

1 **Amodiaquine Hydrochloride -**
2 **Draft revised Poisons Information Monograph for peer review**

3
4
5 PHARMACEUTICALS

6
7 1. NAME

8
9 1.1 Substance

10 Amodiaquine Hydrochloride (INN)

11
12 1.2 Group

13 Antimalarials: 4-aminoquinolines

14
15 1.3 Synonyms

16 Amodiachin Hydrochloride

17 Amodiaquini Hydrochloridum

18
19 1.4 Identification numbers

20
21 1.4.1 CAS number

22 86-42-0

23 6398-98-7 (amodiaquine dihydrochloride, dihydrate)

24 69-44-3 (amodiaquine hydrochloride, anhydrous)

25
26
27 1.4.2 Other numbers

28
29
30 1.5 Brand names,

31 Basoquin

32 CAM-AQ1

33 Camoquin

34 Camoquinal

35 Flavoquin

36 Fluroquine

37 Miaquin

38 SN-10,751

39
40 Formulations containing combinations of amodiaquine and other antimalarial drugs are also
41 available, e.g. Camoprime Infatabs (containing 75 mg amodiaquine + 15 mg primaquine).

42
43 1.6 Manufacturers, Importers

44
45 Basoquin (Parke, Davis, UK)

46 Camoquin (Parke, Davis, Spain, Switzerland, UK)

47 Flavoquin (Roussel, France)

2. SUMMARY

2.1 Main risks and target organs

After oral administration amodiaquine hydrochloride is rapidly absorbed, and undergoes rapid and extensive metabolism to desethylamodiaquine which concentrates in red blood cells. It is likely that desethylamodiaquine, not amodiaquine, is responsible for most of the observed antimalarial activity, and that the toxic effects of amodiaquine after oral administration may in part be due to desethylamodiaquine. Chloroquine, a 4-aminoquinoline derivative which resembles amodiaquine structurally, is widely distributed into the body tissues, especially in liver, spleen, kidney, lungs, brain, and spinal cord. It binds to melanin-containing cells in the eyes and skin. In the blood, chloroquine concentrates in the erythrocytes and binds to platelets and leucocytes. Since the structure and spectrum of activity of these two 4-aminoquinoline derivatives are very similar, it is likely that the distribution of desethylamodiaquine in man mirrors that of chloroquine.

2.2 Summary of clinical effects

Gastrointestinal tract: anorexia, nausea, vomiting, diarrhoea, melanosis.

Haematopoietic system: leucopenia, agranulocytosis, aplastic anaemia, pancytopenia.

Liver: toxic hepatitis.

Skin: lichenoid reaction, urticaria, pigmentation of mucous membranes and skin.

Nervous system & muscles: hallucinations, neuronitis, polymyositis.

Eye: corneal irritation, keratitis, retinitis, retinal degeneration.

Heart: heart block.

The usual signs and symptoms of an overdose are headache, vertigo and vomiting; the more severe manifestations including cardiac arrhythmias, convulsions and coma. The most dramatic feature is visual disturbance, including sudden loss of vision, which is usually transitory. Other symptoms include itching, cardiovascular abnormalities, dyskinesia, neuromuscular and haematological disorders, and hearing loss.

2.3 Diagnosis

Nausea, vomiting, diarrhoea, headache, drowsiness, blurred vision, blindness, convulsions, coma, hypotension, cardiac arrhythmias, cardiac arrest and impaired respiration are the characteristic features of amodiaquine poisoning. Electrocardiography (ECG) may show inverted or flattened T waves, widening of QRS, ventricular tachycardia and fibrillation. Hypokalaemia may be present. High serum amodiaquine levels confirm the diagnosis.

2.4 First aid measures and management principles

Treatment of overdosage is supportive and must be prompt since acute toxicity can progress rapidly, possibly leading to vascular collapse and respiratory and cardiac arrest. Because of the importance of supporting ventilation, early endotracheal intubation and mechanical ventilation may be necessary.

Early gastric lavage followed by administration of activated charcoal may provide some benefit in reducing absorption of the drug. These should be preceded by measures to correct cardiac and severe cardiovascular disturbances, if present, and by respiratory support.

1 Diazepam IV may control seizures and other manifestations of CNS stimulation. Seizures
2 caused by anoxia should be corrected by oxygen and other respiratory support.

3
4 Defibrillators and cardiac pacemakers may be required.

7 3. PHYSICO-CHEMICAL PROPERTIES

9 3.1 Origin of the substance

10 Synthesized from 4,7-dichloroquinoline and 4-acetamido-diethylamino-o-cresol. Alternative
11 synthesis from 2-aminomethyl-p-aminophenol and 4,7-dichloroquinoline (The Merck Index,
12 1983). US patents 2,474,819 : 2,474,821 (1949 to Parke, Davis)

14 3.2 Chemical structure

15 Aminodiaquine Hydrochloride is 4-[(7-chloro-4-quinoly)amino]- 2-[(diethylamino)methyl]
16 phenol dihydrochloride dihydrate.

17
18 Structural formula: $C_{20}H_{22}ClN_3O \cdot 2HCl \cdot 2H_2O$ _
19 STRUCTURAL FORMULA;pim030.gif

20
21 Molecular weight: 464.8

23 3.3 Physical properties

25 3.3.1 Properties of the substance

26 A yellow crystalline powder, odourless (or almost odourless) with a bitter taste.

27
28 Soluble 1 in 22 parts water 1 in 70 parts ethanol (96%) Practically insoluble in benzene,
29 chloroform and ether.

30
31 A 2% solution in water has a pH of 2.6 - 4.6. pH of 1% aqueous solution : 4.0 to 4.8
32 (Merck, 1989)

33
34 Decomposition: 150-160 °C 3.3.2

35
36 Properties of the locally available formulation: To be added by the Poison Control Centre.

38 3.4 Other characteristics

40 3.4.1 Shelf-life of the substance

41 No data available.

43 3.4.2 Shelf-life of the locally available formulation

44 To be added by the Poison Control Centre.

46 3.4.3 Storage conditions

47 Store in an air-tight container, in child-resistant packaging out of the reach of children.

49 3.4.4 Bioavailability

50 To be added by the Poison Control Centre.

52 3.4.5 Specific properties and composition

53 To be added by the Poison Control Centre.

4. USES

4.1 Indications

For the treatment of *P. vivax*, *P. ovale* and *P. malariae* infections (WHO 2007). It is at least as effective as chloroquine, and is effective against some chloroquine-resistant strains, although resistance to amodiaquine has been reported (Sweetman, 2005). It can be used for the treatment of uncomplicated *P. falciparum* infection, but cross-resistance with chloroquine exists in some areas. It should preferably be used as part of combination therapy with other antimalarials, for example artesunate (WHO 2004).

Amodiaquine hydrochloride has been tried in the treatment of giardiasis and hepatic amoebiasis. It has also been tried, with variable success, in the treatment of lepra reactions, lupus erythematosus, rheumatoid arthritis, and urticaria.

4.2 Therapeutic dosage

4.2.1 Adults

Amodiaquine is given as the hydrochloride, but doses are expressed in terms of amodiaquine base. Amodiaquine hydrochloride 260 mg is approximately equivalent to 200 mg of amodiaquine base (Sweetman 2005).

For the treatment of uncomplicated falciparum malaria, in terms of amodiaquine base: initially 7.5 mg/kg twice daily for 1 day then 5 mg/kg twice daily for 2 days; total dose, 35 mg/kg over 3 days (WHO 2004).

4.2.2 Children

Amodiaquine is given as the hydrochloride, but doses are expressed in terms of amodiaquine base. Amodiaquine hydrochloride 260 mg is approximately equivalent to 200 mg of amodiaquine base (Sweetman 2005).

For children over 20 kg body weight, in terms of amodiaquine base: initially 7.5 mg/kg twice daily for 1 day then 5 mg/kg twice daily for 2 days; total dose, 35 mg/kg over 3 days (WHO 2004).

Because of the narrow margin between the therapeutic and toxic concentrations in children, amodiaquine should not be administered parenterally in this age group (AHFS, 1988) (see section 7.2.1.2).

4.3 Contraindications

The US Center for Disease Control (CDC) has stated that any possible prophylactic advantage that amodiaquine may afford is not justified by the possible risk of agranulocytosis associated with the use of the drug (CDC, 1985). The manufacturer of Camoquin (Parke-Davis) has advised in a data sheet to health professionals that the prophylactic use of amodiaquine as a first line agent has been restricted to chloroquine-resistant areas (Neffel et al., 1986). They have also stated that agranulocytosis has occurred in association with the use of amodiaquine in malaria prophylaxis. Although agranulocytosis has been reported following the sole use of amodiaquine, most cases have occurred when other anti-malarials have been taken concurrently. Therefore, the prescribing physician should assess the advantages and disadvantages of amodiaquine in malaria prophylaxis but if the decision is

1 made to so prescribe the drug, concomitant use with other anti-malarials should be
2 performed to assure that blood values and liver function tests remain within normal limits.

3
4 Because amodiaquine may concentrate in the liver, the drug should be used with caution in
5 patients with hepatic disease or alcoholism, and in patients receiving hepatotoxic drugs.
6 Children are especially sensitive to 4-aminoquinoline derivatives (see Section 7.2.1.2).

7
8 Because of the narrow margin between the therapeutic and toxic concentrations in children,
9 amodiaquine should not be administered parenterally in this age group (AHFS, 1988).

10
11 Amodiaquine is contraindicated in patients who are hypersensitive

12 13 14 5. ROUTES OF ENTRY

15 16 5.1 Oral

17 This is the usual route of administration for therapeutic use.

18 19 5.2 Inhalation

20 Unknown.

21 22 5.3 Dermal

23 Unknown.

24 25 5.4 Eye

26 Unknown.

27 28 5.5 Parenteral

29 Amodiaquine has been given by both constant rate intravenous injection and constant rate
30 infusion in volunteers and patients (White et al., 1987). Because of the narrow margin
31 between the therapeutic and toxic concentrations in children, amodiaquine should not be
32 administered parenterally in this age group (AHFS, 1988).

33 34 5.6 Other

35 Unknown.

36 37 38 6. KINETICS

39 40 6.1 Absorption by route of exposure

41 Oral

42 After oral administration amodiaquine hydrochloride is rapidly absorbed, and undergoes
43 rapid and extensive metabolism to desethylamodiaquine which concentrates in blood cells. It
44 is likely that desethylamodiaquine, not amodiaquine, is responsible for most of the observed
45 antimalarial activity, and that the toxic effects of amodiaquine after oral administration may
46 in part be due to desethylamodiaquine (Winstanley et al., 1987).

47 48 6.2 Distribution by route of exposure

49 Oral

50 After oral administration of amodiaquine (600 mg) to 7 healthy adult males, amodiaquine
51 underwent rapid conversion to desethylamodiaquine. The peak concentration of
52 amodiaquine was 32 ± 3 ng/ml at 0.5 ± 0.03 h. The peak concentrations of amodiaquine in
53 whole blood and packed cells were 60 ± 10 and 42 ± 6 ng/ml respectively, reached at $0.5 \pm$
54 0.1 h in both. Thereafter the concentration of amodiaquine declined rapidly, and was

1 detectable for no more than 8 h. Mean peak plasma concentration of the metabolite
2 (desethylamodiaquine) was 181 ± 26 ng/ml respectively. Times to peak for whole blood and
3 packed cells were 2.2 ± 0.5 and 3.6 ± 1.1 h respectively (Winstanley et al., 1987).

4
5 After oral administration of amodiaquine (306.2 mg) to 8 volunteers the pharmacokinetics of
6 amodiaquine and its metabolites, mono and bis-desethylamodiaquine were studied.
7 Amodiaquine disappeared rapidly from the plasma and blood, whereas monoamodiaquine
8 appeared rapidly as a hepatic first pass effect. Amodiaquine was little excreted in urine and
9 bis-desethyl amodiaquine formation from monoamodiaquine was low. Blood
10 monoamodiaquine concentrations were higher than plasma levels, with a
11 monoamodiaquine/amodiaquine concentration ratio of 5 to 10. This mirrored strong uptake of
12 monoamodiaquine by white blood cells (Laurent et al 1993)

13
14 The mean distribution volume is about 20 to 40 l/kg with a marked interindividual variability.

15
16 Although in use for more than 40 years, there exists little information regarding the disposition
17 of amodiaquine in man. Chloroquine, a 4-aminoquinoline derivative which resembles
18 amodiaquine structurally, is widely distributed into the body tissues, especially in liver, spleen,
19 kidney, lungs, brain, and spinal cord. It binds to melanin-containing cells in the eyes and
20 skin. In the blood, chloroquine concentrates in the erythrocytes and binds to platelets and
21 leucocytes. Since the structure and spectrum of activity of these two 4-aminoquinoline
22 derivatives are very similar, it is likely that the distribution of desethylamodiaquine (the major
23 active metabolite of amodiaquine) in man mirrors that of chloroquine.

24 25 Parenteral

26 The distribution half times observed after intravenous injection (3 mg base per kg over 10
27 minutes) to seven healthy adult male volunteers (geometric mean 1.7; range 0.4 to 55
28 minutes) were significantly faster than those observed after intravenous infusion (10 mg base
29 per kg over 4 hours) to 10 adult patients with falciparum malaria (geometric mean 22.2;
30 range 5 to 126 minutes). The plasma concentration time profiles were biphasic.

31
32 After bolus injection the apparent volume of the central compartment (1.1; range 0.3 to 3.6
33 l/kg) was one-quarter of that estimated after the infusion (4.6; range 0.5 to 29.3 l/kg). The
34 authors of the study suggested that there was probably an additional distribution phase in the
35 malaria patients obscured by the slower rate of infusion: it was possible that had the
36 volunteers been able to tolerate a larger dose, a triphasic elimination profile may have
37 become apparent (White et al., 1987).

38 39 6.3 Biological half-life by route of exposure

40 Oral

41 Amodiaquine 600 mg was given by mouth (see section 6.2), the apparent terminal half-life of
42 amodiaquine was 5.2 ± 1.7 (range 0.4 to 5.5) minutes and the geometric mean of the
43 estimated elimination phase half-lives was 2.1 (range 0.5 to 5.7) hours (White et al., 1987).

44 45 6.4 Metabolism

46 Amodiaquine is metabolized via desethylation, oxidation and glucuronoconjugation. Hepatic
47 first-pass metabolism in the liver is high. The main metabolic pathway of amodiaquine leading
48 to N-desethylamodiaquine is via cytochrome CYP 2C8 isoenzyme (Parikh et al 2007).

49
50 When amodiaquine is given orally relatively little of the parent compound is present in the
51 blood. Hepatic biotransformation to desethylamodiaquine (the principal biologically active
52 metabolite) is the predominant route of amodiaquine clearance with such a considerable first
53 pass effect that very little orally administered amodiaquine escapes untransformed into the
54 systemic circulation (Winstanley et al., 1987).

6.5 Elimination by route of exposure

Amodiaquine is eliminated principally by biotransformation. Approximately 2 % is eliminated unchanged in urine. The mean elimination half life of amodiaquine after intravenous administration is about 5 hours (range 1 -12 hours). N-des-ethylamodiaquine is slowly eliminated with a terminal $t_{1/2}$ of 1-18 days, with high interindividual variability.

Amodiaquine and desethylamodiaquine have been detected in the urine several months after administration (Winstanley et al., 1987).

7. PHARMACOLOGY AND TOXICOLOGY

7.1 Mode of action

7.1.1 Toxicodynamics

Amodiaquine, a 4-aminoquinoline similar to chloroquine in structure and activity, has been used as both an antimalarial and an anti-inflammatory agent for more than 40 years. The mode of action of amodiaquine has not yet been determined. 4-Aminoquinolines depress cardiac muscle, impair cardiac conductivity, and produce vasodilatation with resultant hypotension; they depress respiration and cause diplopia, dizziness and nausea.

7.1.2 Pharmacodynamics

In general, 4-aminoquinoline derivatives appear to bind to nucleoproteins and inhibit DNA and RNA polymerase. High drug concentrations are found in the malaria parasite's digestive vacuoles (AFHS, 1988). After oral administration amodiaquine hydrochloride is rapidly absorbed, and undergoes rapid and extensive metabolism to desethylamodiaquine which concentrates in blood cells. It is likely that desethylamodiaquine, not amodiaquine, is responsible for most of the observed anti-malarial activity, and that the toxic effects of amodiaquine after oral administration may, in part, be due to desethylamodiaquine (Winstanley et al., 1987).

7.2 Toxicity

7.2.1 Human data

7.2.1.1 Adults

It is likely that the fatal dose for amodiaquine would be similar to that of chloroquine phosphate (2 to 3 g, adult) (Ellenhorn and Barceloux, 1988) since amodiaquine appears to completely parallel the adverse effects of those seen with chloroquine when equivalent doses are used.

Oral doses of 34 mg/kg over a 6 week period in a male, and 160 mg/kg over a 14 week period in a female caused agranulocytosis (RTECS 1985-86).

Three patients suffered from fulminant hepatitis within 23, 59 and 22 weeks after having ingested a total dose of 16, 26 and 15 g, respectively, of amodiaquine for the prophylaxis of malaria (Bernuau et al 1988),

7.2.1.2 Children

Children are especially sensitive to 4- aminoquinoline derivatives; fatalities have been reported following accidental ingestion of relatively small doses of chloroquine (a 4-aminoquinoline derivative similar in structure and activity to amodiaquine). The toxic

1 dose range for oral chloroquine phosphate in children is 0.75 to 1 g (Ellenhorn &
2 Barceloux, 1988). Severe reactions and fatalities have also occurred in children
3 following parenteral administration of chloroquine (AFHS, 1988) (see section 4.2.2).
4

5 7.2.2 Relevant animal data

6 No data on the toxicity of amodiaquine after repeated oral administration to animals are
7 available. Single dose toxicity studies showed: LD50 (mouse, intraperitoneal) 225 mg/kg
8 LD50 (mouse, oral) 550 mg/kg LDLo (mouse, intraperitoneal) 137 mg/kg (as
9 dihydrochloride; no toxic effect noted) (RTECS, 1985-1986).
10

11 7.2.3 Relevant in vitro data

12 No data available.
13

14 7.3 Carcinogenicity

15 No data available.
16

17 7.4 Teratogenicity

18 Although no data are available for amodiaquine, chloroquine, a structurally similar 4-
19 aminoquinoline with the same spectrum of activity and similar adverse reaction profile, is
20 known to cross the placental barrier. A woman during four of her eight pregnancies was
21 given chloroquine (250 mg daily from the sixth week after conception); two of these children
22 were congenitally deaf with instability of gait. One child had chorioretinitis of the type
23 associated with chloroquine toxicity in the adult. A third exposed child had hemihypertrophy
24 and developed a Wilm's tumour (Shepard, 1986).
25

26
27 A 1985 report summarized the results of 169 infants exposed in utero to 300 mg of
28 chloroquine base once weekly throughout pregnancy. The control group consisted of 454
29 non-exposed infants. Two infants (1.2%) in the study group had anomalies (tetralogy of
30 Fallot and congenital hypothyroidism) compared to four control infants who had defects
31 (0.9%). Based on these data the authors concluded that chloroquine does not have a
32 strong teratogenic effect, but a small increase in birth defects could not be excluded (Wolfe &
33 Cordero, 1985).
34

35 It is generally believed that the benefits of chloroquine therapy in pregnant women exposed
36 to malaria outweigh the potential risks of the drug to the foetus. Chloroquine does not
37 appear to be excreted in appreciable amounts in the breast milk (Anderson, 1977).
38

39 7.5 Mutagenicity

40 In vitro (Ames test) and in vivo tests (sister chromatid exchange and chromosome aberration
41 tests) showed that amodiaquine, like chloroquine, is slightly mutagenic (Chatterjee et al
42 1998).
43

44 7.6 Interactions

45 Since magnesium trisilicate and kaolin are known to decrease the gastrointestinal absorption
46 of chloroquine when administered simultaneously, it is likely that this also follows for
47 amodiaquine (Ellenhorn & Barceloux, 1988). Concomitant administration of chloroquine at
48 recommended doses for malaria suppression of chemoprophylaxis during pre-exposure
49 prophylaxis of rabies with intra-dermally administered rabies vaccine may interfere with the
50 antibody response to the vaccine. However, the clinical significance of this interaction
51 remains to be clearly established but should be considered and may have relevance in the
52 case of amodiaquine (AHFS, 1988).
53
54

1
2 **7.7 Main adverse effects**

3 Oral administration of a single dose of amodiaquine may be followed by abdominal
4 discomfort, nausea, vomiting, headache, dizziness, blurring of vision, mental and physical
5 weakness, and fatigue. These symptoms are usually mild and transient.

6 More severe adverse reactions include blood disorders including leukopenia and
7 agranulocytosis, hepatitis, visual disturbances (retinopathy associated with long-term, high-
8 dose therapy); rarely rash, pruritus, skin pigmentation, neuromyopathy (WHO 2004).

9 The incidence of severe adverse reactions is estimated to be between 1 in 1000 and 1 in
10 5000 (Sweetman 2005).

11
12
13
14 **8. TOXICOLOGICAL ANALYSES AND BIOMEDICAL INVESTIGATIONS**

15
16 **8.1 Material sampling plan**

17
18 **8.1.1 Sampling and specimen collection**

19
20 8.1.1.1 Toxicological analyses

21 8.1.1.2 Biomedical analyses

22 8.1.1.3 Arterial blood gas analysis

23 8.1.1.4 Haematological analyses

24 8.1.1.5 Other (unspecified) analyses

25
26 **8.1.2 Storage of laboratory samples and specimens**

27
28 8.1.2.1 Toxicological analyses

29 8.1.2.2 Biomedical analyses

30 8.1.2.3 Arterial blood gas analysis

31 8.1.2.4 Haematological analyses

32 8.1.2.5 Other (unspecified) analyses

33
34 **8.1.3 Transport of laboratory samples and specimens**

35 8.1.3.1 Toxicological analyses

36 8.1.3.2 Biomedical analyses

37 8.1.3.3 Arterial blood gas analysis

38 8.1.3.4 Haematological analyses

39 8.1.3.5 Other (unspecified) analyses

40
41 **8.2 Toxicological Analyses and Their Interpretation**

42 8.2.1 Tests on toxic ingredient(s) of material

43 8.2.1.1 Simple Qualitative Test(s)

44 8.2.1.2 Advanced Qualitative Confirmation Test(s)

45 8.2.1.3 Simple Quantitative Method(s)

46 8.2.1.4 Advanced Quantitative Method(s)

47
48 8.2.2 Tests for biological specimens

49 8.2.2.1 Simple Qualitative Test(s)

50 8.2.2.2 Advanced Qualitative Confirmation Test(s)

51 8.2.2.3 Simple Quantitative Method(s)

52 8.2.2.4 Advanced Quantitative Method(s)

53 8.2.2.5 Other Dedicated Method(s)

1	8.2.3 Interpretation of toxicological analyses
2	
3	8.3 Biomedical investigations and their interpretation
4	
5	8.3.1 Biochemical analysis
6	
7	8.3.1.1 Blood, plasma or serum
8	8.3.1.2 Urine
9	8.3.1.3 Other fluids
10	
11	8.3.2 Arterial blood gas analyses
12	8.3.3 Haematological analyses
13	8.3.4 Interpretation of biomedical investigations
14	
15	8.4 Other biomedical (diagnostic) investigations and their interpretation
16	
17	8.5 Overall Interpretation of all toxicological analyses and toxicological investigations
18	
19	8.6 References
20	
21	
22	9. CLINICAL EFFECTS
23	
24	9.1 Acute poisoning
25	9.1.1 Ingestion
26	Amodiaquine (a 4-aminoquinoline derivative), exhibits symptoms of overdose typical of
27	the 4-aminoquinoline class of anti-malarial drugs. Symptoms include headache,
28	drowsiness, visual disturbances, vomiting, hypokalaemia, cardiovascular collapse and
29	cardiac and respiratory arrest. Hypotension, if not treated, may progress rapidly to shock.
30	Electrocardiograms (ECG) may reveal atrial standstill, nodal rhythm, prolonged
31	intraventricular conduction time, broadening of the QRS complex, and progressive
32	bradycardia leading to ventricular fibrillation and/or arrest (AFHS, 1988).
33	
34	9.1.2 Inhalation
35	No data available.
36	
37	9.1.3 Skin exposure
38	No data available.
39	
40	9.1.4 Eye contact
41	No data available.
42	
43	9.1.5 Parenteral exposure
44	See section 9.1.1 (oral exposure). Cardiovascular effects may be more commonly
45	observed.
46	
47	9.1.6 Other
48	No data available.
49	
50	9.2 Chronic poisoning
51	
52	9.2.1 Ingestion

1 The more severe adverse reactions include blood disorders including leukopenia and
2 agranulocytosis, hepatitis, visual disturbances (retinopathy associated with long-term, high-
3 dose therapy); rarely rash, pruritus, skin pigmentation, neuromyopathy (WHO 2004).

4 9.2.2 Inhalation

5 No data available.

6 9.2.3 Skin exposure

7 No data available.

8 9.2.4 Eye contact

9 No data available.

10 9.2.5 Parenteral exposure

11 See section 9.2.1 (oral exposure). Cardiovascular effects may be more commonly
12 observed.

13 9.2.6 Other

14 No data available.

15 9.3 Course, prognosis, cause of death

16 Because the 4-aminoquinoline derivatives are rapidly and completely absorbed from the GI
17 tract, symptoms of acute toxicity may occur within 30 minutes following ingestion of the drug.
18 Death has occurred within two hours following vascular collapse and respiratory and cardiac
19 arrest. Children are especially sensitive to 4-aminoquinoline derivatives; however, reports of
20 suicides have indicated that the margin of safety in adults is also small.

21 Without prompt effective therapy, acute ingestion of 5 g or more of chloroquine in adults has
22 usually been fatal, although death has occurred with smaller doses. Fatalities have been
23 reported following ingestion of relatively small doses of chloroquine (e.g., 750 mg or 1 g of
24 chloroquine phosphate in a three-year-old child).

25 9.4 Systematic description of clinical effects

26 9.4.1 Cardiovascular

27 Chronic

28 T-wave changes and prolongation of the QT-interval are not uncommon during high-dose
29 treatment with 4- aminoquinoline congeners. These are probably not significant in
30 themselves (Tester-Dalderup, 1984).

31 A slight prolongation of PR, QRS, and QTc was noted in one study but these changes
32 were considered clinically insignificant. They did not correlate with plasma concentrations
33 of either amodiaquine or desethylamodiaquine (the major metabolite), and it is thought they
34 might have been related to disease rather than amodiaquine (White 2007)

35 Acute on chronic

36 Acute intoxication with chloroquine, a 4-aminoquinoline congener structurally similar to
37 amodiaquine, is associated with cardiac arrest. Complete heart block was observed in a
38 Nigerian male treated with high doses for about two years. First degree right bundle-
39 branch block was recorded in another male who had taken 8 to 10 tablets of 250 mg
40 chloroquine weekly for about three years; sudden death was attributed to a Stoke-Adams
41 attack.

1 Focal convulsions followed by irregular heart action and cardiac arrest were reported
2 during the iv administration of 250 mg chloroquine over a five-minute period. Acute
3 overdosing is reputed to be particularly dangerous if the drug is given intravenously or if
4 taken by young children (Tester-Dalderup, 1984). Sudden hypotension may occur, with
5 absence of peripheral pulses, vasodilatation, cyanosis of the lips and face, arrhythmias
6 and cardiac arrest often seen early. The ECG may reflect bradycardia, atrial standstill, a
7 widened QRS, prolonged intraventricular conduction time, inverted or flattened T waves,
8 S-T segment depression, ventricular tachycardia, and nodal rhythm, prolongation of QT
9 interval, complete heart block, ventricular fibrillation, and cardiac arrest (Ellenhorn &
10 Barceloux, 1988).

11 12 13 14 9.4.2 Respiratory

15 Acute

16 Rapid superficial breathing, Cheyne-Stokes breathing, sudden apnoea, respiratory failure,
17 or, terminally, respiratory arrest may be observed (Ellenhorn & Barceloux, 1988).

18 19 9.4.3 Neurological

20 21 9.4.3.1 CNS

22 Chronic

23 Four patients experienced involuntary movements, usually with speech difficulty after
24 large, but not excessive, doses of amodiaquine (Akindele & Odejide, 1976). Lethargy
25 and drowsiness have been reported as early side effects following therapeutic doses
26 (Glickman, 1959). Additional neurological effects following other 4-aminoquinoline
27 derivatives have been described. These may occur with amodiaquine therapy but have
28 not been reported.

29
30 A range of mental changes attributed to the use of chloroquine has been described
31 namely agitation, aggressiveness, confusion, personality changes, psychotic symptoms
32 and depressions (Tester- Dalderup, 1984).

33 34 Acute

35 Abnormal involuntary movements similar to those that occur in Parkinsonism have been
36 reported in some patients treated with amodiaquine. The movements mainly affected
37 the tongue and the facial muscles. In some patients the limbs were affected with
38 tremor and ataxia. The symptoms usually started within 24 hours of taking the drug.
39 Left untreated, the disturbance remitted spontaneously with 48 hours, but it could be
40 terminated within two hours by giving anticholinergic drugs like benzhexol and
41 benztropine (Salako, 1984).

42 43 9.4.3.2 Peripheral nervous system

44 Chronic

45 Peripheral neuritis has also been described in association with chloroquine (Tester-
46 Dalderup, 1984).

47 48 9.4.3.3 Autonomic nervous system

49 No data available.

50 51 9.4.3.4 Skeletal and smooth muscle

52 Chronic

53 Neuromyopathy, and myopathy have also been described in association with
54 chloroquine (Tester-Dalderup, 1984).

1
2
3
4
5 9.4.4 Gastrointestinal

6 Chronic

7 Nausea, vomiting and diarrhoea have been reported (Glickman et al., 1959). 9.4.5
8 Hepatic Chronic Hepatitis developed in seven patients taking amodiaquine for malaria
9 prophylaxis for 4 to 15 weeks. Liver dysfunction recurred in two patients when
10 amodiaquine was administered subsequently (Larrey et al., 1986) (see section 9.4.11).

11
12 9.4.6 Urinary

13 9.4.6.1 Renal

14 Chronic

15 Although no data are available for amodiaquine, it should be noted that haemolysis and
16 acute renal failure reportedly occurred in a few patients with glucose-6-phosphate
17 dehydrogenase deficiency receiving chloroquine (AFHS, 1988).

18
19 9.4.6.2 Other

20 No data available.

21
22 9.4.7 Endocrine and reproductive systems

23 No data available.

24
25 9.4.8 Dermatological

26 Chronic

27 A mild degree of itching with or without a rash can follow the use of amodiaquine in all
28 races. However, in Africans, a more severe itching has been reported (see below). The
29 itching has a curious biting or pricking character, and affects all parts of the body
30 including the scalp, the palms of the hands, and the soles of the feet. It is often
31 unassociated with urticaria or any other kind of rash. It begins within a few hours of
32 taking the drug and often continues for between 48 and 72 hours. It is usually severe
33 enough to make sleep impossible for as long as it lasts. The itching occurs in all age
34 groups but it is unusual for it to be experienced on the first exposure to the drug. Once
35 itching has started, it usually runs its course of 48 to 72 hours, irrespective of treatment
36 with antihistamines. However, prophylactic administration of an antihistamine usually
37 prevents or reduces the severity of the reaction (Salako, 1984).

38
39 Pruritus occurred in 14 (27%) of 52 patients with malaria treated with amodiaquine (25
40 mg/kg) over three days. Although the pathogenesis of this adverse reaction is still
41 unknown, it occurs mainly in black Africans, and appears to run in families, suggesting a
42 genetic basis (Sowunmi et al., 1989).

43
44 Other dermatological effects have been reported for chloroquine, which may also occur
45 following amodiaquine therapy. These include pigmentary changes of the skin and
46 mucous membranes, skin eruptions resembling lichen planus, and various dermatoses
47 which may be aggravated by exposure to ultraviolet light. Additionally, bleaching of hair
48 has been reported occasionally with chloroquine and occurs most frequently in light-
49 haired individuals. Hair bleaching may affect eye lashes and axillary, pubic, scalp, and
50 body hair, and is usually evident after 2 - 5 months post-therapy (AFHS, 1988).

51
52 9.4.9 Eye, ear, nose, throat: local effects

53 Chronic:

1 4-Aminoquinolines cause two typical effects involving the eye, namely keratopathy and
2 retinopathy. Both are associated with the administration of the drug over longer periods
3 of time; the level of daily doses and total doses is of importance. Retinopathy,
4 sometimes irreversible, was reported following treatment with amodiaquine hydrochloride
5 200 mg daily (Grant, 1986). Ototoxicity has been reported in association with the use
6 of the 4-aminoquinoline derivative chloroquine (Tester-Dalderup, 1984).

8 9.4.10 Haematological 9 Chronic

10 Amodiaquine has reportedly caused blood dyscrasias at therapeutic doses. Sporadic
11 cases of severe neutropenia were reported as early as 1953, but occurred more
12 commonly in patients receiving amodiaquine in anti-inflammatory doses for rheumatoid
13 arthritis. However, in 1986, seven cases were described in travellers returning to the UK
14 who were taking amodiaquine for malaria prophylaxis. The frequency of neutropenia
15 among these has been estimated at about 1 in 2000. Similar findings were reported in
16 Switzerland. In all, 23 cases of agranulocytosis associated with the use of amodiaquine
17 were reported in the 12-month period ending in March 1986, seven of which were fatal.
18 Most cases involved a dosage of 400 mg weekly over periods of three to 24 weeks (WHO,
19 1987).

21 9.4.11 Immunological 22 Chronic

23 The mechanism for amodiaquine hepatotoxicity is unknown. It has been postulated that
24 an immunoallergic mechanism is consistent with some extra-hepatic manifestations
25 possibly due to hypersensitivity and with the prompt increase in serum aminotransferase
26 levels after re-challenge (Larry et al., 1986). However, other co-workers favour a toxic
27 rather than an immune mediated mechanism (Nefitel et al., 1986) (see section 9.4.5).

29 9.4.12 Metabolic

31 9.4.12.1 Acid-base disturbances
32 No data available.

34 9.4.12.2 Fluid and electrolyte disturbances
35 Hypokalaemia has been reported.

37 9.4.12.3 Others
38 No data available.

40 9.4.13 Allergic reactions 41 Chronic

42 The pathogenesis of the itching (see section 9.4.8) may be a hypersensitivity or genetic
43 reaction, but is still a matter of debate (Salako, 1984; Sowunmi et al., 1989).

45 9.4.14 Other clinical effects No data available.

47 9.4.15 Special risks

48 Variable CYP2C8 activity owing to genetic variation and drug interactions may have
49 important clinical implications for the efficacy and toxicity of amodiaquine (Parikh et al
50 2007).

52 Pregnancy

53 Little information is available on amodiaquine use during pregnancy. Between 1948 and
54 1990 only 6 papers reported amodiaquine use in pregnancy. Six studies on amodiaquine

1 delivered by mass drug administration gave inadequate information on safety (Thomas et
2 al 2004).

3
4 Although no data are available for amodiaquine, chloroquine is known to cross the
5 placental barrier. A 1985 report summarized the results of 169 infants exposed in utero to
6 300 mg of chloroquine base once weekly throughout pregnancy. The control group
7 consisted of 454 non-exposed infants. Two infants (1.2%) in the study group had
8 anomalies (tetralogy of Fallot and congenital hypothyroidism) compared to four control
9 infants who had defects (0.9%). Based on these data the authors concluded that
10 chloroquine does not have a strong teratogenic effect, but a small increase in birth
11 defects could not be excluded (Wolfe & Cordero, 1985). It is generally believed that the
12 benefits of chloroquine therapy in pregnant women exposed to malaria outweigh the
13 potential risks of the drug to the fetus.

14 15 16 Breast feeding

17 Chloroquine does not appear to be excreted in appreciable amounts in the breast milk
18 (Anderson, 1977).

19 20 Enzyme deficiencies

21 Since haemolysis and acute renal failure has been reported to occur in a few patients with
22 glucose-6-phosphate dehydrogenase deficiency receiving chloroquine, this should also
23 be considered when using amodiaquine (AHFS, 1988).

24 25 9.5 Other

26 No data available.

27 28 9.6 Summary

29 30 10. MANAGEMENT

31 10.1 General principles

32 Treatment of overdose is supportive and must be prompt since acute toxicity can progress
33 rapidly, leading to vascular collapse and respiratory and cardiac arrest. Because of the
34 importance of supporting ventilation, early endotracheal intubation and mechanical
35 ventilation may be necessary. Early gastric lavage followed by administration of activated
36 charcoal may provide some benefit in reducing absorption of the drug, but should be
37 preceded by measures to correct cardiac and severe cardiovascular disturbances, if
38 present, and by respiratory support. Diazepam iv may control seizures and other
39 manifestations of CNS stimulation. Seizures caused by anoxia should be corrected by
40 oxygen and other respiratory support. Defibrillators and cardiac pacemakers may be
41 required.

42 43 10.2 Relevant laboratory analyses

44 10.2.1 Sample collection

45 Blood should be collected on EDTA and centrifuged at 2000 g for 15 minutes within two
46 hours of collection and the plasma should be frozen at -20 to -40°C. The blood
47 sample should be transported under refrigerated and separated within two hours of
48 collection.

49 10.2.2 Biomedical analysis

50 Regular laboratory investigations should be performed to assure that blood cell counts
51 remain within normal limits. Perform liver function tests and monitor serum electrolytes.
52
53

1 Arterial blood gases should be determined. Electrocardiography is helpful assess
2 cardiotoxicity.

4 10.2.3 Toxicological analysis

5 Measuring the blood levels of amodiaquine and its major metabolite desethylamodiaquine
6 is not considered to be of practical assistance in the clinical management of amodiaquine
7 poisoning. Both simple qualitative and quantitative tests may be found in the USP (1974).
8 A sensitive and selective HPLC method for the determination of amodiaquine in plasma
9 has been reported by Mihaly et al., 1985). This has been modified to permit the
10 determination of both amodiaquine and the major active metabolite,
11 desethylamodiaquine, in plasma, urine, whole blood and packed red blood cells
12 (Winstanley et al., 1987).

14 10.2.4 Other investigations

15 No data available.

17 10.3 Life supportive procedures and symptomatic/specific treatment

18 Treatment is largely supportive. Cardiac and respiratory arrest may quickly supervene,
19 therefore preparations should be made for tracheal airway protection (endotracheal
20 intubation) and mechanical ventilation. Defibrillators and cardiac pacemakers may be
21 required. Check adequacy of tidal volume (normal 10 to 15 ml/kg). Control seizures, if
22 present, before emptying stomach. The seizures may result from the following:

- 23 - anoxia: administer 100% oxygen, begin assisted ventilation;
- 24 - CNS stimulation: diazepam (up to 10 mg iv slowly in adults; 0.1 to 0.2 mg/kg iv slowly in
25 children). If unresponsive: phenytoin (15 mg/kg iv slowly, at up to 0.5 mg/kg/minute, with
26 ECG monitoring);
- 27 - hypotension: intravenous fluids. If unresponsive, administer dopamine: 5 to 15
28 µg/kg/minute (after correction of hypovolaemia); watch for ventricular arrhythmias.

30 10.4 Decontamination

31 This drug is rapidly absorbed, however, if the patient presents less than one hour post-
32 ingestion and the airway is adequately gastric lavage may be given followed by the
33 administration of activated charcoal (adults, 60 to 100 g; children, 30 to 60 g).

35 10.5 Elimination

36 Forced diuresis and/or urinary acidification may increase excretion of unchanged
37 amodiaquine, but neither procedure can be recommended at present on the basis of clinical
38 evidence. Peritoneal dialysis and haemodialysis are not effective. In the case of
39 chloroquine as a comparison, dialysis and haemoperfusion techniques are limited by the
40 high apparent volume of distribution of chloroquine in the tissue. Charcoal
41 haemoperfusion may be effective if begun very early after ingestion in a severely toxic
42 patient. Clinical studies have not established its usefulness. The total body clearance of
43 chloroquine (a 4-aminoquinoline similar to amodiaquine), is increased only slightly after
44 haemodialysis and haemoperfusion.

46 10.6 Antidote treatment

48 10.6.1 Adults

49 There are no antidotes. Treatment with adrenaline and diazepam has been shown to
50 improve survival in cases of severe chloroquine intoxication: adrenaline infusion 0.25
51 microg/kg/min initially, with increments of 0.25 microg/kg/min until adequate systolic blood
52 pressure (more than 100 mmHg); diazepam 2 mg/kg over 30 minutes (loading dose)
53 followed by 1 to 2 mg/kg/day for up to 2 to 4 days (Riou et al 1998).

10.6.2 Children

There are no antidotes. Treatment with adrenaline and diazepam has been shown to improve survival in cases of severe chloroquine intoxication: adrenaline infusion 0.25 microg/kg/min initially, with increments of 0.25 microg/kg/min until adequate systolic blood pressure (more than 100 mmHg); diazepam 2 mg/kg over 30 minutes (loading dose) followed by 1 to 2 mg/kg/day for up to 2 to 4 days (Riou et al 1998).

10.7 Management discussion

Despite the widespread therapeutic use of amodiaquine for the past 40 years, there remains a paucity of both clinical and experimental data on this drug. In particular, there appear to be no useful literature reports from acute amodiaquine poisoning. Further research into the possible role that diazepam may play as an antagonist in acute amodiaquine poisoning is indicated (see section 10.6).

11. ILLUSTRATIVE CASES

11.1 Case reports from literature

Children, oral ingestion

A report (WHO 1979) cites a case in June 1965 from Pakistan. Severe haemoglobinuria had occurred in seven children following ingestion of an unknown amount of Camoprime Infatabs (each tablet containing 75 mg amodiaquine + 15 mg primaquine). No details could be obtained regarding the approximate number of tablets ingested, the age of the children and the circumstances in which the tablets had been taken. However, certain indications strongly suggested that the reported toxic reactions were not related to any regular, supervised drug administration, but were accidents in that the children had got hold of the drug and surreptitiously swallowed a number of tablets.

11.2 Internally extracted data on cases

To be added by the Poison Control Centre.

11.3 Internal cases

To be added by the Poison Control Centre.

12. ADDITIONAL INFORMATION

12.1 Availability of antidotes

No specific antidotes are available.

12.2 Specific preventive measures

Store in an air-tight container, in child-resistant packaging out of the reach of children. The manufacturer of Camoquin (Parke-Davis) has advised in a data sheet to health professionals that the prophylactic use of amodiaquine as a first line agent has been restricted to chloroquine-resistant areas. If the decision is made to so prescribe the drug, concomitant use with other anti-malarials should be avoided and regular laboratory investigations should be performed to assure that blood values and liver function tests remain within normal limits. Because amodiaquine may concentrate in the liver, the drug should be used with caution in patients with hepatic disease or alcoholism, and in patients receiving hepatotoxic drugs. Amodiaquine is contraindicated in patients who are hypersensitive to other 4-aminoquinolines. Since haemolysis and acute renal failure has been reported to occur in a few patients with glucose-6-phosphate dehydrogenase deficiency receiving chloroquine, this should also be considered when using amodiaquine.

1 Children are especially sensitive to 4-aminoquinoline derivatives. Because of the narrow
2 margin between the therapeutic and toxic concentrations in children, amodiaquine should
3 not be administered parenterally in this age group. It is generally believed that the
4 benefits of chloroquine (a 4-aminoquinoline congener similar to amodiaquine in both its
5 structure and activity spectrum) therapy in pregnant women exposed to malaria outweigh
6 the potential risks of the drug to the foetus. The risk to the foetus is greater if it is
7 glucose-6-phosphate dehydrogenase deficient. Chloroquine does not appear to be excreted
8 in appreciable amounts in the breast milk.

10 12.3 Other

11 No data available.

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