

Poisoning by anti-malarial drugs

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Poisoning, deliberate or accidental, with drugs used to treat malaria, seems to be uncommon although data is not available from South Sudan. A study in Uganda suggested around 3% of all cases of poisoning admitted to hospital had taken chloroquine: no other anti-malarial drugs were involved [1].

The commonly used drugs used to treat malaria in South Sudan are artemether with lumefantrine (as “Co-artem” or “Riamet”), artesunate and amodiaquine, quinine and occasionally doxycycline. Chloroquine is infrequently used because of parasite resistance but nevertheless will be included in this review.

Chloroquine and Quinine [2]

Chloroquine¹ and quinine will be considered together as there are similarities in their toxic effects. Both drugs are quickly absorbed by the gastrointestinal tract and symptoms of poisoning usually appear within three hours of ingestion.

The clinical features of poisoning include:

- **Drowsiness, convulsions and coma** and
- **Hypotension** and **cardiac dysrhythmias** (especially ventricular tachycardia and fibrillation) leading to cardiac arrest. Ventricular dysrhythmias may be anticipated from changes on the electrocardiogram (ECG): inversion of T-waves, prolongation of QT interval and widening of the QRS.
- **Respiratory failure.**
- **Diplopia** (double vision), blurred vision, narrowing (constriction) of the visual field (“tunnel” vision) and blindness.

The toxic effects on the cardiovascular system tend to be more severe from **chloroquine** than quinine. Toxicity on the eye (**oculotoxicity**) is the major problem from **quinine** poisoning.

The side effects of pharmacological treatment with quinine are common and become exaggerated when the patient has taken a toxic dose:

- **Nausea and vomiting,**
- **Deafness and tinnitus,**

- **Vasodilatation** (flushing sensation more obvious in a pale skin). This may be exacerbated by the vasodilatation caused by the malaria itself and so cause postural (orthostatic) hypotension.
- **Abdominal pain** (especially epigastric) and
- **Visual impairment.**
- **Hypoglycaemia** may result from stimulation of the pancreatic islet beta-cells. This is more common in pregnancy and infants. The risk is reduced by administering the quinine with glucose. However the nursing and medical staff must be aware constantly of the probability of hypoglycaemia.
- **Thrombocytopenia** may result from an immune mechanism associated with quinine but this is rarely of clinical importance. It may also be part of the disseminated intravascular coagulation syndrome.
- **Rashes** and **angio-oedema** have been described. Itching without a rash is a recognised problem affecting a number of Africans.
- **Confusional states** also occur but distinguishing malaria and quinine as the underlying cause is difficult.
- **Blackwater fever** (haemoglobinuria) is a serious complication.
- **Hypokalaemia** is very common with chloroquine poisoning: even though a facility for serum potassium assay is absent the hypokalaemia should be assumed.

The quantity of **chloroquine** ingested is a useful predictor of the likely symptoms and problems to expect [2] (see table 1).

The ingestion of over 5 grams of chloroquine and systolic hypotension (less than 80mmHg) almost always lead to a fatal result².

If the plasma concentration of **quinine** is less than 10mg/L the symptoms are usually mild but if greater than 15mg/L the risk of permanent visual damage and cardiac dysrhythmias is high.

Management of poisoning

The priority is always to stabilise the poisoned patient with attention to the **Airway, Breathing and Circulation.**

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¹ Chloroquine is a 4-aminoquinolone and comes as a number of salts mainly the phosphate and sulphate.

² An electrocardiogram that shows a QRS duration of >0.12 seconds is also a serious prognostic indicator.

Table 1: The quantity of chloroquine ingested and likely symptoms and signs

Dose Ingested (grams)	Severity	Symptoms / signs
<2	Mild	Visual / vomiting
2 - 3.5	Moderate	Vomiting / visual
>3.5 - 4	Severe	Cardiac toxicity / convulsions.

Ideally management should be carried out in an intensive care facility especially if the patient is shocked with hypotension. Adequate **hydration** should be established. **Mechanical ventilation** may be needed with the added support of very **carefully titrated adrenaline** [3] particularly if there is chloroquine poisoning. Adrenaline may increase the risk of cardiac dysrhythmias.

If the ECG shows an intraventricular block then intravenous 250ml 8.4% **sodium bicarbonate** (i.e. 250 mmol) is indicated.

Gastric lavage should be considered if the patient arrives at the medical unit within one hour of ingesting quinine or chloroquine. If possible activated charcoal 50 – 100G should then be given: this dose may need to be repeated every six hours depending on the clinical response.

There is no evidence that **diazepam** is cardiac protective. It is indicated for convulsions.

Hypokalaemia may increase the risk of cardiac dysrhythmias. It might be tempting to give routinely an intravenous infusion of potassium. However during the recovery period severe “rebound” **hyperkalaemia** may develop. Therefore it is probably wise not to give extra potassium unless frequent serum potassium measurements can be made and the results immediately available.

Artemether and Lumefantrine

These are usually used as a fixed-dose combination artemisinin-based combination treatment (each tablet contains 20 mg artemether and 120 mg lumefantrine) (e.g. “Co-artem”, “Riamet”).

Common side effects include cough, anorexia, nausea and vomiting, diarrhoea, palpitations, joint (arthralgia) and muscle pain (myalgia), headache, dizziness, lethargy and insomnia. The problem with many of these symptoms is that they can be caused by the underlying malarial process. There are also a number of rare but more severe adverse reactions: rash (including urticaria), oedema of mouth and lips, dyspnoea and chest tightness, dysphagia, palpitations, fever, severe headaches and muscle weakness.

Reported experience of overdosage with this drug

combination is sparse. The time after ingestion that each component reaches peak plasma concentration is different: for artemether it occurs at about 2 hours and for lumefantrine at about 6-8 hours. So this could have implications for the onset and duration of toxic effects

The cardiac toxic effects are similar to those from chloroquine and in particular the prolonged QT-interval problem which may lead to serious irregular tachycardia. If the patient is likely to have hypokalaemia then the risk of this complication is increased. If there is a history (or family history) of a heart rhythm disorder or heart failure then this combination antimalarial is probably best avoided. The likelihood of toxicity is increased by taking grapefruit juice as this raises the blood level of the drug. Anti-retrovirals may exacerbate the chance of a prolonged QT as will the use of quinine or chloroquine after a course of artemether - lumefantrine. There are many other drugs which may interfere with the effects of this artemether – lumefantrine combination and include amitriptyline, disopyramide, flecainide, procainamide, quinidine, sotalol,azole antifungals (e.g. fluconazole, ketoconazole), cisapride, clomipramine, fluoroquinolone antibiotics (e.g. ciprofloxacin), imipramine and macrolide antibiotics (e.g. clarithromycin) [4]. The effectiveness of hormonal contraceptives and women should be advised to use an alternative method.

Management of poisoning

Given the similar toxic effects, especially the cardiac ones, to chloroquine and quinine the principles of management should be the same. The benefit of gastric lavage is doubtful but the use of activated charcoal should be considered.

Because of the uncertainties of the effects and outcome of poisoning the patient must be observed carefully (pulse rate and rhythm and blood pressure) and for at least six hours after ingestion. If possible the serum potassium should be measured looking for hypokalaemia. It is always wise to exclude hypoglycaemia. An ECG would indicate the development of a prolonged QT interval and the risk of dysrhythmias.

Artesunate and Amodiaquine

This is another artemisinin-based combination treatment (“Coarsucam”). Amodiaquine is a 4-aminoquinolone similar to chloroquine.

Many side effects have been described including weakness, headache, dizziness, anorexia, nausea, vomiting, abdominal pain, diarrhoea and an itchy rash [5].

Artesunate

As with other artemisinins toxic effects are infrequent

[6]. More serious ones rarely noted include neutropenia, anaemia, haemolysis and hepatitis as indicated by raised liver enzymes.

Amodiaquine

There is a significant and potentially serious risk of neutropenia especially in children infected with HIV [7]. In addition cases of hepatitis have been described. For this reason amodiaquine has been discontinued in some countries. However there appears to be little experience of overdosage. Increased muscle tone, involuntary movements, convulsions and syncope have been described. Because of its similarity to chloroquine the expected problems include

- Hypotension and cardiogenic shock.
- Intraventricular conduction problems: the QRS on ECG becomes widened and the QT interval prolonged.
- Ventricular tachycardia and fibrillation.

Management of poisoning

This is as for chloroquine, quinine and the artemether - lumefantrine combination.

Doxycycline

Generally this is a non-toxic drug although nausea, vomiting and hypersensitivity reactions and rashes may occur. In most cases of overdosage specific measures are not required and gastric lavage is unnecessary. In the unlikely event of frequent or prolonged convulsions then treatment should be along conventional lines with oxygen and intravenous diazepam (10-20 mg in adults; 0.1-0.3 mg/kg body weight in children) or lorazepam (4 mg in adults and 0.1 mg/kg in children). The blood sugar should be checked.

Learning points

1. Experience with managing the toxic effects of antimalarial drugs is limited. However they are very widely used and the opportunities for self-poisoning are great.
2. The potential for serious toxic effects exists especially those affecting the cardiovascular system.
3. The availability of cardiac monitoring is widespread and hence clinical observation (pulse

rate and rhythm, blood pressure, respiratory rate) is crucial.

4. All members of the clinical team should know about the “ABC” i.e. Airway, Breathing and Circulation.
5. The bed-side test for blood sugar is a simple measurement and should never be forgotten as a possible cause of a changed conscious level.

References

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Author's comment

During my research for this review I was amazed to discover how little information seems to be available on experience with the toxic effects of the combination drugs (ACT's). This seems to me to be an excellent opportunity for colleagues in South Sudan to record any experience and report to this journal ... this could be an important contribution to medical science and practice.

Acknowledgement

I am grateful for having access to “TOXBASE” (www.toxbase.org) which is a UK “National Poisons Information Service” commissioned by the Health Protection Agency.