CHAPTER 12

The effect of active and passive smoking on inhaled drugs in respiratory patients

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All combustion processes produce primary and secondary submicrometric aerosol particles. Primary particles are produced directly by incomplete combustion, and secondary particles are formed from gas-phase precursors. When diffused into the atmosphere, each particle is subject to different mechanisms, such as nucleation, condensation, coagulation and surface reaction, by colliding with other particulate and vapour-phase constituents, giving rise to a growth in size and reduction in the total number of particles themselves that take place simultaneously in a very short time, of the order of milliseconds [1].

Environmental tobacco smoke (ETS) is a mixture of condensate and vapour-phase pollutants (>4,000 different chemical substances), and is one of the major sources of indoor aerosol pollution [2]. The condensate phase is formed by particles whose aerodynamic profile shows a major peak in the range 0.1–0.2 μm [3]. It is acknowledged that tobacco smoke and indoor ETS pollution are a worldwide problem [4], and that a relevant percentage of people who are taking inhaled aerosol medication are current smokers (>25% of asthma and chronic obstructive pulmonary disease (COPD) patients) [5, 6]. Moreover, although inhaled corticosteroids (ICSs) are the cornerstone of asthma therapy, their efficacy is dramatically reduced in asthmatic smokers [7].

Alterations in corticosteroid metabolic pathways induced by tobacco smoke have been demonstrated at the cellular level [8]. However, no research to date has been addressed at finding a possible additional explanation for the impairment of ICS effects in smokers, i.e. the interaction between ETS and inhaled drug particles at the moment of inhaled drug actuation by the patient, resulting in a possible growth in the size distribution of the inhaled medication, which represents a critical issue regarding inhaled drug deposition and efficacy [9].

According to pharmaceutical guidelines, ICSs are studied in a clean ambient, and no concern has yet been raised about this issue [10], even though smokers take their medication in highly polluted ambient air, and resistance to ICSs has been reported as a cause of reduced asthma control in asthmatic smokers [11]. The pro-inflammatory properties of tobacco smoke and interference of smoke with glucocorticoid gene expression are considered the primary explanations [12]. However, no study to date has addressed the possible physical interactions of inhaled particles with smoke aerosol in both the airways and the environment polluted by ETS.

The aims of the present study were to: 1) evaluate the possible interactions affecting the aerodynamic profile of dry-powder fluticasone in the presence of tobacco smoke in
an experimental setting; and 2) assess smokers’ behaviour regarding cigarette smoking and timing and place of medication.

**Methods**

A 4-m$^3$ box kept at constant temperature, relative humidity and ventilation was used to analyse the aerodynamic profiles of dry-powder fluticasone (Flixotide 500) dispersed using a direct airflow of 500 L·min$^{-1}$ for 7 min in the presence of either clean air or tobacco smoke generated by a smouldering cigarette. Particle number and classes were measured using a laser-operated instrument (Aerosol Particulate Profiler, model 9012; Metone Instruments, Grants Pass, OR, USA) with a sampling time of 20 s, capable of counting the number of particles in the size ranges 0.70–0.99, 1.00–1.99, 2.00–2.99, 3.00–3.99, 4.00–4.99 and ≥5.00 µm in real time. Each experiment was performed in triplicate. The background-corrected means of the particle counts in the first 80 s after dispersion of fluticasone powder were compared and submitted to statistical analysis (paired t-test).

In order to evaluate the smokers’ behaviour, a self-administered questionnaire was submitted to 16 asthma and 16 COPD patients undergoing treatment with ICSs. The items regarded their current smoking status, the time between lighting a cigarette and ICS medication, the place where they actuate the medication and the possible reasons why they actuate the medication soon after having smoked.

**Results**

In the experiments with clean air, background particles were found at a concentration of <1,000 particles L$^{-1}$, whereas many thousand of particles per litre were observed for the ETS background. As expected, ETS contributed to exceedingly high concentrations of particles in the submicrometric range, with a negligible contribution of particles of ≥3.00 µm in diameter (table 1).

When dispersed in clean air, particles sized 2.00–2.99 µm and ≥5.00 µm contributed ~60% of overall fluticasone particles, whereas 1.00–1.99- and 3.00–3.99-µm particles represented ~30%, and particles sized 0.70–0.99 and 4.00–4.99 µm ~10% of total dispersed fluticasone particles (fig. 1). When fluticasone powder was dispersed in the presence of cigarette smoke, a net decrease in the overall mean ± SD concentration of 0.70–0.99- and 1.00–1.99-µm particles was found, of 5,062 ± 961 and 1,979 ± 901 particles·L$^{-1}$, respectively, whereas an increase in the concentration of larger particles was observed compared to clean air, 1,430 ± 154 versus 788 ± 32, 519 ± 27 versus 370 ± 5, 270 ± 43 versus 207 ± 26 and 946 ± 154 versus 761 ± 53 particles·L$^{-1}$, respectively, for particles of 2.00–2.99, 3.00–3.99, 4.00–4.99 and ≥5.00 µm in diameter (p<0.01) (fig. 2). The shift towards a higher proportion of larger particles accounted for 21% of particles being ≥3.00 µm in the presence of ETS, as compared to 7% in clean air.

**Table 1. Background particle concentration by aerodynamic class**

<table>
<thead>
<tr>
<th>Aerodynamic Class</th>
<th>0.70–0.99 µm</th>
<th>1.00–1.99 µm</th>
<th>2.00–2.99 µm</th>
<th>3.00–3.99 µm</th>
<th>4.00–4.99 µm</th>
<th>≥5.00 µm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clean air particles L$^{-1}$</td>
<td>792 ± 19</td>
<td>438 ± 11</td>
<td>174 ± 7</td>
<td>26 ± 2</td>
<td>6 ± 1</td>
<td>14 ± 1</td>
</tr>
<tr>
<td>ETS particles L$^{-1}$</td>
<td>119768 ± 644</td>
<td>51834 ± 190</td>
<td>5278 ± 68</td>
<td>98 ± 8</td>
<td>168 ± 12</td>
<td>15 ± 2</td>
</tr>
</tbody>
</table>

Data are presented as mean ± sd. ETS: environmental tobacco smoke.
The results of the survey regarding smoking/inhaled medication timing are reported in table 2. The questionnaire was filled in by smokers taking inhalers (n=32), 16 asthma and 16 COPD patients aged 19–76 yrs, with prevalences of heavy and moderate smokers of 37 and 63%, respectively. Most of the smokers smoked at home, and actuated the inhaler in the room in which they usually smoked. Overall, 50% of the smokers actuated the inhaler within 20 min after smoking, whereas 22% actuated it within 5 min. None of the smokers had received suggestions from their doctor regarding smoking/inhaler timing and place.

**Discussion**

The present data suggest that the aerodynamic particle profile of fluticasone powder can be modified by interactions with ETS-derived particles, with an ~15% increase in
particles of \( \geq 3.00 \, \mu m \), considered to be the threshold for particle inhalability. The concentration of tobacco smoke particles used in the present study was in the range of ETS-derived particulate pollution in the real world, but much lower than in mainstream smoke [13]. Thus the observed phenomenon should apply to both passive and active smoking. It might represent another mechanism of steroid resistance for inhaled medications in asthmatic and COPD smokers. Particle-to-particle physical interactions happen very quickly with freshly generated submicrometric combustion particles such as ETS and mainstream tobacco smoke, giving rise to aggregates of larger size. This interaction depends upon temperature, electric charge and the shape of the particles [1]. Thus interaction between mainstream and ETS submicrometric particles with particles from inhaled medications is an expected phenomenon. A similar behaviour has also been shown for hydrofluoroalkane–beclometasone submicrometric particles (data not shown). Inhaled drug particle interactions may occur not only with ETS particles present in the lung of a nonsmoker as a result of ETS-polluted ambient air but also with the extremely high concentration of submicrometric particles that reside in the lung for a few minutes after the last cigarette puff [14].

The present survey of respiratory patients who are current smokers showed that most of them take their medication in the room in which they smoke, and about one out of five within 5 min after the last cigarette puff, thus confirming the worries concerning particle interaction. The clinical impact of the interaction of inhaled medication and smoke-derived particles remains to be evaluated. However, asthmatic and COPD smokers should be advised to administer ICSs after a reasonable time after the last cigarette puff, and should take care to avoid drug inhalation in environments polluted by ETS. This advice should also be addressed to nonsmoker patients taking inhaled medications. Such hints might also apply to indoor pollutants other than tobacco smoke, and to exceptional outdoor conditions involving indoor ambient.

### Table 2. – Smokers’ demographics and behaviour with respect to cigarette/inhaler timing and place

| Age range yrs | 19–76 |
| Males/females n | 14/18 |
| Heavy smoker | 37 |
| Moderate smoker | 63 |
| Asthma | 50 |
| COPD | 50 |
| Smoking at home | 90 |
| Inhaler actuation in room in which smoker usually smokes | 100 |
| Time between last cigarette and inhaler actuation | |
| 5 min | 22 |
| 10 min | 13 |
| 20 min | 15 |
| >20 min | 50 |
| Suggestions from GPs about smoking/inhaler timing/place | 0 |

Data are presented as percentages unless otherwise indicated. COPD: chronic obstructive pulmonary disease; GP: general practitioner. *: \( \geq 20 \) cigarettes day\(^{-1} \); #: \( \leq 20 \) cigarettes day\(^{-1} \).
Summary

It has been demonstrated that ICSs are much less effective in asthmatic smokers. Most smokers are believed to take their asthma medications in the place in which they smoke, and some of them report delivering the inhaled drug just after the last cigarette puff. This behaviour raises the possibility that drug particles might interact with particulate matter present in smokers’ airways due to ETS or residual tobacco smoke (mainstream tobacco smoke polluting the lung after the last puff). The conglomeration of aerosol particles is a well-known physical phenomenon that takes place very quickly and results in an increase in particle diameter. In order to verify such a possibility, the fluticasone dry powder aerodynamic profile was studied in the presence of clean air or ETS; when delivered in the presence of cigarette smoke, a 15% increase in particles sized $\geq 3.00 \, \mu m$ was observed compared to the aerodynamic profile of the drug in clean air. The results of the survey concerning place and timing of smoking/inhaled drug actuation showed that most smokers smoke at home, and actuate the inhaler in the room in which they have smoked. Moreover, 50% of smokers deliver the drug during the first 20 min after smoking, and 22% within 5 min after the last cigarette. None of the smokers had received suggestions from their doctor regarding smoking/inhaler timing and place. These results indicate that ICSs delivered in the presence of tobacco smoke undergo changes in aerodynamic profile, leading to a possible decrease in the percentage of respirable particles. This phenomenon could be one of the explanations for the steroid resistance demonstrated in asthmatic smokers. Smokers should be advised to actuate their ICs after a reasonable time from their last cigarette puff, and should take care to avoid drug inhalation in environments polluted by ETS.

Keywords: Aerosol, environmental tobacco smoke, inhaled drugs, particle interaction, steroid resistance, tobacco smoking.

References


