Delivery Devices for Inhaled Asthma Medication
Clinical Implications of Differences in Effectiveness

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Summary

This review deals with results of comparative clinical studies where 2 or more delivery devices have been used, the lung deposition of the drug has been measured or is known and the clinical efficacy has been documented.

With optimal inhalation technique the lung deposition of inhalation devices is approximately as follows: pressurised metered dose inhalers (pMDIs) 10 to 15% [salbutamol (albuterol) around 20%]; pMDI + spacer 20 to 30%; Rotahaler®, Diskhaler® and Inhalator Ingelheim® around 10%; Easyhaler® 20 to 25%; and Turbuhaler® 20 to 35% of the metered dose depending on the substance.

These differences in deposition figures have been reflected in the results of most single-dose crossover studies with bronchodilator substances. A pMDI is clinically more effective than Rotahaler® and Diskhaler®. Turbuhaler® is more effective than a pMDI. In single-dose studies where expected differences based on deposition values have been undetected, all responses have probably been on the top of the dose-response curves. Studies with a cumulative-dose design have not usually reflected known differences in deposition values between bronchodilator devices. This discrepancy between single-dose crossover studies and cumulative-dose studies seems to be the result of different doses and amounts of drug administered at different time points (especially the first dose) in the cumulative-dose studies. Studies with repeated doses over weeks and months do not reflect
differences in deposition values between bronchodilator devices, since short-acting bronchodilators, irrespective of the delivery system, do not affect the level of airway function in the morning. There are only 2 studies comparing the efficacy of a long-acting bronchodilator given via 2 different devices.

Anti-inflammatory medication is impossible to evaluate without using long screening periods, when the lowest required maintenance dosage of the inhaled corticosteroid has to be individually defined. Comparative studies are meaningless without knowing that patients are neither under- nor over-treated when entering the study. Thereafter, comparisons can be made in studies with a duration of several months. Very few studies fulfil these criteria. However, the results of these types of studies do reflect differences in deposition values between delivery devices. Studies reported so far show that the budesonide Turbuhaler® is clinically approximately twice as effective as a budesonide pMDI or a beclomethasone pMDI with spacer.

The results of short-term studies seem to indicate that fluticasone is twice as effective as beclomethasone, irrespective of pMDI or Diskhaler® delivery system. So far no well-designed double-blind studies have been performed comparing the budesonide Turbuhaler®, with fluticasone via pMDI or Diskhaler®.

No deposition data are available for fluticasone (in pMDI, Diskhaler® or Diskus®/Accuhaler®), or for the most recent device introductions such as the Diskus®/Accuhaler® with any substance. The Easyhaler® (available with salbutamol or beclomethasone) has good deposition values, but has not been compared clinically with Turbuhaler®, Diskhaler® or Diskus®/Accuhaler®.

Even when used properly, delivery devices may deposit very different amounts of drug into the lungs. Also, pMDIs may have different deposition properties. Recent studies with bronchodilators and corticosteroids have shown that there is a good correlation between the amount of drug deposited in the lungs and the level of clinical efficacy.

In order to be efficacious, inhaled drugs intended for treatment of diseases of the airways should reach their local site of action in sufficient amounts. The local action of inhaled β₂-agonists has never been questioned. They are rapidly absorbed from the airway mucosa, have a rapid onset of action and cause a maximum bronchodilation earlier than oral β₂-agonists. For equal levels of systemic effect, e.g. increase in heart rate and tremor, the inhaled drugs result in much greater bronchodilation than the oral drugs. Likewise, the local actions of ipratropium bromide and sodium cromoglycate (cromolyn sodium) are obvious as these drugs are poorly absorbed from the gastrointestinal tract.

It is more difficult to document the topical action of inhaled corticosteroids, as they do not have the same immediate effect as the bronchodilators. It has been postulated that their lung action could be a result of drug reaching the lungs after absorption to the systemic circulation. However, in a placebo-controlled parallel-group study patients with asthma had their minimum requirements of inhaled corticosteroids determined and were then given inhaled or oral budesonide at dosages giving the same area under the plasma concentration-time curve (AUC). The time to relapse was chosen as endpoint. No difference in time to relapse was found between oral budesonide and placebo, whereas patients treated with inhaled budesonide survived significantly longer without a relapse. The antiasthmatic effect could thus be explained