Pharmacokinetics of Sulfadoxine-Pyrimethamine in HIV-Infected and Uninfected Pregnant Women in Western Kenya

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Background. Sulfadoxine-pyrimethamine (SP) is among the most commonly used antimalarial drugs during pregnancy, yet the pharmacokinetics of SP are unknown in pregnant women. HIV-infected (HIV+) women require more frequent doses of intermittent preventive therapy with SP than do HIV-uninfected (HIV-) women. We investigated whether this reflects their impaired immunity or an HIV-associated alteration in the disposition of SP.

Methods. Seventeen pregnant HIV- women and 16 pregnant HIV+ women received a dose of 1500 mg of sulfadoxine and 75 mg of pyrimethamine. Five HIV- and 6 HIV+ postpartum women returned 2–3 months after delivery for another dose. The pharmacokinetics of sulfadoxine and pyrimethamine were compared between these groups.

Results. HIV status did not affect the area under the curve (AUC) or the half-lives of sulfadoxine or pyrimethamine in prepartum or postpartum women, although partum status did have a significant affect on sulfadoxine pharmacokinetics. Among prepartum women, the median half-life for sulfadoxine was significantly shorter than that observed in postpartum women (148 vs 256 h; P < .001), and the median AUC was ~40% lower (22,816 vs 40,106 μg/mL/h, P < .001). HIV status and partum status did not show any significant influence on pyrimethamine pharmacokinetics.

Conclusion. Pregnancy significantly modifies the disposition of SP, whereas HIV status has little influence on pharmacokinetic parameters in pregnant women.

Sulfadoxine-pyrimethamine (SP) is used in some settings for the treatment of uncomplicated malaria in pregnant women, and it is the only drug currently recommended for intermittent preventive therapy during pregnancy (IPTp). The IPTp regimen consists of at least 2 full treatment doses given in the second trimester and third trimester at intervals at least 1 month [1]. Because of the development of resistance, SP is increasingly being replaced by combination therapy for the treatment of malaria in children and adults. However, among pregnant women, the options for prevention are limited, and SP continues to be widely used as IPTp in pregnancy [2, 3].

Because physiological functions are altered during pregnancy, the pharmacokinetics of many drugs, including antimalarials, may be different in pregnant women, compared with nonpregnant women [4, 5]. Complex and constantly changing physiological phenomena during the course of pregnancy complicate the situation [6]. Despite its widespread use, the pharmacokinetics of SP has never been described in pregnant women.

It has also been observed that more frequent doses of IPTp are necessary for HIV+ women to achieve the...
same benefits as HIV− women [7–9]. The risk of malaria infection in immunosuppressed HIV+ persons has been shown to be greater, which partially explains this difference [10]. It is not known whether differences in the pharmacokinetics of SP among HIV+ women might contribute to the reduced efficacy of SP as IPTp or be relevant to the case management of malaria in HIV-infected women. Therefore, we examined the pharmacokinetics of a single dose of SP in HIV+ and HIV− women in western Kenya during pregnancy, and again at 2–3 months after delivery, to determine the effects of pregnancy and HIV infection on the disposition of SP.

SUBJECTS, MATERIALS, AND METHODS

Subjects. The study was conducted at New Nyanza Provincial Hospital in Kisumu from 1999 to early 2000. Primigravid and secundigravid women were included if they had an uncomplicated singleton pregnancy of 16–28 weeks gestation (as assessed by palpation by the midwives in the antenatal clinic), and a hemoglobin level of >8 g/dL. Exclusion criteria included a history of allergies to the study drugs; ingestion of sulfadiazine or other sulfa-containing drugs; a mixed malaria infection on the disposition of SP. The same collection schedule was used for the study repeated during the postpartum period. Levels of sulfadoxine and pyrimethamine in whole blood were determined by high-performance liquid chromatography, performed in accordance with the method described by Green et al. [14]. Interassay variability for sulfadoxine and pyrimethamine was assessed for this study. Standard curve samples for high-performance liquid chromatography analysis consisted of whole blood spiked at the following concentrations: 5, 10, 50, and 100 μg/mL for sulfadoxine and 0.05, 0.1, 0.5, and 1.0 μg/mL for pyrimethamine. Interassay precision (expressed as coefficient of variation [CV]) for sulfadoxine from 18 standard curve runs were 30%, 11%, 6%, and 1%, respectively, for the concentrations stated above, while pyrimethamine showed 77%, 22%, 9%, and 2%, respectively, for the concentrations above. Interassay accuracy (CV) for sulfadoxine was 1%, 15%, 1%, and −1%, and that for pyrimethamine showed 21%, 16%, 3%, and −1%, respective to the concentrations stated above.

After participants provided informed consent and received HIV counseling, HIV testing was conducted using 2 rapid test methods: an initial SeroStrip HIV-1/2 test (Saliva Diagnostic Systems) and a confirmatory Capillus HIV-1/HIV-2 test (Cambridge Diagnostics) performed on all samples that produced a positive SeroStrip result. At all time points when blood samples were obtained for the pharmacokinetic study, blood smears for malaria were performed to assess parasitemia.

Pharmacokinetic analysis. A 1-compartment pharmacokinetic model was used to determine parameters for both sulfadoxine and pyrimethamine. The slope of the least-squares
regression analysis of the natural log of drug concentration versus time was used to calculate the elimination constant \( (k_e) \) and half-life \( (t_{1/2} = -0.693/k_e) \) for each subject. The area under the curve \( (AUC) \) from 0 to 240 h \( (AUC_{0-240}) \) was calculated using the trapezoidal rule applied to the linear regression curve. The AUC from 0 to infinity hours \( (AUC_{0-\infty}) \) was determined by combining \( AUC_{n-240} \) with the area extrapolated from the concentration as determined from the linear regression curve at 240 h divided by the elimination constant of the linear regression curve \( (AUC_{0-\infty} = AUC_{0-240} + C_{240}/k_e) \). The volume of distribution \( (V_{d/f}) \) was calculated from the formula, \( V_{d/f} = \text{dose}/(k_e \times AUC_{0-\infty}) \), and the dose divided by \( AUC_{0-\infty} \) determined the total apparent clearance, Cl/f. Only the patient data sets containing data on blood concentrations from at least the last 3 sampling points (i.e., 96, 120, and 240 h) were used to calculate half-life values. The US Food and Drug Administration recommends that if predose concentration values are greater than 5% of \( C_{max} \), the subject should be dropped from bioequivalency and/or bioavailability study evaluations [15]. Therefore, the AUCs for such subjects were not determined. The time to peak plasma concentration for sulfadoxine and pyrimethamine occurs from 2 to 6 h after administration [16]. The initial time of sample collection in our study was 6 h after administration, therefore a \( C_{max} \) value could not be reliably determined. We estimated the \( C_{max} \) to be close to the concentration at 6 h, and we eliminated the AUC values for subjects in whom predose concentrations were greater than 5% of the concentration at 6 h.

Statistics. Linear regression methods on log-transformed values for half-lives and \( AUC_{0-\infty} \) were used to compare HIV and partum status while controlling for age, parasite count, and malaria status. Generalized estimating equations were used to account for the correlation of multiple observations taken from the same subject. The Student t test was used on log-transformed values to determine differences between groups.

RESULTS

Participants. A total of 95 pregnant women were screened, and blood levels of sulfadoxine and pyrimethamine were obtained for 33 participants. Of the 62 women excluded, 14 had hemoglobin levels of <8 g/dL, 39 women were excluded because their HIV status did not fit the sampling schedule, 1 woman was febrile and had a positive blood smear result, and 8 women refused to participate. The median age of the women included was 20 years (range, 15–30 years) while the median weight was 61.4 kg (range, 47.2–71.0 kg). Gestation time at enrollment ranged from 16–28 weeks (median, 24 weeks); 16 women were HIV+ and 17 were HIV−. There were no significant differences between HIV+ and HIV− women with respect to weight, gestational time, hemoglobin level at enrollment, or age.

None of the women vomited the tablets after intake. Five women missed 1 of the sampling days, and 3 women missed more than 1. Five women reported the use of folic acid during the study period (3 HIV+ women and 2 HIV− women). Eleven pregnant women (8 HIV+ and 3 HIV−) were parasitemic at the start of the study; 1 parasitemic pregnant woman (who was also HIV-infected) had a history of fever in the previous month but her axillary temperature at the time of enrolment was 36.1°C. None of the other parasitemic women had a history of fever. For all the women, parasitemia cleared within 3 days after the study treatment with SP. Severe cutaneous reactions were not observed among participants.

Of the 33 women included in the prepartment analysis, 11 participants (6 HIV+ and 5 HIV− women) returned for the postpartum component of the study at 8.6−11.7 weeks after delivery (median, 10 weeks); they all completed the follow-up schedule. One postpartum woman (who was also HIV+) was parasitemic at the time of enrolment. Among the women who did not participate in the postpartum study, 8 had moved to their rural home or elsewhere, 7 women could not be traced, 5 women refused to participate, and 1 woman died during delivery. There were no significant differences in maternal age, gravidity, or weight (during pregnancy) between women who did and did not participate in the postpartum component of the study; however, women who participated after pregnancy had a higher mean hemoglobin level at enrollment, compared with women who participated only during pregnancy (mean ± SD, 10.8 ± 1.2 g/dL vs. 9.9 ± 1.1 g/dL) \( (P = .04) \).

Sulfadoxine pharmacokinetics. Pharmacokinetic parameters were obtained from whole blood drug concentrations because malaria-infected erythrocytes appear to concentrate sulfadoxine [17]. Linear regression analysis of the control parameters (i.e., age, parasite count, malaria status, and HIV status) did not influence the half-life or \( AUC_{0-\infty} \) values, although partum status did have a significant effect \( (P < .01) \) on sulfadoxine half-life as well as \( AUC_{0-\infty} \). Because the statistical evidence showed that HIV status had no effect on the pharmacokinetic parameters, the values from the HIV+ and HIV− groups were pooled into prepartum and postpartum sets and compared (table 1). The median half-life was significantly shorter during pregnancy compared with the postpartum period \( (148 \text{ h vs } 256 \text{ h}; P < .0001) \). Median \( AUC_{0-\infty} \) were ~40% lower during pregnancy, compared with the postpartum period \( (22,816 \mu \text{g/mL/h vs } 40,106 \mu \text{g/mL/h}; P < .001) \). The rate of clearance was also significantly greater during pregnancy than during the postpartum period \( (65.9 \text{ mL/h vs } 36.9 \text{ mL/h}; P < .001) \), although pregnancy status showed no significant effect on the volume of distribution in our sample group. Because data on the weight of subjects (kg) were available for the prepartum but not the postpartum women, weight-adjusted \( V_{d/f} \) and Cl/f values were calculated only for the prepartum group.

Pyrimethamine pharmacokinetics. Linear regression anal-
Table 1. Comparison of pharmacokinetic (PK) values in the present study with values from published studies of sulfadoxine-pyrimethamine pharmacokinetics in adult whole blood.

<table>
<thead>
<tr>
<th>Drug, by PK variable</th>
<th>Present study</th>
<th>Barnes et al. [21], subjects with acute falciparum malaria&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Edstein et al. [17], healthy subjects&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Prepartum subjects</td>
<td>Postpartum subjects</td>
<td>Patients, no.</td>
</tr>
<tr>
<td>Sulfadoxine 1500 mg dose</td>
<td>1500 mg dose</td>
<td>1500 mg dose&lt;sup&gt;c&lt;/sup&gt;</td>
<td>500 dose mg</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; in h</td>
<td>148 (121–193)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>256 (231–381)</td>
<td>10</td>
</tr>
<tr>
<td>V&lt;sub&gt;f&lt;/sub&gt; in L/kg</td>
<td>0.24 (0.21–0.27)</td>
<td>0.37 (0.27–0.49)</td>
<td>158</td>
</tr>
<tr>
<td>V&lt;sub&gt;f&lt;/sub&gt; in L</td>
<td>15.0 (12.1–16.0)</td>
<td>13.2 (12.6–16.3)</td>
<td>9</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;f&lt;/sub&gt; in mL/h/kg</td>
<td>1.01 (0.92–1.61)</td>
<td>1.36 (0.93–2.18)</td>
<td>158</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;f&lt;/sub&gt; in mL/h</td>
<td>65.9 (47.8–91.6)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>36.9 (35.3–47.3)</td>
<td>10</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;r&lt;/sub&gt; in µg/mL/h</td>
<td>22,816 (16,437–31,373)&lt;sup&gt;d&lt;/sup&gt;</td>
<td>40,106 (31,706–42,463)</td>
<td>161</td>
</tr>
<tr>
<td>Pyrimethamine 75 mg dose</td>
<td>75 mg dose</td>
<td>75 mg dose&lt;sup&gt;c&lt;/sup&gt;</td>
<td>25 mg dose</td>
</tr>
<tr>
<td>t&lt;sub&gt;1/2&lt;/sub&gt; in h</td>
<td>95 (80–119)</td>
<td>102 (69–195)</td>
<td>10</td>
</tr>
<tr>
<td>V&lt;sub&gt;f&lt;/sub&gt; in L/kg</td>
<td>4.92 (4.24–6.00)</td>
<td>3.83 (2.73–5.11)</td>
<td>163</td>
</tr>
<tr>
<td>V&lt;sub&gt;f&lt;/sub&gt; in L</td>
<td>309 (245–372)</td>
<td>329 (253–475)</td>
<td>9</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;f&lt;/sub&gt; in mL/h/kg</td>
<td>37.1 (29.7–45.8)</td>
<td>35.4 (25.8–50.4)</td>
<td>163</td>
</tr>
<tr>
<td>Cl&lt;sub&gt;f&lt;/sub&gt; in mL/h</td>
<td>2162 (1848–2854)</td>
<td>1789 (1628–2930)</td>
<td>165</td>
</tr>
<tr>
<td>AUC&lt;sub&gt;r&lt;/sub&gt; in µg/mL/h</td>
<td>34.7 (26.3–40.6)</td>
<td>42.0 (25.6–46.1)</td>
<td>10</td>
</tr>
</tbody>
</table>

**NOTE.** Cl<sub>f</sub>, mL/h: total apparent clearance; Cl<sub>f</sub>, mL/h/kg: weight-adjusted oral clearance; t<sub>1/2</sub>, half life; V<sub>f</sub>, L: volume of distribution; V<sub>f</sub>, L/kg: weight-adjusted volume of distribution; IQR, interquartile range.

<sup>a</sup> Males and females >12 years old.
<sup>b</sup> Six adult men and 1 adult woman.
<sup>c</sup> Maximum dose.
<sup>d</sup> Significantly different (P<0.001), compared with postpartum values.
ysis revealed that none of the control parameters, that is, age, parasite count, malaria status, HIV status or pregnancy, significantly \((P > .05)\) influenced the pyrimethamine half-life or \(\text{AUC}_{0-\infty}\) values. When grouped into partum and postpartum categories, the median half-life and the \(\text{AUC}_{0-\infty}\) values for pyrimethamine during pregnancy were lower but not significantly so (t_{1/2}, 95 vs. 102 h; \(\text{AUC}_{0-\infty}\), 34.7 vs. 42.0 \(\mu\)g/mL/h; \(P > .05\)) (table 1).

**DISCUSSION**

In this study, we observed differences in pharmacokinetic parameters between pregnant and nonpregnant women for sulfadoxine, and less so for pyrimethamine. HIV status did not seem to influence the pharmacokinetics of SP during pregnancy.

Previous pharmacokinetic studies of SP were commonly performed on the basis of plasma drug concentrations [12, 13, 18–21]. Because the mechanism of action of SP occurs within the red blood cell, we consider whole blood concentrations of drug to be more relevant than plasma concentrations. Edstein [17] reported pharmacokinetic parameters in both whole blood and plasma in 7 healthy adult volunteers (6 men and 1 woman), while Barnes et al. [21] has recently reported pharmacokinetic values for subjects (>12 years old) with acute falciparum malaria. Because these studies report pharmacokinetic values in whole blood from adults, we used these values for comparison with the pharmacokinetic values determined in our study (table 1).

Because elimination half-lives for sulfadoxine and pyrimethamine are independent of dosing [16], a direct comparison of elimination half-lives can be made with those determined by Edstein [17] and Barnes et al. [21] (table 1). Our results show that the half-life values for sulfadoxine in postpartum women (256 h) were similar to those of nonpregnant adults reported by Edstein (227 ± 49 h), however, the half-life during pregnancy was much more rapid (148 h). A lower half-life (possibly in combination with slower absorbance) contributed to the significantly lower \(\text{AUC}_{0-\infty}\) observed in pregnancy in our study.

Median pyrimethamine half-life values for prepartum and postpartum women (95 and 102 h, respectively) were within the range of values reported by Edstein [17] and Barnes et al. [18] (119 and 78 h, respectively). The median weight-adjusted \(V_{d}/f\) value in pregnant women (4.92 L/kg) observed in the present study was slightly higher than the values reported by Edstein (3.71 L/kg) and Barnes et al. (3.83 L/kg). The median weight-adjusted \(V_{d}/f\) value in pregnant women (37.1 mL/h/kg) was similar to that reported by Barnes et al. (35.4 mL/h/kg), and the \(\text{AUC}_{0-\infty}\) in prepartum women (34.7 \(\mu\)g/mL/h) was less than that in postpartum women (42.0 \(\mu\)g/mL/h), but similar to that reported by Barnes et al. (38.4 \(\mu\)g/mL/h).

Poor absorption of orally administered drugs in pregnant women has been attributed to delayed motility and decreased gastric secretions [6]. Although the volume of distribution is usually increased during pregnancy, we found no significant differences in the \(V_{d}\) for sulfadoxine before and after pregnancy. When adjusted for body weight, the \((V_{d}/f)/BW\) value for pregnant women was 0.24 L/kg. These values were similar to the value reported by Edstein [17] in nonpregnant adults (0.25 ± 0.03 L/kg).

The pregnancy-associated differences in pharmacokinetic parameters that were observed for sulfadoxine were not as apparent for pyrimethamine (table 1). Greater variability in the pyrimethamine analysis may account for less significant differences in the pharmacokinetic values between the prepartum and postpartum groups.

The effect of pregnancy on the elimination of sulfadoxine, compared with pyrimethamine, may reflect the fact that sulfadoxine is excreted primarily unchanged by the kidneys, whereas 20%–30% of pyrimethamine is excreted unchanged in urine [16]. Drugs that are largely or completely eliminated by the kidney in unchanged form are known to have a shorter elimination half-life during pregnancy [6].

HIV status has little influence on the pharmacokinetics of SP, suggesting that the observed differences in the efficacy of 2 doses of IPTp with SP result primarily from differences between HIV+ and HIV− women with respect to host factors, such as the effectiveness of the immune response in aiding with the clearance of parasites that survive drug action or possible differences in endogenous folate levels.

In conclusion, the data suggest that pregnancy, at least in the second trimester, adversely alters the pharmacokinetics of sulfadoxine but has little influence on those of pyrimethamine. This is remarkable, given that SP is the antimalarial most commonly used during pregnancy in Africa, but the results are consistent with the recent findings from other pharmacokinetic studies conducted at the Thai-Burmese border with the artemisinins, lumefantrine, atovaquone, and proguanil; all studies show that pregnancy modifies the drugs’ disposition, which results in much lower concentrations of the parent drug or metabolites in pregnant women, compared with nonpregnant adults [4, 5]. In many countries where malaria is endemic, antenatal care may be delayed until well into the third trimester. It is likely that the pharmacokinetic differences observed in the second trimester may be even more pronounced in the third trimester, given the differences in physiological conditions. Therefore, second trimester SP kinetics may have more marked implications for IPTp in the third trimester.

Defining the relationship between drug levels and the therapeutic response to SP is complex because of the synergistic interaction between sulfadoxine and pyrimethamine that depends on the drug-resistance genotype of the parasite and corresponding degree of resistance [21, 22]. Our results justify further dose-optimization studies with SP to determine whether...
higher or more frequent doses are required in pregnant women. We have no evidence that HIV infection had an effect on the disposition of SP in pregnant women.

Acknowledgments

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References