

Letter to the Editor: Incorrect conclusions regarding deposition of conventional mometasone furoate (MF) nasal spray

To the Editor,

The article "Regional deposition of mometasone furoate nasal spray suspension in humans"¹ uses validation in nasal casts, regional deposition of radio-labeled drug in healthy subjects, and a literature review to conclude: "MF [mometasone furoate] aqueous suspension deposited more of its metered dose in humans to the turbinates and middle meatus of the nasal cavity than demonstrated in the literature by other nasal sprays." This prominent conclusion is unsupported and incorrect due to crucial unreported limitations. In this study, the subjects were reportedly trained in the administration "technique described in the package insert"; however, actual administration was by a technician, likely biasing deposition patterns and decreasing variability.²

Also, as expected with conventional nasal sprays, deposition was concentrated near the nasal valve and head of the inferior turbinate (in casts and *in vivo*).^{2,3} Unfortunately, the implications of this highly concentrated deposition (*e.g.*, Fig. 5) for an accurate estimation of regional deposition are not recognized. When a vertical line that separates the anterior-posterior regions is defined exactly in the area of highest concentration, even minor differences in the line position cause major shifts in relative distribution between as-defined "anterior" and "posterior" segments.⁴ We appreciate the authors' use of the method we developed by using a vertical plane at the head of the inferior turbinate visualized by superimposing vertical magnetic resonance imaging sections to delineate anterior-posterior nasal segments.⁴ However, this line is more anterior than in many previous studies and most likely more anterior than the corresponding line in the cast (see Figs. 1, 5, and 11, Hughes 2008).³⁻⁵ This renders suspect the comparison of regional deposition in the cast versus humans.

With the sensitivity of this "anterior-posterior" result to the dividing line, the unreserved comparative conclusion, "60% of the mometasone furoate spray deposited into the posterior nasal cavity," whereas "most other nasal spray deposition studies showed less than 25% in the posterior nasal cavity, with more than 50% in the anterior regions," would appear at best only weakly supported.¹ Weakness becomes inaccuracy in light of the fact that, in the only human γ -deposition

study that applied the same vertical dividing line (omitted from the article⁵), the conventional spray pump produced nearly identical anterior (25.4% versus 26.0%) versus posterior (60.1% versus 60.4%) deposition as reported for MF in this study. Lastly, all "posterior" are not the same. Results of previous studies indicate conventional nasal sprays poorly access target regions for deep nasal inflammation, in part, due to inferior (low) deposition of their "posterior" delivery (*i.e.*, the floor of the nasal cavity, not the middle meatus).² This could have been, and has been, studied by using both vertical and horizontal segmentation.^{2,5}

As the authors suggest, upper-posterior regions of the nasal cavity (*e.g.*, the middle meatus) are important locations in common nasal inflammatory diseases. Delivery of marketed MF with a conventional nasal spray has not been shown to reach those regions better than other conventional nasal sprays. However, in other studies that did test self-administration and did use both vertical and horizontal regional quantification, another technology has demonstrated such superiority.^{2,5}

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Response,

We appreciate the comments by Dr. Djupesland and Dr. Mahmoud about our article given their background in this area as inventor and developer of the bidirectional nasal delivery device, for which they has included citations. Whereas Devadason *et al.*¹ pro-

vided standards for quantifying regional lung deposition imaging, no standards exist for quantifying regional nasal deposition. The issues raised by Dr. Djupesland and Dr. Mahmoud point to the need for discussion and development of standards in this area. The comment suggests that the drug administered by a technician may be more likely to deposit in the posterior nasal cavity. The basis, described in this review,² was from comparing a study with self-administered radiolabeled insulin ($n = 6$), which resulted in a majority deposition in the anterior region, to cromoglycate ($n = 5$) by a technician, which showed posterior nasal cavity deposition. Using these two separate and very small studies to draw conclusions is inappropriate because nothing was controlled between the studies.

We note that our product is commercially marketed. Our technicians ensured that the U.S. Food and Drug Administration–approved patient instructions were followed in the 12 healthy subjects, and our conclusions presume that the patient instructions were followed. Our study was not a human factors study intended to assess variability, user interaction, or patient instructions: a type of study recommended by the U.S. Food and Drug Administration in a complete response to a product associated with Dr. Djupesland. Such studies could be of considerable benefit for nasal devices. We note that two recent nasal deposition articles do not state how patients were dosed, whereas we did.^{3,4} Also, variability was similar to that reported by Leach *et al.*³ for this product.

Dr. Djupesland and Dr. Mahmoud express concern about the anterior-posterior line. We recognize that, across many years of articles, variation exists on the “posterior nasal cavity.” We considered further dividing the posterior nasal cavity but were concerned about resolution. After reviewing images from our study, we can state that deposition from our spray was primarily toward the middle and inferior portions of the region we defined as the posterior nasal cavity. We acknowledge that the OptiNose (OptiNose US Inc., Yardley, PA) device may better target the upper posterior region. However, we are confident in anterior versus posterior deposition because of the rate of mucociliary clearance. The rapid clearance, within 15 minutes, confirms deposition into this region. We have further back-calculated the deposition by using models by Gonda and Gipps⁵ to confirm the initial deposition. We only used the nasal cast as a discriminatory tool to validate the radiolabeling. We did not use the nasal cast to compare *in vivo* and *in vitro* deposition. Further, our cast was an earlier generation of the one pictured

in Hughes *et al.*⁶ and we know that deposition was different.

Dr. Djupesland and Dr. Mahmoud also suggested that one of their articles showed similar deposition of a nasal spray when compared to their bidirectional device.⁷ However, we were not confident in his statement that the deposition is similar because both the rate of mucociliary clearance and the initial images appear different. These dissimilarities could be due to differences between the nasal sprays: his ($n = 7$) was a solution and used a test formulation that had not progressed into further development. Ours was a commercial suspension, with non-Newtonian viscosity behavior that would affect deposition and mucociliary clearance. Ours also used a different number of sprays per nostril. This is why we qualified our statement with the word “most.”

Recently published nasal deposition studies differ by many variables. We do not think that the studies by one research group should be held as a standard to criticize, in written form, the studies of others. Rather, there needs to be greater discussion at scientific conferences and working groups on standards for these studies. This way, guidelines, similar to those developed by Devadason *et al.*¹ for lung deposition studies, can be developed for nasal regional deposition studies for the overall benefit of development groups such as ours, Dr. Djupesland’s company, and others.

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