Letters to the Editor

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Dear Editor

Equivalent therapeutic ratio, of salbutamol given by Turbuhaler® and Diskus® (Respir Med 2000, 94: 574–577)

It was with mixed feelings that I read the article by Arvidsson et al. in a recent issue (1). In their introduction, the authors state that ‘… clinical studies have demonstrated equivalent, or even improved efficacy of these two drugs when delivered via pMDI as compared with Turbuhaler’. The authors use five references to support their statement. A closer look at these five references, however, shows that they do not in any way support this statement.

If anything it should be the other way around. This could possibly be due to carelessness as reference 1 is used in another article (2) by the same group in a correct way. Another example of carelessness is obvious in the reference list. Reference 1 is given with incomplete author list and the title is not correct. Also in reference 7, the title is not given correctly, even though the article is from the same research group.

In addition, contrary to that stated in the article a direct comparison between lung deposition after inhalation via Turbuhaler and Diskus has been performed and was published before the article was submitted (3). In that study it was shown that lung deposition for budesonide Turbuhaler was 34-1% and for fluticasone Diskus it was 12-6% of the nominal metered dose. These data are in line with separately published lung deposition data for Diskus, 16-6% (4) and Turbuhaler, 32% (5) Also in another study a significantly higher lung deposition was observed for Turbuhaler as compared with Diskus (6). This is readily available information that should lead the ‘no-difference’ outcome to be interpreted with caution.

In the present study, the authors use a cumulative design to compare two different inhalers with the same active drug. They show a dose–response over the dosing interval but do not find any difference between the dose–response curves for the two inhalers. They interpret the absence of a difference as the presence of a similarity, which, of course, is against basic statistical common sense. In addition, we performed and published, before the present study was submitted, a study where we compared salbutamol Turbuhaler 50 µg with salbutamol Turbuhaler 100 µg in a cumulative design (7). In total, 400 and 800µg were given on the two study days. In spite of the known two-fold difference in dose given, there was no difference between the two cumulative dose–response curves. This absence of a difference we of course did not interpret as the presence of a similarity. It would have been ridiculous to claim that 50 equalled 100!

Figure 1 is hard to interpret as the bold line is denoted by squares for the first three points and with triangles for the other three points. For the dotted line it is the other way around. A mix-up of data? If the lines in the picture are correct (leaving the denotation apart) then it is hard to understand the numerical analysis as given in the Results section. In addition, it can be questioned if it is correct to connect the baseline value with the first point after drug intake on a dose scale. The baseline point, being zero, lies infinitely far off to the left on a logarithmic scale. A more fair presentation would have been to correct the three dose–response curves for differences in baseline before presenting the information in the figure. It is also more correct to analyse comparative device studies on the dose, rather than the effect, scale. With the given equivalence limits on the effect scale it would then also most probably have been able to show that two consecutive doses from the same device were equivalent to each other.

The authors state that devices should be compared on an equal microgram dose basis, but this statement is not supported by any reference. It is not obvious why an equal-dose comparison would be scientifically more strict than for instance an equal-number of inhalations comparison. A possible scenario, in a cumulative dose response study, is that in an arm where a higher microgram dose was used the full effect of the given dose is not obtained. In any comparisons between drug devices we are looking for differences. If no significant difference can be shown this could in the single case be due to that the devices were not compared on equal microgram doses, or equal number of inhalations. If a significant difference was shown it was a significant difference.

Finally, the statement that ‘… Turbuhaler has been suggested to give more peripheral deposition …’ is not supported by any reference. In the two available scintigraphic studies where regional deposition of inhaled drug was compared between Turbuhaler and pMDI, the one study showed very similar regional deposition (8) while the other one showed a more central (!) deposition when the drug was inhaled via Turbuhaler as compared with pMDI (9).

I look forward to a discussion on the matters raised.

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References

Dear Editor

Response to Prof. Borgström re: paper by Arvidsson et al. (Respir Med 2000; 94: 574–577)

We have received the letter by Prof. Borgström, employed by AstraZeneca R&D in Lund, regarding our recently published study comparing the effects of salbutamol given either by the Turbuhaler® or the Diskus® device (1). Prof. Borgström is bringing up a series of unrelated issues, but the key question is whether it is appropriate to use a cumulative dose–response design when comparing the clinical effects of bronchodilators.

Briefly, our study compared the effects of salbutamol given by two different inhalation devices, the Turbuhaler® and the Diskus®. We found that there were no, or very small, differences in the bronchodilating effects of salbutamol given by either device, in a dose range of 200–3200 μg. Importantly, we documented a clear dose–response relationship in FEV₁ over this dose range (2-2–2-51), which is important when comparing the potency of treatments.

Prof. Borgström argues that the initial dose of a β₂-agonist may influence the effects of a second dose, and thus that the results of findings at the higher levels of the dose–response curve may be more difficult to compare. Interestingly, however, Astra’s documentation for the Turbuhaler® is based on cumulative dose–response studies (2–5). Furthermore, there is a massive published documentation regarding the appropriateness of using cumulative dose–response designs in bronchodilator studies. In addition to these scientific arguments, it may however be even more important to remember that asthma patients, in real life, use multiple doses from an inhaler when they experience worsening of asthma. Thus, cumulative dosing may very well be appropriate when comparing the effects of different inhaled drugs. Regardless of this, we found no difference in the effects of salbutamol Turbuhaler® or Diskus® at the lowest dose used (200 μg). Also, a study performed in Southampton, U.K., showed no clinically relevant difference in maximal bronchodilating effect when therapeutic doses of salbutamol were given via Turbuhaler® either as two consecutive doses or as two divided doses separated by different time intervals (6).

We were careful to compare the same microgram doses, in contrast to some more recent publications evolved from studies sponsored by AstraZeneca (7,8). We did this to avoid any advantage for any of the used inhalers. Our conclusion must be, however aggravating it may be for Prof. Borgström, that there is no or little difference in the effects of salbutamol given by either Turbuhaler® or Diskus®, in the types of patients we have included in the present study.

Prof. Borgström had some additional comments. One of these has been addressed in a recent erratum. Importantly, it is not required to reference studies published only as abstracts, as these have not been peer reviewed. It is extensively argued that the Turbuhaler® gives better peripheral deposition than other devices, and in a publication by Thorson et al. at AstraZeneca, it is stated that ‘the systemic availability of budesonide, calculated as a geometric mean and expressed as percentage of the metered dose, was 38% for Turbuhaler® and 26% for p-MDI’ (9). We are not stating that there is a greater peripheral to central deposition, but rather a greater total peripheral lung deposition, using the Turbuhaler® device. This argument, extensively used at scientific meeting and in marketing situations, may however be untrue as described in Prof. Borgström’s letter, thus arguing against any improved therapeutic ratio of a drug given by Turbuhaler® vs. any other device.

Importantly, we have high respect for Prof. Borgström’s competence in this field, but we feel that it also must be important to consider clinical implications of studies comparing different devices. ‘In vivo veritas’ as stated by Prof. Borgström previously (10).

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