

CORRESPONDENCE

Two letters to the Editor re:

Lung deposition of budesonide from Turbuhaler® is twice that from a pressurized metered-dose inhaler (P-MDI).

Thorsson, *et al. Eur Respir J* 1994 7: 1839–1844.

To the Editor:

In their article entitled "Lung deposition of budesonide from Turbuhaler® is twice that from a pressurized metered-dose inhaler (P-MDI)", THORSSON *et al.* [1], conclude that by administering budesonide *via* the Turbuhaler instead of the MDI, the same degree of asthma control can be achieved with a lower dose which, in turn, reduces the risk of undesired systemic effects. The implication is that the Turbuhaler performs better than MDIs in general, despite the lack of data from multiple-dose studies to support such an argument.

Data that have recently been generated by us using the Andersen Cascade Impactor may give a different explanation for the findings of THORSSON *et al.* [1]. We have compared the fine particle fraction dose (*i.e.* particles of <6 µm) of the budesonide (Bud) MDI with fluticasone propionate (FP) MDI, and the data were as follows:

Drug/Device	% of dose delivered (ex-valve) <6 µm (±SEM)
FP 50 µg MDI	49 (±1.3)
Bud 50 µg MDI	29 (±1.3)
FP 250 µg MDI	42 (±1.0)
Bud 200 µg MDI	26 (±0.8)

These data are consistent with those of OLSSON [2] and demonstrate that the pharmaceutical performance of the budesonide MDI is quite different from the fluticasone propionate MDI and, indeed, the budesonide Turbuhaler. This difference in pharmaceutical performance of the budesonide MDI could explain the findings of THORSSON *et al.* [1]. The above data also demonstrate that data for the budesonide MDI cannot be extrapolated more generally to other MDIs.

It is likely that these differences in fine particle fraction will only be of relevance in single-dose studies in volunteers, where a two-fold difference in particle size can be detected. In multiple-dose studies in patients, the much greater variability in drug delivered to the lung up to 10 fold between patients, will negate any differences seen in single-dose studies. In addition, the increased deposition, as reflected by the fine particle fraction, tends to be in the more peripheral part of the lung and neither β-agonists nor inhaled steroids, when used to treat asthma, are efficacious when landing in peripheral airways.

Therefore, any differences in lung deposition need to be supported by clinical data to determine whether they are clinically relevant. Indeed, there are data which show no difference, in terms of improvements in lung function, between the MDI and Turbuhaler in multiple-dose studies with ipratropium bromide [3], terbutaline [4, 5] and budesonide [6] as well as single-dose and cumulative dose studies with terbutaline [7, 8].

It is clear, therefore, that caution has to be taken in the interpretation of the clinical relevance of lung deposition studies, both in terms of extrapolation to other drugs in the same device and also different drugs and devices.

References

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Advantage of breath-actuated inhalers versus metered-dose inhalers

To the Editor:

In a recent paper, THORSSON *et al.* [1] reported the results of an experimental comparison of lung deposition of budesonide from Turbuhaler® and from a pressurized metered-dose inhaler (MDI). The administration of budesonide via Turbuhaler® gave rise to a lung deposition which was approximately twice that of a MDI, with less variability. The authors suggested that a less well-controlled inhalation procedure than that used in their study could have resulted in a greater difference between the two devices. This suggestion is confirmed by clinical studies showing that breath-actuated inhalers are used more correctly than MDIs [2, 3].

These results are particularly crucial, since drug administration by inhalation is currently the most widespread treatment for asthma, MDIs are the most popular inhalation devices to administrate these drugs, and their misuse is frequent, both in hospitalized [4] and in private practice patients. In a recent study, we assessed the frequency of, and factors related to, misuse of MDIs in asthmatic patients of French private practice [5].

Two hundred and sixty four chest specialists or general practitioners completed questionnaires for three consecutive asthmatic patients aged >6 yrs and currently using MDIs: 668 adults (aged 48±19 yrs, 52% males) and 100 children (aged 12±2 yrs, 72% males) were included. Patients demonstrated how they used the MDI. Adequate technique (deep inspiration synchronized with inhaler activation, followed by breath holding for 5 s) was used by 33% of adults and 26% of children; optimal technique (same, plus shaking the inhaler before use and activating it only once) was used by 22% of adults and 20% of children. The questionnaires also included questions on the characteristics of patients (sex, age, educational level, smoking habits, and size of the town of residence);

characteristics of asthma (frequency of attacks, history of hospitalizations for asthma, impact of asthma on daily life, and treatment); and any previous instruction in the use of inhalers. Previous instruction was the factor most closely correlated with correct use. However, among adults that received instruction in the use of inhalers, only 39% applied adequate technique and 27% optimal technique.

Since the problems related to instruction in the use of MDIs and to its lack of effectiveness in the long-term have not been solved, the improvement of drug delivery might be achieved by using dry powder breath-actuated inhalers.

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REPLY

From the authors:

We read with great interest the letters from LIARD *et al.* ("Advantage of breath-actuated inhalers versus metered-dose inhalers") and from FULLER *et al.* commenting on our article "Lung deposition of budesonide from Turbuhaler® is twice that from a pressurized metered-dose inhaler P-MDI" [1]. In our article, we concluded that the lung deposition of budesonide *via* Turbuhaler is approximately twice that of a P-MDI, with less variability. Turbuhaler gives a more favourable ratio of the contribution from pulmonary absorbed drug to the overall systemic availability, which indicates that the same degree of asthma control can be achieved with a lower dose than from the P-MDI. We also cited clinical studies where this has been confirmed [2, 3].

The difficulties in handling a P-MDI optimally is a well-known problem [4, 5]. The study summarized by LIARD *et al.* in the accompanying letter to the editor, confirms the abundant misuse of P-MDIs, with only 38.6% of the asthmatic patients being able to use an adequate technique. The authors arrive at the same conclusion as we did in our paper, *i.e.* improvement of drug delivery might be achieved by using dry powder breath-actuated inhalers.

Dr Fuller and colleagues, in their letter, seem to agree with this conclusion but suggest that differences in the fine particle fraction dose might explain the difference in lung deposition obtained between Turbuhaler and P-MDI. They also supply data indicating that the fraction of fine particles (<6 µm) is larger for fluticasone P-MDI than for budesonide P-MDI. They claim, however, that the fine particle fraction of the dose does not contribute to the clinical efficacy of the drug, as it is expected to be

deposited too peripherally to elicit the desired topical effect. If Dr Fuller and colleagues are correct in their hypothesis, the fluticasone P-MDI formulation would be expected to give a less favourable risk-benefit ratio, as the fine particle fraction not contributing to the desired anti-asthma effect should still be expected to give undesired systemic effects.

We are, however, unaware of the evidence showing that the fine particle fraction does not contribute to the overall anti-asthma effect. On the contrary, budesonide Turbuhaler has a higher fine particle dose than budesonide P-MDI and evidence of a better clinical effect [2, 6]. If the fine particle fraction contributes to the clinical effect of the drug, and as budesonide and fluticasone have been shown to be approximately equipotent topically [7], budesonide Turbuhaler as well as fluticasone P-MDI would perform better than budesonide P-MDI. This seems indeed to be the case, as suggested by studies from AYRES *et al.* [8], LANGDON and THOMPSON [9], AGERTOFT and PEDERSEN [2] and ENGEL *et al.* [10]. The last two studies are multiple-dose studies comparing the effect of budesonide Turbuhaler with budesonide P-MDI. The claim by Dr Fuller and colleagues, that such data are lacking is, thus, not correct. There is also strong evidence of a good correlation between deposition data and clinical effect for several anti-asthma drugs: there is an approximate 2:1 relationship to P-MDI formulations both in deposition and clinical efficacy for terbutaline Turbuhaler®, salbutamol Turbuhaler®, and ipratropium bromide Turbuhaler® [11–13].

Finally, as agreed by Fuller and colleagues in their letter, each system of drug and inhaler should be regarded as a separate entity, with unique properties regarding therapeutic potency and side-effects. Our article specifically discusses budesonide P-MDI and budesonide Turbuhaler and does not make any claims about Turbuhaler performing better than P-MDIs in general. Hence, each combination of drug and inhaler should be documented separately in well-designed studies. Unfortunately, clinical studies of suboptimal design are sometimes used to compare inhaled steroids. With a shallow dose-response relationship, two different doses of the same drug may give similar effects in such studies. Thus, in trials where the outcome is "no difference", the conclusions could have been predetermined by the doses chosen in the study design. Well-controlled single-dose studies can never replace well-designed, multiple-dose, double-blind clinical studies, but may be very useful in the interpretation of clinical findings and also to form a bridge between *in vitro* performance of a pharmaceutical formulation and its clinical properties.

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