nonmarketed solution also containing a surface-active ingredient (Tween 20). Four subjects were given the solution while in a recumbent position and then asked to complete an

intricate pattern of head turns to maximize the likelihood of prompt absorption. Absorption was found to be rapid and complete; systemic availability was 100%. This formulation was not developed for commercial use and is not commercially available anywhere in the world.

In a separate, more relevant open-labeled, crossover study³ of 17 healthy volunteers, the rate and extent of systemic uptake of budesonide after administration of different commercially available formulations was assessed. Subjects received single doses of intravenous budesonide 400 µg and intranasal budesonide aqueous nasal spray (BANS; Rhinocort Aqua) 400 µg, budesonide via Turbuhaler 800 µg, and budesonide via pressurized metered-dose inhaler (pMDI; Rhinocort Nasal Inhaler) 800 µg in random sequence, with a 6-week washout period between doses. The doses were administered according to patient-use instructions. The absolute systemic availability of budesonide for each formulation was calculated as

$$AUC_{niv} \times Dose_{iv} / AUC_{iv} \times Dose_{niv},$$

where *Dose* represents the delivered dose to the subject, not the dose leaving the drug container (the delivered dose to the subject is equal to the delivered dose from the applicator minus the amount recovered from the surface of the nasal applicator, the outside of the nose, and in exhaled air).

The mean systemic availability of the 2 formulations of intranasal budesonide suspension marketed in the United States was 21% (95% CI, 16.9% to 25.9%) after administration of the pMDI formulation and 31.4% (95% CI, 23.8% to 41.3%) after administration of BANS. When the systemic availability was calculated as the “delivered dose” (that is, the delivered dose from the applicator—referred to as the *metered dose* in the reference), the systemic availability of the pMDI formulation was 12.6% (95% CI, 10.5% to 15.1%) and that of BANS was 29% (95% CI, 22.9% to 36.7%).

These studies illustrate the importance of formulation, the importance of the definition of delivered dose used when calculating systemic availability, and the possible importance of body posture on the assessment of the rate and extent of systemic uptake of systemic corticosteroids.

Given the concern of patients and their physicians about systemic availability of intranasal corticosteroids and the resulting potential safety implications, clarification of these data is important so that physicians can be accurately informed.

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