Short Report: Increased Risk of Early Vomiting among Infants and Young Children Treated with Dihydroartemisinin-Piperaquine Compared with Artemether-Lumefantrine for Uncomplicated Malaria

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Abstract. Artemether-lumefantrine (AL) and dihydroartemisinin-piperaquine (DP) are highly efficacious antimalarial therapies in Africa. However, there are limited data regarding the tolerability of these drugs in young children. We used data from a randomized control trial in rural Uganda to compare the risk of early vomiting (within one hour of dosing) for children 6–24 months of age randomized to receive DP (n = 240) or AL (n = 228) for treatment of uncomplicated malaria. Overall, DP was associated with a higher risk of early vomiting than AL (15.1% versus 7.1%; P = 0.007). The increased risk of early vomiting with DP was only present among breastfeeding children (relative risk [RR] = 3.35, P = 0.001) compared with children who were not breastfeeding (RR = 1.03, P = 0.94). Age less than 18 months was a risk factor for early vomiting independent of treatment (RR = 3.27, P = 0.02). Our findings indicate that AL may be better tolerated than DP among young breastfeeding children treated for uncomplicated malaria.

Artemisinin-combination therapies (ACTs) currently represent first-line treatment of uncomplicated *Plasmodium falciparum* malaria throughout most of the world and exhibit excellent efficacy and the potential to minimize development of drug resistance.1 Of the numerous highly effective ACTs currently available, clinical choice often depends on adverse effect profiles, cost, and ease of administration.1 Artemether-lumefantrine (AL) is the most widely used ACT, accounting for 75% of the 100 million ACT treatments each year.2 Dihydroartemisinin-piperaquine (DP) is emerging as a favorable antimalarial option with comparable clinical efficacy to AL, prolonged post-treatment prophylaxis, and a simple once-a-day dosage regimen.3–6

The ACTs appear to be well-tolerated and serious toxicities are rare.1,4,5,7 Early vomiting (vomiting within one hour of dosing) has been reported in 3% of courses of AL and DP in adults. However, this rate increased to 10%8 or 11%4 in children. Little tolerability data exists for ACTs in infants and young children in Africa, the most susceptible population to malaria-related morbidity and mortality. Early vomiting (vomiting within one hour of dosing) has been previously associated with younger age4 and vomiting before treatment8 and has been shown to reduce the effectiveness of non-ACT antimalarial therapies because of reduced drug absorption.8 Furthermore, vomiting after antimalarial drug administration may discourage patients from taking further doses of the medication.9 The purpose of this study was to compare the risk of early vomiting after administration of AL or DP for the treatment of uncomplicated malaria in infants and young children in Africa.

A total of 351 participants 6 weeks to 9 months of age were enrolled as part of a larger longitudinal cohort study in eastern Uganda. Participants received all medical care at a dedicated study clinic, which was open seven days a week. Episodes of uncomplicated malaria were diagnosed by positive thick blood smear, fever (tympanic temperature ≥ 38.0°C or history of fever within 24 hours), and absence of symptoms indicative of severe malaria. Participants were randomized to receive either AL (Co-artem; Novartis, Basel, Switzerland) or DP (Duo-cotecxin; Holleypharm, Chiong City, People’s Republic of China) at the time the first episode of symptoms indicative of severe malaria. Participants were re-administered. Evening doses of AL were administered by the parent/guardian at home; dosage times and instances of early vomiting were recorded for all new cases of uncomplicated malaria that occurred during May 31–November 7, 2008.

All DP doses and morning doses of AL were administered by study nurses, and participants were monitored for one hour. Early vomiting (within one hour) was recorded and the dose was re-administered. Evening doses of AL were administered by the parent/guardian at home; dosage times and instances of early vomiting were reported to study staff the next day.

Data were double-entered into Microsoft (Redmond, WA) Access and analyzed using Stata version 10 (StataCorp, College Station, TX). Data were evaluated with an intention-to-treat analysis that included all episodes of uncomplicated malaria in participants who were assigned treatment with study drugs during the study period. Because of the low numbers (3 reported cases for 684 doses) of evening vomiting with AL and the bias inherent in comparing the one day clinical doses of DP with the morning clinic doses and evening parent/guardian administration and side effect reporting of AL, we examined the risk of vomiting after the morning clinic doses only. The risk of any early vomiting during the three days of study drug therapy was calculated by using simple proportions because all participants received all their doses.

Generalized estimating equations with exchangeable correlation and robust standard errors were used to measure the associations between the following covariates (AL versus DP)
DP, age, breastfeeding status, human immunodeficiency virus [HIV] status, and use of trimethoprim/sulfamethoxazole [TS] prophylaxis) and the risk of early vomiting, adjusting for repeated measures in the same patient. A multivariate model was then created based on established associations between each covariate and early vomiting. The relative risk (RR) and 95% confidence intervals (CIs) of recurrent malaria associated with early vomiting during 28 days and 63 days of follow-up (standard durations of follow-up by World Health Organization guidelines for antimalarial efficacy trials) were calculated by using generalized estimating equations and adjusting for antimalarial treatment, age, breastfeeding status, and repeated measures in the same study participant. A P value < 0.05 was considered statistically significant.

A total of 468 treatments were administered during the study period: 228 malaria episodes were treated with AL and 240 episodes were treated with DP. There were no significant differences in the median temperature (AL: 38.5°C; DP: 38.6°C) or mean parasite density (AL: 26,000 cells/μL; DP: 29,000 cells/μL) at the time of diagnosis or in the prevalence of participants vomiting before administration of antimalarial therapy (AL: 39 of 228; DP: 33 of 240) between the two treatment arms. The median ages and age ranges of the children at the time of malaria diagnosis were similar between the AL group (median = 1.3 years, range = 0.7–1.9 years) and the DP group (median = 1.3 years, range = 0.7–1.9 years); percentages of participants > 18 months of age for children receiving AL and children receiving DP (20% and 25%, respectively; P = 0.38) were comparable. At the time of malaria diagnosis, 45% of the participants in the AL arm were breastfeeding compared with 43% breastfeeding in the DP arm (P = 0.57). All participants who were still breastfeeding at the time of malaria diagnosis were also receiving supplemental food and cow’s milk (partially breastfeeding).

There were similar percentages of children who were infected with HIV or exposed to HIV in each treatment arm: 9% were infected with HIV and 51% were exposed to HIV in the AL group and 9% were infected with HIV and 47% were exposed to HIV in the DP group (P = 0.63). Of the 44 episodes among HIV-infected participants, 95% were receiving antiretroviral therapy in both treatment groups. Among children who were infected with HIV or exposed to HIV, 39% were receiving TS prophylaxis in the AL arm and 34% were receiving TS prophylaxis in the DP arm (P = 0.36).

For AL, the risk of early vomiting on days 0, 1, and 2 were 3.1%, 3.1%, and 0.9%, respectively, with a total risk for any vomiting of 7.1% for the entire course (Figure 1). For DP, the risk of early vomiting on days 0, 1, and 2 were 7.1%, 3.3%, and 4.7%, respectively, with a total risk for any vomiting of 15.1% for the entire course (Figure 1). There were only two participants with early vomiting after drug administration on more than one day, both in the DP arm. Episodes of vomiting multiple times after drug administration on a single day were uncommon; there were nine episodes in the DP group and two episodes in the AL group.

The overall risk of early vomiting was twice as high among children who received DP compared with children who received AL (RR = 2.17, P = 0.007). In examining the risk of early vomiting in a multivariate analysis, we found no association between early vomiting and HIV status or TS prophylaxis. The risk of early vomiting was significantly higher in all participants less than 18 months of age, regardless of antimalarial study drug used (RR = 3.27, P = 0.02) (Table 1). Use of DP was found to only be associated with early vomiting among those participants who were breastfeeding (RR = 3.35, P = 0.001). There was no difference in early vomiting between antimalarial groups among participants no longer breastfeeding (RR = 1.03, P = 0.94) (Table 1). Early vomiting did not result in an increased risk of recurrent malaria during 28 days (RR = 1.24, 95% CI = 0.71–2.17, P = 0.46) or 63 days (RR = 1.21, 95% CI = 0.96–1.51, P = 0.10) of follow-up.

In this analysis of early vomiting within a randomized control trial comparing AL and DP for treatment of children with uncomplicated malaria, those participants who received DP were at increased risk for early vomiting compared with those who received AL. However, the increased risk of early vomiting with DP was only observed among our breastfeeding participants. We also observed an increased risk of early vomiting in children less than 18 months of age regardless of the antimalarial therapy used.

Despite the increased rate of early vomiting among the breastfeeding children receiving DP in our study, we did not observe an increased risk of recurrent malaria in this population within 28 or 63 days of follow-up. This result conflicts with previous studies with mefloquine monotherapy, which demonstrated an increased risk of treatment failure associated with early vomiting.\textsuperscript{8,9} This discrepancy can most likely be attributed to the use of extremely efficacious ACTs for treatment of uncomplicated malaria and re-dosing of study medication after each episode of early vomiting. Outside of our clinic, parents or guardians who must buy a course of therapy for their ill child may choose not to re-dose vomited medications because of increased expense or fear of repeated vomiting.\textsuperscript{9}

We observed an overall early vomiting risk of 15.1% with DP, which was significantly higher than that in previous studies of older children and adults receiving DP (3–11%)\textsuperscript{10} and likely caused by the 25% early vomiting risk among breastfeeding children less than 18 months of age receiving DP. The mechanism responsible for the increased risk of early vomiting among breastfeeding participants using DP is not known. However, the temporal relationship suggests that the gastric mucosa of breastfed infants is more susceptible to the
proemetic effect of piperaquine than that in weaned infants. Further work is required to determine whether the co-administered milk may also affect this interaction. However, the lack of effect with AL suggests that the mechanism is specific to DP, most likely piperaquine.

Regardless, the risk of early vomiting among this young, breastfeeding population at high risk of malaria morbidity and mortality has not been previously reported, and the impact of early vomiting among infants and young children may be substantial. Our study suggests that caution should be used when administering DP to breastfeeding children and that re-dosing instructions should be considered with all young children taking ACTs. Further clinical studies and pharmacovigilance are needed to confirm these findings and to investigate whether the advantages of AL tolerability in an unsupervised community setting outweigh the prolonged post-treatment prophylaxis and improved adherence expected with once a day administration of DP.16

Received March 13, 2010. Accepted for publication July 20, 2010.

Acknowledgments: We thank the clinical study team and our administrative staff for their assistance, the children for participating in this study, and their parents and guardians for their cooperation.

Financial support: Children in this study were enrolled in programs supported by the U.S. President’s Emergency Plan for AIDS Relief and by Cooperative Agreement Number U62P204421 from the Department of Health and Human Services/Centers for Disease Control and Prevention, National Center for HIV, Viral Hepatitis, STD, and TB Prevention, Global AIDS Program. This study was also supported by the Doris Duke Charitable Foundation. Grant Dorsey is a recipient of a Clinical Scientist Development Award, and Taylor G. Sandison was supported through the Puget Sound Partners in Global Health and National Institutes of Health/National Institute of Allergy and Infectious Disease grant K23-AI082553. Dihydroartemisinin-piperaquine study drugs were provided free of charge by Holleypharm (Chiongqing City, People’s Republic of China).

Disclosure: None of the authors have any conflicts of interest. The corresponding author had full access to all data in the study and takes final responsibility for the decision to submit the paper for publication.

Disclaimer: The contents of this manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the Centers for Disease Control and Prevention or the Doris Duke Charitable Foundation.

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REFERENCES


<table>
<thead>
<tr>
<th>Age</th>
<th>No. early vomiters/total treatments in first group (%)</th>
<th>No. early vomiters/total treatments in second group (%)</th>
<th>RR for early vomiting† (first group vs. second group) (95% CI)</th>
<th>P</th>
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<tbody>
<tr>
<td>&lt;18 months vs. age ≥ 18 months</td>
<td>48/358 (13.4)</td>
<td>4/110 (3.6)</td>
<td>3.27 (1.24–8.59)</td>
<td>0.02</td>
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<tr>
<td>DP use vs. AL use (not breastfeeding)</td>
<td>9/133 (6.8)</td>
<td>7/100 (7.0)</td>
<td>1.03 (0.43–2.48)</td>
<td>0.94</td>
</tr>
<tr>
<td>DP use vs. AL use (breastfeeding)</td>
<td>27/107 (25.2)</td>
<td>3.35 (1.67–6.70)</td>
<td>0.001</td>
<td></td>
</tr>
</tbody>
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*RR = relative risk; CI = confidence interval; DP = dihydroartemisinin-piperaquine; AL = artemether-lumefantrine.
†RR and CIs were generated by using generalized estimating equations adjusted for repeated measures in the same patients with a multivariate model including antimalarial drug, age, breastfeeding, and an interaction term between breastfeeding and antimalarial treatment.