



An investigation into the potential cardio toxic interaction of quinine and artemether/lumefantrine (coartem®) when used sequentially in the treatment of Malawian children with severe malaria anaemia

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Objective



- To determine the frequency of QTc prolongation in children receiving Coartem 12 hours after the last dose of parenteral quinine in the management of severe malaria anaemia



Methods (1)



Study sites in Malawi:

- Queen Elizabeth Central Hospital, Blantyre and Chikwawa District Hospital, Chikwawa.

Study design and inclusion criteria

- Open-label study
- Informed consent, aged 4-59 months, microscopic diagnosis of *P. falciparum* malaria and a
- haemoglobin of $<5\text{g/dL}$ on admission



Methods (2)



ECG recordings & readings

- CardioView 3000-cardioViewMITU 4.41®: Speed 50mm/s, sensitivity 20mm/mV.
- Twelve-lead ECGs were recorded at: 0 hours (12 hours after the last quinine dose), 6 hours (6 hours after the 1st dose of Coartem), and 78 hours (6 hours after the last dose of Coartem).
- RR, PR, QRS, QT and QTc intervals were recorded and the corrected QT interval (QTc) was calculated using Bazett's formula ($QTc = QT/\sqrt{RR}$).
- QTcs values at 6 hours and 62 hours were compared against the baseline value (hour 0) using the *paired t-test*
- The dichotomous QTc endpoints included: absolute QTc values of >450 , >480 , and >550 msec QTc, a relative increase of $>25\%$ relative to baseline.



Results (1)



- 132 patients were recruited between May 2005 and April 2007 (68 at Blantyre and 64 at Chikwawa)
- All patients showed *P. falciparum* malaria on enrolment with 10 patients remaining parasitaemic at 0 hour
- The mean haemoglobin at 0 hour was 7.4g/dl, though on admission all patients had $Hb < 5.0g/dl$.



Results (2)

Hour	0 <i>n</i> =132	6 <i>n</i> =132	62 <i>n</i> =123
Mean QTc (SD) <i>Hour 0</i>	438.9 (25.0)	438.9 (25.0)	439.1 (25.2)
Mean QTc (SD) <i>post-Coartem®</i>		433.9 (25.0)	434.8 (23.3)
Mean difference from baseline (95% CI)		-5.0 (-9.1 to -0.8)	-4.3 (-9.6 to 1.0)
<i>Paired t-test</i>		<i>p</i> =0.02	<i>p</i> =0.12
Absolute signal			
QTc in ms			
>500	1/132	1/132	2/123
>480	7/132	5/132	3/123
Relative signal compared to Hour 0			
>25%		0/132	1/123



Discussion & Conclusions



- The mean QTc decreased from 439ms before Coartem, to 434 and 434ms, 6 hours after the first dose and last dose of Coartem (paired t-test $p=0.02$ and $p=0.1$, respectively).
- None of the children had a QTc interval >550 msec. QTc increase $>25\%$ compared to baseline was observed in only 0.8% (1)



Future perspectives



- No ECG changes suggesting clinically relevant cardiotoxic interactions were found when Coartem[®] is given 12 hours after the last dose of parenteral quinine in these children recovering from severe malaria
- This suggests that Coartem[®] maybe safe to administer after quinine