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Unbound piperaquine exposure in children and pregnant women receiving dihydroartemisinin-piperaquine as malaria chemoprevention

Usman Aslam-Mir[1], Howard Hong[1], Xay Pham[1], Richard Kajubi[2], Meghan E. Whalen[1], Norah Mwebaza[2], Erika Wallender[1], Grant Dorsey[1], Philip J. Rosenthal[1], Francesca T. Aweeka[1], Liusheng Huang[1]

[1]University of California, San Francisco, San Francisco, CA, United States, [2]Infectious Diseases Research Collaboration, Kampala, Uganda

Contact: Liusheng Huang, Ph.D.
Dept. of Clin. Pharm. at UCSF
Tel: 415-502-2594
Email: Liusheng.huang@ucsf.edu

Introduction

- Dihydroartemisinin-piperaquine has been studied for malaria prevention due to the long elimination half-life of piperaquine (PPQ).
- Only unbound PPQ transverses biological membranes and exerts pharmacological effects at active sites-- digestive vacuole (Yellow core in **Figure1**). PPQ is protonated and trapped in the acidic digestive vacuole
- Mechanism of action: PPQ binds to heme Fe^{3+} in digestive vacuole to prevent hemozoin formation
- Young Children and pregnant women have distinct physiological conditions that may alter drug-protein binding.
- We previously reported a reduced exposure of PPQ (protein-bound and unbound) in children and pregnant women, but unbound PPQ exposure has not been studied.

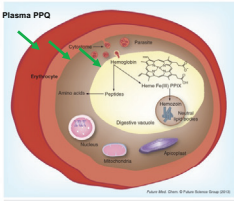

Figure 1 Active sites of piperaquine
Source: DOI:10.4155/fmc.13.113

Method

- *Clinical Trial design*: The study was a part of a large study carried out between December 2014 and May 2017 in Tororo, Uganda. Enrollment for pharmacokinetic (PK) study is shown in **Figure 2**.

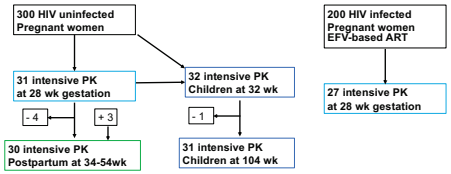

Figure 2. Study population

- *Drug administration and PK sampling*: Dihydroartemisinin-piperaquine was given once daily for 3 days at standard doses every 4 weeks or 8 weeks for malaria prevention. PK samples were collected post last dose at 0, 0.5, 1, 2, 3, 4, 6, 8, and 24 hr for unbound and total PQ determination in venous plasma.
- *Determination of unbound PPQ*: unbound PPQ was separated from plasma with Microcon Ultracel centrifugal filter devices (NMWL 10k), mixed with IS (PPQ-d_6) and injected into UPLC-MS/MS system (**Figure 3**). The calibration range was 20 – 5000 pg/mL.

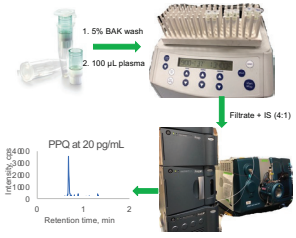

Figure 3. unbound PPQ quantitation

PK data analysis: Noncompartmental analysis was performed with Phoenix WinNonlin version 8.3.1 (Certara, Princeton, NJ) using the linear up- log down trapezoidal rule. PK parameters C_{max} and $AUC_{0\text{-}24h}$ were calculated for both total and unbund PPQ for comparison. Fraction of unbound PPQ (f_u) was calculated with each paired concentration ($PPQ_{unbound}/PPQ_{total}$). Stata version SE14.1 was used for the statistical analyses.

Results

HIV+ women were older than HIV- pregnant women (p<0.01) but their weights were similar, so the age difference is not expected to impact on drug-binding proteins. (**Table 1**). PK data for children are shown in **Table 2** and **Figure 4**. PK data for pregnant women are shown in **Table 3** and **Figure 5**. The f_u is shown in **Figure 6**.

Table 1. Demographic data of study participants

	Children		Pregnant women at 28 wk gestation		Adults
	32 wk (n=32)	104 wk (n=31)	HIV- (n=31)	HIV+ (EFV, n=27)	n=30
Age (yr)	0.61	2	23 (18, 31)	30 (18, 43)*	24 (19, 32)
Weight (kg)	7.53 (6.01, 9.03)	10.6 (8.37, 12.9)	57.5 (45.2, 83.2)	57.6 (43.7, 72.8)	52.9 (38.5, 72.9)
Height (cm)	68 (62, 71)	83 (77, 89)	163 (150, 179)	163 (147, 176)	162 (148,174)
BMI	16.8 (13.0, 19.6)	15.5 (13.8, 17.7)			
Hemoglobin (g/dL)	10.4 (8.6, 12)	11.5 (9.7, 12.4)	12.0 (10.3, 16.8)	11.6 (8.1, 19.2)	13.9 (11.8, 16.3)
Female	14	14			30
Male	18	17			

Table 2. PK parameters of piperaquine in children receiving dihydroartemisinin-PPQ as chemoprevention

	Children					
	32 weeks	104 weeks	Adult	104 wk/32 wk	32 week/adults	104 week/adults
PK parameters	GM; 95%CI (n = 32)	GM; 95%CI (n = 31)	GM; 95%CI (n = 30)	GMR (p value)	GMR (p value)	GMR (p value)
Total PPQ						
C_{max}, ng/mL	345 (279, 427)	309 (266, 359)	497 (392, 630)	0.896 (0.69)	0.694 (0.0037)	0.622 (0.0002)
T_{max}*, hr	4.03 (3.06, 6.01)	4.02 (2.03, 6.05)	3.06 (2.07, 4.03)	0.998 (0.21)	1.32 (0.0085)	1.31 (0.41)
$AUC_{0\text{-}24h}$, hr·µg/mL	3.88 (3.24, 4.64)	3.45 (3.04, 3.91)	5.47 (4.41, 6.79)	0.889 (0.29)	0.709 (0.0034)	0.631 (<0.0001)
Unbound PPQ						
C_{max}, ng/mL	2.35 (1.84, 3.01)	2.28 (1.90, 2.74)	2.97 (2.29, 3.85)	0.970 (0.95)	0.791 (0.13)	0.768 (0.043)
T_{max}*, hr	3.03 (2.06, 4.42)	3.05 (2.03, 4.1)	3.08 (3.00, 4.07)	1.01 (0.86)	0.984 (0.83)	0.990 (0.85)
$AUC_{0\text{-}24h}$, hr·ng/mL	23.0 (18.5, 28.7)	23.0 (19.5, 27.1)	28.1 (21.7, 36.3)	1.00 (0.978)	0.819 (0.071)	0.819 (0.041)
f_u (%)**	0.658 (0.618, 0.701)	0.718 (0.685, 0.753)	0.520 (0.501,0.539)	1.09 (0.0064)	1.27 (<0.0001)	1.38 (<0.0001)
$AUC_{free/total}$ (%)	0.594(0.514, 0.686)	0.666 (0.594, 0.746)	0.513 (0.469, 0.560)	1.12 (0.22)	1.16 (0.13)	1.30 (0.001)

Table 3. PK parameters of piperaquine in pregnant women receiving dihydroartemisinin-PPQ as chemoprevention with or without concomitant EFV-based ART

	Pregnant alone (P)	Preg+EFV	Non-pregnant (NP)	P/NP	Preg+EFV/P	Preg+EFV/NP
PK parameters	GM; 90%CI (n=31)	GM; 90%CI (n=27)	GM; 90%CI (n=30)	GMR (p value)	GMR (p value)	GMR (p value)
Total PPQ						
C_{max}, ng/mL	404 (332, 491)	333 (277, 400)	497 (392, 630)	0.813 (0.13)	0.824 (0.067)	0.670 (<0.01)
T_{max}*, hr	3.08 (3.00, 4.03)	4.00 (2.03, 5.98)	3.06 (2.07, 4.03)	1.01 (0.71)	1.30 (0.78)	1.31 (0.65)
$AUC_{0\text{-}24h}$, hr·µg/mL	4.58 (3.85, 5.44)	3.77 (3.25, 4.38)	5.49 (4.42, 6.81)	0.834 (0.11)	0.823 (0.019)	0.687 (<0.01)
Unbound PPQ						
C_{max}, ng/mL	2.41 (1.83, 3.19)	2.40 (1.88, 3.07)	2.97 (2.29, 3.85)	0.811 (0.20)	1.00 (0.95)	0.808 (0.14)
T_{max}*, hr	3.98 (3.02, 4.03)	4.00 (2.98, 4.07)	3.08 (3.00, 4.07)	1.29 (0.71)	1.01 (0.81)	1.30 (0.72)
$AUC_{0\text{-}24}$, hr·ng/mL	23.6 (18.8, 29.5)	24.2 (19.1, 30.5)	28.2 (21.8, 36.5)	0.837 (0.12)	0.975 (0.87)	0.858 (0.13)
f_u (%)**	0.533 (0.510, 0.557)	0.641 (0.602, 0.682)	0.520 (0.501,0.539)	1.03 (0.66)	1.20 (<0.01)	1.23 (<0.01)
$AUC_{free/total}$ (%)	0.515 (0.464, 0.570)	0.640 (0.543, 0.754)	0.514(0.471, 0.562)	1.00(0.90)	1.24 (<0.01)	1.25 (<0.01)

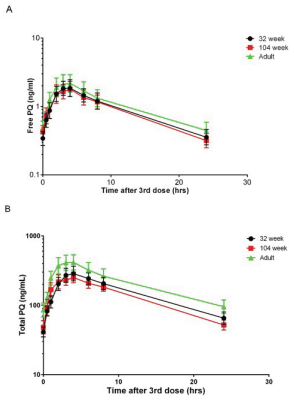

Figure 4. Mean plasma concentration versus time profile for PPQ in children aged 32 weeks (black line), the same children aged 104 weeks (red line), and the adults (green line). Error bars represent 95% confidence interval. Top, unbound PQ; bottom, total PQ

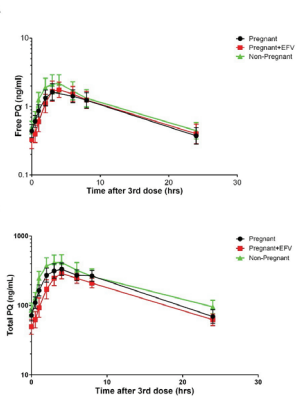

Figure 5. Mean plasma concentration versus time profile for PPQ in HIV-infected pregnant women with concomitant EFV-based ART (red line), HIV-uninfected pregnant women (black line), and postpartum women (green line). Error bars represent 95% confidence interval. Top, unbound PPQ; bottom, total PPQ

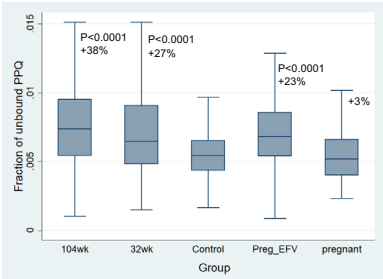

Figure 6. Box plot of fraction of unbound PPQ in children and pregnant women.104wk, children at 104 weeks of age; 32wk, children at 32 weeks of age; control, adult postpartum women. Preg_EFV, HIV infected pregnant women with concomitant efavirenz-based antiretroviral therapy; Pregnant, HIV uninfected pregnant women.

Conclusions

1. Increased fraction of unbound PPQ in children partially compensated for reduction of total PPQ exposure.
2. Increased fraction of unbound PPQ in the context of efavirenz partially compensated for reduction of total PPQ exposure. Data suggest binding site replacement drug-drug interaction.
3. Dose adjustment only based on total PPQ exposure may not be accurate

References

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This work was supported by the National Institutes of Health (R21 AI153848, 4P01HD059454, R01AI117001, and P30AI022763)