Asthma inhalers and subsurface enamel demineralisation: an in situ pilot study

R. TOOTLA, G. KOTRU, M.A. CONNOLLY, M.S. DUGGAL, K.J. TOUMBA

ABSTRACT. Aim The purpose of this pilot study was to identify the subsurface enamel demineralising potential of two possible acidogenic lactose-based powders and their corresponding generic pump inhalers. Methods Ten healthy non-asthmatic adults participated in a 3-leg randomised crossover study including a 10% sucrose control. A twice-daily 400 µg dose of inhaler was applied in vitro to a demineralised enamel slab on the buccal flange of a mandibular removable appliance before in situ placement for 14 days each. Lesion parameters were determined using transverse microradiography and digitised image analysis. Results Minimal demineralisation occurred with sucrose, both pump and one powder inhaler. The remaining powder was associated with remineralisation (p = 0.29). Overall, mean lesion depth increased (p = 0.12). Conclusion Asthma inhalers failed to demonstrate a significant acidogenic/cariogenic effect.

KEYWORDS: Asthma inhalers, Enamel demineralisation, Dental caries.

Introduction

In the United Kingdom prescription medication for asthma accounts for 83% of the total annual expenditure on respiratory drugs (Office of National Statistics, U.K., 1999); in the USA, 6% of child asthmatics are on active treatment (ISAAC, 1998) with $1.1 billion (30%) being spent on prescribed medication annually.

All inhaled asthma drugs are available in aerosol metered-dose (pump) and dry-powder forms. Age appropriate inhaler devices are recommended (British Thoracic Society guidelines, BNF: 2001) as coordinating actuation and inspiration precisely enough with a pump or to inhale forcefully enough when wheezy to use a dry-powder, may prove very difficult in children. Almost 30% of adult asthmatics have inadequate pump technique with 80% of the drug deposited in the oropharynx [Lipworth, 1996]. Dry-powders require a minimum inspiratory effort of 30L/min, precluding their use in children below age 6 years [Pederson, 1996]. Oropharyngeal deposition remains high at 60% of the delivered dose [Lipworth, 1996].

Protagonists for an association between asthma and dental disease are abundant [McDerra et al., 1998; Shaw et al., 2000], with more recent emphasis on the possible role of asthma inhalers. Sympathomimetics (β2-agonists) reduce salivary flow rate and may contribute to the dental caries experience of asthmatics [Ryberg et al., 1987, 1991].

Additional risk factors include unhealthy diet modifications, sugar containing oral medications [Storhaug, 1985] and increased frequency of cariogenic drinks intake due to thirst and desire to rid the mouth of an inhaler’s unpleasant taste. Plaque pH studies following inhaler use have shown that pumps with spacers [Kargul et al., 1998] and lactose-based powders [Lenander-Lumikari et al., 2000; Tootla et al., 2004] decrease plaque pH and, therefore, might be acidogenic.

Lactose-based powders are inherently the most acidic when compared with all other inhalers [O’Sullivan, 1998; Tootla et al., 2004]. Cariogenicity research, using the intra-oral cariogenicity test (ICT), will enhance our knowledge of the relationship of asthma medication to dental caries.

The aim of this study was, therefore, to assess the in situ subsurface enamel demineralising potential of selected inhalers using transverse microradiography and digitized image analysis.

Material and methods

Ethical approval was obtained from the Leeds Regional Ethics Committee (Leeds, England).

A power calculation of this 5-leg single blind crossover study determined a sample size of 10 subjects as sufficient. Ten healthy, non-medicated, dentate adult volunteers who previously participated...
in the pH study on inhalers [Tootla et al., 2004], having fulfilled the criteria for cariogenicity studies [Harper et al., 1986; Stookey et al., 1992; Zero et al., 1992] provided informed consent to participate. The acquisition of suitable human premolars, creation of white spot lesions, sectioning of teeth to produce control and experimental slabs, their sterilisation and storage mirrored that of Amaechi et al. [1998, 1999] and Duggal et al. [2001].

A mandibular removable Hawley appliance was made for each volunteer and an experimental enamel slab attached to the buccal flange was covered by 0.15 mm Dacron gauze for plaque retention prior to each leg [Pollard, 1995] which lasted for 14 days.

Test inhalers comprised two lactose-based powders that previously produced the greatest acidogenic challenge, i.e. Becodisk® (beclamethasone dipropionate + 25 mg lactose/dose) and the combination Seretide Accuhaler® (fluticasone propionate + salmeterol + 12.5 mg lactose/dose), and their pump equivalents: QVAR® and Seretide®, respectively (Tootla et al., 2004). A 10% sucrose rinse served as the positive control. As ethical considerations precluded inhalation of medication by healthy volunteers for extended periods, a twice-daily extraoral application of 400 µg of inhaler onto the enamel slabs, embedded in the appliance, was considered an acceptable alternative prior to intraoral placement. Pumps were directly sprayed but the powders were dismantled, revealing the foil blisters containing a standardized powdered drug dose that was tipped onto the enamel slabs. For the positive control, the flange housing the enamel slab was extraorally immersed in 10 ml of the 10% sucrose solution provided for 1 minute, the same amount of time that it took for inhaler application.

Subjects adhered to a non-fluoride protocol and wore their appliances continuously, except during food and beverage consumption. An initial two-week lead-in period allowed acclimatisation to appliance use and for adjustments. Prior to each leg a two-day lead-in period allowed the acquisition of plaque on the enamel slabs.

The full trial took four months to complete comprising five distinct two-week periods with one week between tests. A compliance check was built into the volunteer diaries and a four-day diet history recorded.

Following the intra-oral periods, enamel slabs were sectioned (80-100 µm thick) and radiographed according to Duggal et al. [2001]. A trained examiner blindly quantified the resulting microradiographs in an image analysis system (Inspektor Systems, Amsterdam, The Netherlands) by means of a Leica Leitz DMRB optical microscope (Leica DMR Modular System, model 020-525.024, Optivision Ltd., W. Yorkshire, England).

The microradiographic image was scanned under standard conditions of light intensity and magnification (150 x) via a video camera connected to a computer. Lesion parameters were expressed in terms of mineral loss, ΔZ (vol%·µm), and lesion depth, Lδ (µm).

Using SPSS 11.1, the normality of data was determined with the Shapiro-Wilk test. Mineral loss/gain and lesion depth of the control and test samples were tested by paired and unpaired t-test within groups and between groups (i.e different test regimens) by ANOVA. Values of p <0.05 were accepted as statistically significant.

Results

All lesion parameter data were normally distributed, except for a few outliers with sucrose. Although parametric tests were considered robust following statistical advice, the non-parametric equivalents were also applied and confirmed the same findings. The mean mineral loss of control sections was 1,234 ±164.2 vol%·µm, ranging from 876.6 vol%·µm to 1,561.1 vol%·µm. For the mean 14-day lesion parameter change, all inhalers except Becodisk® produced demineralisation (Fig. 1) and an increased lesion depth of enamel slabs (Table 1). The absolute and percentage change differences in mineral loss between test groups were not statistically significant, the same was true for comparison between devices for each generic drug. The control lesion depths ranged between 36.5 µm and 63.4 µm. The mean change in lesion depth can be seen in Table 1 with a significant change observed only with the sucrose control (p<0.005). A wide inter-subject variation was observed across inhalers for both experimental lesion parameters, not so with the sucrose control.

Discussion

The in situ model and ICT experiment used in the present study conformed to the guidelines of the proceedings of the 1985 [Harper et al., 1986] and 2000 [Curzon and Hefferren, 2001] Cariogenicity Workshops on Technological Advances in Intra-Oral Model Systems. Adults instead of children participated as the caries rate and response to preventive treatment are similar between them [Zero et al., 1992; Stookey et al., 1992] and adults are more likely to comply with clinical protocols and scheduled
appointments [Tahmassebi et al., 1996]. The ethical dilemma of unnecessarily medicating healthy volunteers at length with several asthma inhalers was the main consideration for choosing in vitro application [Koulourides et al. 1976], although this method fails to imitate normal usage. Pump application closely mimicked intraoral use and dismantling the powder devices resulted in a marked deviation from normal practice, a probable confounder.

The standardised test conditions minimised dietary effects.
Given evidence that a thrice-daily carbohydrate consumption under fluoride-free conditions results in significant enamel demineralisation [Duggal et al., 2001], the twice-daily maximum adult inhaler dose used in the present study conformed to guidelines for standard of care in moderate/severe adult asthmatics (BNF 2001). A negative control was excluded, as the primary focus of this study was to determine the acidogenicity/cariogenicity of asthma inhalers rather than to deduce their ‘safe for teeth’ level; these medications will continue to be used by the asthmatic population for many years to come.

Baseline lesion parameters, in the present investigation, were within accepted norms for cariogenicity studies [Strang et al., 1988]. Bearing in mind that this was only a pilot study, longer study legs, a higher frequency of daily exposure and a larger sample size might have identified any potentially significant differences in 14-day mineral loss. Seretide Accuhaler® contained 25 mg of lactose in the final dose; it has an inherent pH of 4.97 ±0.41 and a titratable acidity of 0.62 µmols OH- ions [Tootla et al., 2004]. Whilst the presence of lactose, low inherent pH and plaque pH responses can explain the demineralisation observed with Seretide Accuhaler® it failed to explain the remineralisation observed with Becodisk®, which contained 50 mg of lactose in the final dispensed dose. Becodisk® has a slightly higher inherent pH of 5.23 ±0.36, but twice the titratable acidity of the Seretide Accuhaler®, it also produces a greater oral pH response [Tootla et al., 2004]. Which of the two parameters, inherent pH or titratable acidity, is more influential on subsurface enamel demineralisation remains questionable. Despite the ‘safe’ inherent pH values, absence of lactose and relatively harmless oral pH responses of QVAR and Seretide pumps [Tootla et al., 2004], some subsurface enamel demineralisation was observed with both.

Asthma inhalers, regardless of lactose content or vehicle of delivery, behaved similarly to a twice-daily 10% sucrose rinse, associated with equivocal or minimal subsurface enamel demineralisation. There is no existing evidence in the dental literature to support a subsurface enamel demineralising potential with a twice-daily 10% sucrose rinse over a two-week period. Hence, the clinically significant cariogenic effect of inhalers remains unknown. The result of this pilot study failed to corroborate the previous pH studies with inhalers [O’Sullivan et al., 1998; Kargul et al., 1998; Lenander-Lumikari et al., 2000; Tootla et al., 2004]. The effect of normal oral fluctuations and protection afforded by saliva cannot be undermined.

<table>
<thead>
<tr>
<th>Test Inhaler</th>
<th>Mean value (µm)</th>
<th>± SD</th>
<th>SEE</th>
<th>± 95% Confidence Interval</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>I Mean change</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Becodisk</td>
<td>-0.61</td>
<td>7.32</td>
<td>2.59</td>
<td>-6.74, 5.51</td>
<td>0.12</td>
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<tr>
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<td>7.66</td>
<td>2.42</td>
<td>-8.27, 2.69</td>
<td></td>
</tr>
<tr>
<td>Seretide Accuhaler</td>
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<td>8.44</td>
<td>6.42</td>
<td>-18.26, 2.69</td>
<td></td>
</tr>
<tr>
<td>Seretide MDI</td>
<td>-8.90</td>
<td>13.43</td>
<td>4.48</td>
<td>-19.23, 1.43</td>
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</tr>
<tr>
<td>Sucrose</td>
<td>-1.84</td>
<td>3.15</td>
<td>1.05</td>
<td>-4.26, 0.58</td>
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<tr>
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<td></td>
<td></td>
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<td>5.37</td>
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<td>7.53</td>
<td>2.51</td>
<td>-10.64, 0.94</td>
<td></td>
</tr>
</tbody>
</table>

µm = lesion depth expressed in micrometers; ± SD = standard deviation of the mean; SEE = standard error estimate of the mean.

Note: the mean percentage change per test inhaler is determined as an average percentage of the sum of the individual percentage changes in lesion depth for each enamel section per test.

**TABLE 1 - Mean change and mean percentage change in lesion depth according to test inhaler and sucrose control across all subjects (n = 10).**
lack of similar in situ work on asthma inhalers renders interpretation of the present findings challenging. As the in vitro use of the inhalers failed to simulate normal medication usage in asthmatics, the results of the present pilot study should be viewed within this context.

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**References**


