Thorax 1995;50:590–592

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[1] 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.[2] 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.[3] 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.
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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.[1] 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.[2] 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.[3] 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,[4] 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.
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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".[1] 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.[1] 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.[2] 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,[3] methods,[4] or techniques[5] using crossover study designs. Unlike other in vivo studies we have reported the reproducibility of the method.[4] 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".[5] 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.[1] This suggests negligible buccal absorption which is consistent with that previously reported,[6] 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.[5] The consensus statement,[7] 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[8] 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

inhalation technique is not fully addressed, despite the FDA recommendation that the technique should be trained using an Inspirease, a spacer device. The problem of a consistent inhaler technique when patients use MDIs has been extensively reported[9–11] and hence could affect the reproducibility of any method related to lung deposition in asthmatics, despite extensive training of the technique. Furthermore, this variability of salbutamol deposition would be enhanced by the pathophysiology of a patient's respiratory tract.[12] Variability of the bioassay will also be introduced by the training effect of the inhalation technique with respect to steroid therapy, hyperresponsiveness due to previous bronchoprovocation, and the length of salbutamol washout periods. Furthermore, the protocol is very demanding on the asthmatic subjects and our projection is that the drop out rate will be high which, together with the strict inclusion criteria, may introduce bias. Nevertheless, to answer the criticism in the two letters, we are planning clinical studies to compare our urinary excretion method with a bronchoprovocation test and the influence of inhaler technique will be studied first.

In vivo deposition studies using a radiolabel[13] have indicated that the bronchodilator response seems to depend on the total amount delivered to the lungs.[14–16] A recently reported abstract, using labelled salbutamol aerosols, has shown differences in regional lung deposition related to the technique and, when total lung deposition was high, there was a corresponding increase in the amount delivered to the different regions of the lungs.[17] This is why we will evaluate the influence of inhaler technique in our bronchoprovocation studies. An ongoing study in our laboratories is showing a linear relationship between one, two, three, four, and five (n = 12 subjects) inhaled salbutamol doses from an MDI and the amount renally excreted. This suggests that an increase in dose delivered to the lungs produces a simultaneous increase in the renal elimination of salbutamol.

Finally, Drs Watson and Lewis state that a significant number of patients claim that they find generic salbutamol inhalers to be less effective than the original branded products. This information should be reported to the regulatory authorities. All inhaled products contain patient information leaflets describing the inhaler technique which should be used, and examination of these reveals different instructions. It may be the confusion created by these differences which causes patients to complain. If the pharmaceutical industry cannot agree on the standardisation of the information on how to use an MDI, then perhaps the British Thoracic Society should provide these guidelines. Any argument that different techniques are recommended because of the MDI formulations, characteristics, etc is not substantiated in the literature.

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Diffuse pulmonary fibrosis and Hermansky–Pudlak syndrome

Dr Reynolds and colleagues (June 1994;**49**: 617–8) report a case of interstitial fibrosis of the lung proven at necropsy in a patient with Hermansky–Pudlak syndrome (HPS). They mention that they had identified 18 more cases in the literature.

The exact number of patients with HPS and pulmonary fibrosis or restrictive lung disease is difficult to determine as several cases seem to have been published on more than one occasion without correct cross referencing. Based on our search of literature we estimate that approximately 50 patients with HPS and pulmonary fibrosis or restrictive lung disease have been observed (bibliographic data in two) including the two necroscopic cases we published. Women seem to be affected more often than men. Only very few reports exist on pulmonary fibrosis in siblings with HPS.[1–3]

Contradictory data exist regarding the identification of ceroid in lungs of HPS patients with pulmonary fibrosis. Pigment-laden macrophages were seen in some patients[4] but not in others.[5] In one case no ceroid was reported at open lung biopsy when fibrosis already existed, but was identified at necropsy.[6]

In the first of two brothers with HPS and interstitial fibrosis we observed numerous pigment-laden macrophages in the lungs at necropsy but none in the second, despite him having more severe pulmonary fibrosis. The deposition of ceroid cannot therefore be the only cause of pulmonary fibrosis in patients with HPS.

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Combined chemotherapy and radiotherapy in advanced pulmonary blastoma

We were interested to read the recent case report of Dr Chin *et al* (August 1994;**49**: 838–9) describing a case of pulmonary blastoma in an adult presenting as a chronic loculated effusion.

We admitted a 57 year old man in 1991 with left shoulder pain, hoarseness, dyspnoea and Horner's syndrome. Chest radiography revealed a 11 × 12 cm mass in the upper zone of the left hemithorax. At fibreoptic bronchoscopy the left vocal cord was paralysed and the left upper lobe bronchus obliterated with a necrotic lesion. Because of the localisation of the lesion, transthoracic lung biopsy was performed and histological examination revealed a pulmonary blastoma. A computed tomographic scan revealed mediastinal invasion by the mass. No distant metastases were detected. The patient was inoperable and conflicting results have been reported regarding the use of chemotherapy, radiotherapy alone, or in combination.[1–3] We gave combined modality treatment using cisplatin, etoposide, and adriamycin as chemotherapy.

After two cycles of chemotherapy 6000 cGy radiotherapy was given to the lesion and a 75% regression was noted in the tumour