Cardiac safety of dihydroartemisinin-piperaquine and sulfadoxine pyrimethamine among pregnant women with and without asymptomatic parasitaema in Tanzania: results from an open-label, parallel-group, randomised phase II trial

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Abstract

Background:
Dihydroartemisinin-Piperaquine (DP) can induce transient prolongation of the corrected QT interval (QTc) and is a candidate for use with sulfadoxine-pyrimethamine (SP) in intermittent preventive treatment of malaria in pregnancy (IPTp). Pregnancy can alter pharmacokinetics of antimalarial drugs. Acute malaria infection can increase QTc prolongation. Whether DP alters cardiac function in pregnant women with or without asymptomatic parasitaemia is not well characerised.

Methods:
This was an open-label, parallel-group, randomised phase 2 study among pregnant women in Handeni, Tanzania (NCT02909712). Women were screened for *P. falciparum* by microscopy and, if positive, received a rapid diagnostic test (RDT). If RDT-positive, they received DP or SP, and the next microscopy-negative woman was randomly allocated to receive DP or SP. Enrolment and allocation continued in this alternating manner to reach 200 (50/group): Grp 1 (neg; SP), Grp 2 (pos; SP), Grp 3 (neg: DP), Grp 4 (pos: DP). Standard 12-lead ECGs were used to record cardiac function in triplicate. DP groups were measured on day 0 (predose), day 2 (predose and hours 3,4,5,6,7,8), and day 7; SP groups had day 0 (predose), and day 7 ECGs.

Results:
DP resulted in QTcF prolongation that peaked ~30 msec at 5-h post dose 3 on day 2 (schedule: days 0,1,2). The mean maximum increase was slightly more in group 4 compared to group 3 (33.1 vs 29.1 msec). On day 7, QTcF returned to baseline in group 3; a small and non-clinically significant increase of 3.4 (90%CI: 0.3, 6.5) msec was still present among RDT-positive women. QTcB measurements were similar. There was a marked decrease in heart rate (HR) among all DP recipients on day 2, which appeared greater in group 4 compared to group 3 (13.3 vs 8.9 bpm), baseline HR was higher in group 4 than group 3 (92.7 vs 88.5 bpm). This

potentially represents a regression towards the mean. On day 7, HR had returned to baseline in both groups.

Conclusion:
Parasite presence did not alter the effect of DP on the different ECG parameters with the possible exception of HR. No marked differences were observed between pregnant women with and without asymptomatic parasitaemia.

Keywords: intermittent preventive treatment of malaria in pregnancy (IPTp), sulfadoxine-pyrimethamine, dihydroartemisinin-piperaquine, QTC prolongation, cardiac function