The cardiotoxicity of antimalarials

Report of the WHO Evidence Review Group
Meeting on 13-14 October 2016

Malaria Policy Advisory Committee (MPAC) Meeting
22-24 March 2017, World Health Organization, Geneva, Switzerland
Presentation Outline

• Malaria treatment, preventive therapy and MDA
• WHO plans to review the cardiotoxicity of antimalarials
• List of studies included in the review
• Panel members, participants, observers & secretariat
• Process for review by ERG, MPAC and ASCoMP
• Summary of findings and proposed recommendations
The benefits of antimalarial medicines

Case management

- The clinical objectives of treating uncomplicated malaria are to cure the infection as rapidly as possible and to prevent progression to severe disease. The public health objectives of treatment are to reduce onward transmission of the infection to others and to prevent the emergence and spread of resistance to antimalarial drugs.

Preventive therapy

- The administration of full treatment courses to vulnerable groups to prevent malarial illness by maintaining therapeutic drug levels in the blood throughout the period of greatest risk. Current WHO-recommended malaria preventive therapies are IPTp, IPTi and SMC.

Mass drug administration

- The coordinated administration of full treatment courses to as much of the at-risk population as possible to clear infections from asymptomatic individuals, to reduce onward transmission and to prevent re-infection during periods of post-treatment prophylaxis.
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 reduce malaria morbidity and mortality rapidly 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.
Quinoline antimalarials and structurally-related compounds have long been associated with cardiovascular side effects:

- Exacerbation of malaria-related orthostatic hypotension, e.g., quinine, chloroquine, mefloquine;
- Acute hypotension with rapid parenteral injection, e.g., chloroquine, quinine, quinidine;
- Sinus bradycardia, e.g., mefloquine;
- QRS complex widening, e.g., quinidine, quinine, chloroquine;
- QT interval prolongation, e.g., halofantrine, quinidine, quinine, chloroquine, amodiaquine, piperaquine.
QT prolongation and cardiotoxicity

A prolonged corrected QT interval (QTc) is a sensitive but not specific indicator of increased risk of torsade de pointes (TdP), a polymorphic ventricular tachycardia that can degenerate in some cases to ventricular fibrillation and lead to sudden cardiac death. Drugs which prolong the QT interval are variably associated with life-threatening ventricular tachyarrhythmias in a small proportion of patients.

The QT interval represents the ventricular action potential, i.e. the interval between ventricular depolarization and repolarization. QT prolongation increases vulnerability to premature action potentials during the late phase of repolarization which may trigger torsade de pointes (TdP).
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 QT interval prolongation

Experience with both QT/QTc interval-prolonging medicines and the congenital long QT syndrome suggests:

• A QT/QTc interval >500ms is associated with a higher risk of TdP and sudden cardiac death;

• Among drugs with QT/QTc interval-prolonging potential, antiarrhythmics have been associated with TdP in 1–5% of exposed subjects, while non-cardiovascular drugs have been associated with much lower risk, e.g., one in 100,000 for moxifloxacin;

• TdP degenerates into ventricular fibrillation in ~10% of cases.

• Apart from drug-induced QT interval prolongation, several risk factors decrease the repolarization reserve and facilitate the development of arrhythmias in individual patients.

**Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk.**
Quinoline antimalarials and structurally-related compounds have been associated with cardiovascular side effects. Antimalarial medicines that prolong the QT interval include quinine, chloroquine, amodiaquine, mefloquine, lumefantrine and piperaquine. All are recommended currently by WHO for malaria treatment (alone or in fixed-dose combinations with artemisinin derivatives).

Quinidine is associated with significant cardiotoxicity and is recommended for the treatment of severe malaria with careful clinical and ECG monitoring only if no other antimalarials are available.

Halofantrine induces marked QT interval prolongation, has been associated with over 30 reports of sudden cardiac death and has never been recommended by WHO for treatment of malaria.
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 to plan a review of the cardiotoxicity of antimalarials.

- The experts recommended that WHO analyses 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 also possible exposure to concomitant medicines which prolong the QTc interval. There was consensus not to include drug associated “syncope” to avoid many confounders.

- ERG plans were presented to the WHO Advisory Committee on Safety of Medicinal Products and to the Malaria Policy Advisory Committee.
Objectives

• Inform the risk assessment for antimalarial cardiotoxicity

• Evaluate the risk of sudden unexplained death following exposure to quinoline antimalarials (Vigibase, MDA, WWARN, Pharma)

• Examine PK/PD studies of the main ACTs to evaluate the dose-response effect and risk factors for QTc interval prolongation

• Evaluate comparative clinical trials of dihydroartemisinin-piperaquine and other piperaquine-containing combination antimalarials to characterise PK/PD relationships for piperaquine in healthy volunteers compared to malaria patients

• Identify evidence sources and gaps, and provide recommendations for additional studies to inform risk assessments
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<td>3. Adverse drug reactions associated with <strong>DHA-piperaquine</strong></td>
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### Evidence compiled for ERG (cont’d)

**Evidence**

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<th>Number</th>
<th>Description</th>
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| 6      | Research networks contributing individual patient data | 1. MORU, SMRU, and OUCRU studies on quinine, chloroquine, halofantrine, mefloquine, artemunate-mefloquine, artemether-lumefantrine, and DHA-piperaquine  
2. INESS phase 4 prospective observational study to evaluate safety of DHA-piperaquine in public health facilities in East, West, and Southern Africa  
3. WANECAM phase 3b/4 randomised trial on pyronaridine-artesunate versus DHA-piperaquine versus artemunate-amodiaquine versus artemether-lumefantrine for treatment of repeated episodes of uncomplicated malaria in West Africa |
| 7      | Product Development Partnerships and Regulators clinical trial data and study reports | 1. MMV phase 1 and phase 2b studies on OZ439-piperaquine  
2. DNDi phase 2b studies on artemunate-mefloquine and artemunate-amodiaquine  
3. FDA phase 1 study on halofantrine |
| 8      | Pharmaceutical companies contributing safety reports and individual patient data | 1. Safety database case reports of sudden deaths after halofantrine (GSK)  
2. Safety overview of artemether-lumefantrine based on information from global clinical trials and proprietary safety database reports (Novartis)  
3. Clinical study reports and individual patient data from phase 1 food and phase 4 studies on artemunate-amodiaquine (Sanofi)  
4. Results from phase 1 studies on ferroquine-artesunate and ferroquine-OZ439 (Sanofi)  
5. Electrocardiology safety assessment report of pyronaridine-artesunate based on information from pre-clinical to phase 3b studies (Shin Poong)  
6. Meta-analysis on clinical use of piperaquine (Sigma Tau)  
7. Safety overview of DHA-piperaquine based on information from sponsored clinical trials and proprietary safety database case reports (Sigma Tau)  
8. Pre-clinical study on TdP risk of DHA-piperaquine versus other antimalarial drugs (Sigma Tau)  
9. Clinical study reports and individual patient data from phase 1 food, phase 2, and phase 3 studies of DHA-piperaquine (Sigma Tau) |
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Panel Members
• Karen BARNES
• Josep BRUGADA (Co-chair)
• Xin Hui CHAN (Rapporteur)
• Albertino DAMASCENO
• Milou-Daniel DRICI
• Nilima KSHIRSAGAR
• Peter KREMSNER
• Eugène van PUIJENBROEK
• Nicholas WHITE (Co-chair)

Participants
• Rita BAIDEN
• Pras JAGANNATHAN
• Eva Maria HODEL
• Yasmin KHAN
• Feiko ter KUILE
• Clement NARH
• Issaka SAGARA
• Joel TARNING
• Anja TERLOUW
• Pascal VOIRIOT
• David WESCHE
Observers

Representatives of:
- MMV (Stephan DUPARC)
- Novartis (Cornelis WINNIPS)
- Sanofi (Marie-José CABANIS & Rita MERINO)
- Shing Poon (Robert M. MILLER & Jangsik SHIN)
- Sigma Tau (Marco CORSI & Giovanni VALENTINI)
- Sun Pharma (Victoria BODEA)
- WWARN (Philippe GUERIN)

WHO Secretariat
- Pedro ALONSO
- Andrea BOSMAN
- Noha IESSA
- Piero OLLIARO (partial)
- Peter OLUMESE
- Shanthi PAL
- Pascal RINGWALD (apologies)
- Marian WARSAME (partial)
DAY 1 – Plenary sessions

• Pre-clinical and clinical basis for drug-induced QT prolongation
• Review of Antimalarial Cardiotoxicity
• Sudden Death in Antimalarial Therapy
  • WHO ICSR database, MDA operations, DP repeated doses review, case management review
• Studies of Antimalarial effects on the ECG
  • Halofantrine, Artemether-lumefantrine, Artesunate-amodiaquine, Artesunate-pyronaridine, OZ439/Ferroquine, Dihydroartemisinin-piperaquine
DAY 2 morning – Plenary session

• PK/PD Analyses of Antimalarial Effects on the ECG
  • Pooled data from Cardiabase supported studies
  • Pooled data from studies shared with WHO for ERG review
  • DHA-PPQ intermittent preventive therapy
  • INESS / Sigma Tau & MORU healthy volunteer studies

• Planned next studies and reviews
  • WWARN piperaquine pooled data analysis plan

DAY 2 afternoon – Closed session for ERG Panel and WHO

• Development of draft recommendations
Questions for the ERG panel

1. What is the frequency of sudden death attributable to the cardiotoxicity of different antimalarial medicines?

2. What is the frequency of life-threatening ventricular tachyarrhythmias and torsade de pointes (TdP) after treatment with antimalarials which prolong the QT interval?

3. Which factors increase the frequency of life-threatening ventricular tachyarrhythmias after exposure to antimalarial medicines which induce QT prolongation?

4. Which strategies for malaria treatment (including preventive) can reduce the risk of life-threatening ventricular tachyarrhythmias after exposure to antimalarial medicines which induce QT prolongation?

5. Is the risk of cardiotoxicity after exposure to piperaquine containing medicines higher than that of chloroquine?

6. Is the risk of cardiotoxicity of piperaquine containing medicines higher in healthy volunteers compared to malaria patients?

7. What evidence sources and gaps can be identified, and what additional studies are recommended to inform the risk assessment for antimalarial cardiotoxicity?
Evidence Review Group on the cardiotoxicity of antimalarial medicines
Summary of findings and proposed recommendations
Questions for the ERG panel

1. What is the frequency of sudden death attributable to the cardiotoxicity of different antimalarial medicines?
   - Halofantrine has been associated with >30 sudden deaths attributed to cardiotoxicity, considered an unacceptable risk.
   - Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most extensively studied antimalarial drugs. There have been no sudden deaths attributed to cardiotoxicity following artemether-lumefantrine. One possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported among ~200,000 individuals with close follow-up after treatment - consistent with risk of fatal cardiotoxicity associated with QT/QTc interval-prolonging medicines in current use.
   - Reported deaths following chloroquine and hydroxychloroquine have been associated with overdose or use in chronic indications other than the treatment of malaria.
This analysis suggests that the risk of sudden unexplained death following DHA-piperaquine is one in 193,974 individuals treated in studies with confirmed active follow-up over 3 days from starting drug treatment.
Pharmaceutical company safety databases

The Sigma Tau safety database yielded three cases of possible serious cardiovascular events following DHA-PPQ. These were reviewed by the ERG panel which considered the first case consistent with vasovagal syncope rather than TdP. The second and third cases were thought unlikely to be causally related to the drug in view of limited absorption in the very brief time from drug administration and after repeated vomiting respectively.

<table>
<thead>
<tr>
<th>Period</th>
<th>Halofantrine (Halfan®)</th>
<th>AL (Coartem®/Riamet®)</th>
<th>DHA-PPQ (Eurartesim®)</th>
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<tbody>
<tr>
<td>Sales figures† (doses)</td>
<td>23.2 million^</td>
<td>&gt;840 million</td>
<td>2.8 million</td>
</tr>
<tr>
<td>Sudden unexplained or cardiac deaths</td>
<td>36</td>
<td>0</td>
<td>1</td>
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†Pharmaceutical company sales figures represent a proportion of the total sales of these antimalarials, which are mostly sold as generics (with the exception of halofantrine). ^Halofan® sales figures were available only up until 2012, while global safety database information was available to October 2016; the product was discontinued in April 2016, so it is unlikely that up-to-date sales figures would be much higher than those reported here.

- The Sigma Tau safety database yielded three cases of possible serious cardiovascular events following DHA-PPQ. These were reviewed by the ERG panel which considered the first case consistent with vasovagal syncope rather than TdP. The second and third cases were thought unlikely to be causally related to the drug in view of limited absorption in the very brief time from drug administration and after repeated vomiting respectively.
2. **What is the frequency of life-threatening ventricular tachyarrhythmias and torsade de pointes (TdP) after treatment with antimalarials which prolong the QT interval?**

   - **Halofantrine** has been associated with dose- and concentration-dependent QTc interval prolongation at therapeutic doses in healthy volunteers and malaria patients; it has also been associated with conduction abnormalities, TdP, syncope and sudden death.

   - No episodes of TdP or life-threatening ventricular tachyarrhythmias have been documented following dihydroartemisinin-piperaquine or artemether-lumefantrine.

   - A QT/QTc interval >500ms has been associated with increased risk of TdP and sudden cardiac death. **DHA-piperaquine** has been associated with a QTc interval >500ms in 0.6% of individuals exposed, while **artemether-lumefantrine** has been associated with a QTc interval >500ms in 0.2–0.3% of individuals exposed.
Questions for the ERG panel

3. Which factors increase the frequency of life-threatening ventricular tachyarrhythmias after exposure to antimalarial medicines which induce QT prolongation?

- The general risk factors for TdP should also be considered risk factors for antimalarial medicines that prolong the QT/QTc interval, including:
  
i) concomitant medications that can induce QT/QTc interval prolongation (see [http://crediblemeds.org](http://crediblemeds.org)) or potentiate the effects of QT/QTc interval-prolonging drugs,
  
ii) structural heart disease,
  
iii) genetic defects of cardiac ion channels,
  
iv) electrolyte abnormalities such as hypokalaemia,
  
v) bradycardia
  
vi) hepatic impairment.
4. Which strategies for malaria treatment (including preventive) can reduce the risk of life-threatening ventricular tachyarrhythmias after exposure to antimalarial medicines which induce QT prolongation?

- No data are available to predict the risk of drug-induced TdP and life-threatening tachyarrhythmias in the general population and in specific population subgroups, or to quantify risks for individual antimalarials.
- In individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmia, or who are already taking medicines that can prolong the QT/QTc interval, antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution. If possible, closer monitoring is advised when giving quinine, chloroquine, artesunate-amodiaquine or dihydroartemisinin-piperaquine to such individuals.
Change in QTc induced by antimalarials

HV = healthy volunteers, mal = patients with uncomplicated malaria.
Effects of antimalarials on the ECG

- **Halofantrine** was associated with the greatest QTc interval prolongation of the antimalarial drugs studied.
- **Chloroquine** has been associated with a larger QTc interval prolongation than DHA-PPQ in healthy volunteers.
- **DHA-PPQ** and **ASAQ** have been associated with comparable degrees of QTc interval prolongation in malaria patients, although more data on amodiaquine are needed.
- QTc interval prolongation associated with **DHA-PPQ** has been found to be similar in both malaria patients and healthy subjects.
- **AL** has been associated with smaller QTc interval prolongation than **DHA-PPQ** in malaria patients and in healthy subjects.
- **Pyronaridine-artesunate** was associated with the smallest QTc interval prolongation of the antimalarials studied.
Questions for the ERG panel

5. **Is the risk of cardiotoxicity after exposure to piperaquine containing medicines higher than that of chloroquine?**
   
   • **No.** Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, provides no evidence of a significant difference in the risk of cardiotoxicity following exposure to the currently recommended doses of piperaquine, chloroquine or amodiaquine.

6. **Is the risk of cardiotoxicity of piperaquine containing medicines higher in healthy volunteers compared to malaria patients?**
   
   • **No.** Review of pharmacovigilance and clinical data, along with preliminary results from PK/PD modelling, provides no evidence of a difference in the risk of cardiotoxicity of piperaquine-containing medicines in healthy volunteers compared to malaria patients.
Questions for the ERG panel

7. What evidence sources and gaps can be identified, and what additional studies are recommended to inform the risk assessment for antimalarial cardiotoxicity

- Exploration of alternative dosing strategies to further minimize the cardiotoxicity risk associated with antimalarial medicines, through field trials and PK/PD modelling, including:
  - Age-based dosing in children
  - Weekly drug administration in MDA

- Identification of genetic polymorphisms and other pre-existing conditions that may contribute to the risk of repolarization-related cardiotoxicity, through:
  - Further investigation of individual outliers in antimalarial drug safety studies
  - Further investigation of special risk groups such as malnourished children
  - Pooling data from potential trial participants with a QTc interval >450ms at screening
7. What evidence sources and gaps .... (cont'd)

- Direct comparison of the cardiotoxicity risk of antimalarial drugs in different populations, through:
  - Pooled PK/PD and statistical analyses of individual patient data on QTc interval prolongation
  - Further nested PK/PD studies, especially in populations exposed to MDA
  - Preclinical in vitro and in vivo assays conducted by independent laboratories
  - More evidence is needed with respect to chloroquine, amodiaquine and primaquine.

- Centralization and standardization of the format of reporting adverse events following antimalarial medicines, particularly deaths, in order to improve signal detection for cardiotoxicity, including:
  - Spontaneous reports to international and national pharmacovigilance centres
  - Serious adverse event and loss to follow-up reporting from clinical trials
  - Active pharmacovigilance strategies in populations exposed to MDA

- Harmonization of ECG measurement methodologies in antimalarial cardiotoxicity safety studies.
Conclusions and draft recommendations

1. Apart from halofantrine, antimalarial medicines that prolong the QT/QTc interval, such as quinine, chloroquine, artesunate-amodiaquine and dihydroartemisinin-piperaquine, have been associated with a low risk of cardiotoxicity.

2. Drug-induced QT/QTc interval prolongation is a surrogate indicator for increased risk of drug-induced torsade de pointes (TdP), a potentially lethal polymorphic ventricular tachycardia. Risk factors for drug-induced QT/QTc prolongation include female gender, structural heart disease, genetic defects of cardiac ion channels, electrolyte disturbances, bradycardia, hepatic impairment, and concomitant use of medications that prolong the QT/QTc interval or increase drug levels. Antimalarial medicines that can induce QT/QTc interval prolongation should be used with caution in individuals with known heart disease, a family history of sudden unexplained death consistent with cardiac arrhythmias, or who are already taking medicines that can prolong the QT/QTc interval.
3. Dihydroartemisinin-piperaquine and artemether-lumefantrine have been the most intensively studied antimalarial drugs. No sudden deaths have been attributed to cardiotoxicity following artemether-lumefantrine. However, among ~200 000 treated individuals with close follow-up, one possible sudden cardiac death associated with dihydroartemisinin-piperaquine was reported. This finding is consistent with the risk of fatal cardiotoxicity associated with other QT/QTc-prolonging medicines in current use.

4. Review of pharmacovigilance, clinical and preclinical data, along with preliminary results of PK/PD modelling, reveals no evidence of a significant difference in the risks of cardiotoxicity following exposure to piperaquine, chloroquine or amodiaquine at the current recommended doses. The risks of cardiotoxicity of piperaquine-containing medicines are probably similar for healthy volunteers and malaria patients.
Drug-induced TdP and life-threatening ventricular tachyarrhythmias are very rare events, and there are no simple screening tests to identify people at risk. Further studies are needed to identify genetic polymorphisms and other pre-existing conditions that may contribute to the risk of drug-induced cardiotoxicity. More evidence on the potential cardiotoxicity of chloroquine, amodiaquine and primaquine is needed.