the most well-esteemed equipment careful calibration of the calibrators is mandatory (6). We did adopt the principles of traceability to international standards throughout our study and on the basis of this our results should be weighted.

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References


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Dear Sir


In the discussion section of this report, in which the relationship between lung deposition of inhaled drugs and clinical efficacy is discussed, there is an error in the interpretation of one of the papers dealing with inhaled sodium cromoglycate.

In the reference to the study by Laube et al. (1) it is stated correctly that differences in the rate of inhalation of sodium cromoglycate were associated with differences in regional lung deposition and the decreased penetration seen with more rapid inspiration was associated with reduced protection against allergen challenge. The report then goes on to state that this study correlates well with previous work using a PK technique, showing that rapid inhalation of sodium cromoglycate was associated with reduced total lung deposition. The reference quoted is that of Richards et al. (2). This in fact shows the complete opposite. The study showed that the inspiratory flow rates measured of 184±14, 101±4, 57±31 min⁻¹ gave lung deposition, as determined by AU C̄/D₂₄₀ of 1245±220, 657±90 and 413±69 ng ml⁻¹min⁻¹ respectively.

The differences in these studies illustrate the differences in the techniques used in drug administration. Laube et al. used a 1 mg pressurized metered dose inhaler (MDI) with the drug being placed into and inhaled from a 750 ml spacer. In these circumstances optimal lung deposition, distribution and protection against allergen challenge is given by slow inspiration. Richards et al. used a dry powder inhaler, the Spinhaler, and the drug was inhaled from a gelatine capsule. Using this method of administration, rapid inspiration provides greater lung deposition and greater protection. In the first case the particle size characteristics of the inhaled drug is determined by the dose size, the nozzle of the metered dose inhaler, and the spacer. In the second case the particle sizes are largely determined by the efficiency with which the particular device breaks up the large particles in the capsule into smaller sizes. This in turn is largely determined by the speed of inhalation through the device. Thus the two systems are entirely different in the way in which they produce optimal deposition within the lung. In the case of metered dose pressurized inhalers, inhalation should be slow, around 301min⁻¹. In the case of the Spinhaler, a dry powder system, inhalation rates in excess of 1201min⁻¹ are required.

An additional relevant study in this context is also by Richards et al. (3,4) which measures the protective effect of inhaled sodium cromoglycate against AMP-induced bronchoconstriction using different inspiratory flow rates. The drug was administered with the Spinhaler from gelatine capsules. The inspiratory flow rates achieved were 221±87, 108±3 and 59±31 min⁻¹. The lung deposition was 3318±925, 1702±378 and 1073±218 ng min ml⁻¹. The PC₂₀AMP at each inspiratory rate were 136, 40 and 15. Again, using a patient driven inhaler more rapid inhalation gave greater lung deposition and greater protection against challenge.

The report concludes that in vitro measurements of aerosol fine particle fraction has a key role to play in the development of new pharmaceutical products and in quality control. A multistage apparatus should be used over the particle size range 0.5–1.0 μm. In Europe, apart from Germany, the most widely used inhaled product of sodium cromoglycate is the 5 mg dose⁻¹ MDI. Applying these criteria to the data provided in the paper by Newman et al. (4), using the 5 mg MDI, the lung deposition as estimated by the fine particle fraction would be 15% of the inhaled dose. That demonstrated by the radiolabelled
product was 8.8% of the dose. A recent paper by Aswania et al. (5), which used urinary output, calculated the percentage of the inhaled dose delivered to the lung at between 2 and 3%. In view of the disparity between these three sets of figures, it may still be necessary to carry out controlled clinical trials with each new inhaled product in order to determine clinical efficacy and bioequivalence. The use of in vitro particle size estimation may be suitable for quality control purposes as long as it is recognized that it does not reflect lung deposition or distribution or implied bioavailability.

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References


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Sir,

Response to letter from
Dr A. M. Edwards in assessing lung deposition of inhaled medications.
(Respir Med 1999; 93: 123–133)

We thank Dr Edwards for his interest in our consensus statement. He is correct in his comment; the reference we quoted was not appropriate to the point being made, and shows the difficulty in pulling together key points from a variety of inputs at a workshop. It is clear from numerous publications that lung deposition from breath-actuated dry-powder inhalers increases with increasing inspiratory flow rate, in contra-distinction to the situation with metered dose inhalers.

We entirely agree that in vitro measurements of aerosol fine particle fraction are not reliably predictive of lung deposition, and we made the point that their principal value was in quality control. The data Dr Edwards quotes support our statement that ‘The FPF (fine particle fraction) measured by in vitro methods generally overestimates the lung deposition measured using in vivo systems’. The disparity between the two in vivo measurements he quotes (radiolabelled lung deposition and urinary output) is difficult to evaluate since they were not made in the same subjects under the same conditions. Bioequivalence could be established (in theory) by comparing radiolabelled lung deposition of two different products, or urinary excretion of two different products, but not by comparing radiolabelled deposition of one with urinary output of another; whereas the ‘gold standard’ for comparing clinical efficacy is to carry out a clinical trial.

Our consensus statement was intended to summarize the current state-of-the-art and clarify the value and correct use of the various methods of estimating lung deposition of inhaled medications, and to review the potential for new or improved methods to increase the accuracy of these estimations, with the possibility that eventually surrogate in vivo methods might be able to replace some of the clinical testing required today.

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Dear Editor

Bovine TB alert

Koch’s discovery of the tubercle bacillus in 1882, and of ‘Old Tuberculin’ soon afterwards, paved the way for cattle TB control schemes by test and slaughter or reactors. His mistaken view that bovine TB was not a risk to man, at least led to exhaustive studies of TB. Bang pioneered such work in Denmark and noted in 1892 [cited in Francis (1) :

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It is found that the tuberculin test is no more perfect than are other things in this world. Sometimes it fails. Animals with a very real degree of tuberculosis will sometimes fail to react, and the same applies to animals with a very slight degree of the disease. Further, a positive reaction has been observed several times in animals in which no tuberculous changes were found on