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Urinary recovery and kinetics of sulphamethoxazole and its metabolites in HIV-seropositive patients and healthy volunteers after a single oral dose of sulphamethoxazole

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1 The urinary excretion of sulphamethoxazole and its metabolites was compared between healthy volunteers and HIV-seropositive patients in order to get a better understanding of why HIV seropositives are more predisposed to idiosyncratic toxicity of sulphonamides.
2 A single 800 mg oral dose of sulphamethoxazole was administered to seven healthy volunteers and seven asymptomatic HIV seropositives without previous use of sulphonamides.
3 Urine was collected for 4 days and drug analysis was by h.p.l.c.
4 No difference was observed between seropositive and seronegative individuals in the urinary recovery of sulphamethoxazole, N4-acetyl-, 5-hydroxy-, N4-acetyl-5-hydroxy-sulphamethoxazole and the N1-glucuronide conjugate. However the recovery of the hydroxylamine metabolite of sulphamethoxazole was significantly lower in the HIV seropositives (0.50 ± 0.51 vs 2.23 ± 0.85%; 95% CI on the difference, −0.90 to −2.55; P = 0.0006).
5 Sulphamethoxazole hydroxylamine may be a factor in the susceptibility of HIV infected individuals to sulphonamides.

Keywords sulphamethoxazole pharmacokinetics sulphamethoxazole hydroxylamine drug adverse reaction HIV infection metabolism

Introduction

The frequency of adverse reactions to sulphonamides is much higher in HIV-seropositive individuals (6–80%) as compared with seronegative individuals (<5%) [1–10]. It has been postulated that the reactive hydroxylamine metabolites of sulphonamides mediate these adverse reactions [11–13]. Toxicity is more likely to occur when scavenging system for such reactive intermediates is deficient, e.g. glutathione deficiency in HIV infection [14–15]. In vitro studies have confirmed the relationship between increased toxicity of hydroxylamines towards lymphocytes of HIV-infected individuals and decreased glutathione concentrations in these cells [16].

The known metabolism (Figure 1) of sulphamethoxazole (SMX) involves acetylation leading to N4-acetyl sulphamethoxazole (N4-SMX), glucuronidation leading to N1-glucuronide conjugate (SMX-gluc) and oxidation [17–18]. The latter reactions are cytochrome P450 mediated [19] and take place at the C5 carbon atom, leading to 5-hydroxysulphamethoxazole (5OH-SMX) and N4-acetyl-5-hydroxy-sulphamethoxazole (N4-5OH-SMX), as well as at the N4 nitrogen atom leading to the unstable and toxic hydroxylamine metabolite (NOH-SMX) [20]. Hydroxylamines can undergo auto-oxidation to nitroso derivatives, a process prevented by glutathione.

We have previously reported the formation and elimination of SMX and all its known metabolites in healthy volunteers after administration of a single oral dose [21, 22]. We now report a similar study in
HIV-seropositive individuals in order to obtain more insight into the reasons why HIV seropositives are more predisposed to sulphonamide toxicity.

Methods

Subjects

Seven healthy volunteers (4 M, 3 F) aged between 23 and 50 years (mean 34 years) and seven HIV-seropositive volunteers participated in the study after approval of the Ethics Committee of Academic Hospital, Nijmegen. Routine biochemical assessments (including liver function) were within normal limits in all participants. The HIV-seropositive individuals (6 M, 1 F) were aged between 31 and 53 years (mean 39 years), were all asymptomatic, CDC class II, had a mean CD4 count of 294 ± 111/mm$^3$ (range 140–480/mm$^3$) and were without previous sulphonamide treatment after seroconversion.

Written informed consent was obtained from all participants. An 800 mg dose of sulphamethoxazole was administered orally in two gelatine capsules after an overnight fast. Two volunteers participated twice in the study in order to determine the reproducibility.

Sampling procedures

Blood samples were only taken from the healthy volunteers while urine samples were collected from both healthy volunteers and seropositives. Blood samples were obtained by fingertip puncture at 1, 2, 4, 6, 8, 10, 12, 24, 32, 36, and 48 h after drug administration. Plasma was separated immediately by centrifugation and stored at −20°C until analysis. Urine was collected over 96 h and three 5 ml aliquots were stored immediately at −20°C until analysis.

Sample treatment and drug analysis has been described in detail elsewhere [18].

Data analysis

Curve fitting of the plasma concentration- and renal excretion rate-time curves was carried out using a one compartment model with first order drug absorption ($r^2 < 0.98$) and pharmacokinetic parameters calculated using the Medi-ware® computer program [23].

The following parameters for N4-SMX were calculated from the renal excretion rate-time profiles: elimination half-life ($t_{1/2,e}$), lag time ($t_{lag}$), time at which maximum excretion occurs ($t_{max}$), mean residence time (MRT = $V_d$/CL + 1/$k_a$ + $t_{lag}$), maximal renal excretion rate ($U_{max}$) and area under renal excretion
rate-time curve (AUC\(\text{in}\)). AUC values were calculated using the linear trapezoidal rule with extrapolation to infinity.

In addition, \(t_{\text{lag}}, t_{\text{max}}, t_{\text{max}}\) and MRT were calculated for N4-SMX in plasma of healthy volunteers. \(t_{\text{lag}}\) was also estimated for NOH-SMX in plasma of healthy volunteers.

Statistics

95% confidence intervals on the differences of the means for unpaired (or paired when appropriate) observations were determined.

Results

The urinary recoveries of parent drug and metabolites were similar in both HIV-negative and HIV-positive subjects with the exception of the urinary excretion of NOH-SMX (see Table 1). The recovery of the hydroxylamine metabolite of sulphamethoxazole was lower in HIV seropositives compared with healthy volunteers. The results of the two volunteers that participated in the study twice were similar.

For healthy volunteers the value (mean ± 1 s.d. or median) of \(t_{\text{lag}}, t_{\text{max}}, t_{\text{max}}\) and MRT of N4-SMX calculated from the renal excretion rate-time profiles was 10.34 ± 1.42 h, 7.48 h, 0.34 ± 0.24 h and 19.40 ± 2.85 h respectively. The 95% confidence interval on the difference between the mean \(t_{\text{lag}}, t_{\text{max}}, t_{\text{lag}}\) and MRT for N4-SMX calculated from the plasma metabolite concentration-time curves [22] and the renal excretion rate-time profiles were -0.51 to 2.87, -1.93 to 0.28, -0.44 to 0.76 and -0.89 to 2.44 respectively. Also the half-lives of N4-SMX and NOH-SMX in urine of healthy volunteers did not differ statistically (\(P > 0.8\)).

The pharmacokinetic parameters of N4-SMX in urine of healthy volunteers and HIV seropositives are listed in Table 2. Only the maximum excretion rate (\(U_{\text{max}}\)) of N4-SMX was significantly different in the two groups.

Table 1 Urinary recovery of sulphamethoxazole and its metabolites in seven healthy volunteers and seven HIV seropositives (expressed as percentage of the dose of sulphamethoxazole) after an oral dose of 800 mg sulphamethoxazole. Mean values ± s.d. and 95% confidence intervals on differences between the mean values are given.

<table>
<thead>
<tr>
<th></th>
<th>HIV seropositives (n = 7)</th>
<th>Healthy volunteers (n = 7)</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N4-SMX</td>
<td>50.27 ± 8.63</td>
<td>43.21 ± 6.25</td>
<td>-1.72 to 15.84</td>
<td>0.11</td>
</tr>
<tr>
<td>SMX</td>
<td>12.66 ± 5.02</td>
<td>14.64 ± 3.80</td>
<td>-7.18 to 3.20</td>
<td>0.42</td>
</tr>
<tr>
<td>N1-gluc-SMX</td>
<td>12.68 ± 2.68</td>
<td>9.66 ± 3.00</td>
<td>-0.29 to 6.33</td>
<td>0.07</td>
</tr>
<tr>
<td>N4-50H-SMX</td>
<td>5.50 ± 1.59</td>
<td>5.20 ± 1.07</td>
<td>-1.28 to 1.88</td>
<td>0.68</td>
</tr>
<tr>
<td>50H-SMX</td>
<td>3.64 ± 1.94</td>
<td>2.70 ± 1.19</td>
<td>-2.82 to 0.94</td>
<td>0.29</td>
</tr>
<tr>
<td>NOH-SMX</td>
<td>0.50 ± 0.51</td>
<td>2.23 ± 0.85</td>
<td>-0.90 to -2.55</td>
<td>0.0006</td>
</tr>
<tr>
<td>Total</td>
<td>83.9 ± 6.23</td>
<td>78.25 ± 5.23</td>
<td>-1.04 to 12.35</td>
<td>0.09</td>
</tr>
</tbody>
</table>

N4-acetylsulphamethoxazole (N4-SMX), sulphamethoxazole (SMX), N1-glucuronic acid conjugate (SMX-gluc), N4-acetyl-5-hydroxy-sulphamethoxazole (N4-50H-SMX), 5-hydroxysulphamethoxazole (50H-SMX) and sulphamethoxazole hydroxylamine (NOH-SMX).

Table 2 Pharmacokinetic parameters of N4-acetylsulphamethoxazole in urine of HIV seropositives and healthy volunteers after an oral dose of 800 mg sulphamethoxazole. Mean values ± s.d. (\(t_{\text{max}}\) is median and range) are given as well as 95% confidence intervals (CI) on the differences between the mean values.

<table>
<thead>
<tr>
<th></th>
<th>HIV seropositives (n = 7)</th>
<th>Healthy volunteers (n = 7)</th>
<th>95% CI</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(t_{\text{lag}}) (h)</td>
<td>8.69 ± 2.12</td>
<td>10.34 ± 1.42</td>
<td>-3.74 to 0.46</td>
<td>0.11</td>
</tr>
<tr>
<td>(t_{\text{max}}) (h)</td>
<td>7.48* (5.60–8.57)</td>
<td>6.56* (5.96–11.06)</td>
<td>-2.05 to 1.41</td>
<td>0.69</td>
</tr>
<tr>
<td>(t_{\text{lag}}) (h)</td>
<td>0.57 ± 0.48</td>
<td>0.34 ± 0.24</td>
<td>-0.22 to 0.67</td>
<td>0.29</td>
</tr>
<tr>
<td>MRT (h)</td>
<td>17.43 ± 2.11</td>
<td>19.40 ± 2.85</td>
<td>-4.89 to 0.96</td>
<td>0.17</td>
</tr>
<tr>
<td>(U_{\text{max}}) (mg h(^{-1}))</td>
<td>23.28 ± 6.16</td>
<td>17.16 ± 3.27</td>
<td>0.37 to 11.87</td>
<td>0.04</td>
</tr>
<tr>
<td>AUC(_{\text{in}}) (mg)</td>
<td>478 ± 90</td>
<td>405 ± 53</td>
<td>-12.55 to 158.83</td>
<td>0.09</td>
</tr>
</tbody>
</table>

\(t_{\text{lag}}\) = half-life, \(t_{\text{max}}\) = time at which maximum excretion occurs, *expressed as median (range), \(t_{\text{lag}}\) = lag time, MRT = mean residence time, \(U_{\text{max}}\) = maximum renal excretion rate, AUC\(_{\text{in}}\) = area under renal excretion rate-time curve.
Discussion

The formation and elimination of sulfamethoxazole and all its known metabolites in healthy volunteers and HIV-seropositive individuals were compared to understand better the predisposition of HIV seropositives to sulfonamide toxicity. Only the urinary recovery of sulfamethoxazole hydroxylamine differed between healthy volunteers and HIV-seropositive individuals. No difference was observed in urinary recovery of SMX, N4-SMX, SMX-gluc, N4-SOH-SMX and 50H-SMX. The formation of the latter metabolite is, like NOH-SMX and probably 50H-SMX, catalysed by cytochrome P450 [20]. These findings suggest that there is no difference in oxidation, acetylation and glucuronidation of SMX in healthy volunteers and HIV-seropositive individuals. The reduced urinary recovery of the hydroxylamine metabolite may be explained by secondary metabolism of an unstable compound that can be further oxidized to reactive metabolites [20]. This process is prevented e.g. by glutathione. Glutathione protects cells from the toxicity of NOH-SMX largely by preventing its further oxidation to reactive metabolites [20]. These results suggest that the formation of the hydroxylamine metabolite is similar in both groups but that only HIV seropositives further metabolize NOH-SMX. This could explain the increased frequency of adverse reactions and the diminished recovery of NOH-SMX in this group of individuals.

The renal excretion rate-time profile of N4-SMX was taken as the main parameter for comparison of the metabolic and kinetic behaviour of SMX in healthy volunteers and HIV seropositives. Although the maximum renal excretion rate (Umax) was different, other parameters like tmax, ti, MRT and AUC were not. It may therefore be concluded that the renal excretion of N4-SMX does not differ between seropositive and healthy volunteers.

References


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