Theophylline and ethylenediamine pharmacokinetics following administration of aminophylline to septic patients with multiorgan failure

P. Toft, L. Heslet, M. Hansen and N.A. Klitgaard

1 Department of Anaesthesiology and Intensive Care and 2 Department of Clinical Chemistry, Odense University Hospital, Odense, Denmark

Received: 31 January 1991; accepted: 19 September 1991

Abstract. The pharmacokinetics of theophylline and ethylenediamine were examined in 6 patients with septicemia and multiorgan failure (MOF). The patients received a bolus injection of 4 mg/kg aminophylline. Aminophylline is the ethylenediamine salt of theophylline. The clearance of theophylline was reduced in all our patients ranging from 10 – 66% of the value obtained in healthy volunteers. The median t1/2β was 18.8 h (range 5.8 – 25.5) compared to a normal value of 6 h. The median clearance of ethylenediamine was 54% of the normal value, while the peripheral volume of distribution was increased to 650%. Due to this t1/2β was 2.3 (2.0 – 2.7) h, which is 5 times the normal value of 0.55 h. There was no correlation between clearance of theophylline and ethylenediamine. As theophylline has a narrow therapeutic range, routine monitoring with measurements of serum theophylline is mandatory in patients with MOF.

Key words: Theophylline – Ethylenediamine – Pharmacokinetics – Sepsis – Multiorgan failure

Theophylline is used as a bronchodilator in patients with obstructive airway disease and is often chemically combined with ethylenediamine to increase its solubility. Aminophylline, the ethylenediamine salt of theophylline containing 80% of theophylline by weight, is regarded as being ideal for intravenous use [1, 2]. The therapeutic effect of theophylline is related to its concentration in plasma. Concentrations below 6 – 8 µg ml⁻¹ are ineffective. If the concentration is maintained above 20 µg m⁻¹, toxic effects ranging from nausea to cardiac arrhythmias ensue. Above 40 µg ml⁻¹ seizures and cardiopulmonary arrest can occur [3 – 5]. Therefore, adverse reactions to aminophylline are usually manifestations of the toxic effects of theophylline. In addition, adverse reactions to aminophylline resulting from hypersensitivity reactions to its ethylenediamine component have been reported [6 – 8]. Patients with sepsis and multiorgan failure (MOF) may require i.v. theophylline in order to relieve bronchospasm or to increase diaphragmatic contractility which can be decreased in sepsis.

The combined pharmacokinetics of theophylline and ethylenediamine has only been described in healthy volunteers [1, 2]. The purpose of the present study was to examine the pharmacokinetics of theophylline and ethylenediamine in critically ill patients with MOF and hence unpredictable metabolic function, which might cause unwanted toxic effects. We were especially interested to investigate if there was any correlation between the elimination of theophylline and ethylenediamine and whether any reduction in theophylline elimination could be predicted from the liver parameters.

Methods

Six patients participated in the investigation. Inclusion-criteria were septicemia with shock and respiratory failure necessitating treatment with pressor agents and artificial ventilation. All patients had MOF defined as 2 or more organ dysfunctions. In addition the liver, kidneys, gastrointestinal and haematological systems might have been affected (Table 1). None of the patients suffered chronic hepatic disease or received drugs that could modify theophylline clearance before their acute illness.

All the patients were treated with antibiotics, received ordinary parenteral nutrition and were sedated with midazolam and morphine. Sodium and potassium were within the normal range for all the patients. Patients with renal failure who were treated with haemodialysis and patients with disseminated intravascular coagulation were excluded. The protocol was approved by the local Ethics Committee.

Each patient received a bolus injection of aminophylline (4 mg/kg) administered as a continuous intravenous infusion with a duration of 15 min. Blood samples 5 ml were obtained from a cannula placed in the radial artery of the contralateral arm before the start of infusions and at 5, 10, 15 min during the infusion. After the infusion was stopped blood was sampled every 10 min for 1.5 h, every 0.5 h for the next 1.5 h and every 1.0 h for the least 3 h. Serum was separated and stored at −20°C until analysis. Theophylline and ethylenediamine concentrations in serum were measured by high pressure liquid chromatography (HPLC) as described by Coigreave and Caldwell [9].

The post-infusion pharmacokinetics of theophylline and ethylenediamine were calculated according to a two compartment open model using least squares regression and the method of residuals [10]. The zero time intercepts were calculated manually.

Whether the calculated correlation coefficients deviated from nil correlation was tested with Students t-test. P<0.05 was considered significant.

Results

The clinical data and laboratory findings are presented in Table 1. The liver parameters were affected for all patients.
included, while serum-creatinine was elevated in half of the patients. The patient with pyrexia of unknown origin presented with an enlarged liver and spleen, developed sepsis with MOF and died. At the autopsy no focus was found. Two patients received a fluoroquinolone antibiotic, which is known to depress theophylline elimination. The serum drug concentration-time curves for theophylline and ethylenediamine were analysed for both compounds assuming a two compartment model (Fig. 1). The calculated pharmacokinetic parameters are presented in Table 2.

Two of our patients had a normal elimination half life of theophylline (t 1/2 β), but in the remaining patients t 1/2 β was prolonged 3–4 times compared to the values measured in normal volunteers (Table 2). There was no statistically significant correlation between liver and renal parameters and prolonged elimination of theophylline. The peripheral volume of distribution (Vp) was moderately enlarged as compared with reference values, while the clearance (CL) of theophylline was reduced to 10%–66% of the reference value in all of our patients (Table 2). The mean peripheral distribution volume of ethylenediamine in our patients was 5 times larger and the mean clearance diminished by 54% as compared to the reference values. All of our patients had a prolonged elimination half life of ethylenediamine. The mean t 1/2 β was prolonged 3–6 times compared to reference value (Table 2). There was no statistically significant correlation between clearance of theophylline and clearance of ethylenediamine (r = 0.12) nor was there any positive correlation between t 1/2 β of theophylline and t 1/2 β of ethylenediamine (r = -0.79).

In our 6 patients we did not observe neither toxic reactions to theophylline or hypersensitivity reactions to ethylenediamine.

Table 1. Clinical data and laboratory results

<table>
<thead>
<tr>
<th>Pt. no.</th>
<th>Age</th>
<th>Sex</th>
<th>Weight</th>
<th>%O2 on ventilator</th>
<th>Pressor agents</th>
<th>Antibiotics</th>
<th>Serum-creatinine (μmol/l)</th>
<th>Serum-albumin (g/l)</th>
<th>ALAT a</th>
<th>Prothrombin time (μ/l)</th>
<th>a.f. b</th>
<th>Bilirubin (μmol/l)</th>
<th>Suspected focus</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>47</td>
<td>F</td>
<td>65</td>
<td>50</td>
<td>Dopamine, Dobutamine, Noradrenaline</td>
<td>imipenem (a tienamycin)</td>
<td>323</td>
<td>25</td>
<td>18</td>
<td>0.54</td>
<td>232</td>
<td>115</td>
<td>intra-abdominal</td>
</tr>
<tr>
<td>2</td>
<td>31</td>
<td>M</td>
<td>60</td>
<td>70</td>
<td>Dopamine, ciprofloxacin (a fluoroquinolone)</td>
<td>penicillin</td>
<td>64</td>
<td>18</td>
<td>111</td>
<td>0.51</td>
<td>245</td>
<td>218</td>
<td>pyrenia of unknown orgin</td>
</tr>
<tr>
<td>3</td>
<td>68</td>
<td>M</td>
<td>62</td>
<td>60</td>
<td>Dopamine, Noradrenaline</td>
<td>cefuroxime</td>
<td>72</td>
<td>17</td>
<td>82</td>
<td>0.57</td>
<td>804</td>
<td>11</td>
<td>pulmonary</td>
</tr>
<tr>
<td>4</td>
<td>75</td>
<td>M</td>
<td>70</td>
<td>50</td>
<td>Dopamine, Dobutamine, Noradrenaline</td>
<td>ampicillin metronidazole</td>
<td>202</td>
<td>28</td>
<td>9</td>
<td>0.45</td>
<td>186</td>
<td>7</td>
<td>intra-abdominal</td>
</tr>
<tr>
<td>5</td>
<td>69</td>
<td>M</td>
<td>65</td>
<td>40</td>
<td>Dopamine, Dobutamine, Noradrenaline</td>
<td>ampicillin metronidazole</td>
<td>377</td>
<td>22</td>
<td>53</td>
<td>0.30</td>
<td>374</td>
<td>102</td>
<td>intra-abdominal</td>
</tr>
<tr>
<td>6</td>
<td>75</td>
<td>F</td>
<td>87</td>
<td>40</td>
<td>Dobutamine, Noradrenaline</td>
<td>ciprofloxacin metronidazole</td>
<td>91</td>
<td>20</td>
<td>12</td>
<td>0.46</td>
<td>253</td>
<td>74</td>
<td>intra-hepatic</td>
</tr>
</tbody>
</table>

a Alanine amino transaminase
b Alkaline phosphatase

Fig. 1. Plasma concentration-time curves for theophylline (△) and ethylenediamine (○) following the intravenous infusion of aminophylline 4 mg/kg to 6 patients with septicaemia and MOF. Mean values (+SD)