WHO plans for reviewing the cardiotoxicity of antimalarial medicines

Malaria Policy Advisory Committee (MPAC) Meeting
14 - 16 September 2016
Salle A, World Health Organization, Geneva, Switzerland
Presentation Outline

- New indications of antimalarial medicines, e.g. SMC and MDA
- QT prolongation and risk of life-threatening arrhythmias
- The cardiotoxicity of antimalarial medicines
- WHO plans to review of the cardiotoxicity of antimalarials
- List of studies included in the review
- Panel members, participants, observers & secretariat
- Outline Agenda
The objective of MDA in the context of transmission reduction to provide therapeutic concentrations of antimalarial drugs to as large a proportion of the population as possible in order to cure asymptomatic infections, to prevent re-infection during the period of post-treatment prophylaxis and, in some circumstances, to interrupt transmission.

To impact on transmission, MDA requires high coverage of the target population which, in turn, demands a high level of community participation.

Mass drug administration rapidly reduces the prevalence and incidence of malaria in the short term. However, if transmission is not interrupted or importation not prevented, transmission eventually returns to pre-intervention levels, unless the vectorial capacity is reduced and maintained to a very low level.
Based on a recent evidence review, the WHO Malaria Policy Advisory Committee made the following recommendations on the role of MDA:

1. **Use of MDA for the elimination of *P. falciparum* malaria** can be considered in areas approaching interruption of transmission where there is good access to treatment, effective implementation of vector control and surveillance, and a minimal risk of re-introduction of infection.

2. **Use of time-limited MDA** to rapidly reduce malaria morbidity and mortality may be considered for epidemic control as part of the initial response, along with the urgent introduction of other interventions, as well as in complex emergencies, during exceptional circumstances when the health system is overwhelmed and unable to serve the affected communities.
A lengthened QT interval is a biomarker of drug-induced hERG potassium channel block and risk of torsade de pointes (TdP) which can lead to sudden death. The risk is not specific and the relation between QTc prolongation and TdP is not entirely clear. Only some drugs which lengthen the QT interval are associated with life-threatening ventricular tachyarrhythmias and only a small proportion of patients with prolonged QT interval develop them.
Torsade de Pointes (TdP)

- The ECG in torsade de pointes (TdP) shows a polymorphic ventricular tachycardia giving the illusion that the QRS complex twists around the isoelectric baseline. It is haemodynamically unstable causing a sudden drop in arterial blood pressure, leading to dizziness and fainting. Most episodes of TdP revert to normal sinus rhythm within a few seconds, but may also persist and degenerate into ventricular fibrillation, which will lead to sudden death in the absence of prompt medical intervention.
Drug induced QTc prolongation and TdP

- TdP as a drug side effect has been a major reason for withdrawal of medications from the market, in spite of the unclear relations between drug-induced prolongation of the QTc interval and predictors of life-threatening ventricular tachyarrhythmias.

- The US-FDA is investing in a research programme to identify better predictors of drug-induced torsade de pointes, with the aim of superseding the current Thorough QT (TQT) study requirements for registration. This programme is expected to be completed over the next two years, and involves *in vitro* studies, use of detailed ECG recordings in clinical studies with exposure–response analysis, and ECG studies of multichannel block by multiple drugs to identify combined hERG potassium channel and inward calcium or late sodium current block, which may lower TdP risk.
Antimalarials and QTc prolongation

• Several quinoline antimalarial medicines are associated with prolongation of the QT interval, namely chloroquine, quinine, mefloquine and piperaquine (in fixed-dose combination association with dihydroartemisinin), all recommended by WHO for malaria treatment. Quinidine is associated with significant cardiotoxicity and is no longer in use for malaria treatment. Halofantrine induces marked increase in QT prolongation, has been associated with over 30 reports of sudden cardiac death and has never been recommended by WHO for treatment of malaria.

• Studies on the effects of antimalarials on QT interval prolongation may lead to systematic overestimation of drug-induced effects in malaria patients as anxiety, fever and fasting shorten the QT interval – which normalises with recovery. The QT should be corrected for the heart rate, preferably using the Fridericia correction (QTcF), to improve the detection of patients at increased risk of ventricular arrhythmia.
Plans for WHO review of cardiotoxicity

• On advice from WHO/EMP, EMA and US-FDA, the WHO Global Malaria Programme consulted a small group of expert cardiologists and QTologists on a plan a review of the cardiotoxicity of antimalarials.

• The experts recommended that WHO analyse large individual patient data series for documentation of sudden unexplained death following drug exposure. The documentation of torsade de pointes in ECG recordings even in a single death should be taken as strong indicator of the mechanisms of drug-induced death. The analysis should include not only the quinoline antimalarial medicines, but also possible exposure to concomitant medicines which prolong the QTc interval. There was general consensus that search and analysis of drug associated “syncope” was unnecessary as it will be influenced by too many confounders.
Objectives

• Inform the risk assessment for antimalarial cardiotoxicity
• Evaluate the risk of sudden unexplained death following exposure to quinoline antimalarials (Vigibase, WWARN, Pharma)
• Evaluate the dose-response effect and risk factors of QTc prolongation from PK/PD studies of the main ACTs
• Evaluate PK/PD relationships for piperaquine in healthy volunteers compared to malaria patients from comparative clinical trials of dihydroartemisinin-piperaquine and artefenomel-piperaquine
• Identify evidence sources and gaps, and provide recommendations for additional studies to inform risk assessments
### List of studies considered for review

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<tr>
<th>Study Description</th>
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<tr>
<td><strong>Vigibase: analysis of ADR reports</strong></td>
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<td>- analysis of sudden deaths and torsade de pointes with halofantrine</td>
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<td>- analysis of ADR reports of DHA-PQP</td>
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<td>- analysis of unexplained sudden death for antimalarials</td>
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<td><strong>Meta-analysis of sudden deaths in ongoing DP MDA studies</strong></td>
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<td><strong>Safety meta-analysis of repeated DP dosing (LSTM and CDC)</strong></td>
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<td><strong>WWARN pooled analysis of sudden death among infected patients</strong></td>
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<td><strong>INESS PK/PD analysis of multicenter trial data to assess piperaquine – QTc relationship</strong></td>
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<tr>
<td><strong>Cardiabase pooled analysis: WANECAM, OZ439-PQP, DP, ASAQ</strong></td>
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<td><strong>Healthy volunteer study in Thailand (PK/PD analysis)</strong></td>
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<td><strong>DP IPT in infants, schoolchildren and pregnant women in Africa and Asia (UCSF, LSHTM and LSTM)</strong></td>
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<td><strong>Review of cardiotox safety data for individual antimalarials (research, PDP and Pharma)</strong></td>
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<td><strong>Evaluation of QTc effect of Oz439+piperaquine in healthy volunteers and infected patients</strong></td>
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ERG Panel Members

- Karen BARNES
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- Nilima KSHIRSAGAR
- Peter KREMSNER
- Eugène van PUIJENBROEK
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- Philip SAGER
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Participants

- Rita BAIDEN
- Abdoulaye DJIMDE
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- Yasmin KHAN
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- Joel TARNING
- Anja TERLOUW
- Pascal VOIRIOT
- David WESCHE
Observers

Representatives of:
• MMV
• WWARN
• GSK
• Novartis
• Roche
• Sanofi
• Shing Poon
• Sigma Tau

WHO Secretariat
• Pedro Alonso
• Andrea BOSMAN
• Noha IESSA
• Peter OLUMESE
• Shanthi PAL
• Pascal RINGWALD
DAY 1 – Plenary sessions

- Review of Principles of Electrophysiology and Methods for Assessing Cardiotoxicity
- Literature Review of Antimalarial Cardiotoxicity
- Sudden Death in Antimalarial Therapy
  - WHO ICSR database, MDA operations, IPTp-DP, literature review
- Studies on Antimalarial effects on the ECG
  - Halofantrine, Artemether-lumefantrine, Artesunate-amodiaquine, OZ439/Ferroquine, Dihydroartemisinin-piperaquine, artesunate-pyronaridine, artemisinin naphtoquine (?) and arterolane-piperaquine (?)
DAY 2 – Plenary session

- PK/PD Analyses of Antimalarial Effects on the ECG
  - Pooled data from Cardiabase
  - Pooled data from studies shared with ERG
  - DHA-PQP intermittent preventive therapy
  - INESS / MORU healthy volunteer studies
- Planned next studies and reviews
  - WWARN piperaquine pooled data analysis plan

DAY 2 – Closed session for ERG Panel and WHO

- Development of draft recommendations
Discussion