β-agonist safety and the elephant in the room?

We read with interest the recent paper by Weatherall et al who presented data from a meta-analysis of the relative safety of long-acting β-agonists (LABAs).1 In 2008 the FDA reported on the safety of LABAs and concluded that the nature and magnitude of risk needs to be confirmed. When adverse outcomes are reported relatively infrequently in clinical trials, it is difficult to interpret the value of such analysis and a more thorough examination of these index cases may yield more meaningful information about individual risks per se.

Polymorphisms in the β2-adrenoceptor have long been linked to differences in response to β2-agonists after chronic dosing. In asthma, the prevalence of the genotype Arg-Arg-16 is approximately 15% and of Arg-Gly-16 is 45%.2 In patients with asthma using frequent β2-agonists, there is an increased risk of asthma exacerbation per copy of Arg16 allele (OR 1.64; 95% CI 1.22 to 2.20; p=0.001).3 Could this be the elephant in the room for better understanding risk?

In a recent multicentre study assessing salmeterol as an add-on to inhaled corticosteroids in genotype-selected patients (the LARGE study), patients with the Gly-Gly-16 genotype had a 2.4-fold greater improvement in bronchial hyper-reactivity (BHR) with salmeterol than with placebo (p=0.0001), while patients with the Arg-Arg genotype had no such benefit (p=0.87).4 Lee et al have previously shown similar differences in response to BHR for patients with the Gly-Gly genotype compared with individuals carrying either one or two copies of Arg16 (table 1).5 Furthermore, this paper demonstrated differences in patients with Arg16 in their response to the full agonist formoterol compared with the partial agonist salmeterol. These findings are in keeping with the discussion by Weatherall et al which suggested that there may be different risks in different drugs from the same drug class.

It is common practice for respiratory physicians to measure levels of thiopurine methyltransferase before administration of the drug azathioprine in pulmonary fibrosis. This test identifies individuals with genetic polymorphisms which predispose to an adverse reaction to the drug. Perhaps the time has come to join up the dots and start assessing individual risk to β2-agonists rather than continuing to count cases.

P A Williamson,1 P M Short,1 L McKinlay,1 C N A Palmer,2 B J Lipworth1

1Asthma and Allergy Research Group, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK; 2Biomedical Research Centre, University of Dundee, Ninewells Hospital and Medical School, Dundee, UK

Correspondence to Professor Brian Lipworth, Asthma and Allergy Research Group, University of Dundee, Ninewells Hospital and Medical School, Dundee DD1 9SY, UK; brianlipworth@googlemail.com

Competing interests None.

Table 1 Change in bronchial hyper-reactivity as a doubling dilution shift for formoterol and salmeterol in genotype-specific patients as change from placebo after chronic dosing

<table>
<thead>
<tr>
<th>Drug</th>
<th>Genotype</th>
<th>Doubling dilution (dd) shift</th>
<th>&gt;1 dd (improvement)</th>
<th>±1 dd (no change)</th>
<th>&gt;1 dd (worsening)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Formoterol</td>
<td>Arg-Arg and Arg-Gly</td>
<td>17%</td>
<td>23%</td>
<td>60%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gly-Gly</td>
<td>27%</td>
<td>44%</td>
<td>29%</td>
<td></td>
</tr>
<tr>
<td>Salmeterol</td>
<td>Arg-Arg and Arg-Gly</td>
<td>35%</td>
<td>46%</td>
<td>18%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Gly-Gly</td>
<td>50%</td>
<td>39%</td>
<td>11%</td>
<td></td>
</tr>
</tbody>
</table>

After data from Lee et al.

REFERENCES

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