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Bioavailability of salbutamol

We read with interest the paper of Hindle and Chrystyn (May 1994;49:549-53) in which the lung bioavailability of salbutamol (Ventolin, Allen & Hanburys, Uxbridge, UK) was augmented by 53.4% by using a Nebuhaler (Astra Pharmaceuticals, Kings Langley, UK) as assessed by 30 minute urinary excretion of salbutamol in normal volunteers. In this respect, measuring the plasma concentration of salbutamol, peak levels occur within five minutes of inhalation, in keeping with rapid lung absorption, and it is this which will therefore largely determine systemic β_2 -mediated effects of inhaled salbutamol.^{1,2} That lung bioavailability determines systemic effects is supported by two studies.^{3,4} Firstly, salbutamol given by inhalation but not by mouth spraying produces a tachycardia and, secondly, mouth washing does not attenuate the systemic effects of inhaled salbutamol.

On the basis of the data of Hindle *et al* one might predict that the use of the Nebuhaler should increase the systemic β_2 effects of salbutamol in comparison with a metered dose inhaler. This was not found to be the case, however, in the study where systemic β_2 responses to cumulative doubling doses of salbutamol (100-2000 μ g) were compared in normal subjects using a metered dose inhaler and Nebuhaler as no differences were seen between the systemic dose-response curves.⁵ Although it may not be possible to extrapolate between the two studies, the inference is that measurements of 30 minute urinary salbutamol excretion may not be a true reflection of lung bioavailability, which may be directly measured using peak plasma concentration. Indeed, this is supported by a study where the increased plasma salbutamol concentration with a modified actuator device compared with a metered dose inhaler was associated with a left shift in the dose-response curve for a number of β_2 -mediated systemic effects.²

There have been recent concerns regarding the bioequivalence of generic salbutamol metered dose formulations, particularly with regard to safety evaluation in terms of systemic β_2 effects. Thus, if it is

required to quantify the systemic bioequivalence of generic inhaled salbutamol formulations, the use of direct pharmacokinetic evaluation of lung bioavailability using plasma salbutamol concentration along with measurement of systemic β_2 responses may be more appropriate than using an indirect surrogate pharmacokinetic parameter such as 30 minute urinary salbutamol excretion.

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AUTHOR'S REPLY The amount of salbutamol eliminated in the urine during the first 30 minutes after inhalation is an index of the dose delivered to the lungs, hence the term "relative bioavailability" to the lung.¹ It is useful for the comparison of two inhaled products or methods when used by a patient. Furthermore, the method can differentiate between the fractions of dose delivered to the body by the pulmonary and oral routes. This is also true for plasma salbutamol concentrations,² when measured after the inhalation of a first dose rather than following cumulative dosing. Peak plasma concentrations five minutes after inhalation,² together with the polar and basic properties of salbutamol, are consistent with the large renal excretion we have reported in the first 30 minutes after an inhalation.¹ Measurement of plasma salbutamol concentrations and the urinary excretion method do not indicate regional deposition in the lung and, therefore, are both indirect techniques.

The finding of greater deposition to the lung when a Nebuhaler was used with a metered dose inhaler (MDI) by Hindle *et al*³ is consistent with that reported by others.^{4,5} During our study³ we did not measure systemic effects of salbutamol but subjects did report that tremor, between 5 and 20 minutes after inhalation, was greater when spacers were used. Lipworth and Grove cannot find an explanation for the greater lung deposition with spacers³⁻⁵ because a previous report has shown that extrapulmonary β_2 adrenoceptor responses were the same when

an MDI was used with and without a spacer.⁶ This may be due to the specially prepared MDIs delivering 100 and 500 μ g per actuation used in their studies which could have affected the in vivo respirable fractions with and without the Nebuhaler. Furthermore, a cumulative dosing schedule was used and the systemic effects could be influenced by the total delivery of salbutamol to the body from the modified MDIs via pulmonary and oral routes. Lipworth *et al*⁶ do refer to this in their conclusion by stating that "improved lung delivery with a pear-shaped spacer (PSS) may have compensated for reduced oropharyngeal deposition and gut absorption". Hence, without a measurement of the amount of salbutamol delivered to the body no comparison can be made between the study of Lipworth *et al*⁶ and those which demonstrate greater lung depositions with the Nebuhaler.³⁻⁵

Finally, we sympathise with the concerns of Lipworth and Grove with respect to the bioequivalence of inhaled products. We have shown that, using the same MDI, a variation in the technique significantly alters the amount of drug delivered to the lungs⁷ and that an efficient technique cannot be detected by subjective methods.⁸ If this occurred during a clinical study, especially the four period, two sequence randomised crossover design proposed by the FDA, then the issue of bioequivalence could be misrepresented. The need to carry out some simultaneous measure of lung deposition is highlighted by the confusion of Lipworth and Grove. Direct methods of measuring lung deposition require a modification to the aerosol and thus cannot be used in bioequivalence studies. Although the plasma salbutamol concentration measurements and the urinary excretion method are indirect methods, they do provide an indication of the relative in vivo respirable fractions delivered to the patient.

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