Importance of Using Markers of Dilution When Measuring Inflammatory Mediators in Nasal Lavage Fluid

To the Editor—In their recent article on nasal cytokine production in children with upper respiratory infections (URIs), Noah et al. [1] state “accurate calculation of the volume of epithelial lining fluid in respiratory lavage fluid is not possible with current techniques.” While this may be true in bronchoalveolar lavage (BAL), it is not the case with nasal lavage.

I have used inulin as an exogenous marker of dilution when performing nasal lavages to study IgA and total protein and cytokine production in infants 1–31 months old with acute viral wheezing [2, 3]. By measuring the inulin concentration in the wash solution and in the lavage fluid obtained, the proportion of nasal lavage fluid consisting of nasal secretions can be calculated. This allows the substance being measured (e.g., tumor necrosis factor [TNF]-α) to be expressed per volume of nasal secretions by use of the simple formula: \(\frac{[\text{TNF-\alpha}]_{\text{nasal wash}}}{[\text{TNF-\alpha}]_{\text{nasal secretions}}} = 1 - \frac{\text{[inulin]}_{\text{nasal lavage fluid}}}{\text{[inulin]}_{\text{nasal wash}}}.\) It is not possible to differentiate the nasal (epithelial) lining fluid recovered from the rest of the nasal secretions, but that is unimportant.

Inulin, a chemically inert polysaccharide, is safe and easy to measure. Its use in nasal lavage was first described in 1970 [4], and it has recently been used in BAL [5]. There were early problems due to the difficult and inexact inulin assay, but by using an easier and more robust assay [6], I obtained a coefficient of variation of <2% for the method. I have also compared the use of exogenous inulin with that of endogenous urea, the method still in favor for calculating dilution factors in BAL, and found that the urea method underestimates the dilution factor in the majority of samples [7].

The concentration of a substance in nasal lavage fluid does not necessarily reflect its concentration in the nasal lining fluid. Simply measuring a substance in nasal lavage fluid ignores the tremendous variability in dilution between samples, which is a particular problem when looking at paired data from the same subject. In almost 100 nasal lavage samples, I found that the proportion of lavage fluid consisting of nasal secretions ranged from 4% to 48%, with a mean (SD) of 25.6% (9.1%). Amounts were similar for infected and recovered states and for wheezing and nonwheezing infants.

Furthermore, without standardizing solute concentrations to nasal lining fluid, comparisons cannot be made between different centers. The TNF-α levels during URI in the study by Noah et al. [1] were 15–350 pg/mL (median, ~50) and in similar patients, we found a range of <20–7000 pg/mL (median, 293) nasal lining fluid [3]. These differences may well be due to the dilution of the samples in the former study.

In conclusion, nasal lavage is a useful noninvasive technique for study of inflammation in the upper respiratory tract. However, expressing concentrations of mediators per volume of lavage fluid limits interpretation. The answer is to use markers of dilution, and inulin is recommended.

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References