Clinical

Dose-response relationships in determining the safety:efficacy ratio

A. LEFF

Section of Pulmonary and Critical Care Medicine, Department of Medicine, University of Chicago, Chicago, U.S.A.

The development of inhaled agonists selective for $\beta_2$-adrenoceptors and high potency corticosteroids has improved the treatment of asthma. The delivery of the drugs to the site of action reduces the systemic exposure and hence reduces adverse systemic events. Together, these factors have resulted in improved toxicity:therapeutic ratios. Long-acting $\beta_2$-agonists, such as salmeterol and formoterol, and high efficacy corticosteroids, such as fluticasone propionate and budesonide, now are available for clinical use. Because suboptimal treatment of asthma causes increased morbidity and mortality, and increased costs to society, these compounds are of particular value. Risk factors associated with fatal and near-fatal asthma have been identified, and it would appear that drug treatment by metered dose inhaler per se does not cause increased asthma fatality as an independent risk factor.

Mortality associated with asthma is considerably lower than for many other diseases. For a given therapy, therefore, the acceptable level of side effects will be very low and the expected levels of efficacy very high. This makes asthma therapy a challenging area.

$\beta$-agonists in the Treatment of Asthma

The development of $\beta$-adrenoceptor agonists, originally based on the structures of adrenaline and noradrenaline, has resulted in compounds with specificity for $\beta_2$-adrenoceptors, such as salbutamol and terbutaline, and, more recently, the long-acting $\beta_2$-agonists, salmeterol and formoterol (see Table 1). As formoterol is not yet available in the USA, this article focuses solely on salmeterol. After inhalation of a 50 $\mu$g dose, salmeterol produces peak bronchodilation 1-2 hours after dosing, equivalent to that obtained with 200 $\mu$g of salbutamol (1). Furthermore, salmeterol-induced bronchodilation lasts as long as 12 hours, compared with approximately 4 hours for salbutamol. This long duration of action results from repeated stimulation of the active site of the $\beta_2$-adrenoceptor by the molecule's polar 'head', while the long, nonpolar side-chain remains anchored to the hydrophobic exosite of the receptor (2).

Because of the relatively slow onset and long duration of action, salmeterol is particularly useful for regular prophylactic treatment, rather than immediate symptomatic relief. In clinical trials, salmeterol has frequently been used as a replacement for other bronchodilators and added to existing regimens (including corticosteroids, sodium cromoglycate, nedocromil or ketotifen). In one study, salmeterol 12.5, 50 and 100 $\mu$g twice daily was compared with placebo in 614 patients with mild to moderate asthma (3). In the patients receiving salmeterol, there was a dose-related increase in peak expiratory flow rate and dose-related reduction in diurnal variation in pulmonary function. Significant symptomatic improvement with salmeterol also was reported, with the 50 $\mu$g twice daily dose producing the optimal balance of efficacy and tolerability, based both on patients' and physicians' overall assessments. Moreover, in patients with moderate to severe asthma, salmeterol 50 or 100 $\mu$g twice daily has been reported to cause dose-related improvements in peak expiratory flow rate, as well as reductions in the use of an additional bronchodilator as rescue medication (4).
DOSE-RESPONSE RELATIONSHIP IN DETERMINING THE SAFETY-EFFICACY RATIO

Table 1. Selectivity of some β-adrenoceptor agonists.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Airway smooth muscle (β₂-adrenoceptor)</th>
<th>Cardiac tissue (β₁-adrenoceptor)</th>
<th>Selectivity ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoprenaline</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Fenoterol</td>
<td>0.6</td>
<td>0.005</td>
<td>120</td>
</tr>
<tr>
<td>Formoterol</td>
<td>20.0</td>
<td>0.05</td>
<td>400</td>
</tr>
<tr>
<td>Salbutamol</td>
<td>0.55</td>
<td>0.0004</td>
<td>1375</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>8.5</td>
<td>0.0001</td>
<td>85,000</td>
</tr>
</tbody>
</table>

*Potency expressed as relative to isoprenaline (=1.0)

The long duration of action of salmeterol means that the drug is particularly useful in preventing nocturnal asthma symptoms. In a study of 17 patients with nocturnal asthma, salmeterol 50 or 100 µg twice daily was more effective than placebo in improving overnight peak expiratory flow rates and objective measurements of sleep; the 100 µg dose reduced significantly the requirement for rescue salbutamol during the night (5,6). Using a visual analogue scale to determine sleep quality, Ullman et al. (7) reported that patients receiving salmeterol 50 µg twice daily, rated quality of sleep higher than those receiving salbutamol 200 µg four times daily. In addition, several other placebo-controlled studies have demonstrated that awakenings, occurring as a result of nocturnal symptoms, are reduced by salmeterol 50 or 100 µg twice daily (3,4,8).

Comparative studies of salmeterol with other inhaled, short-acting, β₂-adrenergic agonists, using large numbers of patients with varying asthma severity, have shown salmeterol 50 µg twice daily to be more effective than salbutamol 200 µg four times daily or terbutaline 300 µg four times daily in increasing peak expiratory flow rates and in reducing day and night time symptoms, diurnal variation and rescue salbutamol use. A meta-analysis of nine clinical trials comparing salmeterol with slow-release theophylline indicated significantly improved clinical responses in patients receiving salmeterol (11).

Inhaled corticosteroids in the treatment of asthma

Inhaled corticosteroids are used in various doses, depending upon the severity of asthma requiring treatment and on the delivery device being used. Because of differences in receptor affinity, lipophilicity and delivery devices, it is not appropriate to assess potential toxic effects of these agents as dose equivalents. Hence, toxicity assessments for these drugs must be made at comparable levels of efficacy. The clinical efficacy of fluticasone propionate is twice that of beclomethasone dipropionate (BDP) or budesonide, both of which in turn are twice as effective as triamcinolone acetonide. However, the safety of these compounds at the various doses needs to be taken into account, since increased efficacy could also mean increased systemic activity and adverse events.

One of the key benefits of using inhaled corticosteroids is their ability to reduce the dosage of oral steroids (and hence reduce the systemic adverse events associated with these drugs) in those patients requiring them for effective asthma management. Noonan et al. (12) reported a study in which patients with severe asthma symptoms who were dependent on oral corticosteroids received either inhaled fluticasone propionate, 750 or 1000 µg twice daily, or placebo. Following 16 weeks of treatment, both fluticasone propionate-treated groups had increased forced expiratory volume in 1 second (FEV₁) values and peak expiratory flow rates (PEFR), the higher dose of fluticasone propionate caused significantly greater improvements than the lower dose. In addition, most patients receiving fluticasone propionate were able to either discontinue or significantly reduce the accompanying dose of oral steroids without worsening of their asthma (Table 2). Thus, night awakenings, rescue salbutamol use and patient-rated asthma symptoms were significantly reduced by fluticasone propionate, but there was no significant difference in these parameters between the two doses (Table 2). Thus, the additional improvement in symptom score for the higher dosage group compared with the lower one was modest in clinical terms.

Chervinsky et al. (13) also found that fluticasone propionate, 25, 100 and 500 µg twice daily, was more effective than placebo in controlling mild to moderate...
Table 2. Effect of fluticasone propionate (750 or 1000 µg twice daily) or placebo for 16 weeks on various outcome measures of patients with severe asthma. Data from Ref 12

<table>
<thead>
<tr>
<th>Variable</th>
<th>Placebo</th>
<th>FP 750 µg twice daily</th>
<th>FP 1000 µg twice daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morning PEF (L/min)a</td>
<td>332 -15.0</td>
<td>307 40.1**†</td>
<td>378 83.2**†</td>
</tr>
<tr>
<td>Evening PEF (L/min)</td>
<td>367 -24.1*</td>
<td>342 19.8*</td>
<td>422 54.1*†</td>
</tr>
<tr>
<td>Salbutamol use (puffs/day)</td>
<td>9.2 0.91</td>
<td>8.9 -3.04**</td>
<td>8.2 -3.97**</td>
</tr>
<tr>
<td>Nocturnal awakening</td>
<td>0.74 0.11</td>
<td>0.61 -0.32**</td>
<td>0.68 -0.63**</td>
</tr>
<tr>
<td>Prednisone dose (mg)</td>
<td>10.2 1.6</td>
<td>9.5 -6.6**</td>
<td>10.2 -9.3**†</td>
</tr>
<tr>
<td>Asthma symptom score</td>
<td>1.01 0.02</td>
<td>0.77 -0.36</td>
<td>0.80 -0.56**</td>
</tr>
</tbody>
</table>

*p<0.05 versus baseline
**p<0.05 versus placebo
†p<0.05 versus FP 750 µg twice daily.

Abbreviations: FP: fluticasone propionate; PEF: peak expiratory flow.

As asthma, as assessed by FEV₁, forced vital capacity and PEF measurements. Over the 8-week treatment period, there were significant improvements in PEF rates and symptom scores, while night-time awakenings and use of rescue salbutamol declined significantly. Physician global assessments rated fluticasone propionate as either effective or very effective in 55-85% of patients; treatment was judged ineffective in 4-17%. In addition, fluticasone propionate caused a marked reduction in the number of severe episodes of asthma and increased the probability of patients remaining in the study (Fig. 1).

To obtain an overview of the efficacy:toxicity ratios of the various inhaled corticosteroids, meta-analyses have been performed of all trials of fluticasone propionate, budesonide (14), and BDP (15), in which morning PEF was measured prior to any medication.

Risk factors associated with fatal asthma

Spitzer et al. (17) suggested an apparent association between increased risk of death or near death from asthma and regular use of β₂-agonist bronchodilators. However, this study also showed that patients receiving theophylline and inhaled corticosteroids had increased risk. This study was, however, subject to confounding by failure to analyse severity of illness. Subsequent studies from the same population of patients showed no correlation between β₂-agonist MDI use and serious adverse events in asthmatic patients (18).

Asthma therapy usually focuses on improvements in clinical condition and patient’s quality of life. However, a study by Marquette et al. (19) examined...
the long-term prognosis of near-fatal asthma. They reported that a subset of patients 40 years old, who had previously been intubated because of life-threatening asthma, had a mortality rate of approximately 40% by the end of 5 years. Potential risk factors associated with fatal asthma (sudden onset fatal asthma or fatal asthma syndrome) include prior frequent hospitalisation, especially if previously intubated, and steroid dependency. The incidence of fatal asthma varies considerably among countries. The reasons for this cannot be easily identified, but it is extremely unlikely to be drug-related as the same drugs are used in most developed countries. In the USA, socio-economic factors have been shown to be important risk factors. Over a 10 year period, between 1978 and 1987, the incidence of fatal asthma was 3 times greater and increasing among black compared with white Americans, where it decreased slightly (20). Changes in mortality rate may not be related to drug treatment, lack of drug treatment, or a change in disease. For example, in Chicago, the increase in deaths occurring as a result of tuberculosis increased eight-fold, while during the same period, asthma-related deaths increased three-fold.

Summary

There is strong emphasis in the new treatment guidelines issued by The Expert Panel of NHLBI that asthma should be treated as a disease of stages. Treatment should not only be directed to a particular stage, but should initially be focused on the highest level for that stage to gain control of the disease as quickly as possible. Long-acting $\beta_2$-Agonists and inhaled corticosteroids, either alone or in combination, significantly improve the clinical signs and symptoms of asthma. Administration of $\beta_2$-adrenergic agonists by inhalation results in no significant loss in their effectiveness, but a significant decrease in their systemic activity, resulting in improved efficacy:safety ratios. Systemic adverse events are usually observed only at very high inhaled dosages, and even at these doses, drug therapy does not appear to be related to asthma mortality.

References


