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REVIEW OF SIDE EFFECTS AND TOXICITY OF CHLOROQUINE

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Chloroquine, which belongs to the 4-aminoquinoline group of compounds, has been one of the most widely used antimalarials for some 30 years. The present document which reviews its side effects and toxicity is the second in a series of such reviews of the pharmacological and toxicological aspects of antimalarial drugs in current use. The first, which dealt with primaquine and other 8-aminoquinolines, was recently issued under the symbol WHO/MAL/79.905. These reviews, which have been arranged for by WHO under the auspices of the Malaria Action Programme, are intended to serve as reference material for scientists responsible for the development of WHO-supported research on the chemotherapy of malaria. However, it is hoped that by making these reviews also available to other interested scientists through their issue in the WHO/MAL information series, they will also serve to reactivate or broaden interest in chemotherapeutic research which is an indispensable source of tools for malaria control.

The toxic effects of chloroquine depend on dosage and duration of administration, and these in turn depend on the condition under treatment. Therefore the present review will consider the side effects and toxicity of chloroquine not only with regard to its use for the treatment and suppression of malaria, but also with regard to the relatively high doses required for the treatment of "collagen diseases" such as lupus erythematosus and rheumatoid arthritis.

1. MINOR SIDE EFFECTS

With the doses recommended for malaria suppression or treatment, side effects are rare, and, when they do occur, they are usually slight. They generally consist of gastrointestinal disturbances (nausea, vomiting, abdominal pain, anorexia), dizziness, headache, and occasionally pruritus. Though unpleasant, these symptoms tend to be mild, of short duration, and without adverse consequences. Their incidence can be reduced to a very low level by avoiding excessive doses and by not taking chloroquine on an empty stomach but always with some food or after a meal.

Pruritus or itching as a side effect of chloroquine appears to be more frequent and important, at least in Nigeria, than was previously supposed. Alving et al. (1948) in their detailed studies on the chronic toxicity of chloroquine mentioned skin eruptions, but no itching, in two out of 20 subjects receiving 500 mg of chloroquine base once weekly. Berliner et al. (1948) reported generalized itching in only one of the subjects on 400 mg of chloroquine base daily. According to Ekpechi & Okoro (1964) about 8% to 15% of patients in Nigeria treated with a single dose of chloroquine (10 mg/kg) complained of a widespread prickling sensation, affecting mainly the hands, feet and scalp, beginning six to eight hours after drug administration and lasting for two to three days. In over half of the cases, the sensation was sufficiently severe to be incapacitating. Antihistamines were found to have no effect on this pruritus. Recently, Olatunde (1977) has again drawn attention to this side effect which is more than a mere nuisance in Nigeria. It appears that chloroquine can first be taken without adverse effect, but that sensitivity develops after several treatments. Itching generally starts 24 to 48 hours after taking the drug and in some cases may be so severe as to produce psychotic changes. It is independent of the presence or absence of malaria parasites in the blood. Subjects who have experienced this unpleasant reaction are unwilling to take chloroquine for treatment of subsequent malaria attacks. The best solution seems to be to prevent further malaria attacks by regular chemoprophylaxis using either daily proguanil or weekly pyrimethamine.

An unusual toxic reaction, consisting in chloroquine-induced involuntary movements, has been reported by Umez-Eronini & Eronini (1977). Treatment with oral or parenteral chloroquine was followed by involuntary movements such as protrusion of the tongue, twitching of facial muscles, excessive salivation, difficulty in swallowing, and turning the neck to one side. Two of the patients developed the same symptoms when given chloroquine again. Over a period of five years, the authors have treated more than 25 000 malaria patients in Nigeria with chloroquine, and five of the patients presented this reaction (i.e. an incidence of less than 1/5000). The same symptoms had previously been reported, also from Nigeria, in four

patients treated with amodiaquine (Akindele & Odejide, 1976). In both of these papers there is some uncertainty as to the doses used as these are stated only in terms of number of tablets.

Torrey (1968) presented the histories of four patients who had epileptic seizures thought to be due to chloroquine. All patients were being treated for amoebiasis with chloroquine in doses ranging from 1.35 to 6.3 g base given over three to 14 days. (For at least two patients the chloroquine doses were higher than those used for antimalaria purposes.) Concurrently with chloroquine, all four patients had received one or more amoebicides and antibiotics, e.g. diiodohydroxyquin, 2 g daily for 20 days; emetine, 60 mg daily for 14 days; oxytetracycline, tetracycline and paromomycin for varying periods. This raises some doubts as to whether chloroquine alone was responsible for these seizures.

Another uncommon reaction to chloroquine has been reported by Boulle & Achard (1964), who observed in one patient the appearance of pigmentation of the gums after prolonged malaria prophylaxis with chloroquine (300 mg base once weekly for one year).

Finally, Onori (1963) pointed out that pigmentation of the skin would appear to occur occasionally under prolonged chloroquine prophylaxis at a weekly dosage of 300 mg base.

2. ACUTE TOXIC EFFECTS OF SINGLE HIGH DOSES

Acute chloroquine poisoning following the accidental or intentional ingestion of a massive overdose has been reported for two main groups of cases; (1) young children who accidentally got hold of the drug and swallowed a large number of tablets; (2) adults who deliberately ingested a massive overdose for committing suicide.

2.1 Accidental poisoning in young children

Available published reports (1961-1978) on acute chloroquine poisoning in children comprise 25 cases, aged 17 months to six years, who accidentally swallowed toxic or fatal doses of chloroquine. In the five children who alone managed to survive, either the dose had been relatively small, or remedial measures had been instituted at a very early stage. In practically all of the cases the amount of chloroquine accidentally ingested is either unknown or can be given only as a rough estimate.

Cann & Verhulst (1961) were the first to report on acute chloroquine poisoning in children. They described seven cases of which six were fatal. The estimated amounts of chloroquine ingested ranged from 450 mg to 1.5 g base. In the six fatal cases, death occurred within only one to three hours after drug ingestion, with sudden collapse and respiratory and cardiac arrest, despite all resuscitative efforts (tracheal intubation with oxygen, cardiac massage after opening the chest, etc.). One boy aged three years died two-and-one-half hours after having swallowed an estimated dose of 450 to 600 mg base, which represents two to three times the highest single dose recommended for this age.

The lowest reported fatal dose is 300 mg chloroquine in a three-year-old boy who died of cardiac failure one hour after drug intake (Clyde, 1966). However, Clyde points out that results of tissue analysis suggested a higher intake of drug. The boy was on a weekly suppressive dose of 150 mg base - twice the recommended dose for this age - which had probably led to a certain saturation of the tissues. Markowitz & McGinley (1964) reported the case of a two-year-old child who recovered after having swallowed exactly five coated chloroquine tablets of 300 mg base each, or a total dose of 1.5 g base. Vomit contained fragments of pink-coated tablets. Gastric lavages were started 45 minutes after drug intake, and each return yielded many fragments of pink-coated, undissolved tablets, the coating having delayed dissolution and absorption of the drug.

Some of the reported fatal cases were due to ingestion of combined chloroquine-primaquine tablets containing 300 mg base and 45 mg base, respectively. Carson et al. (1967) reported the fatal poisoning of a child aged 18 months, who had been seen playing with chloroquine-primaquine tablets (brought home from Viet Nam by a relative) and who had swallowed an unknown

number of these tablets. He was brought to hospital six hours later in a comatose state and died within 30 minutes. Di Maio & Henry (1974) presented 27 cases of fatal poisoning due to ingestion of an overdose of chloroquine-primaquine tablets. Six of these cases were in children aged 11 months to four years. The 11-month-old boy died one hour after ingestion of four combined tablets (1.2 g chloroquine base + 180 mg primaquine base). Death was probably due mainly if not exclusively to the chloroquine content, the toxic effects of primaquine being much slower in onset.

Larkworthy (1971) reports the history of a two-year-old girl who swallowed an unknown number of chloroquine tablets, vomited two-and-one-half hours later, became unconscious and died one hour later on arrival at hospital. At autopsy, a total of 22 tablets, many of them partially digested, were recovered from various parts of the upper gastrointestinal tract, representing an intake of at least 3.3 g base. Another two-year-old child swallowed about 45 ml of chloroquine syrup providing some 600 mg base. Vomiting with a saline emetic was immediately induced and the child recovered. In one instance (McCann et al., 1975), a two-year-old child having ingested an unknown amount of chloroquine, was kept alive for about 47 hours after drug ingestion, by means of a multitude of energetic measures, including peritoneal dialysis which, however, removed little of the drug. On the twenty-seventh hour of dialysis the heart again stopped and the child could not be revived.

Some cases of acute fatal poisoning in children have resulted from faulty drug administration by adults. Wilkey (1971) reported two such cases of overdosage. A boy aged three years suddenly collapsed with twitching and died. Inquiries disclosed that parents had given him four "adult chloroquine tablets" (= 600 mg base ?) for a feverish illness shortly before death. Another boy, aged 18 months, weighing 6 kg, was admitted to hospital and, due to a misunderstanding, was given an intramuscular injection of 5 ml chloroquine, equivalent to 200 mg base. The child died about 10 minutes later. The injected dose of 200 mg base, or 33.3 mg/kg body weight, represents nearly seven times the maximum recommended intramuscular dose for children, which is 5 mg/kg. Some eight cases of sudden death of children following intramuscular injection of an overdose of chloroquine have been reported in the literature, and certainly many more have occurred but have not been published.

The outstanding features of acute chloroquine poisoning in children are the relatively narrow margin of safety between the therapeutic and toxic doses, the rapid onset of severe toxic symptoms, and the often fatal outcome, death due to respiratory failure and cardiac arrest occurring within one to three hours after drug ingestion. The very rapid lethal effect of an overdose, especially when given parenterally, probably indicates that the unchanged chloroquine is the toxic agent, and not some metabolite or degradation product. Most authors agree that the acute toxic effects of chloroquine are exerted mainly on the heart.

There is no specific antidote to counteract the acute toxic effect of an overdose of chloroquine, and only supportive measures are available. Since chloroquine is rapidly absorbed after ingestion, gastric emptying, either by induction of emesis or by gastric lavage, is the most important measure and must be undertaken as soon as possible. Respiration must be maintained by whatever means are available, if possible by endotracheal intubation with oxygen. This should be done before gastric lavage, to prevent aspiration. Cardiac massage and cardiac stimulants are recommended, and vasopressors to counteract hypotension.

2.2 Voluntary poisoning in adults

Deliberate poisoning by ingesting a large number of chloroquine tablets has become a frequent method for committing or attempting suicide, and the literature on such cases is already extensive. Since 1955 and up to the present (1978), at least 335 cases of voluntary acute chloroquine poisoning have been reported and each year the number continues to increase, particularly in Africa (Carayon et al., 1968; Bondurand et al., 1972; Champagne, 1975; Frija, 1975). Of the 335 cases of acute poisoning, 135 resulted in death while 200 recovered, either because remedial measures could be initiated at a very early stage, or because the ingested doses had been rather low: less than 1.0 g or less than 1.5 g of the base (Frija, 1975; Champagne, 1975; Charles et al., 1975).

Among the 135 fatalities, 16 occurred in young women who had swallowed large amounts of chloroquine in attempts to abort themselves, though chloroquine has no abortifacient effect (Le Breton & Garat, 1962; Tabbara, 1962; Ollivier & Quicke, 1962; Camps & Robinson, 1971; Armand et al., 1971).

The estimated amounts of chloroquine ingested which produced toxic or lethal effects ranged from less than 1.0 g (Champagne, 1975) to as much as 26.7 g of the base (Kiel, 1964). Although the exact quantities of chloroquine ingested are seldom known and only estimates can be given, it would appear from the reports of Ollivier et al. (1958) and Bellevaux & Vanderick (1958) that a single dose of 1.5 to 2.0 g of chloroquine base may be fatal. Most authors consider that for an average adult 1.5 g of chloroquine base is a toxic dose, and 2.0 g (30-35 mg/kg) is a lethal dose (Pille & Palancade, 1963; Constantin & Charmot, 1966; Fauran & Sankalé, 1970; Champagne, 1975).[1] It may be noted here that, according to Pille et al. (1958) a daily dose of 1.2 g chloroquine base administered in certain cases of severe lupus erythematosus has been tolerated for at least a few days; this dosage, however, appears to be a limit which should not be exceeded.

As already mentioned with regard to accidental poisoning in children, the impressive feature of acute chloroquine intoxication is the rapid appearance of severe toxic manifestations and the often fatal outcome, usually occurring within two or three hours after drug ingestion. Clinical symptoms of acute chloroquine intoxication may be divided into three categories: neurological, respiratory and cardiovascular (Frija, 1975). Neurological manifestations include drowsiness, which is an early and frequent symptom, visual disturbances (photophobia, diplopia) and finally convulsive seizures. Death is often preceded by hyper-excitability or convulsions. Respiratory difficulties are frequent and may vary from rapid, superficial breathing to frank arrest. Sudden apnoea may occur during resuscitation efforts, and is often followed by cyanosis. Cardiovascular manifestations include vasodilatation and hypotension, a sudden fall in blood pressure, being one of the most frequent symptoms of acute chloroquine intoxication. There is decreased myocardial contractility and finally cardiac arrest. The depressive effects of chloroquine on the cardiac muscle, such as depression of excitability and impairment of conductivity, are similar to the effects observed with quinine and quinidine (Cann & Verhulst, 1961).

Because of the early toxic manifestations and their severe consequences, it is important that therapeutic measures be initiated very rapidly. In the absence of a specific antidote, gastric lavage should be carried out immediately even if the patient has vomited. Some authors have pointed out that chloroquine being rapidly absorbed, gastric lavage is useless if symptoms have already appeared. It would seem however that while initial absorption is rapid, as shown by the early appearance of symptoms, complete absorption of the ingested amount is prolonged. Constantin & Charmot (1966) were able to recover chloroquine by gastric lavage as late as two-and-one-half hours after ingestion. According to Bondurand et al. (1972), if the drug is taken on an empty stomach, absorption is rapid and almost complete and severe toxic manifestations may appear within 30 minutes; but if the tablets are taken after a meal, absorption is delayed and slow, and symptoms may not appear until some two hours or more after ingestion.

Carayon et al. (1968) found that already one hour after drug ingestion little chloroquine was left in the stomach whereas there was still a considerable amount in the duodenum, as shown by their new method: surgical lavage of the small intestine. They give the history of three patients who had swallowed lethal doses of chloroquine and who were profoundly comatose despite intensive measures taken. Laparotomy was performed (without anaesthesia) and the small intestine was washed out. All three patients so treated showed rapid improvement and recovered. In a previous series of four severe intoxications in which only conventional treatment had been given, three patients died. The only patient who was saved had been admitted to hospital 15 minutes after having swallowed 100 tablets of Nivaquine, or 10 g of the base.

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[1] Since the single dose recommended by WHO for an adult is 600 mg base or 10 mg/kg, the margin of safety is not very large.

For a large number of fatal cases autopsy findings and results of toxicological tissue analysis are given.   Autopsy findings are nonspecific and usually the only abnormality found is marked oedema and congestion of the lungs, consistent with respiratory failure.   Oedema of the brain was found in some patients (Kiel, 1964;   Di Maio & Henry, 1974;   Wilkey, 1973; Van den Heede et al., 1973).

As regards tissue levels of chloroquine, the highest concentration is usually found in the liver, with high levels also being found in the kidney, lung and spleen, but little in the brain.   According to Armand et al. (1971) the cardiac muscle retains much more chloro- quine than any other muscle.   Blood levels found after death may vary considerably.   There are also great variations in the tissue distribution of chloroquine found in different subjects.   This probably reflects the different time intervals between drug ingestion and death.   High blood levels and low levels in the liver may be found when death has occurred very rapidly, without sufficient time for deposition of chloroquine in the liver. Van den Heede et al. (1973) found the smallest chloroquine concentration in the liver, in a patient who .had died less than two hours after drug ingestion.

In several cases of "sudden unexplained death", the diagnosis of chloroquine intoxication has been made only by toxicological analysis of autopsy specimens (Ollivier et al., 1958; Larribaud et al., 1961;   Tabbara et al., 1962;   Bäumler & Lüdin, 1963;   Klug & Schneider, 1970;   Lazarini et al., 1974;   Prouty & Kuroda, 1958).

3.   CHRONIC TOXIC EFFECTS

Medium or high daily doses of chloroquine (150-750 mg base) taken continuously over long periods may give rise to toxic effects due to the selective accumulation of chloroquine in certain tissues.   This property of chloroquine has been well known since the early investi- gations carried out by Berliner et al. (1948) who showed that most of the ingested chloroquine is stored in the tissues and only a small part of the daily dose (10-25%) is excreted in the urine.   Soon after its introduction as an antimalarial, chloroquine which is also an anti- inflammatory drug became increasingly used for the treatment of "collagen diseases" (mainly rheumatoid arthritis and lupus erythematosus), the symptomatic relief of which required the prolonged administration of much higher doses than those needed for antimalarial purposes. The wide use of chloroquine for treatment of diseases other than malaria has brought with it a variety of previously unrecognized toxic reactions, such as ocular complications, possibly ototoxic effects and neuromyopathies.

3.1   Ocular complications

3.1.1   Following high daily doses used for the treatment of collagen diseases

Long-term toxic effects of chloroquine include ocular changes following prolonged administration of the drug at a high dosage.   These were first reported by Hobbs & Calnan in 1958.   Two kinds of eye damage have been observed: keratopathy and retinopathy.

3.1.1.1   Keratopathy

This consists in corneal opacities which lead to difficult accommodation, blurred vision, seeing halos around lights and which are caused by the scattered deposition of a granular opaque material in the corneal epithelium, probably composed of chloroquine or its metabolite (Hobbs & Calnan, 1958;   Zeller & Deering, 1958).   The frequency of keratopathy following chloro- quine administration is difficult to estimate.   Corneal changes do not always produce symptoms and are visible only by slit-lamp biomicroscopic examinations.   No strict relation seems to exist between the duration of treatment or the total dose ingested and the development of keratopathy.   In some cases, corneal changes may appear after several weeks, in other cases the cornea may remain unaffected after several years of treatment with high doses.   The reported incidence varies considerably with different authors.   When high daily doses of chloroquine are taken for prolonged periods, keratopathy may be expected in 10-50% of patients. According to Lloyd & Hiltz (1965) the incidence is 30-70%, whereas Scherbel et al. (1965), who studied a series of 408 patients, reported an incidence of only 10%.

There seems to be general agreement on the fact that corneal changes do not cause permanent visual defects and are always reversible. Cessation of chloroquine therapy seems to result in absorption of the corneal deposits within a few months, and no cases of lasting impairment of the cornea due to chloroquine are known.

3.1.1.2 Retinopathy

Retinal lesions, consisting in changes in the fundus of the eye due to the deposition of chloroquine, are less frequent than keratopathies, but are much more serious. Unless they are recognized in the early, asymptomatic stage, they may lead to permanent impairment of vision, and even to blindness.

Retinal changes following long-term chloroquine therapy with medium or high doses were first described by Hobbs et al. (1959) and Sternberg & Laden (1959). Since then, a considerable number of reports on this toxic effect have been published of which only a small part are listed with the references at the end of this review.

Typically, chloroquine retinopathy consists of granular or stippled pigmentation of the macula, or of a patchy macular depigmentation, surrounded by a clear zone of depigmentation, which in turn is encircled by another ring of pigment; the whole pattern resembles a "doughnut" or "bull's eye" and is often referred to by these terms. Ophthalmological findings may include peripheral constriction of visual fields, attenuation of retinal vessels and impairment of central vision (Hobbs et al., 1959). At a later stage there may be diffuse depigmentation in the periphery of the retina.

Most authors have reported that these retinal lesions are irreversible and may even progress for long periods after chloroquine treatment has been discontinued (Hobbs et al., 1959; Okun et al., 1963; Henkind et al., 1964; Burns, 1966).

The irreversible nature of retinal damage occurring after prolonged chloroquine administration has been explained by the histopathology. Wetterholm & Winter (1964) reported that the pathology was a destructive lesion of the rod and cone elements of the retina, with accumulation of pigment-laden cells in the outer retinal layers.

Studies carried out in animals by Zvaifler et al. (1963) and by Bernstein et al. (1963) showed that chloroquine was stored in high concentrations in the uveal tract of the rabbit and rat. Concentrations of chloroquine in the iris, choroid and pigment epithelium of the retina were found to be much greater than that in the liver, which is usually considered to be the site of highest chloroquine deposition. The absence of chloroquine in the same tissues of albino rats suggested that the binding of chloroquine was with the melanin pigment. According to Bernstein & Ginsberg (1964) the chloroquine bound to the melanin-containing tissues of the eye may interfere initially with the metabolism of the retinal pigment epithelium, and this may secondarily produce rod and cone destruction.

Lawwill et al. (1968) were able to determine the chloroquine concentration in human eyes, obtained from eight patients subjected to enucleation, who had taken chloroquine for various periods, some of them in the immediate pre-operative period. The concentration found in choroid and pigment epithelium was much higher than in other eye tissues, indicating that chloroquine is selectively accumulated in the human choroid and pigment epithelium. Long-term retention in these tissues was demonstrated by measurable amounts in the eye of one patient who had taken his last dose of chloroquine 16 years previously. Their data also confirmed that the degree of chloroquine accumulation is related to the dosage and the duration of treatment, i.e. to the total amount ingested.

Dosage is the principal factor in the development of retinopathy. Most of the cases reported occurred in patients who had received massive doses - 300 mg to 750 mg daily - for more than one year, or total doses largely exceeding 100 g. Voipio (1966) suggested that the risk of retinal damage first appears at a total dose exceeding 100 g of the base, and Carr et al. (1966) found that retinopathy developed only in persons whose total chloroquine intake exceeded 100 g of the base. It was much more frequent when a total dose of 8 g/kg body weight had been ingested, or a total dose of 560 g for a 70 kg person.

Arden & Kolb (1966) have reported that the electro-oculogram was significantly lower even in patients having taken only 1 g/kg or less, or a total dose of 60-75 g for an adult. If it is admitted that a total dose exceeding 1 g/kg may eventually lead to irreversible retinopathy, this would mean that an adult of 75 kg should not take more than 75 g of chloroquine. At a once weekly dose of 300 mg base, the total intake per year would be 15.6 g of the base. Thus an adult could continue on 300 mg chloroquine once weekly for about five years before reaching a dangerous level at which retinopathy might develop.

Apart from variations in individual susceptibility, age seems to be an important factor in the development of retinal lesions in patients taking chloroquine for treatment of connective-tissue diseases. Scherbel et al. (1965) found that in both chloroquine-treated and untreated groups the incidence of ocular complications was definitely higher in the older age-groups. Elman et al. (1976) analysed the effect of age on ocular findings in 270 patients with rheumatoid arthritis who had received chloroquine in total annual doses of 70-75 g. The period of treatment lasted up to 15 years, and the maximum total dose given was 1330 g (probably of chloroquine diphosphate). The frequency of maculopathy, or slight macular changes, increased with the total doses received only in the older age-groups (over 63 years).

The actual incidence of retinopathy due to chloroquine is difficult to assess. Most authors report only on selected cases in which retinopathy has occurred, without mentioning the number of patients similarly treated who did not develop retinopathy. Except for the more recent publications, reports on retinopathy apparently caused by chloroquine are inconclusive because the condition of the retina before chloroquine treatment had not been determined.

Depending on the authors, retinopathy has been observed in 0.5% to 14% of patients. Arden & Kolb (1966) reported an overall incidence of 13% (29/211), but in those patients who had taken more than 8 g/kg it was 40%. Scherbel et al. (1965) reported an incidence of 0.5% (2/408) in patients treated with 150 mg chloroquine base daily for one to nine years, whereas in a group not treated with chloroquine the incidence was 0.9% (3/333). Magendie (1965) tabulated all available data reported in the literature from March 1957 to June 1965 for 161 cases of ocular damage, apparently due to chloroquine or other 4-aminoquinolines. For many of these patients the doses used were unreasonably high, e.g. 600 mg daily for several years; many others among these patients are doubtful cases as neither the doses nor the duration of treatment can be given. For none of the patients are pretreatment ophthalmological data available. According to Magendie, if one takes into account the thousands of patients with collagen diseases who have been treated with chloroquine, the number of 161 cases of ocular damage which he was able to gather shows that the incidence is rather low.

Today it is recommended that all patients under prolonged chloroquine treatment with medium or high doses be kept under regular ophthalmological supervision, in order to detect any retinal changes at an early, asymptomatic stage when they may be reversible. Numerous tests have been described for the detection of retinopathy, e.g. electro-oculography, electroretinography, fluorescein angiography. However, according to Appleton et al. (1973), none of these tests seems to be of value in detecting early retinal damage due to chloroquine.

3.1.2 Following daily or weekly doses used for malaria suppression

3.1.2.1 Daily doses of 100 mg chloroquine base

Several cases of ocular alterations (corneal deposits or retinal pigmentary changes, or both) have been reported after prolonged and continuous intake (10 years or more) of daily doses of chloroquine for malaria suppression. Available data, concerning nine cases, are summarized in Table 1. The reports are all of French origin since the regimen of 100 mg Nivaquine (base) daily was adopted almost exclusively by the French and the francophone countries. In addition, there is a report by Védy (1975) on retinopathy caused by chloroquine in the prevention of malaria in children, but unfortunately this paper was not available to this reviewer.

TABLE 1.   CASES OF OCULAR DAMAGE AFTER PROLONGED MALARIA PROPHYLAXIS
WITH DAILY DOSES OF 100 MG CHLOROQUINE BASE[a]

Author	Patient	Duration of daily intake of 100 mg chloroquine base	Total dose	Results of ophthalmological examinations
Paufique et al. (1964)[b]	F. 39 years	10 years	365 g	Blurred vision; corneal deposits. Macular pigmentation; central scotoma; vascular constriction. Abnormal electroretinogram (ERG).
François & Becker (1965)[c]	F. 48 years	"Many years"	?	Reduced vision; corneal deposits. Macular pigmentation; central scotoma. Blood vessels normal. Normal ERG.
	M. 52 years	"Many years"	?	Cornea normal. Macular degeneration; reduced vision; central scotoma. Normal ERG.
Ravault (1965)	F. 39 years (missionary nun, living in Ivory Coast)	10 years	365 g	Reduced visual acuity. Bilateral macular pigmentation. Abnormal ERG.
	+ 3 other missionary nuns	About 10 years	About 365 g	Bilateral macular degeneration and pigmentation.
Trojan (1975)	M. 48 years (living in Togo)	15 years	547 g	Reduced vision; corneal deposits and opacities. Funduscopic examination normal. Two months after discontinuation of prophy- laxis, corneal changes had disappeared and vision was normal.
	F. 56 years (living in Togo)	20 years	730 g	Reduced vision. No corneal alterations. "Bull's eye macula"; vascular constriction. Five years after discontinuation of prophylaxis no amelioration.

[a] Data from Védy (1975) could not be included as the original report was not available to this reviewer for consultation.

[b] Data cited by Magendie (1965).

[c] These authors do not state the reason for chloroquine administration.

3.1.2.2 Weekly doses of 300 mg chloroquine base

There is no documented evidence that a once weekly dose of 300 mg chloroquine base may cause retinal damage. According to Appleton et al. (1973), already in 1966 and 1967, returning Viet Nam veterans, who had taken 300 mg chloroquine base weekly for two or three years, were screened for ocular damage, and no significant differences were found between Viet Nam returnees and controls.

Many authors consider that a total cumulative chloroquine dose of 60 g base is a critical level at or above which retinopathy may develop. With a once weekly dose of 300 mg, the total intake per year would be only 15.6 g, but in a five-year period it would amount to about 80 g. This uncertainty regarding the dangerous level for ocular toxicity of chloroquine induced Appleton et al. (1973) to carry out a study on 57 United States Foreign Service personnel who had taken the usual weekly dose of 300 mg chloroquine base (without primaquine) for five or more years while stationed in malaria endemic areas. The duration of chloroquine prophylaxis ranged from five to 26 years; five subjects had used the drug for more than 10 years, corresponding to a total intake of over 160 g of the base. Screening was done by the perimetric method of Wetterholm, as this was the only method which has yielded some positive results in previous surveys for the detection of early retinal changes. When tested by this method, together with 30 control subjects who had never taken chloroquine, none of the 57 experimental subjects could be demonstrated to have an arcuate visual field defect of the type observed in previous studies. The authors concluded that a once weekly dose of 300 mg chloroquine base for malaria suppression could be ingested over at least a five-year period without causing retinal damage.

3.2 Ototoxicity

Chloroquine has also been incriminated as a cause of "nerve deafness". However, while ocular damage associated with high chloroquine dosage over long periods appears to be well established, the same cannot be said with regard to auditory damage due to chloroquine, the incidence of which seems to be extremely low.

Scherbel et al. (1958) reported "reversible vestibular dysfunction, apparently caused by chloroquine treatment of rheumatoid arthritis in a small percentage of patients. The symptoms were tinnitus and a sensation of imbalance on rapid turning of the head. Usually these reactions subsided spontaneously within a few weeks without reduction of dosage".[1]

In a subsequent paper by Scherbel et al. (1965) on the study of 741 patients, no reference is made to auditory symptoms, nor have such side effects been mentioned by other authors reporting on the treatment of collagen diseases with high doses of chloroquine. Therefore, if these symptoms do occur, they do not seem to be frequent.

Only four cases of partial loss of hearing following chloroquine treatment have been reported.

Dewar & Mann (1954) reported the case of a patient with lupus erythematosus who was receiving 900 mg chloroquine weekly. After seven months, treatment was discontinued because of anorexia. Four weeks later, the patient complained of deafness, tinnitus and vertigo. She could not hear conversational voices at a distance of more than 2 ft (0.609 m) from either ear. Tuning-fork tests indicated bilateral nerve deafness. An audiograph revealed uniform loss of air and bone conduction. The result of caloric testing was within normal limits. Eight months later an audiograph showed no change and the nerve deafness seemed likely to be permanent. The authors did not give details as to the age of this patient, other drugs used, etc.

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[1] Quoted from Hart & Naunton (1964) and Lindquist & Ullberg (1972), the original paper not being available to the reviewer; references to this paper by Scherbel et al. (1958) do not indicate the number of patients, the doses used or duration of treatment.

The second case was reported by Toone et al. (1965). A 16-year-old girl with rheumatoid arthritis was first given a daily dose of 125 mg chloroquine for six months. The dose was then reduced to 125 mg three times a week. Three months later, impairment of hearing was suspected, but there was no deficit on gross testing. Treatment on the reduced schedule was continued for 38 months. After a total of 44 months of continuous therapy, audiological examination revealed 30% hearing loss in both ears. The drug was stopped immediately, but six months later hearing loss had progressed to 70%. Tests repeated five months later showed no auditory improvement and the hearing loss appeared to be permanent.

Sataloff & Vassallo (1970) mentioned somewhat incidentally the case of a 24-year-old former Peace Corps volunteer stationed in Africa "who developed a precipitous high-frequency hearing loss with ringing tinnitus after ingestion of antimalarial medication containing chloroquine phosphate. The loss started at 1000 hertz with a sudden 30 decibel drop and ranged up to 65 decibel loss at 10 000, 12 000 and 14 000 hertz. The hearing loss has stabilized but ringing tinnitus persists". The authors do not indicate doses and duration of chloroquine prophylaxis, nor possible other medication.

Finally, there is the patient of Dr J. F. Dulac, Chief of the Joint Medical Service in Geneva. This patient had been stationed in Africa from 1966 to 1971 and during this period he had taken chloroquine, 300-600 mg base per week, for malaria prophylaxis. In 1970 he began complaining of bilateral progressive deafness. An audiogram taken in March 1976 revealed high-frequency hearing loss. With reference to this patient, Dr R. Hausler (Clinique Universitaire d'Oto-Rhino-Laryngologie, Hôpital Cantonal, Geneva, personal communication) pointed out the following in his letter of 18 October 1976 to Dr Dulac:

"This type of bilateral progressive hearing loss in the high frequencies may result from the administration of ototoxic drugs (Schuknecht, 1974). But there have been no indications that cochlear damage might result from the chloroquine doses needed for malaria prophylaxis. It should however be noted that the ototoxic effect of a drug may greatly vary in different individuals. Renal insufficiency may considerably increase the risk of auditive impairment. It is also known that the concurrent intake of other ototoxic drugs (certain antibiotics, or diuretics), even in very small doses, may have a cumulative effect resulting in important lesions of the inner ear.

"While the possibility of an ototoxic effect of chloroquine in this patient cannot be excluded, more precise data regarding a possible renal insufficiency and the intake of other drugs would be desirable."[1]

No further information on this case seems to have been forthcoming.

Two more cases may be added as reported by Hart & Naunton (1964). According to these authors, it seems that chloroquine, when taken /at an excessive dosage/ by the mother during pregnancy, can have an ototoxic effect on the developing foetus. The case histories of two children (child 3 and child 5) are given; both showed severe bilateral cochleo-vestibular paresis and child 3 suffered from marked bilateral hearing loss and child 5 from complete deafness. The mother of these children suffered from lupus erythematosus and had been treated with chloroquine, 300 mg base daily, throughout the two pregnancies (see also section 4.2). Subsequently Matz & Naunton (1968) reported that child 3 died at the age of seven years from an epithelial ependymoma of the right cerebellum, and histopathological examination of the right temporal bones from the deceased child showed the following:

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[1] Translated and abstracted from French original.

"The middle ear and otic capsule are normal. The cochlea shows complete absence of the organ of Corti in most areas, but in a few areas it is represented by a small mound of undifferentiated cells. Hair cells are absent. The stria vascularis, the tectorial membrane, limbus and the position of Reissner's membrane are normal. Peripheral nerve fibres are absent except for a possible few near the apex. The ganglion cells are reduced mainly in the basal coil, the total count being 19 700. The sensory cells in the vestibular system, including the saccule, are present but show moderate degeneration, interpreted as due to post-mortem autolysis."[1]

From the above histopathological findings, Lindsay (1973) readily concludes:

"The toxic effect of chloroquine on the ear in this instance has resulted in sub-total absence of cochlear sensory cells and the peripheral nerve fibres. Supporting cells of the organ of Corti were also absent in most areas. Structures known to be exposed to the endolymph, including the stria, tectorial membrane and the cochlear duct volume, were not affected and the spiral ganglion showed a reduced population mainly in the basal coil. The findings closely resemble those seen in the late stage of senso-rineural degeneration produced by certain of the ototoxic drugs in the postnatal period /references not given/. Degenerative changes in the peripheral vestibular system were not clearly evident. Clinical indications of vestibular paralysis and CNS changes as well as other abnormalities had been evident in the two brothers exposed to the drug."

To sum up, there have been four cases of partial loss of hearing in persons who had taken chloroquine in various dosages and for varying periods. Two of the four subjects had taken chloroquine for malaria prophylaxis, one of them in doses of 300-600 mg base weekly for about five years (Dr Dulac's patient, 1976). No relevant data are available for the Peace Corps volunteer mentioned by Sataloff & Vassallo (1970). The two other patients had received chloroquine in much higher doses, either for lupus erythematosus (Dewar & Mann, 1954) or for rheumatoid arthritis (Toone et al., 1965). In three of these four cases, other possible causes or contributing factors were not considered. In addition, Hart & Naunton (1964) have reported ototoxic effects, apparently due to chloroquine, in two children whose mother had been treated with 300 mg chloroquine base daily, throughout the two pregnancies.

These six cases represent all the information reported so far on an ototoxic effect of chloroquine. When one considers the very large number of patients in the last 30 years who have taken chloroquine either for antimalarial purposes or, at much higher doses, for long-term treatment of collagen diseases, then the number of six cases of ototoxicity, possibly due to chloroquine, appears to be very small indeed.

Lindquist & Ullberg (1972) have suggested that the affinity of drugs for melanin is an important mechanism also in the development of drug-induced ototoxic lesions. They point out that the anatomy of the inner ear is similar to that of the eye, in that melanin-bearing cells are situated in the vicinity of the sensory cells. In the inner ear, heavy deposits of melanin are normally present in the planum semilunatum of the ampullae and in the stria vascularis of the cochlea. These structures form the fluid that nourishes the receptor cells. Damage to these cells may thus occur secondarily to lesions in the melanin-containing cells. Lesions in the melanin-containing stria vascularis have been found almost constantly in animals treated with ototoxic drugs, such as certain antibiotics.

Dencker & Lindquist (1975) have studied the distribution of labelled chloroquine in the inner ear of young rats, using autoradiography. Results of their investigations showed that after intravenous injection of ^{14}C-chloroquine in a pigmented rat, there was a heavy accumulation and retention of the drug in the melanin-containing tissues of the inner ear, e.g. the stria vascularis in the cochlea and the planum semilunatum in the ampullae. No accumulation was observed in the endolymph, perilymph, sensory cells, and nerves. A high retention was observed as long as one year after the administration of a single dose of ^{14}C-chloroquine.

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[1] Summary quoted from Lindsay (1973), the original paper not being available to this reviewer.

According to the authors, an ototoxic effect of chloroquine may be caused by accumulation of the drug in the melanin-containing vascularized areas of the inner ear, leading to degenerative changes in the stria vascularis and other tissues. This may secondarily damage the receptor cells.

3.3 Myopathy

Myopathy, also referred to as neuropathy or neuromyopathy, is a further toxic effect following the inconsiderate use of chloroquine for the treatment of certain chronic diseases, mainly rheumatoid arthritis. Myopathy has been observed in patients receiving prolonged treatment courses with overdoses of chloroquine for symptomatic relief in diseases such as rheumatoid arthritis, arthritis, arthralgia, etc.

In the various reported cases the clinical picture of chloroquine myopathy was essentially the same: after several months of treatment with daily doses of 300 mg base, patients complained of weakness in their legs, they had difficulty in using their legs and were unable to climb stairs because of weakness in the thighs, but there was usually no pain or other sensory symptom. If treatment was continued, even at a reduced dose, the weakness in the legs increased, with distinct wasting of both quadriceps muscles, absence of knee and ankle reflexes, and generalized muscle weakness, involving also the upper limbs (Millingen & Suerth, 1966; Blom & Lundberg, 1965; Ebringer & Colville, 1967).

Loftus (1963) reported myopathy in four patients who developed progressive muscle weakness of the legs while receiving daily doses of 300 mg chloroquine base. The first symptoms appeared three to 11 months after the start of treatment. The dose was then reduced to 150 mg daily, but a few weeks later patellar and Achilles reflexes were absent and there was marked weakness of the quadriceps. When chloroquine was finally stopped (after five to 22 months of continuous treatment), recovery took several months, with very slow return of muscle function and reflexes. Ebringer & Colville (1967) reported the case of a 49-year-old patient who had been treated with 150 mg chloroquine base daily for three years, apparently for no other cause than "numbness and pain in the right shoulder". After 18 months her legs became weak, giving way beneath her, and she had difficulty in walking upstairs; after two years, she complained of blurred vision; and after three years of continuous therapy her muscles had become so weak that she could hardly get out of bed and, when walking, she had to hold on to furniture: all tendon reflexes were absent. In addition, she had developed keratopathy and retinopathy. Chloroquine was finally stopped, and after three months she had somewhat improved.

Histological examination of muscle biopsy specimens shows marked vacuolar degeneration of muscle fibres. In two fatal cases with cardiac involvement about 50% of the muscle fibres showed vacuolation (Hughes et al., 1971).

According to Hughes et al. (1971), most authors have attributed the muscular weakness to the myopathy, but some have suggested that there is neural involvement and the term "neuromyopathy" is sometimes used, although the evidence in the literature for central or peripheral nervous involvement is slender. According to other authors, e.g. Girard et al. (1973) and Karstorp et al. (1973), a neurogenic component is indicated by the absence of knee and ankle jerks with moderate or no weakness of the corresponding muscles.

Two cases of myopathy have been reported which were due to an overdosage of chloroquine taken for malaria suppression. These two cases are of interest in that they occurred in young, healthy persons, not suffering of diseases or taking other medication which could have contributed to the effect of chloroquine.

Girard et al. (1973) reported in detail the case of a 24-year-old African male nurse in Upper Volta who had been taking, for malaria prophylaxis, a daily dose of 400 mg chloroquine base since about three years, when the first symptoms of muscular weakness appeared. He then increased the dose to 600 mg base daily and continued for a further one-and-one-half years, when he had to be hospitalized because of extreme weakness, considerable weight loss, general amyotrophy and myasthenia and absence of knee and ankle reflexes. Microscopic examination of

a muscle biopsy specimen showed numerous vacuolar degeneration with the formation of true lacunae where the sarcoplasm had completely disappeared. Ophthalmological examination showed diffuse corneal opacities. Examination of the fundus was difficult because of the corneal deposits, but there seemed to be no major abnormalities. After seven months, recovery was nearly complete with respect to the neuromyopathy, but visual disturbances still persisted.

The second case was reported by Karstorp et al. (1973). A young Swedish woman living in Kenya took "for safety" 600-900 mg chloroquine base weekly instead of the prescribed 300 mg. After one year, she noticed a gradually increasing weakness in her legs; a month later it was found that knee and ankle reflexes were absent. She was transferred to Sweden where moderate atrophy of her thighs, marked weakness of hip flexion and absence of reflexes were noted. Routine investigations revealed no abnormality, but an electromyogram from the quadriceps muscle showed abnormalities consistent with a peripheral nerve lesion. Biopsy of the quadriceps showed no abnormalities. Chloroquine was discontinued and one month later muscle strength had improved and ankle jerks had returned. Three months later muscle strength and knee jerks were normal.

4. POSSIBLE TERATOGENIC EFFECTS OF CHLOROQUINE

4.1 Animal experiments

According to available data, the chloroquine doses required to demonstrate teratogenicity in animals (rats) are very high and hardly comparable with the doses needed for antimalarial purposes.

Dyban (1967) carried out studies on the effect of chloroquine on embryogenesis in rats, using oral doses from 250 mg to 1500 mg/kg body weight, corresponding to about 62 to 375 mg for a rat of 250 g. Chloroquine in a dose of at least 500 mg/kg increased the post-implantation mortality of embryos to 25%, as compared with 7-9% in the controls. Embryos on the ninth day of development were most sensitive to the drug. In order to produce malformations, a chloroquine dose of at least 550 mg/kg, given on the eighth or ninth day of development, was necessary. With a chloroquine dose of 1000 mg/kg, malformations were obtained in 47% of the embryos. Only the eyes, and no other organ, became malformed (kind of malformation not specified). This dose of 1000 mg/kg is 100 times higher than the maximum single dose recommended for humans.

Lindquist & Ullberg (1972), by means of whole-body autoradiography, studied the general distribution of chloroquine in various organs of albino and pigmented mice after intravenous injection of ^{14}C-labelled chloroquine. Non-pregnant mice and mice at early or late stages of pregnancy were used. Doses of chloroquine diphosphate ranged from 0.22 mg per non-pregnant mouse to 0.45 mg and 0.75 mg for mice at late or early stage of pregnancy, respectively. (It may be noted that these doses, though administered intravenously, are comparable to the oral doses used for antimalarial purposes in humans.) One of the important findings on embryo-toxicity was that in the pigmented pregnant mice the labelled chloroquine rapidly passed through the placenta wall and accumulated in the eyes of mouse foetuses. This occurred in the early as well as in the late stages of pregnancy. High accumulation of chloroquine was also observed in the inner ear of pigmented mouse foetuses at a late stage of development. Accumulation in the melanin-containing tissues was observed as early as five minutes after injection, thus indicating the likelihood of unchanged chloroquine being bound. No such accumulations were observed in albino mouse foetuses. The authors do not mention any malformations.

Landauer (1978) found that when carbachol or neostigmine is injected into chicken eggs concurrently with chloroquine, the incidence of malformations in chick embryos (short, crooked neck and muscle hypoplasia) is about twice that observed with each of the two cholinomimetic compounds alone. However, chloroquine alone, at the same dose, caused these effects, only on rare occasions, in the developing chick embryos. Among the embryos treated after 24 hours of incubation with 0.2 mg chloroquine/egg, three of the 73 survivors on the eighteenth day of incubation presented the typical neck muscle defects and hypoplasia of the leg muscles. But

treatment at later stages did not produce this effect. When about the same doses of chloro-quine were injected after 48, 72 and 96 hours of incubation, abnormalities of the eyes (enlargement or absence of eyes) were found in 2-9% of the surviving embryos. According to the author, the eye defects encountered in chick embryos treated with chloroquine might well be of similar origin as those recorded by Udalova (1967) in rat foetuses, the mothers of which had been treated with chloroquine (see also Dyban, 1967). However, the defects found in chickens were too scattered in incidence to be readily interpreted.

4.2 Observations in humans

Despite the wide use of chloroquine for over 30 years in malaria treatment and suppres-sion and, since 1953 or earlier, in the treatment of other diseases, few observations have been reported on the effect of chloroquine administration during pregnancy. Available information is limited to some random observations or to isolated cases. The few data which could be collected are given below.

Berberian & Dennis (1948) conducted a field trial in Lebanon in which the population under once weekly chloroquine administration included five women, four to eight months pregnant. Three of the women, who experienced acute attacks of malaria, were successfully treated with a three-day chloroquine course and subsequently maintained on a once weekly suppressive dose (300 mg base) for seven to 14 weeks. The other two women received only the once weekly suppressive dose for 11 and 18 weeks, respectively. All five women, while still on a once weekly chloroquine dose, were delivered of normal infants at term.

Watson et al. (1950) reported on a field trial carried out in Taiwan during which "10 pregnant women received the drug /300 mg chloroquine base once weekly for six months/ and eventually came to term and delivered normally. There were no cases of miscarriage or abortion during the study".

Kjaer (1955) reported the case of a woman five months pregnant taking one chloroquine tablet of 300 mg base once weekly for malaria prophylaxis. On one occasion she ingested an overdose of chloroquine, because the calcium tablets, which she also took, had been inadver-tently mixed with the chloroquine tablets. The patient had marked toxic reactions, including severe nausea and vomiting, double vision and depressed respiration. Recovery was complete after 36 hours, with no adverse effect on the pregnancy. It was impossible to determine the amount of chloroquine ingested. It could have been as much as 2.1 g of the base (seven tablets), or as little as 0.9 to 1.2 g base (three to four tablets). Four months later she was delivered of a healthy infant. Seen again when three years old, the child was normal in all respects.

Merwin & Winkelmann (1962) give the case history of one patient with lupus erythematosus who had had two spontaneous abortions and who delivered a normal healthy child after having taken 150 mg chloroquine base daily for one year and throughout her pregnancy. The authors state: "It is apparent that gestation may progress normally during therapy for lupus erythematosus with antimalarial drugs".

Dziubinski et al. (1962) reported their observations of six women with acute lupus erythematosus who had a total of 10 pregnancies and who were treated with steroids or both steroids and antimalarials /chloroquine/ during their pregnancies. They concluded that it is possible to use antimalarials of the 4-aminoquinoline type "in low and effective doses /presumably 150 mg base daily/ throughout pregnancy where indicated to control the toxic symptoms of systemic lupus erythematosus without adversely affecting the pregnancy. Both steroids and antimalarials may be used conservatively without harm to the mother or foetus".

Hart & Naunton (1964) were the first to suggest that chloroquine when used in excessive doses for the treatment of lupus erythematosus might cause injury to the human foetus. Their report is briefly summarized below.

The patient, a woman of 30, had been suffering from discoid lupus erythematosus since nine years and, during the last seven years, had had seven pregnancies. During four of her pregnancies - the second, third, fifth and sixth - she had been taking daily doses of 300 mg

chloroquine base. One of these pregnancies, the sixth resulted in an abortion, and the other three in children, all full-term but with certain congenital defects:

child 2, who had been exposed to a daily dose of 300 mg chloroquine base from week 0 to week 6 of gestation, was born apparently healthy. At the age of four years he had a left Wilms' tumour removed. At the age of six years, examination showed a hemihypertrophy of the left side, the left leg and the left arm being longer and larger than the right leg and arm.

The audiometry test and the vestibular system (caloric test) were normal. No results of funduscopic examinations are given for this child;

child 3, who had been exposed to 300 mg chloroquine base daily throughout the entire gestation period except for the first week, was born full-term. Immediately after birth he had a convulsion which recurred three times during the next six weeks, despite sedation with phenobarbital. Subsequent development was normal, but at the age of six months he was suspected to be deaf.

Otoneurological examination at the age of five years showed a marked bilateral symmetrical hearing loss. The caloric test indicated severe bilateral vestibular paresis. Locomotor ataxia and other signs seemed to indicate posterior column defects. Funduscopic examination revealed the same peripheral mottled pattern of the pigment and the same tigroid streak pattern as was present in the mother. (Child 3 died at the age of seven; see section 3.2);

child 5, who had been exposed to daily chloroquine doses throughout the entire gestation period, was born full-term but had a slow physical and mental development, understanding little of what was said to him.

When examined at the age of three years, it was not possible to test him audiometrically. Caloric tests showed severe bilateral vestibular paresis. Funduscopic examination showed the same uneven, peripheral distribution of the pigment as was present in child 3 and in the mother.

The children of the first, fourth and seventh pregnancy, who had not been exposed to chloroquine during gestation, were all apparently healthy, normal children. Audiometry and vestibular system tests were normal, but on none of these three children was funduscopic examination made.

Examination of the mother after she had been taking chloroquine "on and off for over 6 years" showed audiometry and caloric tests to be normal. Funduscopic examination of the eyes showed a "bilateral mottled appearance in the chorioretinal pattern. In addition, the periphery of the fundus revealed a very fine pigmentary change with occasional clumps of pigment, associated with areas of retinal thickening in a "tigroid streak pattern". The same pattern was found in the two children with hearing defects (child 3 and 5). Assuming that the mother had taken 300 mg chloroquine base daily for at least two years, the total amount of chloroquine ingested was about 220 g.

The paper by Hart & Naunton (1964) is certainly open to some criticism. The authors themselves admit that the chloroquine doses exceeded the maximum recommended doses (p. 410). The left hemihypertrophy of child 2 and the abortion which terminated the sixth pregnancy were probably not related to the chloroquine medication. For child 2, who had been exposed to chloroquine only during the first six weeks of gestation, audiometry and vestibular system tests were normal and, contrary to the authors' statement (p. 411), the presence of retinal pigmentary changes has not been proved for this child as no funduscopic examination seems to have been carried out. Nevertheless, the fact remains that two pregnancies, during which 300 mg chloroquine base daily had been taken continuously from week 0 or 1 to week 40, resulted in two children with congenital defects of the hearing system and with retinal pigmentary changes, the latter having been observed also in the mother.

The above findings reported by Hart & Naunton (1964) have given rise to considerable concern as to the safety of chloroquine during pregnancy and have led to a number of comments (Anonymous, 1964, 1965, 1971a; Klumpp, 1965; Stone, 1965), none of which refers to the unduly high doses used.

Paufique & Magnard (1969) reported a further observation suggesting that chloroquine, when taken at an excessive dosage during pregnancy, may have some harmful effect on the human foetus. A woman, while living in the Congo, had taken for malaria prophylaxis a daily dose of "2 tablets of Nivaquine" (tablets of 100 mg or 300 mg not indicated by authors) over a period of three years and throughout her two pregnancies. Later, the two children, aged 17 and 15 years, respectively, were living in France where they underwent an ophthalmological examination because of "retinal degeneration". The 17-year-old girl had suffered from reduced visual acuity since early childhood. Examination of the fundi showed small, scattered pigmentary deposits at the periphery, and a large pigmented and atrophic macular zone. The younger sister also presented central retinal degeneration, but there was no peripheral pigmentation. In the absence of other possible causes (examination of the parents was normal), the authors considered it highly probable that the Nivaquine medication of the mother during her pregnancies had been responsible for the retinal lesions in the two children.

Some important points of the above short note (Paufique & Magnard, 1964) require clarification. In particular, the chloroquine dose actually taken by the mother is not clear. On p. 466 it is stated that she took two tablets of Nivaquine daily. Nivaquine tablets may contain 100 mg or 300 mg chloroquine base. For daily malaria prophylaxis tablets of 100 mg are used and, in this case, the mother would have taken 200 mg daily, or twice the maximum recommended dose. However, in the last paragraph on p. 467, when stating that "1 tablet per week would have been sufficient", the authors obviously refer to tablets of 300 mg. In this case, the mother would have taken a daily dose of 600 mg base, or six times the maximum recommended dose. It would also be important to know for how many years the two children had lived in the Congo and whether they, too, had taken daily doses of Nivaquine for several years.

In the above case reported by Paufique & Magnard (1964) as well as in that reported by Hart & Naunton (1964), the chloroquine doses taken by the mothers for several years and throughout pregnancy were much in excess of those needed for malaria suppression. In all published comments and references to these two papers, this aspect of dosage and duration of therapy has been completely neglected.

It appears now well established that chloroquine, when taken at an excessive dosage for prolonged periods, accumulates in certain tissues, preferentially in the melanin-containing structures of the retina, and in the inner ear. There is also some evidence that chloroquine passes across the placenta; this is not surprising, since most drugs do so to some extent (Moya & Thorndyke, 1962). According to Soares et al. (1957), who carried out some studies in connexion with chloroquinized salt distribution in Brazil, chloroquine, given in daily doses of 20-45 mg base to pregnant women for three to five days before delivery, passes readily across the placenta, the drug content in the maternal and foetal blood being found to be the same in most cases. Experiments carried out in pregnant mice by Ullberg et al. (1970) and by Lindquist & Ullberg (1972) showed that chloroquine rapidly crossed the placenta and accumulated in the eyes of the foetuses, at both early and late late stages of development. At a late stage of development, high accumulation was also observed in the inner ear of mouse foetuses. While this is no proof that the same will occur in humans, the possibility should be kept in mind, and it would be prudent to advise against the use of heavy doses of chloroquine (more than 100 mg base daily) during pregnancy.

It has rightly been pointed out that the question of possible teratogenicity of chloroquine would never have arisen if chloroquine had been used exclusively for antimalarial purposes for which it was originally intended. The toxicity of chloroquine and other 4-aminoquinolines has been well evaluated with respect to the doses required for treatment and suppression of malaria, and with these doses only occasional minor side effects have been observed.

Since about 1954, chloroquine has been used also for long-term therapy of so-called collagen diseases, based on high daily doses the safety of which has never been established. (The highest dose that had been used was 300 mg base daily given to human volunteers for only 77 days - Alving et al., 1948.) Unexpected toxic effects occurred and received wide publicity, without relating these effects to the unduly high and prolonged dosage used. This created widespread though unfounded alarm regarding the safety of chloroquine for antimalarial purposes.

During the general discussion of a Symposium on Malaria (Cahill, 1969), held by the Tropical Disease Center, St Clare's Hospital, New York, and the Merck Company Foundation, in May 1969, several participants once more raised the question of whether or not chloroquine could safely be given for malaria prophylaxis during pregnancy, especially during the first trimester. Answers were as follows:

According to Dr Cahill, Director of the Tropical Disease Center:

"Chloroquine has been very widely used for many years throughout the world and there are no documented examples of human teratogenic side effects." . . . "Chloroquine, therefore, can be prescribed for women at all stages of pregnancy, and should be prescribed for those entering malarious areas."

A more detailed answer, based on personal experience, was given by John Frame:

"I take care of Protestant missionaries and their families. During the past 15 years I have taken care of approximately 1,000 women of the child-bearing age who have taken chloroquine for varying periods. I do not know of a single complication from this drug, and I have very good records of these women and their children. There are about 3,500 children in these families. I do not know of any case of teratogenicity we could ascribe to chloroquine. I do know of two or three persons who had children born with major deformities, but these have been divided between those who have taken chloroquine and those who never did. I think statistically we could say that chloroquine probably can be completely acquitted of responsibility."

It should have been added that these statements refer to the chloroquine doses normally used for malaria treatment or prophylaxis, and that these doses have proved perfectly safe to the human foetus, in contrast to the much higher doses which are used for long-term therapy of collagen diseases and which may not be equally safe.

Taking into account the very wide use of chloroquine as an antimalarial for some 30 years, it can reasonably be assumed that any increased incidence of congenital malformations following the use of chloroquine for treatment or suppression of malaria would certainly have been noticed, and sooner or later would have been reported.

RESUME

Le présent document est le deuxième d'une série passant en revue les effets pharmacologiques et toxicologiques des antipaludiques d'usage courant. Les effets toxiques de la chloroquine, qui appartient au groupe des amino-4 quinoléines, dépendent de la posologie et de la durée d'administration du médicament qui eux-mêmes sont fonction de l'affection traitée. Aux doses recommandées pour le traitement suppressif ou curatif du paludisme, les effets secondaires sont rares et lorsqu'il s'en produit, ils sont habituellement bénins et consistent généralement en troubles gastro-intestinaux, en vertiges et en céphalées; on peut réduire leur incidence à un très faible niveau en évitant des doses excessives et ne prenant pas la chloroquine à jeun. A l'occasion, des prurits et une pigmentation cutanée peuvent également se produire.

Des effets toxiques aigus suivant l'ingestion d'une surdose massive de chloroquine ont été signalés dans des cas d'intoxication accidentelle chez les jeunes enfants et d'empoisonnement volontaire chez les adultes. La littérature publiée disponible (1961-1968) sur l'intoxication aiguë par la chloroquine chez les enfants porte sur 25 cas, âgés de 17 mois à 6 ans, dont 5 ont survécu. Par ailleurs, l'intoxication délibérée par ingestion d'un grand nombre de comprimés de chloroquine est devenue une méthode fréquemment usitée de suicide ou de tentative de suicide et la littérature (1955-1978) sur de tels cas est déjà abondante. Sur les 335 cas d'intoxication volontaire qui ont été rapportés, 135 ont eu une issue fatale.

Après avoir passé en revue les effets secondaires mineurs et les effets toxiques aigus de prises uniques élevées, le document étudie les effets toxiques chroniques de la chloroquine. Peu après son introduction comme antipaludique, la chloroquine, qui est également un anti-inflammatoire, a été de plus en plus utilisée pour le traitement des "maladies du collagène", surtout de l'arthrite rhumatoïde et du lupus érythémateux, dont le traitement symptomatique implique l'administration prolongée de doses beaucoup plus élevées (doses quotidiennes de 150 à 750 mg de chloroquine base par exemple) que pour le traitement du paludisme. L'usage généralisé de la chloroquine pour ces maladies s'est accompagné de diverses réactions toxiques non décelées auparavant, attribuables à l'accumulation sélective du médicament dans certains tissus et, en particulier, à son affinité avec la mélanine contenue dans certains tissus, les tissus oculaires par exemple. Ces réactions adverses comprennent des complications oculaires, des effets ototoxiques et des myopathies.

A la suite de l'administration prolongée de chloroquine à dose élevée, deux sortes d'affections oculaires ont été observées : des kératopathies, consistant en opacités cornéennes, et des rétinopathies, consistant en modifications du fond de l'oeil. La fréquence des kérato-pathies est difficile à estimer. L'incidence signalée varie considérablement d'un auteur à un autre. Cependant, on peut s'attendre à l'apparition d'une kératopathie chez 10 à 50 % des malades auxquels sont administrées des doses élevées de chloroquine pendant de longues périodes. Les modifications cornéennes n'entraînent pas d'altération permanente de la vision et sont toujours réversibles. Les lésions rétiniennes sont moins fréquentes que les kératopathies, mais beaucoup plus graves; si elles ne sont pas reconnues au stade asymptomatique précoce, elles risquent de provoquer une altération permanente de la vision et même la cécité. Plusieurs cas d'altérations oculaires (dépôts cornéens, modifications pigmentaires de la rétine, par exemple) ont été observés après 10 ans ou plus d'administration quotidienne de 100 mg de chloro-quine base. En revanche, il n'y a pas de preuve documentée de lésion rétinienne provoquée par le médicament administré à raison de 300 mg de chloroquine base par semaine.

La chloroquine a également été incriminée comme cause de "surdité nerveuse". Toutefois, si l'association entre les affections oculaires et l'administration prolongée de doses élevées du médica-ment paraît bien établie, il n'en est pas de même en ce qui concerne les lésions auditives, dont l'incidence semble extrêmement faible.

Des myopathies, appelées aussi neuropathies et neuromyopathies par certains auteurs, ont été observées chez des malades en traitement prolongé recevant des surdoses de chloroquine pour le soulagement symptomatique de maladies du collagène telles que l'arthrite rhumatoïde, l'arthrite et l'arthralgie.

En dernier lieu, le document étudie les effets tératogènes possibles de la chloroquine. Selon les données expérimentales disponibles, les doses de chloroquine requises pour mettre en évidence un effet tératogène chez les animaux (rats) sont très élevées et peu comparables aux doses utilisées pour le traitement antipaludique. Chez les humains, seules quelques observa-tions sur les effets de l'administration de chloroquine pendant la grossesse ont été rapportées; en fait, la question d'une action tératogène possible de la chloroquine n'aurait jamais été soulevée si le médicament avait été utilisé exclusivement pour le traitement antipaludique. Compte tenu du large emploi qui est fait de la chloroquine comme antipaludique depuis quelque 30 ans, on peut raisonnablement supposer que toute augmentation de l'incidence des malforma-tions congénitales à la suite de l'administration de chloroquine pour le traitement suppressif ou curatif du paludisme aurait certainement été remarquée et signalée.

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