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Dapsone Therapy for Malaria During Pregnancy

Maternal and Fetal Outcomes

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Abstract

The need to consider using dapsone in pregnant women for its antimalarial activity is becoming greater in areas where *Plasmodium falciparum* resistance to chloroquine and pyrimethamine-sulfadoxine is rapidly increasing. Dapsone in combination with other antimalarials might provide a valuable alternative for both treatment and prophylaxis. This review assesses the clinical pharmacology of dapsone and its adverse drug reactions in relation to haemolysis, glucose-6-phosphate dehydrogenase (G6PD) deficiency, blood dyscrasias and methaemoglobinaemia. Studies are summarised reporting its use in leprosy, dermatological and other conditions, and malaria, in relation to maternal and infant outcomes. A total of 924 pregnancies were identified during which dapsone therapy was taken. Only limited data are available and this precludes a meaningful quantitative benefit-risk analysis.

Mild degrees of haemolysis consistently occur with continued therapy, although adverse effects may be less likely with intermittent treatment, as most reported adverse effects have occurred with long-term use of dapsone. There are a

number of gaps in knowledge where more data are needed. These include no data on pharmacokinetics in pregnancy and whether these are altered with co-administration of chlorproguanil. Potential complications in women with severe anaemia are unknown and there is no information on haemolytic effects in women or the fetus with G6PD deficiency. The use of dapsone in HIV-infected women in malarious areas could carry increased risks because of the immunosuppressive actions of the drug. Trials of dapsone therapy in pregnancy should be considered in malarious areas where there is good reason for its deployment. Controlled trials have provided data on maternal tolerance, and dapsone in combination with other antimalarial drugs can offer clear benefit in terms of improved birthweight. The use of dapsone combinations should be considered when no good alternative is available and the threat of malaria is the greater risk.

The need to consider using dapsone in pregnant women for its antimalarial activity is becoming greater in areas where *Plasmodium falciparum* resistance to chloroquine and pyrimethamine-sulfadoxine is increasing. Dapsone in combination with other antimalarials might provide a valuable alternative for both treatment and chemoprophylaxis. Dapsone acts against bacteria and protozoa in the same way as sulphonamides, by inhibiting the synthesis of dihydrofolic acid through competition with para-aminobenzoate for the active site of dihydropteroate synthetase. It has been used in combination with pyrimethamine (as Maloprim®)[1] for malaria prophylaxis in pregnancy in only two studies, and two further studies report on its use for treatment of malaria during pregnancy. In one study it was given in combination with chlorproguanil, and with pyrimethamine in the other. In view of the limited experience with the use of dapsone during pregnancy for malaria, this review assesses studies reporting its use for leprosy, dermatological disorders and other conditions in pregnant women. The clinical pharmacokinetics and adverse effects of the drug are reviewed and considered in relation to maternal and infant outcomes. The need to evaluate the drug for treatment of malaria in pregnancy is discussed.

1. Clinical Pharmacology of Dapsone

Dapsone is slowly absorbed after oral administration, and peak serum or plasma concentrations are reached at about 2–6 hours, but considerable variation may occur. A mean absorption half-life of 1.1 hours after oral dapsone 100mg has been reported.[1] Absolute oral bioavailability is calculated to exceed 85%.[2] Serum/plasma concentrations following different doses suggest a linear association between increase in maximum concentration (C_{max}) with an increase in dose (50mg single dose, mean C_{max} 0.72 mg/L; 300mg single dose, mean C_{max} 4.82 mg/L).[3] Steady-state concentrations after daily administration are about twice as high as those resulting from a single dose. About 70–90% of dapsone is bound to plasma protein. The elimination half-life in volunteers ranged from 14.6–82 hours.[2,3] Generally, 90% of a single 100mg dose of dapsone will be eliminated within 9 days.[3] The pharmacokinetics is also influenced by co-administration of rifampicin (rifampin) administered monthly.[4] Three days after rifampicin the elimination half-life of dapsone was reduced from 40.4 to 25.3 hours. Despite this considerable influence the authors considered there was no reason to adjust dapsone doses. The reason that dapsone doses are not adjusted with concomitant intake of rifampicin has its explanation in the fact that blood concentrations normally obtained are already far above the minimum inhibitory concentra-

1 The use of trade names is for product identification purposes only and does not imply endorsement.

tion (MIC). Thus, upon halving of these concentrations, they still remain far above the MIC, but this may be different in other applications.

Dapsone seems to be widely distributed throughout the tissues, crosses the placenta[5,6] and is excreted in breast milk,[7,8] saliva,[1] urine and faeces.[3] Sulphones have been reported in the urine of infants of breast-feeding mothers,[7] showing that dapsone is significantly secreted in breast milk. Concentrations in breast milk of 439 μg/L have been reported in mothers receiving dapsone 50mg daily.[8] The volume of distribution is 1–2L.[3] Pharmacokinetics of dapsone may be different in pregnant women because of dynamic physiological changes, influencing absorption, distribution and elimination, but no data on pharmacokinetics in pregnancy have been reported.

The main metabolite is mono-acetyl dapsone (MADDS), which has a similar half-life to dapsone.[3] Acetylation and deacetylation take place and a constant equilibrium is reached within a few hours of oral administration. The acetylation ratio (ratio of concentration of MADDS to dapsone) shows large inter-individual variation (0.1–2.0), which arises because the activity of N-acetyltransferase is genetically determined. The frequency of these genes controlling acetylation rates varies geographically. No relationship between acetylation capacity and incidence of adverse effects has been demonstrated for dapsone and the therapeutic response is the same in both acetylator phenotypes.[3]

Hydroxylation is the second pathway of dapsone metabolism and may be responsible for the drug's haematological adverse effects.[3] In rats the rank of toxicity agreed with the formation of the hydroxylamine metabolite *in vitro*.[9] N-Hydroxylation of dapsone is by multiple enzymes of the cytochrome P450 (CYP) system, particularly by CYP2C8/9.[10] The levels of expression of these CYP enzymes may be an important determinant of individual susceptibility to the toxic effects of dapsone, and may influence the ability of enzyme inhibitors to block dapsone toxicity *in vivo*.[11] Inductors of CYP enzymes reduce the half-life of dapsone, probably through increased formation of N-hydroxy dapsone.[12] Dapsone and its metabolites are eliminated primarily by urinary excretion, predominantly in the form of glucuronide conjugates. Only minor amounts of MADDS or its conjugates are found in the urine. N-hydroxylation is a major metabolic pathway as up to 40–50% of the excreted dapsone may consist of N-hydroxy metabolites. Analysis of bile revealed the formation of dapsone hydroxylamine and its glucuronide in rats and humans.[9]

Genetic factors are therefore likely to be important in relation to dapsone toxicity because of hydroxylation. Clustering of cases of hyperpigmented dermal macules, which occurred in 4% of children following administration of pyrimethamine-dapsone for malaria chemoprophylaxis, suggested the possible involvement of genetic factors in the pathogenesis of these skin lesions.[13] Race-linked differences in serum concentrations of dapsone and MADDS have also been described during malaria prophylaxis, which may partly have a genetic basis.[14]

2. Adverse Drug Reactions with Dapsone

Dose recommendations are empirical and not established on the basis of pharmacokinetics. The most frequent adverse effects are haemolysis and methaemoglobinaemia. Other adverse effects are rare, especially at doses <300 mg/day.[15] At concentrations <5 mg/L (which is within the therapeutic range) the risk of dapsone-dependent adverse effects is very low. Deaths associated with its administration have been rarely reported and occur from agranulocytosis, aplastic anaemia and other blood dyscrasias.[16,17]

The toxic dose of dapsone is close to its therapeutic dose. While severe poisonings have been observed after doses of 1–1.5g in adults,[18,19] recovery without sequelae has been reported in adults after ingestion of doses up to 15g.[20] Overdose of dapsone during pregnancy has been reported in a single patient, and caused severe maternal methaemoglobinaemia, but infant outcome was not reported.[21] The fetus may be at risk because of hypoxaemia that could occur with methaemoglobinaemia and haemolysis. With acute overdose, symptoms may

appear within a few minutes to 24 hours following ingestion and methaemoglobinaemia may last for up to 10 days. Haemolysis is usually delayed but it may persist for 14 days, with haemoglobin returning to normal within 3–4 weeks.

A variety of rare serious adverse reactions have been described, mostly as case reports related to drug sensitisation.[22] These include peripheral neuropathy[23] and several cutaneous reactions (exfoliative dermatitis, erythema multiforme and nodosum, and urticaria),[24] which may be dose dependent. Adverse reactions were thought to occur after several weeks of therapy over 100mg daily, although a 'dapsone syndrome' was noticed after only 4 weeks of Maloprim® (dapsone 100mg, pyrimethamine 12.5mg weekly) and chloroquine (300mg weekly) for malaria prophylaxis.[25] The syndrome consists of fever, exfoliative dermatitis, hepatitis, lymphadenopathy, leucopenia and mononucleosis arising in the first 6 weeks of treatment. Haemolytic anaemia and agranulocytosis may occur with the relatively low doses used for leprosy and malaria, whereas peripheral neuropathy and hepatitis have only been observed with the higher doses used in the treatment of dermatitis herpetiformis.[26]

2.1 Haemolytic Effects and Glucose-6-Phosphate Dehydrogenase Deficiency

Haematological effects are frequent adverse effects of dapsone. These are generally clinically insignificant.[3] These adverse drug reactions are initially dose related but may lessen with continued treatment.[15] The life span of erythrocytes is reduced when the drug is taken and these effects are related to the dose and period of exposure.[27] A fall of about 1 g/dL of haemoglobin occurred within 7 days of therapy in several volunteers with normal erythrocytes, receiving daily dapsone doses between 50–300mg and producing mean concentrations of dapsone in blood of between 0.4–4.2 mg/L.[28] The haematological effects of dapsone in severely anaemic individuals are not described. However, in a randomised trial in Kenyan children, haemoglobin levels of 5 g/dL or less caused trial exit for 6.9% of children receiving chlorproguanil-dapsone, compared with 1.5% of children receiving pyrimethamine-sulfadoxine.[29] The explanation for this difference may be dapsone-related haemolysis.

In patients with lepromatous leprosy, the drop in haemoglobin level and concomitant increase in serum bilirubin and urinary excretion of urobilinogen, and fall in the serum haemoglobin binding capacity (haptoglobin level) following treatment with dapsone indicated mild intravascular haemolysis.[30] Volunteer studies have also shown haptoglobin levels decrease with dapsone administration, and in leprosy patients normal haptoglobin levels are indicative of poor compliance with dapsone (Eggelte TA, unpublished observations). Serum haemopexin measurement should be of value in the assessment of the severity of the haemolysis caused by dapsone drug treatment in those patients who have a low serum haptoglobin level.[31]

Shortening of erythrocyte survival was seen to be more marked in G6PD-deficient male volunteers than in healthy volunteers receiving the same daily dose of dapsone.[28] Intercurrent infections may increase the severity of drug-induced haemolysis in G6PD-deficient individuals. The administration of daily doses of 200mg may cause severe haemolysis in individuals having fully expressed G6PD deficiency. Degowin et al. considered that marked haemolysis did not occur with daily administration of relatively low doses of 25mg such as those required for the suppression of infection with *P. falciparum*.[28] However, profound haemolytic anaemia has been reported in three G6PD-deficient individuals receiving a low dose of dapsone (25mg in combination with primaquine and chloroquine) daily as prophylaxis for falciparum malaria.[32] None of these studies report the haemolytic effects in females and no larger studies have been reported.

Red cell sequestration appears to take place primarily in the spleen.[28] Malaria-induced splenomegaly, which is common in pregnant women living under holoendemic conditions for malaria,[33] could enhance the haemolytic effect of dapsone. It is likely that denaturation of haemoglobin into insoluble precipitates – Heinz bodies – and damage to the

erythrocyte membrane are the events preceding sequestration.[34] The mechanism(s) through which certain drugs shorten the life span of G6PD-deficient erythrocytes have not been clearly defined.

The most serious haematological adverse effect of dapsone is bone marrow suppression.[35] The available data suggest that this is an idiosyncratic reaction to dapsone that is exacerbated by the concomitant administration of folic acid antagonists.[36] An increase in the incidence of agranulocytosis from 1 : 10 000 to 1 : 2000 was seen in Swedish travellers using twice-weekly Maloprim® chemoprophylaxis compared with once-weekly prophylaxis in British travellers.[37] The incidence in the latter was comparable to that seen in American soldiers receiving daily dapsone chemoprophylaxis.[38] During dapsone treatment of dermatitis herpetiformis, the total risk of agranulocytosis was one case per 3000 patient-years of exposure.[39] The median duration of dapsone treatment for these patients was 7 weeks, with a mean daily dose of 100mg. Megaloblastic anaemia has been encountered in patients receiving dapsone, but may have been a result of folate deficiency, secondary to enteropathy of dermatitis herpetiformis,[40] or to inhibition of dihydropteroate synthetase in patients with acquired immuno-deficiency syndrome,[41] or to combined use with pyrimethamine.[42] Concurrent administration of primaquine may predispose to agranulocytosis or haemolysis.[17]

2.2 Methaemoglobinaemia

In studies with volunteers the height of peak formation of methaemoglobin was linearly related to the dose of dapsone ingested over a 50–400mg range (Eggelte TA, unpublished observations). Methaemoglobin is formed in the reaction of N-hydroxylated metabolites of dapsone (DDS-NHOH) with oxyhaemoglobin, resulting in the oxidation of iron from its ferrous to its ferric form together with formation of DDS-NO and reactive oxygen species.[3] The formed nitroso compound can be reduced back to DDS-NHOH by glutathione. A small number of volunteers with G6PD deficiency did not develop increased methaemoglobinaemia in a chemoprophylactic trial of dapsone.[43,44] However, the formed reactive oxygen species are less well detoxified in these persons leading to higher haemolytic activity. The role of methaemoglobin in the sequence of events leading to haemolysis is subject to controversy.[45] Individuals with certain haemoglobinopathies and methaemoglobin reductase deficiency are more susceptible to methaemoglobin formation and haemolysis.[46] Methaemoglobinaemia has been observed in patients receiving dapsone 25 mg/day for malaria prophylaxis.[44]

Most individuals experiencing dapsone-related methaemoglobinaemia are asymptomatic until approximately 30% of haemoglobin is oxidised, although lower levels are associated with cyanosis. Upon partial oxidation of haemoglobin a change in oxygen affinity may occur, increasing the toxic symptoms more than would be expected from the methaemoglobin levels alone. In adult male volunteers, methaemoglobinaemia exceeding 2% was detected in 10 of 22 volunteers treated with dapsone ≥100mg daily, but not in those who received 25mg or 50mg daily.[28] Peak levels occurred during the second week of treatment. Sulphaemoglobinaemia has been reported in an adult male following acute dapsone overdose.[47]

3. Maternal and Infant Outcomes

Dapsone was not shown to be teratogenic in rats or rabbits at dosages up to 192 mg/kg/day or 200 mg/kg/day, respectively.[48] Information from DRUGDEX® states that ICI Pharmaceuticals (Macclesfield, England) has collected data on over 1000 patients treated with dapsone during pregnancy.[49] They reported no teratogenic adverse effects in newborns born to any patient treated. One manufacturer's product overview information states that because of the lack of animal studies or of controlled human experience dapsone should be given to a pregnant women only if clearly needed.[50] The drug is classified for use in pregnancy as category C by the US FDA. This indicates that risk cannot be ruled out, and this specifically includes the situation where animal studies have shown a risk to the fetus.

The drug should be given only if the potential benefit justifies the potential risk to the fetus.[51]

A literature search was performed and publications were identified by searching Medline to June 2003 with the keyword "dapsone" (no restriction on fields, publication type, age, publication date, language, subsets or sex). Reference lists of publications were also examined. Twenty-six publications were identified, which reported on either the maternal and/or fetal outcomes of dapsone treatment in human pregnancy. The main application has been for therapy of immune-mediated skin disorders; other indications included leprosy and malaria. Three reports were identified which documented its use in pregnancy for other conditions. A total of 924 pregnancies were identified during which dapsone therapy was taken.

3.1 Immune-Mediated Skin Disorders

Higher dosages (maintenance dosage up to 400mg daily) of dapsone have sometimes been employed for the initial therapy of dermatitis herpetiformis or other chronic dermatological disorders, as well as therapy for pemphigoid gestationis (herpes gestationis). How dapsone works in these disorders is uncertain; the action is not related to its antimicrobial properties.[51] It probably acts as an immune-modulator since it inhibits both the alternate pathway of complement activation and polymorphonuclear leucocyte cytotoxicity.[15,52]

Dapsone stabilises neutrophil lysosomes and may impair neutrophil chemotaxis. Although the modes of action of dapsone in reducing inflammation are not precisely known, it appears that neutrophils and neutrophil products are the major targets for this drug.[53] The drug can be N-chlorinated by the myeloperoxidase system and reacts with neutrophils at a number of locations.[54] N-hydroxy dapsone may also bind to surfaces of viable white blood cells in a similar way to N-hydroxy sulphamethoxazole.

Table I summarises eight case reports describing maternal and infant outcomes following dapsone therapy for immune-mediated skin disorders. G6PD status was known for only one case (normal). Two cases received treatment throughout pregnancy,[8,55] two cases during the second trimester,[5,56] two from the third trimester,[57,58] one case post-partum,[59] and for one woman (an overdose) the gestation was not stated.[21] The shortest duration of therapy was 2 weeks, with the majority of women receiving at least several weeks' treatment with a daily dapsone dose of 100mg or more. All women except one also received other drugs.

Dapsone-related complications were reported in three cases: two mothers and their infants who developed haemolytic anaemias,[5,8] and a woman who received an overdose who developed severe maternal methaemoglobinaemia (the outcome in her infant was not reported).[21] A further infant was premature and stillborn with skin lesions, which were extensive denuded areas.[58] While dapsone may have played a role in the death of this child, during dapsone therapy, which was initiated 14 days before the fetus died *in utero*, no adverse effects such as sulfhaemoglobinaemia, methaemoglobinaemia or haemolysis were detected in the mother's blood. Autopsy of the fetus did not shown signs of infection. It is uncertain if the skin lesions were of 'rash-type' or not as this fetus may have been macerated. The use of dapsone alone (100–200mg) for pemphigoid gestationis has recently been reported to give a favourable outcome for four of six treated pregnancies. Treatment mostly commenced from the second or third trimester and no complications were reported for the fetus.[60]

The pemphigoid gestationis may have influenced the outcome in some of these cases as there is a high rate of abortion, stillbirths and fetal anomalies associated with the disease. Lawley et al. reported a 7.7% stillbirth rate and a 23% prematurity rate in a selected series of 40 cases.[61] Others have found no evidence of increased spontaneous abortion or stillbirth in dermatitis herpetiformis.[62]

3.2 Leprosy

Eleven published reports of dapsone therapy for leprosy during pregnancy were identified, including a total of 256 women (table II). G6PD status was not reported for any of these women. Most women

Table I. Maternal and infant outcomes following dapsone therapy for eight single cases of dermatitis herpetiformis, pemphigoid gestationis (herpes gestationis) and pemphigus vulgaris during pregnancy

Case report	Gestation commenced	Dapsone daily dose (mg)	Duration of therapy (w)	Other drugs	Outcome		Reference
					maternal	infant	
Dermatitis herpetiformis							
Case 1	1st trimester	100–150	12	Thyroxine	Post-partum haemolysis (mild)	Neonatal haemolysis	8
	2nd and 3rd trimester	50	24				
Case 2	All trimesters	25–50	40	None	Normal	Normal	55
Case 3	NS	5000	Overdose	Alcohol	Severe methaemoglobinaemia	NS	21
Pemphigoid gestationis							
Case 4	Week 26	400 ↓100 200	5 4	Sulfapyridine	Chronic haemolysis commencing 6d after therapy	Fetal haemolysis at 30w gestation until second postnatal week Normal G6PD	5
Case 5	Week 24	200	16	Prednisone + hydroxyzine hydrochloride	Normal	Normal	56
Case 6	Week 38	100	2	Prednisone	NS	NS	57
Case 7	Post-partum	50–100	28	Prednisone	NS	Well	59
Pemphigoid vulgaris							
Case 8	Week 31	200	2	Prednisone Betametasone Propranolol	Premature delivery Pemphigus exacerbations	Premature (33w) Still birth, denuded skin, heavy adrenal glands	58

d = day(s); **G6PD** = glucose-6-phosphate dehydrogenase; **NS** = not stated; **w** = week(s); ↓ indicates decrease.

Table II. Maternal and infant outcomes following dapsone therapy for leprosy during pregnancy

No. of pregnancies	Dapsone daily dose (mg)	Duration of therapy	Other drugs[a]	Outcome		Reference
				maternal	infant	
26	NS	All trimesters	Rifampicin (rifampin), prednisone, mercaptopurine, ACTH, thiamazole (methimazole)	Anaemia, PET or other complications in 53%	Cleft palate × 1[b] Congenital hip dislocation × 1 15% preterm, 11% wastage[c]	63
13	100	NS	Rifampicin, clofazimine, prednisone	NS	Normal term	70
3	100	NS	Rifampicin	NS	Normal term	71
70	100	NS	Rifampicin, clofazimine, thioacetazone	Leprosy relapses, several cases	NS	68
1	100	All trimesters	None	NS	Methaemoglobinaemia, well at day 12	6
1	300 (weekly) for 1st and 2nd trimesters, 50 (weekly) for 3rd trimester	All trimesters	?None	?Normal	Normal term, hyperbilirubinaemia	64
1	NS	Not last month	?None	Good condition	Normal term, no hyperbilirubinaemia	64
17	100	All trimesters	Rifampicin, clofazimine	Drug reactions × 10	Exfoliative dermatitis × 1 20% preterm 25% low birthweight	65
100	NS	NS	NS	No untoward effects	No untoward effects	67
1	100	From 14 weeks	Rifampicin	Premature delivery	Normal preterm 32 weeks	66
23	NS	NS	?None	Leprosy relapses, 5 cases	NS. Infant separated from mother	72

a Not all cases received all drugs.

b Not known which abnormal outcomes had received dapsone.

c Including ectopics, abortion and stillbirth.

ACTH = corticotropin (adrenocorticotrophic hormone); **NS** = not stated; **PET** = pre-enclamptic toxaemia.

received other drugs in combination therapy for leprosy. Only one woman was known with certainty to have received dapsone alone.[6] The daily dapsone dose of 100mg was nearly uniform across these studies, and for four of the 11 reports therapy was known to have been provided through all trimesters (n = 46).[6,63-65] Maternal complications related to leprosy occurred in at least two studies. A specific dapsone-related complication was reported for one neonate who developed methaemoglobinaemia.[6] One infant developed hyperbilirubinaemia,[64] several were reported as pre-term,[63,65,66] and in one study two babies out of 26 delivered had a congenital abnormality.[63] It is not known whether the mothers of these babies with congenital anomalies had definitely received dapsone. It is difficult in this selected series to directly attribute any of these abnormal outcomes to dapsone, except for the single case of mild neonatal methaemoglobinaemia.[6] No untoward effects were reported for the largest case series (n = 100),[67] and infant outcomes were not reported for the second largest case series (n = 70).[68] Dapsone has been used widely in pregnant women with leprosy and many leprologists have not reported ill effects (D. Lockwood, personal communication). The numbers of leprosy patients who have received dapsone since 1982 is about 11.2 million, which reflects the size of the leprosy experience with dapsone. This experience is important, but it is possible that problems could have gone unobserved. Primary disease from leprosy could independently influence outcome and small placentae, low birthweight, and fetal growth retardation have been described and may confound an assessment of dapsone adverse effects.[69]

3.3 Malaria

Dapsone in combination with other antimalarial drugs has its widest application during pregnancy for the treatment or prophylaxis of *P. falciparum* malaria. Table III summarises information available from three studies and a case report. In one study it was used as single-dose treatment (2.4 mg/kg) in combination with chlorproguanil in 44 pregnant women in a drug sensitivity test with 28-day follow-up.[73] Adverse effects were not noticed but it is not clear how they were assessed and infant outcome was not reported. A single case report of its use in the first trimester in combination with pyrimethamine and chloroquine was associated with severe congenital anomalies and stillbirth.[74] The pyrimethamine also taken by this woman could have induced malformations in the embryo through folate deficiency, as described in rats.[51]

The largest series is reported by Greenwood et al.,[75] in which fortnightly dapsone and pyrimethamine (Maloprim®) was used for chemoprophylaxis of malaria in the Gambia. In this randomised trial, no increase in maternal or neonatal deaths or stillbirths was observed compared with the placebo control group. No methaemoglobinaemia, agranulocytosis or other adverse effects were reported, but it is unclear whether these were assessed. The benefits of parasite clearance on reducing malarial anaemia may have masked any haemolytic effect caused by dapsone therapy. Overall packed-cell volumes were improved in the treated compared with the placebo group. No details of G6PD deficiency were provided. An additional Gambian study in a different group of primigravidae receiving pyrimethamine-dapsone, and who were followed-up carefully, found no significant differences in pregnancy outcome between treatment and placebo groups.[76] The combined data from these two Gambian studies were reanalysed for first pregnancies alone.[77] Five of 206 primigravidae who received Maloprim® died during pregnancy or within 2 months of delivery, as did four of 200 women who received placebo. The subsequent survival of infants born to women in each group was similar.

The risk of acute nonspecific upper respiratory tract infections in healthy men taking pyrimethamine-dapsone for prophylaxis against malaria was reported as significantly increased compared with controls.[78] This suggests that the comparatively small decrease in immunoglobulin levels in adults receiving pyrimethamine-dapsone for malaria prophylaxis may be of clinical relevance.[79]

Table III. Maternal and infant outcomes following dapsone therapy for malaria during pregnancy

No. of pregnancies	Gestation	Dapsone dose (mg)	Dosage frequency	Other drugs	Outcome		Reference
					maternal	infant	
44	NS	150 (2.4 mg/kg)	Single dose	Chlorproguanil (1.2 mg/kg)	Adverse effects not noticed	NS	73
1	Days 10, 20, 30	100	3 doses at 10-day intervals	Pyrimethamine (12.5mg on days 10, 20, 30) Chloroquine (100 mg/day on days 1–30)	NS	Stillbirth, ?ectopia cordis, absent left arm	74
500	All trimesters[a]	100	Every 2 weeks, 1 to ≥10 (mean 4.8) doses	Pyrimethamine (12.5mg every 2 weeks)	Higher PCV and reduced malaria parasitaemia. No increase in maternal deaths compared with placebo group. No methaemoglobinaemia, agranulocytosis or other adverse effects	Improved birthweight among primigravidae. No increase in neonatal deaths or stillbirths compared with placebo group	75
82	All trimesters[a] (mean 24 weeks)	100	2 weekly, mean 10.2 doses	Pyrimethamine (12.5mg every two weeks)	Abortion × 3 (pyrimethamine-dapsone); × 1 (placebo)	Stillbirths × 6 (pyrimethamine-dapsone); × 11 (placebo)	76
					Maternal death[b] × 3 (pyrimethamine-dapsone); × 2 (placebo)	Neonatal deaths × 4 (pyrimethamine-dapsone); × 4 (placebo)	

a No details of numbers of women in first trimester.

b Causes unspecified (related to pregnancy or delivery).

NS = not stated; **PCV** = packed-cell volume.

3.4 Other Conditions

Three further reports encompassing 27 pregnancies were identified for women receiving dapsone for diverse conditions, all of whom received other drugs, including corticosteroids (table IV). In this highly selected series infant outcomes were poor, but it is impossible to attribute these effects directly to dapsone therapy. Five of the 27 babies were reported to be normal or healthy. Haemolytic anaemia or methaemoglobinaemia was not mentioned. The mechanism of action of dapsone in these cases is unclear. A blockade of the reticulo-endothelial system by excessive red cell destruction has been proposed as the mechanism in idiopathic thrombocytopenic purpura.[80] Dose-related haemolytic anaemias have been reported in this condition.[81]

4. Neonatal Outcomes

The newborn infant is particularly sensitive to the development of methaemoglobinaemia because of the increased sensitivity of fetal erythrocytes to oxidising agents causing the formation of fetal methaemoglobin. There is also a transient physiological deficiency of cytochrome B5 (i.e. reduced nicotinamide adenine dinucleotide [NADH]-dependent methaemoglobin reductase) activity in neonates (approximately 60% of normal adult values). The normal volume of distribution of dapsone is low and, regarding the physicochemical properties of dapsone, it is likely that fetal concentrations of dapsone may not be that different from those in the mother, although no data such as cord blood concentrations are available. Administration of dapsone to the mother prior to delivery can cause cyanosis in the neonate at birth.[6] G6PD deficiency and male gender in the fetus could influence the degree of fetal haemolysis, which may occur as male hemizygotes may be at higher risk than female heterozygotes. While transplacental transfer of dapsone could theoretically predispose to hyperbilirubinaemia through competitive binding,[64] kernicterus has not been reported and, in an extensive survey of the published work, Scholer et al. found no cases in which sulphonamides in late pregnancy were proven to cause kernicterus in the newborn infant.[26] Some

Table IV. Maternal and infant outcomes following dapsone therapy for miscellaneous conditions during pregnancy

Condition	No. of pregnancies	Dapsone daily dose (mg)	Duration of therapy	Other drugs[a]	Outcome		Reference
					maternal	infant	
Linear IgA disease	19	50–200	Variable trimesters	Prednisolone, sulfamethoxypyridazine	Disease relapses frequent	Transient blisters × 1 Patent ductus arteriosus × 1	82
Idiopathic thrombocytopenic purpura	1	100	28 weeks to 1 week post-partum	Prednisone, immunoglobulin, splenectomy	Recovered post-partum	Premature (35 weeks), healthy	83
Relapsing polychrondritis	7	NS	NS	Prednisone	Ectopic pregnancy × 2	Normal term × 4 Abortion × 1	84

a Not all women received all drugs.

NS = not stated.

clinicians have recommended the discontinuation of dapsone therapy one month before the expected date of delivery to minimise the theoretical development of kernicterus.[64]

Dapsone is excreted in breast milk in substantial amounts and has been detected in infants' urine. The breast-fed infants of women taking dapsone are at potential risk of developing haemolytic anaemia.[7] The properties of dapsone as a weak base, with high lipid solubility and a long serum half-life, favour excretion in breast milk. Concentrations in milk have been reported by Edstein et al., but do not exceed 0.85 mg/L/day, with milk to plasma ratios ranging between 0.22 and 0.45.[81] The maximum percentage of the maternal dapsone dose that a suckling neonate would ingest has been estimated at 14.3%.[81]

Conflicting statements on the safety of dapsone during breast-feeding have been reported. The WHO Working Group on Drugs and Human Lactation concluded that the use of dapsone during breast-feeding was not safe.[85] Conversely, it is listed by the American Academy of Paediatrics Committee on Drugs as a maternal medication compatible with breast-feeding.[86]

Carcinogenicity has been shown for dapsone in offspring of pregnant and lactating mice and rats, given lifetime treatment (2 years) with maximum tolerated doses (total doses ranged from 10–16mg per rat and 1.2–1.4g per mouse).[87] In these animal studies splenic sarcomas were induced in male rats and induction was dependent on the sex of the animals. The increase in tumour incidence in dapsone-treated animals over that observed in untreated controls was statistically significant, although the increase was relatively low. The investigators concluded that these results provided only limited evidence of carcinogenicity of dapsone in rats. There are no case reports of carcinogenicity in humans.

5. General Discussion

Because current knowledge on the safety of dapsone in pregnant women and their infants is limited, both dapsone and dapsone combinations optimally require further study before they are employed routinely for use in prevention or treatment of malaria in pregnant women. Although a total number of 924 pregnancies were identified during which dapsone therapy had been taken, comparison between these reports is not straightforward as they mostly comprise selected case reports of women with a variety of illnesses which may independently influence pregnancy outcome or dapsone pharmacokinetics. The majority of women had received other drug combinations. Information on pharmacokinetic interactions with dapsone appears to be confined to those drugs employed in leprosy and malaria treatment.[3] For example, rifampicin decreases the half-life of dapsone by a factor of two and pyrimethamine, although it does not alter half-life, does increase the volume of distribution and lower the peak serum concentrations of dapsone. In addition, other drugs may have a direct influence on maternal and fetal wellbeing. It is not possible to judge causality from these case reports and the data do not support a clear link with congenital abnormalities.

Haemolysis consistently occurs with continued dapsone therapy; however, mild degrees of haemolysis are not easily detectable, although serum haptoglobin and haemopexin levels should decrease with therapy if haemolysis occurs. However, haptoglobin levels are also decreased with malaria and it may be impossible to distinguish dapsone-related haemolysis from the mild chronic haemolysis associated with malarial parasitaemia and splenomegaly. The lack of reported untoward haemolytic effects in the studies undertaken in malarious areas is therefore not surprising. A degree of haemolysis always occurs with dapsone therapy but is usually limited with short-term treatment (<1 week) to a fall in haemoglobin level of about ≤1 g/dL. In patients whose malaria is treated, the greater benefit of reduced malarial haemolysis may lead to an average improvement in haemoglobin level.

Several gaps exist in our knowledge – more data are needed in these areas. Firstly, no published data were identified on whether dapsone pharmacokinetics in pregnancy were altered when it was administered in combination with chlorproguanil.

Secondly, carefully collected data are needed on the potential complications and benefits of dapsone (and combinations) in women with severe anaemia. In communities where pregnant women have a high prevalence of severe anaemia, which may reach 10% in highly malarious areas,[88] and especially in those with chronic malaria-related haemolysis and splenomegaly, dapsone-related haemolysis and methaemoglobinaemia may be poorly tolerated.

Thirdly, the lack of information on haemolytic effects in women with G6PD deficiency is a cause for concern, especially since expression of G6PD deficiency in females is so variable. The incidence in African populations varies from under 5% in parts of East Africa to 24% among the Yoruba in Nigeria.[34] The self-limiting nature of the haemolytic anaemia in G6PD-deficient individuals relates to the fact that only older members of the red cell population are destroyed during drug challenge. It is these cells that are most enzyme deficient, whereas newly produced erythrocytes have nearly normal levels of G6PD, which enables them to resist drug-induced destruction.

A further consideration is that nothing is known about dapsone-related haemolytic effects in the G6PD-deficient homozygous female or hemizygous male fetus. As fetal anaemia (cord haemoglobin <12.5 g/dL) is a frequent occurrence in babies born in highly endemic malarious areas,[89] and partly relates to pregnancy malaria,[90] it is important to ensure antimalarial drug use during pregnancy is not associated with enhanced risk of fetal haemolysis. Intra-uterine methaemoglobinaemia is also a potential fetal risk, as newborn infants are more likely to develop methaemoglobinaemia because of a normal transient deficiency of methaemoglobin reductase in neonatal erythrocytes and the increased tendency of fetal haemoglobin to assume the met-configuration.[91]

Fourthly, information is needed on the safety of dapsone (and combinations) in HIV-seropositive women. These women may be at higher risk of adverse drug effects. Higher mortality has been reported in HIV-seropositive men receiving iron supplementation with dapsone compared with aerosolised pentamidine for prophylaxis against *Pneumocystis carinii* pneumonia.[92] Independent of dapsone therapy, iron supplementation may have adversely influenced outcome in these HIV-infected patients.[93] Caution in the use of dapsone in HIV-infected pregnant women may be necessary both because of the increased risk of haemolysis with intercurrent infection, and because of a possible interaction with concurrent use of iron supplements. Haemolysis could be especially marked in HIV-infected women with intercurrent infection and G6PD deficiency.

The approach to filling in these knowledge gaps on the safety of dapsone (and combinations) during pregnancy should be to plan and conduct studies in non-pregnant women as well as pregnant women in the second and third trimester of gestation. Adverse effects may be less likely to occur with intermittent treatment, as most reported adverse effects have been with long-term use of dapsone. Women with severe anaemia and HIV-seropositive women may initially be excluded from trials until more information on safety in groups who may be less at risk for complications becomes available. Eventually, information on even these higher-risk women would be useful to collect because it is they who most require protection from the adverse effects of malaria during pregnancy. Because there is very little information on the use of dapsone in the first trimester, including a lack of published animal data and controlled human data, women in the first trimester are probably best initially excluded and data obtained from surveillance reporting. In all women included in trials, there is a need for G6PD screening and close follow-up of complete blood counts and methaemoglobin levels.

6. Conclusions

The design of trials of dapsone in combination with other antimalarial drug therapy in malarious areas will need to consider several complicating factors, which could potentially limit the widespread use of this drug for malaria treatment or prevention in pregnancy. Currently available data limit the extent to which a meaningful quantitative benefit-risk

analysis can be made. However, controlled trials have provided some data on maternal tolerance and, when used as an antimalarial drug in combination therapy, clear benefits in terms of improved birthweight were achieved.[73,75,76]

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