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Antimalarial Drugs in Systemic Lupus Erythematosus

Use in Pregnancy

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Contents

Abstract

The 4-aminoquinoline radical containing antimalarial drugs are also used in the management of various connective tissue diseases including sytemic lupus erythematosus (SLE) and rheumatoid arthritis. These agents are particularly useful for the management of inflammatory polyarthritis and skin disease. By raising the pH in intracellular compartments, these drugs interfere with normal phagocytic function which consequently enables them to interfere with antigen processing. Other actions include inhibition of platelet aggregation, this is advantageous in patients with phospholipid antibodies (aPL) which are known to predispose patients to recurrent arterial and venous clinical thrombotic events. Hydroxychloroquine has also been demonstrated to reduce serum lipid levels including cholesterol, triglycerides and low density lipoproteins. As it is now known that patients with SLE are at risk for accelerated artherogenesis and premature heart disease, this action may be an added benefit for these patients.

The use of the 4-aminoquinoline radical containing antimalarial drugs during pregnancy is controversial. It is known that these agents can cross the placenta and are deposited in fetal pigmented tissues. These findings have led to the recommendation that these agents should be discontinued in pregnancy for patients with connective tissue diseases even though they have long been recommmended for malarial prophylaxis in pregnant women travelling to malarial infested areas. Flares of SLE disease have been documented when these agents are discontinued and as flares of SLE disease activity are known to be detrimental to pregnancy

outcome in patients with SLE, it is our opinion that these drugs should not be discontinued during pregnancy in a patient with lupus, particularly when the known terminal elimination half life is 1 to 2 months.

1. Introduction

The 4-aminoquinoline antimalarial drugs are anti-inflammatory agents useful for managing patients with discoid lupus erythematosus and systemic lupus erythematosus (SLE).[1-3] These agents are excellent at controlling both the cutaneous and the arthritic manifestations of SLE but they are not indicated for major organ involvement such as renal or cerebral disease.[3] What makes these drugs particularly beneficial for the patient with SLE is that in addition to their anti-inflammatory effect, they also inhibit platelet aggregation,[4,5] making them even more desirable for patients with SLE who also have phospholipid antibodies (aPL) syndrome. Patients with aPL syndrome are predisposed to develop recurrent venous and/or arterial thromboses,[6,7] and one manifestation of this syndrome is recurrent fetal wastage.[8-10] The 4-aminoquinoline antimalarial agents also have the ability to lower serum lipid levels,[11,12] which is obviously useful as patients with SLE are known to be predisposed to develop accelerated atherogenesis and coronary artery disease.[13,14] These 4-aminoquinoline antimalarial drugs are well tolerated in combination with other anti-inflammatory agents such as prednisone, making them important steroid-sparing agents.

Previous studies have demonstrated that stopping the 4-aminoquinoline antimalarial drugs can precipitate a flare of SLE[15,16] and therefore it is our opinion that these drugs should be continued long term in patients with SLE who can tolerate them. As disease activity is associated with increased morbidity for the pregnant patient with SLE and for the developing fetus,[17-19] it really makes no sense to discontinue these agents during pregnancy, particularly if she has aPL syndrome, unless the potential fetal toxicity of these agents outweighs the potential benefits for both mother and fetus. These agents do cross the placenta, and animal studies have demonstrated that they are deposited in fetal tissues.[20] Managing a pregnant patient with SLE who is dependent on the 4-aminoquinoline antimalarial drugs for SLE disease control therefore poses a difficult therapeutic decision. This review discusses the advantages and drawbacks for continuing the 4-aminoquinoline antimalarial drugs throughout pregnancy and the reasons we favour continuing these agents in patients with lupus who become pregnant.

2. Systemic Lupus Erythematosus and Pregnancy

Although some reports have suggested that pregnancy is not associated with flares of SLE disease activity,[21,22] earlier papers had suggested that patients with lupus were more likely to experience flares of disease during pregnancy and the postpartum period.[17,18] Unlike patients with rheumatoid arthritis, 80% of whom can expect a remission of their disease during pregnancy,[23] some patients with SLE improve clinically, some deteriorate and some remain clinically the same during pregnancy.[17] At least 8% of patients with lupus entering pregnancy after the onset of known renal disease can expect a permanent deterioration of renal function.[19] Pregnancy is therefore a particularly dangerous time for the patient with SLE, not only because of the risk of flares of the disease and end organ damage, but also because of a risk of complications of pregnancy such as hypertension and pre-eclampsia.[24,25] Patients with SLE also have an increased rate of fetal wastage and preterm births,[17,18,26] and one recent study reported a neonatal death rate of approximately 10%.[27] One of the factors known to contribute to this increased fetal wastage is disease activity at the time of conception or during the course of the pregnancy.[17,18]

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3. Phospholipid Antibodies and Pregnancy

aPL are associated with an increased predisposition to both arterial and venous thrombosis, and the aPL syndrome is now considered part of the spectrum of autoimmune disease.[6,7,28,29] Some patients with aPL are at risk for recurrent clinical thromboses, although approximately 40% of patients with aPL never experience rethrombosis.[30] Patients who do rethrombose usually develop clinical thrombosis on the same side of the vascular tree. Recent evidence has suggested that a 'second hit' phenomenon is required to trigger clinical thrombotic events in these patients with aPL.[31] These second hit phenomena include pregnancy, the postpartum period, oral contraceptive use, infections and flares of lupus disease activity in patients who have SLE. The pathogenesis of the thrombotic diathesis in patients with aPL remains unclear,[32,33] but many of these second hit phenomena are physiological or pathological states that are known to be prothrombotic.

Recurrent fetal wastage is one of the well recognised clinical presentations seen in patients with aPL,[8-10] and patients with SLE who have additional factors, such as the presence of aPL, can expect increased fetal wastage.[9,10] Patients with aPL syndrome develop placental infarcts that leads to placental insufficiency.[34,35] In addition, the placenta frequently has poor implantation and uterine wall invasion, leading to defective placentation which may be a consequence of disruption of the annexin-V antithrombotic shield.[36] It has been suggested that the pathogenesis of 80% of fetal wastage occurring after 10 weeks' gestation occurs in patients who have aPL syndrome.[37]

Pregnancy is one of the known second hit factors that puts patients with aPL at risk for clinical thrombotic events during gestation and the postpartum period. A flare of SLE disease activity is also a known trigger for clinical thrombosis, so it is very apparent that SLE disease activity should be inhibited at all costs in patients with SLE and aPL syndrome, especially those who are pregnant.

4. The 4-Aminoquinoline Radical-Containing Antimalarial Drugs

4.1 Pharmacokinetics

Chloroquine and hydroxychloroquine are 4-aminoquinoline derivatives.[38,39] They have similar structures, differing only by the replacement of an ethyl group in chloroquine with a hydroxymethyl group in hydroxychloroquine.[39] The plasma half-life of these drugs is about 3 days[40] and their terminal elimination half-life is 1 to 2 months.[41] There is wide tissue distribution, with accumulation in muscle, liver, spleen, kidney, lung, blood cell colonies, adrenal and pituitary glands, and melanin-containing tissues.[42] It is the tissue deposition in the retina that gives major cause for concern, as this is irreversible and can lead to vision loss.[43,44] Careful monitoring can prevent this complication.[45] The tissue deposition of chloroquine has been demonstrated to be approximately 2.5-fold greater than that of hydroxychloroquine[46] and, therefore, chloroquine binds more avidly to corneal and retinal tissues, increasing the risk of retinal toxicity, which is known to be directly related to the total amount of drug given.[47] The major metabolite of these agents is desethylchloroquine, which can reach serum concentrations one-third as great as those of the parent compound.[48] The principal excretory route is via the kidney, and it should be mentioned that these drugs can be found in the urine more than 2 weeks after stopping the medication.[49]

4.2 Mechanisms of Action

The 4-aminoquinoline antimalarial agents are weak bases which enter lysosomal and other acidic compartments, where they are protonated. Once in these acidic intracellular compartments, they raise the pH, thus interfering with the normal phagocytic function of subcellular components that depend upon an acidic milieu.[50] This mechanism of action has many secondary effects that include interfering with receptor recycling, intracellular processing and secretion of proteins, and antigen processing by influencing the binding of antigenic

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peptides to major histocompatibility complex class II molecules.[51-53] These immune effects result in decreased lymphocyte proliferation, interference with natural killer cell activity and alteration of autoantibody production.[54,55] These properties result in decreased production of cytokines and other inflammatory mediators, including the inhibition of phospholipases, antagonism of prostaglandins, stabilisation of lysosomal membranes, decreased release of fibronectin by macrophages and blockage of release of superoxide radicals.[56-59] Defective apoptosis (programmed cell death) is considered to be an important factor contributing to the development of autoimmune disease. Hydroxychloroquine can induce apoptosis in peripheral blood lymphocytes.[60]

As patients with aPL syndrome are predisposed to recurrent clinical thromboses, the inhibition of platelet aggregation and adhesion is particularly useful for the patient with SLE who also has aPL. These patients get a dual benefit from the antimalarial drugs because they are less likely to develop thrombosis and are also less likely to experience a flare of SLE, a known second hit for triggering thrombosis.[30,31]

The lipid-lowering effect of hydroxychloroquine is also particularly useful for patients with SLE, as these patients are known to be at increased risk for developing accelerated atherogenesis and premature coronary artery disease.[13,14] The reason for accelerated atherogenesis in patients with SLE remains unclear, but it is almost certain that the small-vessel vasculitis of SLE contributes to this pathology.[61] We now know that the development of atheromatous plaques is associated with inflammation.[62,63] Corticosteroids are known to elevate serum lipid levels and it has been suggested that corticosteroid therapy, rather than the disease itself, may contribute to this accelerated atherogenesis,[64,65] which is most unusual in young, premenopausal women. Recently, Rahman et al.[66] demonstrated that the lipid-lowering effect of antimalarial drugs was particularly beneficial for patients with SLE who were also taking corticosteroids. The mean serum total cholesterol level was 11% less in patients with SLE taking both corticosteroids and antimalarial drugs than in those taking corticosteroids alone. These findings confirm a previous study by Wallace et al.[12] that demonstrated significant lowering of serum total cholesterol, triglycerides and low density lipoprotein-cholesterol in patients taking hydroxychloroquine. Therefore, the lipid-lowering effect of hydroxychloroquine is an important tool for preventing the secondary effects of SLE that contribute to a bimodal pattern of mortality.[67]

5. Antimalarial Drugs in Pregnancy

Before the malarial parasite developed resistance to the 4-aminoquinoline drugs, hydroxychloroquine was routinely recommended as a treatment of choice for pregnant women travelling to areas where malaria was endemic[68,69] and these drugs were considered 'completely safe during pregnancy'.[69] Contrary to this opinion, however, it is known that the 4-aminoquinoline antimalarial agents do cross the placenta, and Ullberg et al.[20] demonstrated deposits of radiolabelled metabolites of chloroquine in fetal eyes after administering the drug to pregnant mice.

A single case report by Hart and Naunton[70] suggested that congenital disease can occur in offspring exposed to chloroquine *in utero*. These authors described a mother with discoid lupus disease who had seven pregnancies. Throughout three of these she took chloroquine, and in each case the offspring demonstrated a congenital abnormality, leaving the authors to conclude that 4-aminoquinoline antimalarial drugs should be contraindicated during pregnancy.[70] In some instances, treatment with 4-aminoquinoline antimalarial drugs has been grounds for therapeutic termination of pregnancy,[71] which could be argued more strongly if mepacrine (quinacrine) had been taken, as this agent is known to be mutagenic and is known to cause non-surgical sterilisation.[72]

It is difficult to understand how these agents have been used for malarial prophylaxis for many years without apparent fetal toxicity and yet there is a major controversy over their use in pregnant patients

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who have a rheumatic disease. One suggestion has been that the dosage required for malarial prophylaxis (chloroquine phosphate 500 mg/week) is much lower than that required for controlling SLE.[73]

As it is known that the risk of retinal toxicity is related to the total amount of drug given, the current policy for minimising retinal toxicity is to ensure that the daily dosage of hydroxychloroquine does not exceed 6.5 mg/kg in adults.[74] While receiving this drug, patients are also advised to have retinal field eye examinations every 6 to 12 months. Obviously, a dosage that is safe for the developing fetus has not been determined. Fetal toxicity would be expected to be greater with chloroquine than with hydroxychloroquine because of the greater tissue deposition of chloroquine.[46] The problem is that the half-life of these drugs is so long that unless the patient plans for the pregnancy and stops the antimalarial drugs several months before conception, the fetus will still be exposed throughout the entire period of organogenesis even if the antimalarial drug is discontinued as soon as the pregnancy is discovered.

5.1 Breast Feeding

Both hydroxychloroquine and chloroquine are weak bases and are therefore secreted in breast milk. The current belief is that administration of these drugs is compatible with breast feeding, and previous studies have suggested that a nursing infant will ingest between 2.2 and 4.2% of the maternal dose of chloroquine over a 9-day period.[75] However, studies investigating breast milk secretion in the steady state for both hydroxychloroquine and chloroquine are lacking and need to be performed.

6. The University of Connecticut Health Center Experience

It is current policy in the Rheumatology Clinic at the University of Connecticut Health Center to recommend that any woman with SLE who becomes pregnant while taking a 4-aminoquinoline antimalarial drug should continue to receive that drug through pregnancy (table I). Compared with chloroquine (greater tissue deposition), we prefer our patients to receive hydroxychloroquine during pregnancy if at all possible.

Because of concerns for potential fetal toxicity, some women with SLE who are planning a pregnancy wish to discontinue the 4-aminoquinoline drugs before conception. These patients are advised to discontinue the drug at least 3 months before attempting to conceive. They are also in-

Table I. Current recommendations for the use of antimalarial drugs during pregnancy[a]

Unplanned pregnancy	
Patient with SLE	Continue antimalarial drugs
Patients with SLE and aPL syndrome	Continue antimalarial drugs, anticoagulate with therapeutic heparin and low dose aspirin
Patient with primary aPL syndrome	Continue antimalarial drugs, anticoagulate with therapeutic heparin and low dose aspirin
Planned pregnancy	
Patient with uncomplicated SLE	Observe for disease activity if antimalarial drugs are discontinued
Patients with complicated SLE	Add in or increase corticosteroids and observe for disease activity if antimalarial drugs are discontinued
Patients with SLE flares after discontinuation of antimalarial drugs	Restart antimalarial drugs or add/increase prednisone and wait 6 months after disease is under control prior to conception
Patient with SLE and aPL syndrome	Advise patient to continue antimalarial drugs and anticoagulate with heparin and low dose aspirin
Patient with primary aPL syndrome	Anticoagulate with heparin and low lose aspirin

a In each situation, the advantages and drawbacks of continuing or discontinuing the 4-aminoquinoline antimalarial drugs during pregnancy must be discussed at length with the patient. If the patient wishes to discontinue antimalarial drugs, this should be done a minimum of 3 months prior to attempting conception. If antimalarials are continued, hydroxychloroquine, at the lowest possible dosage, is the antimalarial drug treatment of choice during pregnancy.

aPL = antiphospholipid antibody; **SLE** = systemic lupus erythematosus.

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Table II. Maternal disease activity, presence of antiphospholipid antibody (aPL) and pregnancy outcome in patients with systemic lupus erythematosus receiving hydroxychloroquine (HCQ) therapy during pregnancy (patients 2, 5 and 10 each had two pregnancies)

Patient no.	HCQ dosage (mg/day)[a]	Other medications[b] (daily dosage)	Pregnancy outcome	Maternal disease activity	Presence of aPL
1	200	Prednisone 40mg	LB 35wk	Active at first visit	No
2a	200	Prednisone 5mg	LB 39wk	No	No
2b	200	Prednisone 5mg	LB 38wk	No	No
3	200	Prednisone 20-40mg, SC heparin, aspirin	LB 31wk	Mild and intermittent during pregnancy	Yes
4	200 qod	None	LB 40wk	No	No
5a	200	Prednisone 40mg	LB 31wk	Persistently low platelets	No
5b	200	Prednisone 60mg	LB 35wk	Yes	No
6	200	Prednisone 10mg, aspirin	LB 39wk	No	Yes; LAC(+)
7	200	Prednisone 10mg	LB 33wk	Flare after discontinuing HCQ	No
8	200	Prednisone 10mg	LB 35wk	No	No
9	200	Prednisone 10mg	LB 40wk	Active disease at first visit	No
10a	200	Prednisone 15-40mg	LB 36wk	Flare after discontinuing HCQ	No
10b	200	Prednisone 60mg	LB 35wk	Yes	No
11	200	Prednisone 20mg, SC heparin, aspirin	LB 36wk	Mild	Yes

a Unless otherwise specified.

b Administered orally unless otherwise specified.

HCQ = hydroxychloroquine; **LB** = live birth; **LAC(+)** = lupus anticoagulant positive; **qod** = every other day (quaque altera die); **SC** = subcutaneous.

formed that there is a risk of a disease flare and that this could be detrimental to the pregnancy. Our general recommendation for patients with SLE who wish to become pregnant is that their disease should be in remission for at least 6 months before conception.

Our most recent experience with antimalarial drugs being taken during pregnancy is described in table II. Some of the data have been published previously,[76] but these have been updated and include additional patients and pregnancies. In our case series, patient numbers 7 and 10 experienced a flare of SLE when hydroxychloroquine was temporarily discontinued but fortunately the disease was controlled by increasing the dosage of or adding prednisone and restarting the antimalarial drug. It was difficult to control the SLE in patient number 10 during her second pregnancy, and it required increasing dosages of prednisone which in turn aggravated her gestational diabetes.

We now also have long-term information on the development of some of the offspring born to these mothers with SLE. The range of follow-up for the offspring of these pregnancies is 3 months to 24 years. To date none of the offspring have demonstrated any evidence of retinal or other toxicity known to be associated with exposure to 4-aminoquinoline antimalarial drugs, although formal ophthalmological and auditory testing has not been done in all of these children. One male child, born to patient 7, has developed dyslexia, a condition that is known to occur more frequently in male offspring born to mothers with SLE.[77] As far as we know, this problem has never been attributed to the 4-aminoquinoline drugs but appears to be a complication of the mother's disease.

7. Other Published Reports

There are now a small number of published reports documenting continued use of these drugs in the pregnant patient with a rheumatic disease.[78-81] Despite the troubling report from Hart and Naunton,[70] more recent papers suggest that these agents do not pose a serious risk to the fetus even at dosages required to control rheumatic diseases. In a study of 27 pregnancies in 24 months, Levy et al.[78] concluded that neither chloroquine nor hydroxychloroquine appeared to be teratogenic, but they still recommended discontinuing the drug because of

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the cumulative toxic effect. On the other hand, Toubi et al.[79] also reported a similar lack of fetal toxicity in offspring exposed to these agents throughout pregnancy, and recommended continuation of drug therapy throughout pregnancy because of the risk of precipitating a flare of SLE. A small (n = 22) but recent double-blind, placebo-controlled trial of hydroxychloroquine in pregnant patients with systemic or discoid lupus erythematosus determined that, compared with placebo, those receiving hydroxychloroquine had fewer flares of disease and a significant improvement in SLE disease activity index score (SLEDAI) at delivery.[81] The offspring of the patients exposed to hydroxychloroquine did well, and eye and ear examinations at between 1.5 and 3 years of age revealed no clinical deficits.[81] These reports and our current experience with pregnant patients with SLE documented in table II reinforce our opinion that treatment with these agents should be continued throughout pregnancy (see table I). Hydroxychloroquine is preferable to chloroquine and mepacrine must be avoided at all costs.[72]

8. Conclusions

It is clear that the 4-aminoquinoline antimalarial drugs are useful for treating patients with SLE and that discontinuation of treatment with these agents can lead to flares of SLE.

As disease activity is known to be an important factor for determining the outcome of pregnancies in patients with lupus, it does not make sense to discontinue these agents in a patient with SLE just because she is pregnant, particularly as a flare of disease could put both the mother and the fetus at risk. It is also important to remember that these drugs have a very long half-life and stopping treatment as soon as pregnancy is discovered will expose the fetus to the drug throughout the entire period of organogenesis.

Although the numbers of patients who have received these drugs during pregnancy remain small in the rheumatological literature, there is now a growing belief that it is probably not necessary to discontinue these agents, particularly hydroxychloroquine, during pregnancy. In some particularly litigious societies, however, change comes more slowly and, therefore, this trend of continuing antimalarial drugs during pregnancy is occurring more frequently in Europe than it is in the US. With the information we now have, it could be argued, however, that discontinuing the antimalarial drug during pregnancy poses a greater risk to a woman with SLE than if the drug were continued as it was antepartum.

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