Salbutamol inhalation and dental caries

Introduction
Salbutamol (Ventolin®) is a β₂-sympathomimetic drug, which was granted a marketing authorization in 1973. It is indicated for the treatment of reversible airway obstruction in bronchial asthma, chronic bronchitis and emphysema [1]. Both child and adult asthmatics use this inhalation medication, the difference lies in the dosage and vehicle of delivery. Dental caries as an ADR of salbutamol use is well-described in literature and seen regularly by health professionals but is not listed in the SPC.

Reports
Up to September 5, 2007 the Netherlands Pharmacovigilance Centre Lareb received five reports of dental caries in association with salbutamol. In some reports the application form was mentioned, which is shown in table 1. Ventolin Rotadisk® contains lactose. Ventolin® aerosol does not. Lareb received no reports of dental caries on other selective β₂-sympathomimetic drugs.

<table>
<thead>
<tr>
<th>Patient, Sex, age</th>
<th>Drug Indication for use</th>
<th>Concomitant medication</th>
<th>Suspected adverse drug reaction</th>
<th>Time to onset, outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>A M, 9</td>
<td>salbutamol 1 DF as necessary</td>
<td>beclomethasone</td>
<td>dental caries</td>
<td>2 years not reported</td>
</tr>
<tr>
<td>B M, 5</td>
<td>salbutamol inhaler 100 µg QID as necessary</td>
<td>not reported</td>
<td>dental caries</td>
<td>years not reported</td>
</tr>
<tr>
<td>C M, 5</td>
<td>salbutamol aerosole 100 µg TID aerochamber fluticasone 125 µg BID aerochamber</td>
<td>sodium cromoglicate nasal spray</td>
<td>dental caries (8 dmfs*) growth retardation</td>
<td>not reported</td>
</tr>
<tr>
<td>D M, 6</td>
<td>salbutamol inhaler 200 µg as necessary</td>
<td>not reported</td>
<td>dental caries</td>
<td>since start with inhalation powder striking number of holes in teeth not reported</td>
</tr>
<tr>
<td>E F, 6</td>
<td>salbutalol aerosole 100 µg as necessary asthma</td>
<td>none</td>
<td>dental caries</td>
<td>2 months not recovered</td>
</tr>
</tbody>
</table>

* dmfs means decayed, missing or filled surface

Other sources of information

Literature
Dental caries is the result of a disturbed balance between saliva, oral bacteria, tooth structure, the existence of plaque, and dietary substrates [2]. The amount of saliva and of plaque, the saliva pH (SpH) and the plaque pH (PpH) play important
roles. The lower secretion rate of whole saliva consequently means that the availability of biologically active components, like amylase, calcium, secretory IgA, and peroxidase is decreased. The decreased output of antibacterial components favours both bacterial colonization and plaque growth. Furthermore the lowered secretion per minute of calcium and protein implies an unfavourable effect in critical pH [3]. This ‘critical pH’, at which the enamel begins to dissolve in the plaque environment, is not known, although its existence is widely assumed. It is generally accepted that a drop of plaque pH below 6.0 should be considered potentially harmful [4].

In the study by Ryberg et al. asthmatic patients chronically using the β-adrenoceptor terbutaline or salbutamol have a significantly lower secretion rate for whole saliva and higher titres of lactobacilli than healthy non-users [3]. Furthermore, they showed a positive relationship between decreasing saliva secretion rate and an increased dosage of β-agonists [3]. A relative difference between caries prevalence in primary and mixed dentitions has been demonstrated in several studies. Reddy et al. found an increasing prevalence of caries when examining children with primary (70%), mixed (78%), and permanent dentitions (83%), respectively [5]. The higher risk of caries in the more developed mixed or permanent dentition is also shown by Wogellius et al. and by Milano et al. [6,7]. A case-control study with 1-year follow-up showed that salbutamol inhaler increased caries rate compared to control, salbutamol tablets and beclomethasone inhaler [8].

There is also a difference in potential of lowering PpH between pressurized metered dose inhalers (MDIs) and dry powder inhalers (DPIs). The latter contains lactose, which has been shown to depress PpH and SpH more than DPIs. In the study by Kargul et al. the results suggest that asthmatic children on long-term inhaler use have inherently lower oral pH than the normal population and that inhalers, even in the MDI form, whether corticosteroid or β₂-agonist, are potentially acidogenic [2].

Databases
On September 4, 2007 the Lareb database contained 46 reports of dental caries and 227 reports on salbutamol. The reporting odds ratios are shown in table 2.

Table 2. reports of tooth caries associated with the use of salbutamol in the Lareb database and the WHO database in the 2nd quarter of 2007

<table>
<thead>
<tr>
<th></th>
<th>reports of tooth caries on salbutamol (n)</th>
<th>ROR (95%CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lareb</td>
<td>5</td>
<td>34.2 (13.4-87.3)</td>
</tr>
<tr>
<td>WHO</td>
<td>19</td>
<td>8.2 (5.2-13.0)</td>
</tr>
</tbody>
</table>

Discussion
Dental caries affect many patients in Europe [9], and a significant proportion of children in the Netherlands has caries [10]. Dental caries is a well-described adverse drug reaction of salbutamol and other β-agonists, and well-known by dentists and paediatric health-professionals [3-9]. This might explain the low
number of reports in the Lareb database: when an ADR is well-known, it will be less often reported.

Three of the five patients used corticosteroids next to salbutamol. Corticosteroids are weak organic acids and generally are not metabolised by oral bacteria. They therefore should not pose a pH threat, except when lactose-based inhalers are used [4]. Concomitant medication was not reported in the fourth patient. The fifth patient used only salbutamol. So the role of corticosteroids is absent in this patient.

Conclusion

Five case reports of dental caries in the Lareb database are associated with the use of salbutamol. Literature supports the relation and probable mechanisms are proposed.

References