

## LETTERS TO THE EDITOR

### Generic salbutamol metered dose inhalers

I read with interest the recent paper by Drs Chege and Chrystyn (November 1994;49:1162-3) in which similar 30 minute urinary excretions of salbutamol 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<sup>1</sup> have suggested that the amount of some drugs absorbed via the lungs could depend critically upon the site of deposition within the airways. If 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 excretions 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 following an oral salbutamol dose.<sup>2</sup> 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 inadequately 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 with which I 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.<sup>3</sup> 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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- 1 Taylor G, Colthorpe P, Farr SJ. Pulmonary absorption of proteins: influence of deposition site and competitive elimination processes. In: Byron PR, Dalby RN, Farr SJ, eds, *Respiratory drug delivery IV*. Buffalo Grove: Interpharm Press, 1994:25-30.
- 2 Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; 34:311-5.
- 3 Consensus Statement of the British Association for Lung Research. Determining equivalence of inhaled medications. *Respir Med* 1995 (in press).

The demonstration by Drs Chege and Chrystyn of equal urinary excretion following inhalation of different salbutamol products via a Volumatic (November 1994;49:1162-3) is a helpful contribution to the debate about bioequivalence of generic inhalers, being the first *in vivo* comparison in this country of a generic product with the original brand. However, the conclusion implied in the title - "Volumatic usage: some generic inhalers can be used" - cannot be justified from their study.

It is assumed that the contribution of buccal, pharyngeal, and enteral absorption is negligible. A previous study showed that actuating the device into the mouth without inhaling led to a mean excretion of salbutamol in 30 minutes of 8.5% of that found after the optimal inhalation technique.<sup>1</sup> It may be argued that in the current study the use of the Volumatic would reduce pharyngeal deposition - and hence non-pulmonary absorption - but the size of that effect is not known.

Assuming that the results reflect predominantly pulmonary absorption, there is no measure of regional deposition within the lungs. The percentage of particles in the "respirable fraction" (<6.8 µm) from Ventolin (Allen and Hanburys) and Salamol (Baker Norton) salbutamol inhalers has been shown to be similar using a twin stage impinger.<sup>2</sup> However, differences have been found between these manufacturers' beclomethasone inhalers when the distribution of particles within the respirable range was assessed using a high performance multistage liquid impinger.<sup>3</sup> If such differences are also found in the salbutamol products, they might influence regional deposition within the lungs and hence therapeutic effect, but these differences would not be detected by urinary salbutamol excretion.

The subjects in this and previous studies of the urinary salbutamol excretion technique have all been healthy volunteers. We await data to show whether urinary salbutamol excretion relates to airway response in asthmatic patients.

In view of the significant number of patients who claim that they find generic salbutamol inhalers are less effective than the original branded product,<sup>4</sup> clinical trials showing therapeutic equivalence are needed to support this pharmacokinetic evidence before the conclusion implied by the title can be drawn.

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- 1 Hindle M, Newton DAG, Chrystyn H. Investigations of an optimal inhaler technique with the use of urinary salbutamol excretion as a measure of relative bioavailability to the lung. *Thorax* 1993;48:607-10.
- 2 Lee MG, Ireland DS, Dwyer PG, Weir PJ. Comparison of salbutamol in the United Kingdom. *Int J Pharm Prac* 1993;2:172-5.
- 3 Newman SP, Kenyan CJ. Asthma products bioequivalence. *Pharm J* 1994;253:42.

- 4 Phillips M. *First annual report of the West Midlands testing scheme for general practitioners and community physicians*. 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".<sup>1</sup> When a standardised, reproducible, well trained inhalation technique is used by a healthy volunteer, then this measurement is dependent on 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.<sup>1</sup> 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.<sup>2</sup> 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,<sup>3</sup> methods,<sup>4</sup> or techniques<sup>5</sup> using crossover study designs. Unlike other *in vivo* studies we have reported the reproducibility of the method.<sup>4</sup> 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 was activated, swallowed, then had a drink of water".<sup>5</sup> The 30 minute measurement therefore represents the amount of salbutamol delivered to the body by the buccal and oral (gastrointestinal) route. The mean (SD) salbutamol elimination in the 30 minutes after manoeuvre 3 was 0.24 (0.19)% of the inhaled dose, which is similar to the 0.23(0.20)% we previously reported following oral administration of salbutamol solution in the same volunteers.<sup>1</sup> This suggests negligible buccal absorption which is consistent with that previously reported,<sup>6</sup> and hence Drs 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 urinary elimination of salbutamol.<sup>5</sup> The consensus statement,<sup>7</sup> referred to by Dr Newman, states that carefully designed clinical trials are important in the evaluation for therapeutic equivalence of different inhaled medications, but does not detail any methods. The FDA have described a pharmacodynamic bioassay<sup>8</sup> based on bronchoprovocation which could be used to demonstrate the therapeutic equivalence of two inhaled products. However, the reproducibility of this one point determination has not been reported and the problem of