Safety profile of antimalarial medicines

With specific emphasis on the artemisinin derivatives

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Presentation outline

adverse reactions patterns

- Chloroquine, sulfadoxine-pyrimethamine, mefloquine, quinine
  - Amodiaquine
    - Artemisinin derivatives
      - neurotoxicity
      - reprotoxicity
Alternative options to CQ, AQ and SP are at least 10 times more costly

Increasingly complex drug regimens

The gap

Average cost per adult Rx (US$)

SP  CQ  AQ  CQ+SP  AQ+SP  MQ-15  MQ-25  ART+SP  ART+AQ  AM/LUM  ART+MQ-25  Q  Q/D  Q/T
History of synthetic antimalarial drugs

- 1926: pamaquine was discovered (primaquine precursor)
- 1932: mepacrine (quinacrine), acridine compound
- 1936: chloroquine (CQ), structurally related 4-aminoquinoline

> Initially chloroquine was rejected as being too toxic for human use
> The same company (Bayer) then produced 3-methylchloroquine (Sontoquine)
> Only in early 1950s CQ became treatment of choice of malaria throughout the world.
Chloroquine adverse reactions

- Generally well tolerated as antimalarial, but overdose has severe consequences in children
- Overdose can occur with 2-3x daily Rx dose, with rapid intravenous infusion or with intramuscular administration larger than 3.5 mg/kg dose
- Acute intoxication can cause cardiovascular toxicity, which may be fatal - mortality in children is high
- Clinically: hypotension, apnea, seizures, arrhythmias, progressing to cardiac and respiratory arrest
- Hypersensitivity reactions = rashes and pruritus
Chloroquine: organs and systems

- **Cardiovascular**: death recorded with CQ blood concentration of 1 mg/l
- **Nervous system**: neurotoxicity in high doses (vertigo, headache, agitation, confusion, personality changes, depression) - 1:13600
- **Hematological**: leukopenia, agranulocytosis
- **Gastrointestinal**: diarrhoea and vomiting
- **Skin**: pruritus (peak at 24 hrs after intake)
- **Eyes**: retinopathy (reversible only at early stage), rare <250 mg daily dose.
Chloroquine (continued)

- **Second generation effects**: CQ inactivates DNA and crosses the placenta in animals, but no reports of complications to mother or child from CQ treatment during pregnancy

- **Risk factors**: gastric irritation in young children, history of epilepsy, psoriasis

- **Interactions**: antagonistic effect with penicillin, reduced systemic availability of ampicillin, synergistic effect with chlortetracycline
Sulfadoxine-pyrimethamine

- High frequency of adverse effects: hematological, serious skin reactions, polyneuritis, vasculitis, and hepatotoxicity

- Incidence in chemoprophylaxis:
  - all serious reactions = 1:2100 prescriptions (UK);
  - skin reactions = 1:4900 (UK); 1:5000 (US-CDC)
  - death rate = 1:11100 (UK); 1:10000 - 1:25000 (US-CDC)

- Use in prophylaxis discontinued because of severe skin reactions, hepatitis and blood discrasias
SP (continued)

- Hematological: leukopenia, agranulocytosis, thrombocytopenia, megaloblastic anemia
- Liver: from raised serum transaminases to jaundice and granulomatous hepatitis
- Skin: erythema exudativum multiforme, Stevens-Jonson syndrome, toxic epidermal necrolysis, cutaneous vasculitis (within 1st month)
- Risk factors: ipersensitivity to sulfa drugs
- Second-generation effects: Rx of pregnant women without evidence of subsequent abnormalities
Mefloquine adverse reactions

- List of adverse effects grown with experience
- Incidence of adverse effects, same as chloroquine = 40-50%, usually mild
- Most common: nausea, diarrhea, abdominal pain, dizziness, strange dreams, insomnia (dose-dependent)
- Occasional severe neuropsychiatric derangement
- Nervous system: headache, dizziness, vertigo and light-headedness are common (20-90%)
Mefloquine: organs and systems

- Nervous system (continued): neuropsychiatric and neurovegetative reactions at 1:13000 with prophylaxis and 1:215* with therapeutic use - all neuropsychiatric reactions are transient
  - disorientation, hallucinations, agitation, impaired consciousness
  - aggravate and provoke epilepsy

- Second-generation effects: 1 study showed 4x increased risk of stillbirth with MQ Rx in pregnancy

* 1:1000 in Asian, 1:200 in Caucasian or African patients
Quinine adverse reactions

- Overdosage cause marked gastrointestinal intolerance, vertigo, visual disturbances, impaired intracardiac conduction - ingestion of 4-12 g, but a dose of 8 g can be lethal
- Prolonged use leads to « cinchonism » in sensitive individuals: tinnitus, headache, nausea and visual disturbances
- Hypersensitivity reactions: fever, rash and thrombocytopenis purpura
Quinine: organs and systems

- **Cardiovascular**: atroventricular conduction disturbances in most cases due to overdosage
- **Respiratory**: quinine poisoning = respiratory depression
- **Nervous system**: intoxication can be followed by convulsions and coma
- **Endocrine, metabolic**: hypoglycemia due to hyperinsulinaemia
- **Hematological**: thrombocytopenia, acute intravascular hemolysis with renal involvement
Quinine (continued)

- **Eyes**: permanent damage to the retina due to overdosage - principal sign of acute intoxication is sudden onset of bilateral pupil dilatation

- **Ears**: reduction in high-tone auditory acuity

- **Second-generation effects**: quinine crosses placenta, high concentration in the cord blood and is excreted in breast milk - no evidence of teratogenicity after therapeutic use in pregnancy

- **Interactions**: increases action of anticoagulants, not combined with halofantrine because both impair atrio-ventricular conduction
Amodiaquine adverse reactions

- Compared to chloroquine, amodiaquine is more effective and better tolerated for treatment of uncomplicated falciparum malaria.

- Unacceptable incidence of serious toxicity with prophylactic use:
  - all serious reactions = 1:1700;
  - blood disorders = 1:2200;
  - serious hepatic disorders = 1:15650
  - death rate = 1:15500

- GI complaints are common: nausea, vomiting, diarrhea, constipation
Review of amodiaquine safety (I)

The 12th Expert Committee on Selection and Use of Essential Medicines (April 2002) requested more information on safety of AQ treatment in areas of intense malaria transmission.

WHO commissioned a Cochrane systematic review of amodiaquine adverse events. 371 studies reporting adverse were reviewed, including 270 perspective studies. The review concluded that amodiaquine treatment was not associated to increased risk of white cell adverse events, liver toxicity or severe adverse events.
Review of amodiaquine safety (II)

- In addition, WHO analysis of comparative studies with WBC and neutrophil counts included: i) 4 studies comparing amodiaquine treatment to chloroquine and SP; ii) 2 studies comparing amodiaquine to amodiaquine+artesunate; and iii) 1 study comparing SP to artesunate+SP.

- Treatment with chloroquine or SP or amodiaquine (alone or combined with SP or artesunate) is associated with a decline of WBC and neutrophil counts. Power insufficient to detect difference.

- Review by 13th Expert Committee on 1 April 2003.
Artemisinin derivatives

- In animal studies high doses associated with hematopoietic, cardiac and nervous system toxicity (artemether in dogs at 15mg/kg/day for 28 days = serious neurological syndrome).
- No evidence of neurotoxicity in man
- **Cardiovascular:** sinus bradycardia
- **Hematological:** dose-dependent reduction in reticulocyte count
WHO/TDR safety report of artemisinin derivatives for registration of rectal artesunate by US-FDA

- Studies show few side effects of artemisinin derivatives, but this may not illustrate overall incidence of adverse effects in a population.
- Problems of trials: study design to detect adverse effects, and similarity between adverse events and malaria manifestations.
- Common gastrointestinal adverse events. Few cases of reduced reticulocyte counts, anaemia, neutropenia and elevated transaminases (all mild and transient). Low frequency of bradycardia and QT prolongation.
WHO/TDR safety report (continued)

- Limited data on neurological assessments. Four patients had neuropsychiatric adverse events, all spontaneously resolved. Single case report of ataxia and slurred speech in patient receiving oral artesunate for 5 days.
- Nonetheless, this report highlights the importance of continued surveillance and further studies to evaluate the neurotoxic potential of this class of compounds.
WHO current position on the use of artemisinin derivatives in pregnancy

- Animal studies have shown that exposure in early pregnancy can cause death of embryos and morphological abnormalities, while exposure later in pregnancy affects fetal body weight and survival.

- Published data on 607 pregnancies in which artemisinin compounds were given during 2\textsuperscript{nd} or 3\textsuperscript{rd} trimesters show no adverse pregnancy outcomes. Normal outcomes observed in 124 pregnancies exposed in the 1\textsuperscript{st} trimester. Numbers are too small to provide an adequate safety profile of these drugs for malaria treatment in pregnancy.
Artemisinin derivatives in pregnancy

WHO does not recommend artemisinin compounds for treatment of malaria in the 1st trimester, except when considered lifesaving for the mother and other antimalarials are unsuitable. Because of limited safety data, artemisinin compounds should only be used in the 2nd and 3rd trimesters when other treatments are considered unsuitable.

All pregnant women treated with artemisinin compounds should be carefully followed up to document pregnancy outcomes and child development and reported to appropriate authorities.
Conclusions

- Limitations of clinical trials data in sample size, methods for adverse events data collection, assessment and reporting of adverse events, including differentiation of adverse events from expected incidence of disease-related effects.

- Need for pharmacovigilance of artemisinin derivatives (alone or in combination) and of amodiaquine, to evaluate risk of increase in frequency of safety problems with the deployment of these drugs on a large scale.