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COMMENTARY

At the Frontiers of Understanding: Inhaled Aerosols in Neonates

Commentary on articles by Minocchieri et al. on page 141, and Sood et al. on page 159

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Aerosols are well recognized as an effective means of delivery of therapeutic agents. However, our knowledge of aerosol behavior in human subjects becomes increasingly poor as subject age is reduced. The paucity of pediatric data are due in part to issues associated with the use of *in vivo* imaging in infants and children. Being at the very youngest end of the age spectrum, neonates are at the frontiers of our predictive understanding of aerosol deposition. The youngest age for which extensive deposition data for micrometer sized aerosol particles has previously been obtained is that of Swift (1), who measured nasal deposition in a replica of a 6-wk-old female infant as a function of particle size and flow rate. Minocchieri *et al.* (2), in their article in the present issue, have surpassed this previously youngest age by 9 wk, building a replica from an MRI scan of a 3 wk preterm neonate and measuring deposition of a nebulized budesonide aerosol in this replica. Comparing Minocchieri *et al.*'s data to that of Swift's, at flow rates of 1 and 5 L/min, Minocchieri *et al.* find aerosol delivery to the lung is about half that seen in Swift's 6-wk-old subject, while at 10 L/min their data are similar to Swift's. Minocchieri *et al.* note that they find less delivery to the lung than in previously published data in the SAINT replica of a 9 mo old (3). Assuming that infants have similarly large intersubject variations in their extrathoracic airways as seen in adults, a relevant question is how much of these differences is due to intersubject variation at a given age and how much is due to age alone? In other words, does Minocchieri *et al.*'s subject have particularly high nasal deposition for subjects of that age while Swift's subject has particularly low nasal deposition? Or would all subjects that are 9 wk apart at these ages show such dramatic differences in nasal deposition?

In adults, intersubject variability in extrathoracic deposition is a primary cause of intersubject variability in lung dose (4). Recent work in adults and older children has shown that intersubject variability can be collapsed by incorporation of subject-dependent length scales into the relevant dimensionless mechanical parameters that govern aerosol behavior (5–8). Would such a treatment allow prediction of the above differences in infant deposition? This is an intriguing question that arises when reading Minocchieri *et al.*'s work, and the answer is far from being esoteric, since it hints at the hope of *a priori* prediction of neonatal lung delivery. Such predictive power already exists for adult subjects, and is simple enough that it has been incorporated into an on-line calculator (9) that allows the user to quickly predict aerosol deposition, thereby allowing improved drug delivery in adults and older children. Can we extend to neonates the powerful predictive understanding that we currently have in older subjects? Minocchieri *et al.* show that it is possible to obtain *in vitro* aerosol deposition data in replicas of neonatal extrathoracic airways, so the answer to this question will surely not be long in coming.

While the article by Minocchieri *et al.* evokes enticing dreams of *in vitro* prediction of neonatal lung deposition, *in vivo* validation of such predictions is naturally desirable. Indeed, the above-mentioned powerful models in adults have not been extended to infants partly because of the lack of *in vivo* data in infants. Such studies have not been done in the past due to radiologic exposure issues with conventional radioisotope methods of assessing deposition. The article by Sood *et al.* (10), in the present issue, aims at circumventing these radiologic exposure concerns. By showing that magnetic resonance imaging (MRI) can be used to assess regional deposition in newborn pigs using a paramagnetic contrast agent (Gadopentetate dimeglumine: Gd-DTPA) added to a nebulized solution, Sood *et al.* set the stage for *in vivo* studies aimed at improving our poor knowledge of *in vivo* aerosol deposition in infants and children. Although the rapid absorption of Gd-DTPA prevents such studies from being used to develop an understanding of inhaled particulate clearance and disposition, and measurement of baseline T_1 values in subjects before aerosol exposure is needed to put the resulting measured deposition values on a solid quantitative footing, Sood *et al.* present an interesting new tool that may shed light on *in vivo* aerosol deposition in neonates.

Taken together, the studies by Minocchieri *et al.* and Sood *et al.* in this issue suggest that the fog may soon lift on our current relatively poor quantitative understanding of neonatal aerosol

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deposition. The promise of *in vitro* studies following Minocchieri *et al.,* and *in vivo* studies following Sood *et al.,* bodes well for the development and assessment of improved neonatal aerosol drug delivery.

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