What dose fraction represents the respirable dose?

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There would appear to be no evidence in the literature that, for β₂-agonists, particle size distribution is more important than total "respirable dose". Respirable dose has various definitions: ranging from particles <3 μm, to the fraction of particles <5 μm, or even <6-8 μm. This confusion may be because respirable dose has never been adequately defined. Indeed, this may be one of the reasons why central and peripheral effects cannot be distinguished when the 'so-called' respirable dose is changed.

Therefore, consideration needs to be given as to what dose fraction represents the likely respirable dose, before the effects of changing it can be studied.

Three separate studies, which used a pressurised metered dose inhaler (pMDI) (1), a dry powder inhaler (DPI) (2), or a nebuliser (3) to generate an aerosol, all reached the same conclusion, namely that when comparing the effects of small (~5 μm) and large (>5 μm) particles on measurements of lung function, the small particles had a greater effect. However, since large, or even coarse, particles also had a significant effect, using a cut-off point of 5 μm to define the respirable dose is probably too simplistic.

The first study (1), which examined the effect of particle size of terbutaline from a pMDI on the mean change in forced expiratory volume in 1 second (FEV₁), showed that while particles <5 μm had a significantly greater effect on mean improvement in FEV₁, larger particles (up to 15 μm) also improved this measure of lung function. In the study by Persson & Wirén (2), which used a DPI, the percentage of particles <5 μm were 1, 8 and 18% of the fixed total dose. The results showed only a weak correlation between the proportion of particles <5 μm and lung function. The third study (3), which used a nebuliser, again used different percentages of particles <5 μm within the dose, in this case 20, 50 and 80%. The results showed that whilst increasing the percentage of particles <5 μm improved the clinical outcome, this was only significant when 80% of the particles were <5 μm. Thus, these three studies reinforce the observation that while it is better to have small particles, an arbitrary cut-off size of <5 μm may not be appropriate as larger particles also contribute to the effect. In actual fact, a simple cut-off value is unlikely to define the respirable dose, which may be better defined from a probability ascribed to different particles sizes.

Another study (4) showed that reducing the particle size of the aerosol increased the dose of drug deposited in the lung, which also supports the view that total particle dose is more important than particle size distribution.

Using a nebuliser, Johnson et al. (5) compared the effects of small (3.3 μm) and large (7.7 μm) particles on lung function in 8 adults with moderate to severe asthma. The total dose reaching the lung with the small particles was three times that with the large particles (Fig. 1). The relative dose distribution in the central, intermediate and peripheral regions of the lung appeared almost identical for the two nebulisers. Another study (6) also compared the effects of small (1.4 μm) and large (5.5 μm) particles on lung function, but used a fixed lung dose (i.e. the number of small and large particles reaching the lung were the same). In this study, both distribution and bronchodilatation were similar with the two particle sizes. This indicates that reducing particle size results in a higher lung dose, but not in differential deposition.

Zanen et al. (7) also studied clinical effect in relation to particle size, but instead of using poly-disperse aerosols (as in the previous studies), mono-disperse aerosols with emitted particles sized 1.5, 2.8 or 5 μm were used. There was a significantly (p<0.001) greater improvement in FEV₁ with the 2.8 vs 5 μm particles, and there was also a larger improvement with the 2.8 vs 1.5 μm particles. It was
concluded that the most suitable particle size for a $\beta_2$-agonist aerosol formulation was approximately 3 $\mu$m. Patel et al. (8) also reported similar results using a monodisperse aerosol.

What can be concluded from these studies? First, increasing the proportion of particles $<3\,\mu m$ increases the lung dose, which in turn increases the effect of a $\beta_2$-agonist on lung function. If, however, the lung dose is fixed, then increasing the fraction of small particles has no effect. Second, aerosols containing 3 $\mu$m particles appear to be more effective than those containing 5 $\mu$m particles. With a fixed lung dose, however, there is no difference in either deposition or effect with the two different particle sizes. There is no clinical evidence to support beneficial effects of increased lung penetration with reduced particle size.

The problem of defining respirable dose has already been discussed. It may, therefore, be more appropriate to use a probability-based distribution technique that takes the statistical probability of lung deposition for any given particle size into account. Alternatively, we recently compared the distribution of particles from a spacer using a standard impactor 'throat' with that from the cast of an adult airway that extended from the lips to the main stem bronchi (9). The dose passing to the level of the bronchi can be considered a relevant in vitro estimate of the respirable dose. The bias introduced when a single cut-off is used to define the respirable dose is illustrated when the particle size distribution of the

dose actually reaching the bronchial level through such cast is analysed: the major fraction of particles $\leq 4.7\,\mu m$ reach the bronchi, but there is also a significant proportion of larger particles, and this mirrors the clinical data. Therefore, to understand drug deposition and distribution, perhaps the term respirable dose should be re-defined. The human cast method may be useful to define the in vitro correlate of the dose reaching the lung, and could be developed for each age group, because results obtained with an adult model cannot be extrapolated to children or infants.

In summary, respirable dose should not be defined using a simple cut-off particle size; it may be represented by a particle size probability distribution; and using human airway replicates may improve in vitro estimates of the lung dose.

References