Correlation of Serum and Saliva Theophylline Concentrations after Administration of a Sustained Release Preparation

J. H. G. Jonkman1,2, G. H. Koëter3, R. Schoenmaker2, K. de Vries1, J. E. Greving1, and R. A. de Zeeuw1

1Department of Toxicology, Laboratory for Pharmaceutical and Analytical Chemistry, State University, Groningen, 2Laboratory for Drug Analysis, Assen and 3Pulmonary Division of the Department of Internal Medicine, State University, Groningen, The Netherlands

Summary. The correlation between serum and saliva levels of theophylline was investigated in seven healthy volunteers after multiple dose administration of a low dose (300 mg/day) and a high dose (900 mg/day) of a sustained release theophylline preparation (Theo-Dur®). Tablets were taken for five days, at 8 a.m. and 8 p.m. and a last dose was taken on Day 6 at 8 a.m. Fourteen serum and saliva samples were collected simultaneously during the dosing period and for up to 32 h after the last dose. On the 300 mg/day regimen the level in saliva was 55.3% of the serum level, with an overall variability of 6.7% and an intrasubject variability of 10.5%. After 900 mg/day, the saliva concentration was 55.5% of the serum concentration, with an overall variability of 7.6% and an intrasubject variability of 12.7%. A good correlation was found between both determinations \(r=0.99\), which suggests that saliva levels could be used to monitor theophylline after administration of a sustained release tablet.

Key words: theophylline; sustained release preparation, serum level, saliva level

The correlation between serum and saliva concentrations of theophylline has been discussed in the literature for several years, the value of therapeutic monitoring of theophylline by means of salivary concentrations being the main point of debate. Although different authors have used different criteria, it is clear that good and less significant correlations have both been reported.

Koysooko et al. (1974) published the first report about this subject. They suggested an excellent linear relationship between theophylline concentrations in plasma and saliva over a plasma concentration range of 4 to 14 µg.ml\(^{-1}\) (Koysooko et al. 1974; Levy et al. 1974), starting one hour after ingestion of a theophylline solution. They used the non-selective Schack and Waxler method (Schack and Waxler 1949) for analysis. Eney and Goldstein (1976) also found a good correlation between the two estimates 2 h after administration of a hydroalcoholic solution of theophylline.

Galant et al. (1977) reported very low hour-to-hour variability, as well as good week-to-week consistency, of the plasma/saliva ratio in the individual patient after ingestion of theophylline-containing capsules, elixir or aminophylline tablets.

Khanna et al. (1980) found that monitoring of saliva theophylline concentration could be an alternative to measurement of serum concentration in preterm infants receiving aminophylline (intravenously or via orogastric tube), as long as the salivary concentration did not exceed 8 µg.ml\(^{-1}\).

Lena at al. (1980) concluded that, although the ratios between saliva and plasma theophylline concentrations were different between individuals (asthmatic children) after giving theophylline on a long-term basis (mostly sustained release tablets of aminophylline), salivary concentrations of theophylline below 7 µg.ml\(^{-1}\) reflected plasma concentrations below 10 µg.ml\(^{-1}\), i.e. subtherapeutic levels, while saliva concentrations above 7µg.ml\(^{-1}\) were consistent with therapeutic doses.

Less optimistic reports about the usefulness of salivary theophylline measurement to predict plasma theophylline concentrations have appeared in the literature. Knop et al. (1975) did not find a consistent plasma/saliva ratio during the absorption phase of theophylline-containing suppositories, although the correlation improved with time. Cohen et al. (1975) were also unable to confirm the existence of a fixed
Table 1. Details of the subjects

<table>
<thead>
<tr>
<th>Subject</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td>F</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>F</td>
<td>M</td>
<td>M</td>
<td>-</td>
</tr>
<tr>
<td>Age [years]</td>
<td>27</td>
<td>36</td>
<td>28</td>
<td>32</td>
<td>41</td>
<td>26</td>
<td>29</td>
<td>31 ± 5</td>
</tr>
<tr>
<td>Weight [kg]</td>
<td>58</td>
<td>64</td>
<td>74</td>
<td>76</td>
<td>62</td>
<td>67</td>
<td>65</td>
<td>67 ± 6</td>
</tr>
<tr>
<td>Height [m]</td>
<td>1.63</td>
<td>1.64</td>
<td>1.78</td>
<td>1.76</td>
<td>1.71</td>
<td>1.80</td>
<td>1.84</td>
<td>1.74 ± 0.08</td>
</tr>
</tbody>
</table>

ratio between the theophylline level in those two body fluids after ingestion of a microcrystalline theophylline tablet or a theophylline-containing elixir. Hendeles et al. (1977) concluded that saliva theophylline measurements could not be recommended for predictive use in patients with chronic obstructive pulmonary disease. Zuidema (1978), too, suggested that serum/saliva concentration ratios might vary rather widely, even after giving a sustained release preparation.

Finally, Boobis and Trembath (1978) reported a concentration-dependent correlation between plasma and saliva theophylline concentrations. Within the range of 10–20 µg.ml⁻¹, salivary levels were approximately 67% of plasma levels, but at plasma levels of less than 6 µg.ml⁻¹, salivary concentrations fell to less than 40% of the plasma theophylline concentration.

Subjects and Methods

Seven healthy volunteers, weight 67 ± 6 (SD) kg, aged 31 ± 5 (SD) years, were selected and their informed consent to the trial was obtained (Table 1). Smokers were excluded from the study.

A sustained release theophylline preparation (Theo-Dur®) to produce consistent therapeutic serum levels (Weinberger et al. 1978; Koëter et al. 1981) which can be of high importance in practice (Jonkman et al. 1980b), stimulated us to investigate the value of monitoring saliva theophylline levels after multiple doses of this preparation.

Subjects and Methods

Two dosage regimens were used in each volunteer, in cross-over open design, namely intake of 150 mg (= 0.5 Theo-Dur® tablet) and 450 mg (= 1.5 Theo-Dur® tablet) on each occasion. There was an interval of one week between the two studies.

Mixed saliva was collected, the saliva flow being stimulated by chewing Parafilm®, at the same time as blood was drawn.

Serum and saliva samples were stored at −20 °C until analysed. Theophylline concentrations in serum and saliva were determined by a rapid, selective HPLC method (Jonkman et al. 1980a).

Results

On Day 1 slowly increasing serum and saliva theophylline levels were found. Absorption seemed to be slow, due to the sustained release characteristics of the tablets, even broken ones (Koëter et al., 1981).

On Day 6, presumably the steady state situation, both the 150 and 450 mg regimens resulted in a serum concentration - time curve that showed a long-lasting plateau value (Fig. 1).

Maxium serum concentrations, under steady state conditions, were seen on Day 6 either at 11 a. m. or 2 p. m. after the 150 mg dose; after a dose of 450 mg the peak sometimes appeared even later, because the unbroken tablet included in this dose released theophylline more slowly than a broken tablet (Koëter et al. 1981).

Administration of the higher dose resulted in serum theophylline levels which all lay in what is considered to be the therapeutic range of the drug (between 10 and 20 µg.ml⁻¹). The saliva theophylline-time curves appeared to follow the serum theophylline-time curves in all subjects very well (Fig. 1).

The equations of the correlation plots for all measurements for each subject are given in Table 2. It shows a fixed relationship between the theophylline concentrations in the two body fluids, and also the very high correlation coefficient between the levels in them. A typical example of a regression line for the correlation between the serum and saliva theophylline concentrations is show in Fig. 2.

The half-lives of elimination calculated from serum and saliva theophylline data are listed in Table 3.

Discussion

The fixed ratio between the serum and saliva theophylline concentrations was found to be very consistent during all phases of the experiment: absorption (Day 1), steady state (Day 6) and elimination phases.