Low-dose inhaled versus standard dose oral form of anti-tubercular drugs: Concentrations in bronchial epithelial lining fluid, alveolar macrophage and serum

Sir,

Patients with pulmonary tuberculosis could benefit from the use of inhaled anti-tubercular drug (ATD) administration as it would deliver the drug directly at the site of infection.\(^1\) It is also likely that lower doses would be required when the drugs are administered by inhalation.\(^2\)

A ‘proof of concept’ study was undertaken for comparing the concentrations of rifampicin (RIF), isoniazid (INH) and pyrazinamide (Z) in the epithelial lining fluid (ELF), alveolar macrophages (AM) and serum following low-dose administration via inhaled route and those following standard dose administration via oral route.

Following the approval of the Institutional Ethics Committee, healthy volunteers aged 20-50 years without prior history of tuberculosis and with baseline forced expiratory volume at 1 sec (FEV1) over 60% of predicted value for height, weight and gender were enrolled.

Informed consent was obtained prior to enrollment. The subjects were then randomized into two groups: Six subjects in Group A received capsule containing micro-particles of anti-tubercular drugs (ATD, INH 15 mg, RIF 30 mg and Z 75 mg with lactose as a carrier particle) using a dry powder inhaler. The particle size ranged from 1-10 µ with mass median aerodynamic diameter of 2.79 µ. The remaining six subjects in Group B received oral ATD (a tablet containing RIF 500 mg, INH 250 mg and Z 1250 mg) as a single dose at 8 h of fasting. As shown in Table 1 the mean concentrations of INH, Z and RIF achieved in ELF were 220, 15 and 83 times higher in the inhaled group than those in the oral ATD group. Similarly, the median AM intracellular concentrations of INH, Z and RIF

<table>
<thead>
<tr>
<th>Group</th>
<th>Site (units)</th>
<th>Isoniazid (µg/mL)</th>
<th>Pyrazinamide (µg/mL)</th>
<th>Rifampicin (µg/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhaled</td>
<td>Epithelial lining fluid</td>
<td>1601</td>
<td>18381</td>
<td>2585.2</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td>7.25</td>
<td>1240</td>
<td>31.29</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Alveolar macrophages</td>
<td>90.88</td>
<td>1010.67</td>
<td>117.55</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td>0.95</td>
<td>34.32</td>
<td>1.04</td>
</tr>
<tr>
<td>Inhaled</td>
<td>Serum</td>
<td>0.25</td>
<td>1.46</td>
<td>0.45</td>
</tr>
<tr>
<td>Oral</td>
<td></td>
<td>3.75</td>
<td>11.40</td>
<td>6.96</td>
</tr>
</tbody>
</table>

*Peak serum conc; †Mean conc
in inhaled group were 96, 29 and 113 times higher than those achieved in the oral group. The peak serum concentrations of INH, Z and RIF in the inhaled group were negligible and far lower than those for the oral group [Table 1].

As the first step, our study has demonstrated that inhaled ATDs attain appreciably higher levels in the ELF and AM as compared to orally administered drugs. Similarly, inhaled drug administration is associated with lower serum concentrations. Studies on multiple dose pharmacokinetics are required to further investigate our findings.

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References