Pyrimethamine Inhibits Renal Secretion of Creatinine

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The mechanism of increased serum creatinine after administration of pyrimethamine and dapsone was evaluated for six healthy volunteers. Serum parameters, urine sediment, and clearances of creatinine, inulin, and para-aminohippurate were assessed prior to and 28 h after the ingestion of a single, combined dose of 100 mg of pyrimethamine and 200 mg of dapsone. In a second series, the same renal function tests were performed for nine human immunodeficiency virus-infected men before and after 1 month of prophylactic treatment with a weekly dose of 75 mg of pyrimethamine and 200 mg of dapsone to evaluate sustained effects on renal function. Serum creatinine increased within 28 h from 81 ± 14 to 102 ± 16 μmol/liter (P = 0.002) in the healthy volunteers. Blood urea nitrogen, β2-microglobulin, and urine remained normal. Creatinine clearance decreased from 125 ± 27 to 91 ± 26 ml/min (P < 0.02) without changes in inulin clearance. The effect was reversible within 21 days and attributable to pyrimethamine, as determined by administration of each drug alone. The sustained effect of four doses of pyrimethamine and dapsone in human immunodeficiency virus-infected patients consisted of an analogous rise in serum creatinine from 69 ± 17 to 87 ± 32 μmol/liter (P < 0.05). Both creatinine and inulin clearances, however, were unchanged, representing a new equilibrium between creatinine production and elimination at a higher level in serum. Pyrimethamine, thus, may reversibly inhibit renal tubular secretion of creatinine without affecting the glomerular filtration rate. This physiologic effect in pyrimethamine-treated patients must be differentiated from possible organ-related nephropathies.

Consistent and unexplained rises in serum creatinine in volunteers participating in the assessment of bioavailability and toxicity of a planned prophylactic treatment were observed. This treatment used weekly combined doses of pyrimethamine and dapsone for prophylaxis of human immunodeficiency virus (HIV)-associated Pneumocystis carinii pneumonia and cerebral toxoplasmosis (19). Both drugs have only rarely been associated with renal side effects and do not belong to groups of typically nephrotoxic agents (10, 20). Reduction in glomerular filtration rate can occur as a consequence of a drug-induced nephropathy, including acute tubular necrosis, interstitial nephritis, and intratubular obstruction (10, 20). On the other hand, certain drugs, such as cimetidine, trimethoprim, and probenecid, have been shown to reduce tubular secretion of creatinine without causing a reduction in glomerular filtration rate (5, 8, 9, 18, 24). In addition to glomerular filtration, creatinine is also secreted by renal tubules through both the organic anion and the organic cation pathways (15). The tubular secretion accounts for 5 to 40% of the total amount of excreted creatinine in individuals with normal renal function (4, 11, 12, 14, 22) and can be competitively inhibited by drugs with a similar, aromatic structure (8, 23). To evaluate the mechanism of the observed changes in serum creatinine in response to pyrimethamine and dapsone, acute effects on renal function in healthy volunteers who received single doses of both drugs together and separately were measured. The same renal function tests were performed for HIV-infected study participants to estimate the sustained renal effects of both drugs before and 4 weeks after the start of the prophylactic treatment.

MATERIALS AND METHODS

Study design. Six volunteers (five men and one woman), whose mean age ± standard deviation (SD) was 33.3 ± 2.0 years, gave informed consent to participate in the examination of acute effects of the combination of pyrimethamine and dapsone on renal function. All volunteers were healthy, had no known kidney disease, and were not taking any medication. Their weight was 70 ± 5.5 kg. They first underwent baseline tests of renal function as described below. The next day, they received a single, combined dose of 100 mg of pyrimethamine and 200 mg of dapsone after fasting. Renal function tests were repeated 28 h after the ingestion of the drugs. Urine was collected and additional blood samples were drawn on days 0, 1, 2, 4, 6, 14, and 21 for determinations of hematology, serum creatinine, urea, and β2-microglobulin. Five to six weeks later, without any further medication, the same urine and blood analyses were performed before and after the administration of a single dose of 200 mg of dapsone alone and, again, 3 to 4 weeks later and after the administration of a single dose of 100 mg of pyrimethamine.

When the results of the first phase were known, we initiated a prospective study with HIV-infected patients to test the efficacy and toxicity of a combined dose of 75 mg of pyrimethamine and 200 mg of dapsone, administered once weekly, as prophylaxis of both P. carinii pneumonia and cerebral toxoplasmosis (19). The patients had to be immunodeficient (<200 CD4 lymphocytes per μl) or have symptomatic HIV infection; patients with previous cerebral toxoplasmosis or on chronic medication with sulfonamides, trimethoprim, or clindamycin were excluded. To evaluate the sustained renal effects of pyrimethamine-dapsone, urine and blood analyses as well as renal function tests were performed for the first nine study participants before the initiation of treatment and in the 5th week of treatment, after four doses of the drug combination had been taken. The
TABLE 1. Serum values\textsuperscript{a} before and 28 h after the administration of a single combined dose of 100 mg of pyrimethamine and 200 mg of dapsone for six healthy volunteers

<table>
<thead>
<tr>
<th>Serum parameter</th>
<th>Before dose\textsuperscript{a}</th>
<th>After dose\textsuperscript{a}</th>
<th>Change (95% CI)</th>
<th>% Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine ((\mu)mol/liter)\textsuperscript{a}</td>
<td>99 ± 15</td>
<td>117 ± 21</td>
<td>+18 (+10 to +26)</td>
<td>+18.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Creatinine ((\mu)mol/liter)\textsuperscript{a}</td>
<td>81 ± 14</td>
<td>102 ± 16</td>
<td>+21 (+13 to +29)</td>
<td>+26.1</td>
<td>0.002</td>
</tr>
<tr>
<td>Urea (mmol/liter)</td>
<td>5.2 ± 1.2</td>
<td>5.1 ± 1.2</td>
<td>-0.1 (-0.8 to +0.5)</td>
<td>-2.3</td>
<td>NS\textsuperscript{b}</td>
</tr>
<tr>
<td>(\beta)-2-Microglobulin (mg/liter)</td>
<td>1.20 ± 0.15</td>
<td>1.19 ± 0.21</td>
<td>-0.01 (-0.22 to +0.20)</td>
<td>-0.8</td>
<td>NS</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Means ± SDs.
\textsuperscript{b} Jaffe reaction.
\textsuperscript{c} Colorimetry of enzymatic reaction.
\textsuperscript{d} NS, not statistically significant.

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The determination of the second clearance took place 5 ± 1.7 days after the last intake of the prophylactic treatment.

All of the nine patients were men with an average age of 43 ± 11 years and weight of 72 ± 10 kg. Two of them were asymptomatic, five were in Centers for Disease Control stage IVC\textsubscript{2}, and two had previously diagnosed AIDS due to Kaposi’s sarcoma. All nine patients were immunosuppressed with a median CD4 lymphocyte count of 160/\mu\text{L} (range, 60 to 270). All patients were receiving zidovudine, two were additionally receiving fluconazole, one was additionally receiving ketoconazole, and one was additionally receiving maropitant. No drugs other than the prophylactic treatment were administered between the two renal function tests. Written informed consent was obtained from all participants. The study was approved by the ethical committee of our institution.

Renal function tests and biochemical analyses. The clearances of creatinine, inulin, and para-aminomhippurate (PAH) were measured at steady state during four periods of 20 min each, as previously described (16, 17). After fasting, a priming infusion of 4.25 g of inulin and 0.6 g of PAH per 1.73 m\textsuperscript{2} in 150 ml of 0.9% saline solution was given within 10 min and was followed by a constant infusion of 36 mg of inulin and 6 mg of PAH per 1.73 m\textsuperscript{2} per min to sustain steady state. Participants were instructed to drink 1,000 ml of water before and during the test to maintain a urine flow rate above 5 ml/min. Additionally, they were intravenously hydrated with 6 ml of 0.9% saline solution per min. After a 45-min equilibration period, renal function tests were performed during steady state in four consecutive collection periods of 20 min each. During each of the four collection periods, the volume of spontaneously voided urine and arterial blood pressure were measured and samples of blood and urine were collected for determinations of creatinine, inulin, and PAH. The corresponding clearances were calculated as \((U/P) \cdot V\), where \((U/P)\) is the urine-to-plasma concentration of creatinine, inulin, or PAH, respectively, and \(V\) is the urine flow rate (in milliliters per minute) during the collection period. The values for the four collection periods were then averaged and expressed per standardized body surface area of 1.73 m\textsuperscript{2}. The clearance of PAH represents the renal plasma flow. Renal vascular resistance (in dynes \cdot \text{centimeter}^{-1} \cdot \text{liter}^{-1}) was calculated as mean arterial blood pressure/RBF \cdot 80,000, where RBF is renal blood flow (in milliliters per minute), calculated as renal plasma flow/(1 - hematocrit), and 80,000 is the conversion factor necessary to express the resistance in metric units (adapted for the units of mm Hg for blood pressure and milliliters per minute for renal blood flow). Renal vascular resistance was also adjusted to the standardized body surface area of 1.73 m\textsuperscript{2}.

All serum and urine samples were stored at −20°C and analyzed immediately after thawing. Standard laboratory methods were employed. Serum creatinine and urine creatinine were assayed by an enzymatic color test (Boehringer Mannheim Diagnostics; normal serum level, 44 to 97 \(\mu\)mol/liter), inulin was assayed by the colorimetric measurement of fructose produced by hydrolysis of inulin (anthon method), and PAH was assayed by the Bratton-Marshall reaction (7). Coefficients of variance of the inulin and PAH assays for control samples were 1.43 and 4.84%, respectively. Serum creatinine was additionally assayed by Jaffe reaction (normal level, 53 to 115 \(\mu\)mol/liter), blood urea nitrogen was assayed by the urease method (normal level, 2.5 to 7.5 mmol/liter), and \(\beta\)-2-microglobulin was assayed by enzyme-linked immunoabsorbent assay (normal level, 0.01 to 2.40 mg/liter).

Statistical analysis. Every subject served as his own control. Values are presented as means ± SDs; 95% confidence intervals (95% CI) are given for the observed changes. Statistical comparisons were made by paired Student’s \(t\) test. \(P\) values of <0.05 were considered statistically significant.

RESULTS

Acute effects in healthy volunteers. A single combined dose of 100 mg of pyrimethamine and 200 mg of dapsone caused serum creatinine to rise from 81 ± 14 to 102 ± 16 \(\mu\)mol/liter within 28 h (colorimetry; \(P = 0.002\)). The values for urea and

TABLE 2. Results\textsuperscript{a} of renal function tests before and 28 h after the administration of a single combined dose of 100 mg of pyrimethamine and 200 mg of dapsone for six healthy volunteers

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before dose\textsuperscript{a}</th>
<th>After dose\textsuperscript{a}</th>
<th>Change (95% CI)</th>
<th>% Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>125 ± 27</td>
<td>91 ± 26</td>
<td>-34 (-57 to -12)</td>
<td>-27.5</td>
<td>&lt;0.02</td>
</tr>
<tr>
<td>Inulin clearance (ml/min)</td>
<td>116 ± 36</td>
<td>120 ± 25</td>
<td>+4 (+27 to +34)</td>
<td>+3.3</td>
<td>NS\textsuperscript{c}</td>
</tr>
<tr>
<td>Renal plasma flow (ml/min)</td>
<td>580 ± 177</td>
<td>442 ± 49</td>
<td>-138 (-269 to -7)</td>
<td>-23.8</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Renal vascular resistance (dynes \cdot \text{s} \cdot \text{cm}^{-2} \cdot \text{y}^{-1})</td>
<td>8,431 ± 1,666</td>
<td>12,311 ± 4,423</td>
<td>+3,880 (+1,186 to +9,646)</td>
<td>+46.0</td>
<td>0.13 (NS)</td>
</tr>
</tbody>
</table>

\textsuperscript{a} Means ± SDs, adjusted to the standard body surface area of 1.73 m\textsuperscript{2}.
\textsuperscript{b} NS, not statistically significant.
\textsuperscript{c} \(n = 5\).
The administration of a single combined dose of 100 mg of pyrimethamine and 200 mg of dapsone for six healthy volunteers. Values are means ± SDs. Creatinine was measured by Jaffé reaction.

β2-microglobulin remained unchanged (Table 1). Creatinine clearance decreased concurrently from 125 ± 27 to 91 ± 26 ml/min (P < 0.02), while inulin clearance remained stable between 116 ± 36 and 120 ± 25 ml/liter (Table 2). An additional decrease in renal plasma flow from 580 ± 117 to 442 ± 49 ml/min (P < 0.05) was paralleled by a rise in renal vascular resistance from 8,431 ± 1,666 to 12,311 ± 4,423 dynes · s · cm⁻² (available for five volunteers; P = 0.13). The mean arterial blood pressure remained unchanged. Urine analysis results remained normal for all subjects throughout the entire observation period. Specifically, no cells, protein, or crystals were found in the urine sediments.

The time course of serum creatinine, measured by Jaffé reaction, showed a rise from 99 ± 15 to 116 to 117 μmol/liter lasting between days 1 and 4 postexposure (Fig. 1). Thereafter, serum creatinine fell continuously from day 6 to day 21 after drug intake, normalizing at 104 ± 20 μmol/liter on day 21. The highest individual value observed was 150 μmol/liter on day 1.

To determine which drug was responsible for the observed decrease in creatinine clearance, the volunteers were rechallenged with single doses of 200 mg of dapsone and then 100 mg of pyrimethamine, with each dose administered after a drug-free interval exceeding the fivefold half-life time of the drug ingested previously. A 19% increase in serum creatinine occurred after the administration of pyrimethamine, corresponding in magnitude to the rise observed after the administration of pyrimethamine and dapsone together. A single dose of dapsone, however, did not cause any change in serum creatinine (Table 3). This part of the study, thus, determined pyrimethamine to be the substance responsible for the rise in serum creatinine.

**Sustained effects in patients.** Following the administration of four weekly doses of 75 mg of pyrimethamine and 200 mg of dapsone as prophylaxis against P. carinii pneumonia and cerebral toxoplasmosis, serum values of creatinine and renal function tests for nine HIV-infected patients were compared with their pretreatment values. Serum creatinine, measured by colorimetry, increased from 69 ± 17 to 87 ± 32 μmol/liter (P < 0.05). Both creatinine and inulin clearances showed inconsistent courses resulting in marginal, nonsignificant decreases. Renal plasma flow, renal vascular resistance, and mean arterial blood pressure remained unchanged (Table 4). Results of urine analyses remained normal at all times.

**DISCUSSION**

Pyrimethamine has not been associated with any typical renal side effects (10, 20), even though it has been in clinical use for many years. Our study demonstrates for the first time that moderate but consistent rises in serum creatinine occurred after the administration of a single dose of 100 mg of pyrimethamine in persons without any known kidney disease. The acute effects of a combined dose of pyrimethamine and dapsone consisted of a rise in serum creatinine and a fall in creatinine clearance, without changing inulin clearance. A rise in serum creatinine of the same magnitude occurred after pyrimethamine alone but not after dapsone alone. These results confirm that pyrimethamine caused a selective alteration of the renal handling of creatinine without affecting the glomerular filtration rate. Pyrimethamine thus may have selectively blocked the renal tubular secretion of creatinine, which accounts for 5 to 40% of the total amount of excreted creatinine in healthy persons (4, 11, 12, 14, 22), but can increase to well over 40 to 50% in patients with renal disease (2, 14, 23, 24). The same mechanism for rises in serum creatinine was shown previously for trimethoprim (4, 5), cimetidine (8, 9, 24), and probenecid (18). Since both pyrimethamine and trimethoprim have similar 2,4-diaminopyrimidine chemical structures (27), the analogous effect on renal function is not surprising, but it has never been described before.

Despite an acute drop (27.5%) in creatinine clearance, the rise in serum creatinine was only mild to moderate in our healthy volunteers, reaching a peak at 150 μmol/liter (normal level, <115 μmol/liter) in one person and returning to normal within 3 weeks (Fig. 1). Considering the half-life time of 83 ± 14 h for pyrimethamine (3), the rate of normalization was only slightly slower than the serum elimination of pyrimethamine itself. Trimethoprim-induced inhibition of creatinine secretion returns to normal within 7 days (4), reflecting its shorter elimination time (11 ± 1.4 h) (3). The inhibition of creatinine secretion is thus competitive, revers-

**TABLE 3.** Serum values* before and 24 h after the administration of a single dose of either 100 mg of pyrimethamine or 200 mg of dapsone for six healthy volunteers

<table>
<thead>
<tr>
<th>Serum parameter</th>
<th>Dapsone</th>
<th>Pyrimethamine</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>Creatinine (μmol/liter)*</td>
<td>97 ± 16</td>
<td>98 ± 15</td>
</tr>
<tr>
<td>Urea (mmol/liter)</td>
<td>5.3 ± 0.7</td>
<td>5.4 ± 1.0</td>
</tr>
</tbody>
</table>

* Means ± SDs.

* Jaffé reaction.

* NS, not statistically significant.
PYRIMETHAMINE INHIBITS RENAL CREATININE SECRETION

TABLE 4. Serum creatinine and renal function values* before and after 4 weeks of prophylactic treatment with the combined dose of 75 mg of pyrimethamine and 200 mg of dapsone per week for nine HIV-infected patients

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Before treatment</th>
<th>After treatment</th>
<th>Change (95% CI)</th>
<th>% Change</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum creatinine (µmol/liter)</td>
<td>69 ± 17</td>
<td>87 ± 32</td>
<td>+18 (+3 to +34)</td>
<td>+26.7%</td>
<td>&lt;0.05</td>
</tr>
<tr>
<td>Creatinine clearance (ml/min)</td>
<td>124 ± 37</td>
<td>116 ± 31</td>
<td>−16 (−42 to +14)</td>
<td>−11.1%</td>
<td>NS</td>
</tr>
<tr>
<td>Inulin clearance (ml/min)</td>
<td>120 ± 35</td>
<td>108 ± 38</td>
<td>−11 (−35 to +12)</td>
<td>−9.6%</td>
<td>NS</td>
</tr>
<tr>
<td>Renal plasma flow (ml/min)</td>
<td>585 ± 313</td>
<td>569 ± 140</td>
<td>−17 (−257 to +223)</td>
<td>−2.9%</td>
<td>NS</td>
</tr>
<tr>
<td>Renal vascular resistance (dynes x s - cm⁻²)</td>
<td>9,448 ± 3,547</td>
<td>9,576 ± 4,484</td>
<td>+128 (−2,231 to +2,488)</td>
<td>+1.4%</td>
<td>NS</td>
</tr>
</tbody>
</table>

* Means ± SDs, adjusted (except for serum creatinine) to the standard body surface area of 1.73 m².

The use of pyrimethamine with HIV-infected patients for both prophylaxis and treatment is increasing. The knowledge of this mechanism is, therefore, important and should be considered especially when other potentially nephrotoxic drugs are used. Every increase in serum creatinine must lead to careful consideration of other causes of nephropathy, whether they are drug induced or disease associated (10, 20). Although the cooccurrence of renal disease is rare, HIV infection has been shown to coincide with different glomerular and extraglomerular nephropathies (6, 21). The use of pyrimethamine in the treatment of malaria could also result in slight-to-moderate increases in serum creatinine. In contrast, acute renal failure as a possible complication of malaria causes real decreases in the glomerular filtration rate (1, 26) and can be distinguished by additional laboratory parameters.

In conclusion, serum creatinine and urine should be regularly monitored for patients treated with pyrimethamine to allow early evaluation of a possible increase in serum creatinine by differentiating between functional, physiologic changes and true impairment of renal function.

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REFERENCES