Local versus systemic effects of inhaled drugs

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For all drugs, the therapeutic ratio, i.e., the difference between therapeutic effect and adverse effect, should be as large as possible. When focusing on drugs used in the treatment of asthma, particularly β2-agonists and corticosteroids, the therapeutic ratio of these drugs can be considered to be the degree of separation of their effects on lung function from their systemic effects. This is increased by administration via inhalation, resulting in targeting of the drug directly to the site of action. However, all drugs deposited in the airways are eliminated via the systemic circulation, and have, therefore, the potential to cause some systemic side effects.

Short-acting β2-agonists

An early study by Thiringer & Svedmyr (1), showed that lung function improved more with inhaled terbutaline than with systemically administered drug. Furthermore, the systemic side-effects of the beta-2-agonist, given by the inhaled route was substantially reduced, showing that the therapeutic ratio is improved when anti-asthma drugs are given by inhalation.

In some studies, increased deposition of inhaled beta-2-agonists has been found by using different inhalation devices. For example, inhaled terbutaline is deposited to a larger extent in the lung (2) when using the TurbuhalerTM (18–21%) compared with the pMDI (9%). This increased deposition of terbutaline is associated with a more pronounced improvement in lung function (2,3) suggesting that the degree of deposition is important in determining the degree of bronchodilation. However, it is likely that increasing overall lung deposition of a beta-2-agonist will result in larger systemic bioavailability of the drug, and will therefore most likely also increase systemic side effects, such as tremor (4) and changes in serum potassium and heart rate, in parallel with local beneficial effects. Thus, the therapeutic ratio may not necessarily be improved by simply increasing lung deposition. It may be possible to increase the thera-

Long-acting β2-agonists

When an inhaled bronchodilator drug reaches the airway wall, it will have to diffuse through the airway epithelium to reach the submucosa, and then be further transported through the submucosa to the airway smooth muscle, before exerting its effects.

The microenvironmental distribution of drugs in the airways has been mainly discussed in the context of long-acting beta-2-agonists (6). Salmeterol and formoterol are two long-acting, β2-agonists that have been studied extensively, both clinically and in vitro systems. A clinical difference between the two drugs is seen in their onset of action, whereas the duration of effect can be shown to be very similar (7). Thus, both in isolated airway smooth muscle (6,8), and in patients (9,10), the onset of action of formoterol is faster than that of salmeterol.

It has been hypothesised that the different onset of action of these two drugs may depend on their different ways of entering the active site of the beta-2-receptor (6). Both salmeterol and formoterol are lipophilic, and a large proportion of drug in the microenvironment will be taken up into the lipid bilayer of the cell membrane, and a smaller portion will remain in the hydrophilic extracellular space. Salmeterol is taken up to a larger extent into the...
membrane compared with formoterol (6), because of its higher lipophilicity.

The long-acting beta-2-agonists may diffuse into the active site of the beta-2-receptor by two different routes, from the extracellular space and from the lipid bilayer. Formoterol, being less lipophilic than salmeterol, may to a larger extent enter the beta-2-receptor from the extracellular space, a process which will be more rapid than that of salmeterol, which enters exclusively from the lipid bilayer, explaining the faster onset of action of formoterol (8,10).

The duration of effect of both of these beta-2-agonists may in part be explained by the membrane lipid bilayer acting as a depot, allowing drug to be presented to the beta-2-receptor over a prolonged period of time. However, for salmeterol it has also been suggested that binding to an exo-site, within the beta-2-receptor, is important for the long duration of action (11).

Inhaled Corticosteroids

Giving corticosteroids by the inhaled route improves substantially the therapeutic ratio compared with the oral route. For example, inhaled budesonide is suggested to be approximately 30–50 times more potent in improving asthma control than oral prednisolone (12), whereas oral prednisolone is approximately 7 times more potent in inducing steroid-related systemic side-effects (measured as decrease in serum cortisol levels).

Inhaled corticosteroids may have their most pronounced effect in airway epithelial cells, in tissue resident inflammatory cells, and in the endothelium of the airway wall microvasculature. It is therefore likely that the concentration of a corticosteroid within the airway wall is important for its clinical effect, but very little is known about the microenvironmental distribution of inhaled steroids in the lung. In man, inhalation of budesonide and fluticasone propionate results in a high local concentrations of drug in both central and peripheral lung tissue (13–15), within the range showing anti-inflammatory effects in vitro, whereas the concentration in the plasma (13,14) is lower at corresponding time points. This was particularly evident for fluticasone propionate (14), where the high local concentrations were maintained for more than 12h, probably due to slower elimination from the airways (16). This would indicate that there is considerable binding of fluticasone propionate in the lung, which may, in part, result in a prolonged residency time of the drug at the important sites of action, and may result in a longer duration of clinical effect.

When a corticosteroid is given by inhaled route, approximately 15–30% of the emitted dose reaches the lung, and the rest is deposited in the mouth and pharynx. Most of the drug deposited outside the lung will be swallowed and absorbed from the GI tract, but up to 80–99% may be eliminated by first-pass metabolism in the liver. All of the drug deposited in the lung, and the oral portion not eliminated by first pass metabolism, will reach the systemic circulation. One study has investigated whether the fraction of corticosteroid reaching the systemic circulation has any anti-asthma effects (17). Briefly, budesonide was given orally at a dose causing a systemic concentration of the drug, similar to that found after inhaled drug. No beneficial anti-asthma effect was, however, observed suggesting strongly that the most important site of action of inhaled corticosteroids is the airways, and that any systemic anti-inflammatory effects may be unimportant for anti-asthma efficacy.

Conclusions

Improving knowledge of the microenvironmental distribution of topically administered anti-asthma drugs may prove to be important. For example, increased therapeutic ratio may be achieved by decreasing the elimination of inhaled drugs from the airways, thus increasing and maintaining their concentration at the site of airflow obstruction and inflammation in asthma. In the future, the same goal may be reached by targeting the drug to its site of action, by using monodispersed aerosols.

References

16. Derendorf H. This meeting