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ABSTRACT Abstracts, which should be of no more than 250 words, should state clearly why the study was done, how it was carried out (including number and brief details of subjects, drug doses, and experimental design), results, and main conclusions. They should be structured to go under the headings "Background", "Methods", "Results", and "Conclusions".

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- 1 Anderson HR. Chronic lung disease in the Papua New Guinea Highlands. *Thorax* 1979;34:647-53.
- 2 Green AB, Brown CD. *Textbook of pulmonary disease*. 2nd ed. London: Silver Books, 1982:49.
- 3 Grey EF. Cystic fibrosis. In: Green AB, Brown CD, eds. *Textbook of pulmonary disease*. London: Silver Books, 1982:349-62.

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LETTER TO THE EDITOR

Lung bioavailability of generic and innovator salbutamol MDIs

The statement by Clark *et al* (March 1996; 51:325-6) that "the coefficient of variation for urinary salbutamol was approximately double that for plasma salbutamol" cannot be made with confidence until the authors have validated the protocol they are using. Hindle and Chrystyn¹ reported that the relative bioavailability of salbutamol to the lung could be used to compare two inhaled products/inhalation methods by measuring the amount of salbutamol excreted in the urine in the first 30 minutes after inhalation. Their method was to start at time zero, inhale four consecutive doses (with one minute between each dose), and then provide a urine sample at time $t=30$ minutes. The protocol used by Clark *et al* is 12 sequential inhalations over six minutes and then a urine sample is collected for the measurement of salbutamol excretion 30 minutes after completion of the 12 inhalations. Thus, urine is collected over the first 36 minutes compared with 30 minutes for the method of Hindle and Chrystyn. This the authors confirmed during a poster discussion session at the British Thoracic Society's winter meeting in December 1995.

We have recently been involved with further studies to validate our method so that we can extend our work to the use of nebulisers. At present we have data on five healthy volunteers (three women) who swallowed 100 µg salbutamol solutions at $t=0, 2, 4, 6,$ and 8 minutes and provided urine samples at 0, 30, 40, and 60 minutes after swallowing the first salbutamol dose. The mean (SD) rate of salbutamol urinary elimination from $t=0-30, 30-40,$ and $40-60$ minutes was 0.08 (0.11), 0.72 (0.76), and 0.99 (0.38) µg/hour, respectively (data on file). Similar rates following the inhalation of five sequential 100 µg salbutamol inhalations at $t=0, 2, 4, 6,$ and 8 minutes (that is, each separated by two minutes) were 25.80 (5.79), 24.16 (7.54), and 17.60 (6.69) µg/hour, respectively. Thus, interference from the salbutamol delivered to the body by the oral route would be present in the urine samples collected between 30 and 40 minutes after the first inhaled dose. This suggests that the urine samples collected by Clark *et al* over the first 36 minutes after the start of the first inhalation would include salbutamol absorbed by the oral route. The presence of drug from oral absorption could account for some of the greater variability of their results compared with the reported plasma salbutamol concentrations.

Clark *et al* claim that the maximum plasma concentration, C_{max} , after inhalation may be used as a direct measure of absolute drug bioavailability. However, the measurement of C_{max} is an indirect method of bioavailability since it measures salbutamol concentrations in the plasma rather than amounts in the lung. Furthermore, the authors do not present supporting data following oral administration to the 10 healthy men they studied. The absence of intravenous data or direct instillation into the lungs with their method means that it compares relative lung bioavailability, not absolute.

Finally, we question whether the dosing schedule used by Clark *et al* would be rep-

resentative of normal inhaler usage. Although our initial studies have used four inhaled doses, we have now validated our method for one dose² (although most of our work is now concentrating on two doses). In the absence of *in vivo* studies to show that there is no difference in pulmonary deposition and oral ingestion between a few doses and 12 sequential inhalations, the conclusion of Clark *et al* that the two generic MDIs were similar to the innovator can only be applied if 12 consecutive doses are inhaled by men.

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- Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; 34:311-5.
- Tomlinson HS, Corlett SA, Chrystyn H. Effect of dose on the relative lung bioavailability of salbutamol. *J Aerosol Med* 1995;8:127.

AUTHORS' REPLY We thank Dr Chrystyn and colleagues for their helpful anecdotal data on relative urinary excretion of unchanged salbutamol when given by oral and inhaled routes. Their data show that elimination over an extra six minutes would be expected to have a negligible effect on overall bioavailability. From their data at $t=30-40$ minutes the proportion of urinary elimination of unchanged salbutamol was 3% when oral administration (0.72 µg/hour) was compared with inhaled (24.16 µg/hour) administration. Thus, the use of 36 minute urinary salbutamol excretion against 30 minute urinary excretion is unlikely to have any impact in terms of relative lung versus gut components of elimination of unchanged salbutamol.

In this respect, it is known that buccal absorption of salbutamol is negligible¹ and our subjects all rinsed their mouths after each puff, which would obviate a large proportion of gut bioavailability. Furthermore, there is extensive first pass conjugation of the swallowed moiety of inhaled salbutamol.² These factors taken together indicate that 36 minute urinary salbutamol excretion is unlikely to be confounded by gut bioavailability to any significantly greater degree than a 30 minute collection.

Since the method of Dr Chrystyn and colleagues has a detection limit of 50 ng/ml,³ this represents 50-fold lesser sensitivity than our assay (limit 1 ng/ml). Perhaps this explains why Dr Chrystyn continues to try to justify using the urinary method which is both indirect and more variable. This is evidenced by a recent study showing that it is possible to detect a 1.32-fold difference in lung bioavailability between CFC and non-CFC salbutamol formulations with plasma but not with urinary kinetic methods.⁴

We therefore remain firmly of the opinion that direct measurement of plasma salbutamol kinetics is the only way to evaluate directly lung bioavailability in man.

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- Lipworth BJ, Clark RA, Dhillon DP, *et al*. Pharmacokinetics, efficacy and adverse effects of sublingual salbutamol in patients with asthma. *Eur J Clin Pharmacol* 1989;37:567-71.
- Morgan DJ, Paull JD, Richmond BH, *et al*. Pharmacokinetics of intravenous and oral salbutamol and its sulphate conjugate. *Br J Clin Pharmacol* 1986;22:587-93.

- Hindle M, Chrystyn H. Determination of the relative bioavailability of salbutamol to the lung following inhalation. *Br J Clin Pharmacol* 1992; 34:311-5.
- Clark DJ, Lipworth BJ. Lung bioavailability of chlorofluorocarbon free, dry powder and chlorofluorocarbon containing formulations of salbutamol. *Br J Clin Pharmacol* 1996;41:247-9.

BOOK NOTICE

AIDS - A Pocket Book of Diagnosis and Management. 2nd Edition. Adrian Mindel and Robert Miller. (Pp 370; £15.99). London: Arnold, 1995. 0 340 58609 5.

This book represents a successful attempt to incorporate in a practical way the huge amount of information published regarding HIV and AIDS since the first edition in 1990. If anything, the term "pocket book" may understate the quantity of information which is concisely expressed on every aspect of HIV disease.

There are 18 chapters each by different authors with practical experience in their topic, although the editors have maintained throughout a uniformity of style of presentation which is thoroughly readable. Chapters on epidemiology and natural history and international aspects of HIV/AIDS outline the global spread of the disease and the important regional differences in natural history. Each chapter on the main organ systems initially provides a helpful differential diagnosis of common presenting symptoms (including some diagnoses not specific for HIV), then reviews the important conditions in more detail. These reviews are authoritative and well balanced between giving the practice of the author and providing an overview of current literature. The chapter on therapeutic guidelines comprehensively presents treatment regimes for the major opportunistic infections, including drug side effects and drug interactions. Chapters on HIV in pregnancy, paediatrics, and in relation to blood products and intravenous drug misuse provide updated information of great use in counselling patients. Moreover, there is a chapter providing practical guidelines for counselling HIV patients in general. Especially useful and thoughtfully presented is the chapter on aspects of palliative and terminal care.

The book has an index and each chapter is referenced. There are a limited number of black and white illustrations.

This excellent book is particularly recommended to medical students, junior hospital doctors including MRCP students, and general practitioners in high prevalence areas. Chest physicians will find this book useful not only for information on the respiratory manifestations, but also on the diseases of other organ systems likely to coexist in their patients infected with HIV. - DF

NOTICE

European Asthma School

A three-day intensive course on Experimental and Clinical Aspects of Asthma will be held in Ghent, Belgium on 19-21 November 1996. For further information please contact the Department of Respiratory Diseases, University Hospital, De Pintelaan 185, B 9000 Ghent, Belgium. Phone: 32 9 2402611. Fax: 32 9 2402341.