Generic salbutamol metered dose inhalers

I read with interest the recent paper by Drs Chege and Chrsynt (November 1994;49:1162–3) in which similar 30 minute urinary excretions of salbutamol products were reported for the innovator product and for a single generic product. I would like to question what exactly the 30 minute urinary excretion of salbutamol measures. This quantity is obviously related to lung deposition in some way, but what is the nature of that relationship, and is it the same relationship under all circumstances? A variety of factors, including exercise, smoking and, possibly, the disease state, may affect pulmonary drug absorption, although these factors would presumably be allowed for by using subjects as their own controls. However, recent data have suggested that the amount of some drugs absorbed via the lungs could depend critically upon the site of deposition within the airways. Alternatively, this is the case for salbutamol, then two products delivering different amounts of drug to the lungs could show the same 30 minute urinary excretion because their distributions within the airways are different. Conversely, two products delivering the same amount of drug to the lungs could show different 30 minute urinary excrections for the same reason.

The validation of the authors’ method would seem to rely chiefly upon the observation of very low 30 minute urinary excretion of salbutamol delivered as a single dose. While this indicates that the 30 minute urinary excretion following an inhaled dose results from the inhaled drug, it does not tell us what relationship the 30 minute urinary excretion bears to lung deposition. Unless urinary excretion of salbutamol absorbed via the lungs is always complete after 30 minutes, then an arbitrary amount of absorbed drug will be missed by the technique. Bearing in mind these considerations, I feel that, at the present time, the technique remains inadequate validated as a means of assessing drug delivery to the lungs, at least in terms of data available in the public domain.

Drs Chege and Chrystyn make a statement in the discussion of their paper saying that it would agree wholeheartedly, namely that “equal urinary excretions following inhalation from two salbutamol products goes some way to suggesting that they have similar in vivo behaviour”. However, such an observation does not necessarily indicate therapeutic equivalence. There can be no substitute for the demonstration of therapeutic equivalence between inhaled salbutamol products in carefully designed clinical trials that assess pharmacodynamic parameters, as has been suggested by recent guidelines. The 30 minute urinary excretion method is an interesting one, but it is important that data obtained with this technique are not overinterpreted.

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4 Phillips M. First annual report of the West Midlands testing scheme for general practitioners and community pharmacists, West Midlands Regional Health Authority, July 1992.

AUTHORS’ REPLY

We have shown that the amount of unchanged salbutamol excreted in the urine during the first 30 minutes after inhalation from a salbutamol metered dose inhaler (MDI) is the “relative bioavailability of salbutamol to the lung following inhalation”. When a standardised, reproducible, well trained inhalation technique is used by a healthy volunteer, then this measurement is dependent upon the amount of drug delivered to the body via the lungs and the individual’s salbutamol pharmacokinetic parameters. Since salbutamol is a polar and basic chemical, any variability caused by pH changes of the urine is negligible and, because renal function is stable, the clearance of salbutamol should not fluctuate. Our studies have shown that the amount absorbed into the body via the oral route and excreted in the urine during the first 30 minutes after inhalation is small. A high value for the 30 minute urinary excretion of salbutamol does not indicate greater lung deposition in one subject than another because this measurement is influenced by the individual’s renal salbutamol clearance.

Elimination of the salbutamol fraction absorbed via the pulmonary route will not be complete after 30 minutes because the elimination half-life of salbutamol is approximately 1–2 hours. Although some renal elimination of salbutamol delivered to the lungs by the pulmonary route is missed by the 30 minute measurement, as Dr Newman suggests, this does not affect the relevance of the method. The measurement, therefore, is an index which can be used to compare two different inhaled products,1–4 rather than a precise version of the total lung uptake. Unlike other in vivo studies we have reported the reproducibility of the method. At present our studies have focused on salbutamol and thus comparisons with other drugs, mentioned in both letters, are purely speculative.

Drs Watson and Lewis have questioned the influence of buccal absorption but have misinterpreted manoeuvre 3 which states “subjects inhaled to total lung capacity, held their breath and the MDI actuator was actuated” clearly indicating that peak flow was not recorded, hence Dr Watson’s and Lewis’s argument on the influence of non-pulmonary absorption when the Volumatic was used does not apply. Our studies have shown the effect of inhaler technique on the 30 minute measurement of salbutamol. The consensus statement, referred to by Dr Newman, states that carefully designed clinical trials are important in the evaluation for the bioequivalence of different inhaled medications, but does not detail any methods. The FDA have described a pharmacodynamic bioassay based on bronchoprovocation which could be used to demonstrate the therapeutic equivalence of two inhaled products. However, the reproductibility of this one point determination has not been reported and the problem of
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