Cardiac electrical changes during co-administration of artemether-lumefantrine and atazanavir/ritonavir in HIV-infected Nigerian adults

ABSTRACT

Background: Malaria and HIV infections are both major public health problems in Africa with significant morbidity and mortality. Atazanavir and artemether-lumefantrine are used in the treatment of HIV and Malaria respectively which are co-administered when there is co-infection with both diseases. Both drugs are known to independently cause cardiac electrical abnormalities. In addition, atazanavir inhibits CYP3A4 which is the enzyme that metabolizes lumefantrine with the potential for increased cardiac electrical abnormalities. We, therefore, assessed the cardiac electrical activities during the co-administration of atazanavir and artemether-lumefantrine.

Method: Forty-one consecutive HIV-infected adults attending the Anti-retroviral therapy clinic in a Nigeria General hospital were enrolled on the study using the convenience sampling technique. Study participants had electrocardiographic tracings done before (day 0) and after treatment with artemether/lumefantrine (days 3 and 7)

Result: There was an increase in the mean heart rate from day 1 through day 7 but the mean heart rates were within normal limits. In contrast, there was a progressive decline in the mean PR interval from day 0 through day 7 which was not statistically significant. There was also a significant increase in corrected QT interval (QTc) between day 0 and day 3 and day 0 and day 7. Though the value of the mean QTc on day 3 (414.83±34.88ms) and day 7 (411.41 ± 22.63ms) remained within the normal limit, 5% (2) of the participant had prolonged QTc.

Conclusion: The results of this study suggested that there may be potential drug-drug interaction resulting from the co-administration of atazanavir based antiretroviral drug and artemether-lumefantrine especially in the prolongation of QTc interval

Keywords: Cardiac, co-administration, Atazanavir, Lumefantrine, QTc interval

INTRODUCTION

Malaria and HIV infection are both major public health problems in Africa in general and Nigeria in particular. Most Nigerians are at risk of malaria with about 100 million cases while HIV affects up to 3.4 million people accounting for a prevalence of 3.1%.[1] Both are major causes of morbidity and mortality with both topping the list of causes of death in Nigeria.[2] Studies have shown an increase in the incidence of malaria in people living with HIV/AIDS (PLWHA) especially those with low CD4 count.[3,4] Intercurrent infection with Malaria in PLWHA decreases productivity and quality of life of patients. It may cause anorexia and vomiting and it accounts for missed doses of highly active anti-retroviral therapy (HAART) as well as missed clinic appointments. There is also evidence to suggest a transient rise in viral load in PLWHA with intercurrent malaria infection.[5]

Currently, Nigeria ranks second only to South Africa in the population of HIV positive individuals. Malaria in PLWHA will be common. In an effort to increase cure rates and reduce emergence of resistant micro-organisms for both malaria and HIV, combination therapy has been adopted as the gold standards. (WHO 2001 –Combination Rx for malaria, ----HIV reference)

In view of the foregoing, intercurrent infection with and this comes with a lot of clinical, laboratory and pharmacologic impacts. Indeed

In Nigeria, the recommendations for HAART include two nucleoside reverse transcriptase inhibitors (NRTIs) plus a non-nucleoside reverse transcriptase inhibitor (NNRTI) or a protease inhibitor (PI). Atazanavir/ritonavir (ATV/r) is an oral fixed-dose combination tablet of ATV (a Protease inhibitor) with low dose ritonavir, a pharmacoenhancer that significantly increases atazanavir plasma concentrations by cytochrome P450 3A4 (CYP3A4) inhibition.[6] On the other hand, artemisinin-based combination therapy with a preference for artemether-lumefantrine (AL) and artesunate-amodiaquine (ASAQ) in that order is the recommended treatment for malaria. (FMOH 2005, 2011) Co-administration of atazanavir/ritonavir and artemether/lumefantrine could lead to drug-drug interaction.

Atazanavir is known to cause an atrioventricular block, prolonged QT interval and Torsade de pointe.[7,8] Lumefantrine may also cause prolongation of QT interval. However, Atazanavir is both a substrate and inhibitor of the enzyme CYP3A4 while lumefantrine is a

substrate of the enzyme.[6] It is thus rational to expect that co-administration of the two drugs may increase the serum concentration of lumefantrine and the potential for toxicity.

This study looked at cardiac electrical abnormalities which may result from the drug-drug interaction in HIV positive patients on atazanavir taking artemether/lumefantrine combination.

METHODOLOGY

Study design: This was an interventional prospective study

Study area: The study was carried out at a secondary health care facility; General Hospital Ogbomoso. Ogbomoso is located in Ogbomoso south local government area of Oyo State, Nigeria. Malaria is endemic in southwest Nigeria and the HIV prevalence rate is about 5%.

Study participants: Enrollees were confirmed HIV-infected adult Nigerians taking the ritonavir-boosted Atazanavir (second-line ARV) with medium to high adherence according to the modified Morisky adherence scale.[9] They also had clinical features compatible with malaria and tested +ve for malaria on the rapid diagnostic test (FMOH 2001). Other inclusion criteria were the provision of individual informed consent and living within 10 kilometres radius of the study hospital. Patients were excluded if they were less than 18 years of age, had advanced symptomatic HIV infection, had pre-existing heart disease, hypertension, were taking other drugs with similar effects as lumefantrine or atazanavir that may interfere with the result and those who in the judgement of the investigator will not comply with the study protocol. All the female enrollees either had their last menstrual periods within the preceding two weeks of enrolment or were postmenopausal. They all reported not being pregnant.

Procedure: Referral for treatment for malaria was based on malaria symptoms. Such patients were referred for recruitment in the study. History and examination were carried out with a focus to diagnose malaria in prospective enrollees receiving atazanavir/ritonavir. Axillary temperature was taken in each enrolee using a validated digital thermometer.
Each participant had a complete clinical cardiac status assessment with a view to diagnosing pre-existing cardiac disease. The resting pulse rate was taken over 1 minute after subjects have rested for at least 15 minutes. Systolic and diastolic blood pressures were taken with the appropriate cuff of a standardized Accoson sphygmomanometer after resting for 15 minutes. Korotkoff phase 1 and V were taken as systolic and diastolic blood pressure respectively. The subject was classified hypertensive if the value was ≥140mmHg systolic or the diastolic blood pressure was ≥90mmHg in an adult recorded at more than two occasions separated by at least fifteen minutes interval.[10]Enrollees were weighed using a digital weighing scale and the weights were recorded in kilograms (Kg) while height was recorded in metres (m). The body mass index (BMI) was subsequently calculated using the following formula:

$$BMI = \text{weight (kg)} / [\text{height (m)}]^2$$

Malaria diagnosis was based on the result of First response® Malaria Antigen *P. falciparum*, an HRP2-based RDT as recommended by the National malaria treatment guideline (FMOH 2011). First Response rapid card test used was manufactured by Premier medical corporation limited, Kachugam, Nani Daman, (UT) 396 215. INDIA. Each cassette was appropriately labelled with the enrolee's initials, date and study identification number. The test was carried out aseptically according to the manufacturer's instructions. The result of the malaria RTD was recorded as positive, negative or indeterminate. Only prospective enrollees that tested positive were enrolled.

A resting standard 12-lead electrocardiogram was obtained in accordance with the recommendations of American Heart Association specifications[11] using the Zoncare® Digital three-channel ECG machine 1203Q model. The electrodes were applied appropriately on the precordium and limbs with the use of gel to maintain proper contact between the skin and electrodes. Baseline (D0) ECG was carried out before the initiation of six dose regimen of AL treatment for malaria. Each dose consisted of four tablets of Lumartem®. Lumartem® is manufactured by Cipla Limited, plot 9 & 10, Indore SEZ, Pitampura, M.P.-454 775,India. Each tablet of AL contained 20mg artemether and 80 mg of lumefantrine.

The first dose of AL was administered supervised, adequate instruction was given on the dosage and frequency of dosing of subsequent doses. This was done on scheduled time interval and subjects were supervised with regular phone calls and pre-set phone reminder to ensure compliance with medications. They were also monitored for adverse drug reaction.

There were two follow-up visits on days 3 and 7 during which ECG was also done and the tracings were recorded. A structured questionnaire was administered to evaluate clinical progress and detect any adverse drug reaction that might have occurred. ECG tracings were manually read and interpreted by a cardiologist and a senior resident. Parameters evaluated include heart rate, PR interval, QRS duration, QT interval, atrioventricular and intraventricular blocks and other forms of cardiac arrhythmia. The QT interval was corrected for heart rate using Bazett's formula (QTc= $\frac{QT}{\sqrt{R-R}}$).[12]

Data Analysis

Data was entered and analysed using the Statistical Package for Social Sciences (SPSS) package Version 20.0 - California, Los Angelis. Continous data were presented as mean ±standard deviation and categorical variables were presented as percentages.

Paired T-test was used to assess for significant associations between group means in quantitative variables. Statistical significance was taken as $p < 0.05$, and the confidence level.

RESULTS

The cohort of 71 HIV positive patients taking second line antiretroviral (protease inhibitors) were followed up for six months (between 30th of June 2014 and 26th November 2014)

During this time interval 48 of the 70 who had symptoms compatible with malaria and tested positive for malaria with rapid diagnostic test (RDT) were evaluated for enrolment into the study. Two of the volunteers were excluded. One was hypertensive and another one had abnormal baseline ECG at evaluation (frequent ventricular premature contractions). Only 41 0f the enrolled 46 (89.1%) participants completed the study. Three were lost to follow up before day 7.

The demographics

Of the 41 volunteers that completed the study per protocol, 33 (80.5%) were females while 8 (19.5%) were males. The mean age of the participants is 41.27 years (±10.14). Singles among the participants are 2.4%, 53.7% were currently married to their first spouse, 19.5% separated, while 7.3% remarried. The average monthly income was 12000 Naira. Further details of socio-demographic characteristics are shown in Table 1.

Table 1: Sociodemographic characteristics of the HIV patients on atazanavir based regimen treated for malaria

Variable	Female (n =33)	Male (n = 8)	Total (41)	Percentage
Age (Years)				
≤ 20	0	0	0	0
21 – 30	3	1	4	9.8
31 – 40	16	3	19	46.3
41 – 50	8	3	11	26.8
51 – 60	4	1	5	12.2
> 60	2	0	2	4.9

Mean ± SD	**41.27 ± 10.14**			
Marital status				
Single	1	0	1	2.4
Married	18 +3 = 21	4	25	70.0
Widow/Widower	6	1	7	17.1
Divorced	5	3	8	19.5
				7.3
Educational level				
None	6	2	8	19.5
Primary	11	2	13	31.7
Secondary	15	3	18	41.9
Tertiary	1	1	2	4.9
Income (Naira)				
≤ 10,000	25	3	28	68.3
11,000 – 20,000	5	3	8	19.5
21,000 – 30,000	1	2	3	7.3
➢ 30,000	2	0	2	4.9
Body mass index				
Underweight	3	0	3	7.3
Normal	18	3	21	51.2
Overweight	8	5	13	31.7
Obese	4	0	4	9.8

Clinical parameters

The mean axillary temperature on day 0 was 36.58^{o}C ±0.76 with a range of ----- to ----, X number of participants had fever defined as axillary temperature >37.4^{o}C. There was no significant difference between the mean temperature on day 0 and those of days 2 and 3 which were 36.65^{o}C ± 0.35 and 36.67^{o}C ± 0.26 respectively. However, no case of fever was recorded on days 2 and 3.

The mean baseline pulse rate was 83.07 ± 9.77/min and was not statistically different from that recorded on days 3 and 7 of the study.

Both systolic and diastolic blood pressure remained within the normal limit with no significant change throughout the period.

Table 2: Comparison of some clinical parameters measured before and after artemether-lumefantrine

Variable	Day 0	Day 3	P-value	Day 0	Day 7	P-val	Day 3	Day 7	P-val
PR	83.07 ± 9.77	82.35 ± 13.62	0.581	83.07 ± 9.77	85.78 ± 12.39	0.073	82.35 ± 13.62	85.78 ± 12.39	0.072
SBP	116.04 ± 14.61	117.64 ± 13.29	0.842	116.04 ± 14.61	117.41 ± 14.76	0.926	117.64 ± 13.29	117.41 ± 14.76	0.919
DBP	71.61 ± 10.49	74.70 ± 10.57	0.109	71.61 ± 10.49	72.54 ± 9.80	0.886	74.70 ± 10.57	72.54 ± 9.80	0.133
Temp	36.58 ± 0.76	36.65 ± 0.35	0.581	36.58 ± 0.76	36.67 ± 0.26	0.436	36.65 ± 0.35	36.67 ± 0.26	0.661

PR= Pulse rate Temp= temperature

SBP= Systolic blood pressure DBP= Systolic blood pressure

The cardiac electrical activity in HIV-Infected Nigerian adults taking atazanavir/ritonavir

The electrocardiographic parameters before artemether-lumefantrine use reflects the effect of atazanavir on the electrical activity of the heart. The mean heart rate was 77.17 ± 10.21 which is within normal limit.

Though the mean PR interval was 173.19 ± 26.69 which was within normal limit, about 10% had prolonged PR interval. The mean QTc 398.41 ± 27.73 remained within normal limits. None had QTc more than 470ms at baseline.

The cardiac electrical activity during co-administration of artemether-lumefantrine and atazanavir/ritonavir in HIV-Infected Nigerian adults using electrocardiography

There was a progressive increase in the mean heart rate from day 0 through day 7 but the mean heart rate was within normal limit on all the days though not statistically significant.

In contrast, there was a progressive decline in the mean PR interval from day 0 through the day which was not statistically significant.

There was a statistically significant increase in corrected QT interval (QTc) from day 0 to day 3. Though the value of the mean QTc on day 3 remained within the normal limit, 5% (2) of the participant had prolonged QTc.

There was also an observed increase in QTc on day 7 compared to day one which is also statistically significant. There was however a decrease in QTc from day 4 to day 7 which is not statistically significant (Table 3).

Table 3: comparison of the electrocardiogram parameters on days 0, 3 and 7

Variable	Day 0	Day 3	P-val	Day 0	Day 7	P-val	Day 3	Day 7	P-val
HR	77.17 ± 10.21	79.04 ± 13.07	0.266	77.17 ± 10.21	86.48 ± 45.74	0.214	79.04 ± 13.07	86.48 ± 45.74	0.287
PR	173.17 ± 26.69	170.24 ± 22.85	0.323	173.17 ± 26.69	165.87 ± 33.71	0.100	170.24 ± 22.85	165.87 ± 33.71	0.270
QTc	398.41 ± 27.73	414.83 ± 34.88	<0.001*	398.41 ± 27.73	411.41 ± 22.63	0.008*	414.83 ± 34.88	411.41 ± 22.63	0.478

*=statistically significant

HR = Heart rate, PR = PR interval, QTc = Corrected QT interval

DISCUSSION

As patients with HIV/AIDS now have a longer life expectancy with antiretroviral therapy, the rates of cardiovascular disease (CVD) are increasing. One of the most feared complications of the manifestation of CVD is sudden cardiac death (SCD).[13] Many of the SCDs occur in patients not previously diagnosed with CVD which makes the high index of suspicion essential in people living with HIV/AIDS. One of the substrates for ventricular fibrillation which is a major mechanism of SCD is prolonged QTc.

HIV has many effects on the heart and it has been shown to prolong the corrected QT interval, QTc.[14]Likewise, some of the drugs used in the treatment of HIV have been shown to prolong the QTc. Of the antiretroviral drugs (ARVs), protease inhibitors have been demonstrated to block the HERG and therefore prolong the QTc.[15] Indeed there was an FDA alert over the effects of ritonavir-boosted lopinavir on the heart with warning and precautions regarding QTc interval and PR interval prolongation.[16] Atazanavir which is a new protease inhibitor preferred for its convenient once daily dosing and better side effect profile are not free from this QTc prolongation effect. Indeed cases of Torsades de pointes in patients taking atazanavir have been reported.[7]. This study however shows a QTc within the limit of normal in patients taking ritonavir-boosted atazanavir. The observed value may represent an increase more than that found in HIV negative subjects or ARV naïve HIV positive subjects. The mean PR interval also remain within the normal limit but 5% of the study participants showed prolonged PR interval while ritonavir-boosted atazanavir

The finding of prolonging PR and normal QTc is similar to the findings of Busti *et al.*,2006 [17] who studied twenty-one patient who werewas either newly commenced on atazanavir or switched from another drug to atazanavir. ECG was done at baseline, after 2 hours and a month after to evaluate the steady-state level on the PR interval, QTc and QTd. A minor but statistically significant increase in PR interval was seen which is not clinically significant.

In this current study, the mean duration on atazanavir was 13months with a minimum duration of one month and all had medium to high adherence. This ensures a steady-state evaluation of the effect of the ECG.

The finding in this study is however different from the findings in the study by Gianoti *et al.*, 2007[8] who observed no significant changes in the PR interval and corrected QT interval (QTc) but found a significant increase in the QRS duration and new asymptomatic bundle

branch blocks. There was however no baseline ECG done in patients in this study before the commencement of atazanavir. As documented HIV affects the heart in several ways and this observation could be one of the HIV effects on the electrical activity of the heart.

Also, the effect could have been from the other drugs the patients were taking. All the patients in this study were taking Zidovudine, tenofovir, and emtricitabine in addition to the ritonavir-boosted atazanavir though there is no report of similar effect with these other drugs.

Lumefantrine is an aryl-amino alcohol antimalarial with some structural similarities to halofantrine. It also has physic-chemical characteristics similar to halofantrine by being lipophilic and hydrophobic, with very variable oral bioavailability leading to considerable inter-individual variability in plasma concentrations. However, unlike halofantrine, it proved to have little or no detectable cardiac effects over a wide range of plasma concentrations.[18,19] Studies have shown conflicting results on the effect of artemether-lumefantrine on QTc prolongation. While some studies show no significant increase in the QTc prolongation,[18] others showed a significant increase. There are case reports of artemether-lumefantrine causing other cardiac conduction abnormalities. Bigeminy was associated with artemether-lumefantrine in a 46-year-old man which was corrected after withdrawal of the drug.[20]

Significant increases in serum concentration have been demonstrated in other drugs when co-administered with atazanavir due to inhibition of various enzymes involved in the metabolism of those drugs. Rosiglitazone and elvitegravir's serum concentration were increased due to the inhibition of CYP2C8 and CYP3A4/ UGT1A1 respectively.[21,22] No study has so far been carried out to investigate this effect with artemether or lumefantrine. However, lopinavir/ritonavir was found to increase the serum concentration of lumefantrine.[23,24]

Also, there are case reports of atazanavir causing prolonged QTc interval and Tosardes de points, especially when administered with other drugs like methadone[25,26] or macrolide.[27]

This study found a significant increase in the QTc after a standard six-dose artemether-lumefantrine given over a 3day period in HIV-positive patients taking an atazanavir-based regimen, though this remained well within the limit of the normal QT interval. There is an initial rise on day 3 with a slight decline though not down to the baseline. All values were within the normal reference range. This may represent the effect of the theoretical enhanced serum concentration of lumefantrine due to inhibition of its metabolism by Atazanavir, as well as the synergistic effect of atazanavir and lumefantrine on QTc prolongation. However,

a similar study using lopinavir rather than atazanavir did not find a significant increase in QTc, though this was after a single dose of 80/480mg of artemether-lumefantrine. [28]

CONCLUSION

A high index of suspicion should be maintained in HIV-positive patients taking atazanavir when administering other drugs for treating co-morbidities/opportunistic infections as each of these may pose risk for prolonged QTc interval and fatal ventricular arrhythmia. Especially when co-administering drugs that could alter the metabolism of atazanavir or whose metabolism is altered by atazanavir and drugs that can also affect the electrical activity of the heart.

Ethical Approval:

As per international standard or university standard written ethical approval has been collected and preserved by the author(s).

Consent

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

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