

P – ANTIPARASITICS, ISETICIDES, REPELLENTS

P01 – Antiprotozoal agents

P01AB – Nitroimidazole derivatives

Metronidazole – P01AB01 – G01AF01 – J01XD01 – D06BX01

See J01XD01

Tinidazole – P01AB02 – G01AZ99

Patented in 1964

We have been unable to locate references on possible human reproductive effects of this agent.

Studies on laboratory animals

- Owaki et al (1974): nonteratogenic in mice and rats (up to 2 g/kg per os).

Conclusions: There are no specific studies in literature on the use of tinidazole in human pregnancy. The sole evaluation is therefore based on pharmacological analogy with metronidazole (see) and on laboratory animals' studies, which have not revealed any teratogenic activity (records provided by manufacturer for registration, not available in database).

P01AB – Antimalarials

These drugs affect initial tissues of Plasmodia located in the liver, in order to prevent erythrocytes invasion and consequent transmission of the disease (proguanil, primaquine). They are also active against latent tissues not eliminated, once primary hepatic life forms have infected the blood thus causing recurrent erythrocyte infections (chloroquine). Hematic schizonticides, used in malarial prophylaxis are of two types: quick-action type (chloroquine, quinine, quinidine, and mefloquine) and slow-action type (antifolics and tetracyclines).

P01BA – Aminoquinolines

Chloroquine – P01BA01

It is a quinine derivative. Patented in 1946.

Hydroxychloroquine – P01BA02

Patented in 1949.

Case report

- Smith (1966), this family case had been already described by Hart and Naunton (1964): 1 newborn with left hemihypertrophy (and Wilms disease at 4 years of age), 2 newborns with vestibule injury (one of them also showing an adult-chloroquine-toxic type of chorioretinitis), all born to a woman who in 3 of her 7 pregnancies had been administered – and in 2 out of the 3 cases throughout pregnancy – 500 mg/day of chloroquine phosphate for the treatment of SLE (see table). This report has suggested the hypothesis of an association between chloroquine and oto-vestibule impairments.

Pregnancy	Chloroquine exposure	Outcome
1°	no	Healthy male infant

2°	0-6 weeks	Hemihypertrophy, Wilms' disease
3°	Throughout pregnancy	Neonatal convulsions, deafness, vestibule injury, ataxia
4°	no	Healthy male infant
5°	Throughout pregnancy	Physical-mental retardation, vestibule injury, ataxia
6°	no	Miscarriage at 3 months of gestation
7°	no	Healthy female infant

- Ross and Garatsos (1974): one fetus of 14 weeks (VIP) exposed since the beginning of pregnancy did not show any impairments or anatomohistologic signs of oto-vestibule injury.
- Harpey et al (1983): 1 newborn exposed 10 days prior to conception and in the following 45 days to chloroquine, primetamine and dapsone (on 10th, 20th, 30th day following conception), who had abdominal wall and thoracic schisis.
- Suhonen (1983): 1 healthy newborn exposed during the first 6 weeks of pregnancy to hydroxychloroquine in the treatment of maternal SLE. At two years of age he showed no mental or physical anomalies.
- Parke (1988): 9 exposures to antimalarial drugs administered at high dosage throughout pregnancy due to maternal SLE (chloroquine and hydroxychloroquine). 15 pregnancies: 4 miscarriages, 4 stillbirths and 7 healthy newborns.

Cohort studies without controls

- Levy et al (1991): 27 first trimester exposures to chloroquine or hydroxychloroquine due to SLE (11), rheumatoid arthritis (3), and malarial prophylaxis. Outcomes: 6 VIP, 4 miscarriages, 3 stillbirths and 14 healthy newborns with follow-up over periods ranging from 9 months to 19 years of age. They showed no eye or ear defects. In the review made by the authors 215 exposures to chloroquine or hydroxychloroquine were reported: 7 newborns (3.3%) had congenital anomalies.
- Buchanan et al (1955): of 17 exposures throughout pregnancy and 6 first trimester exposures to hydroxychloroquine, all due to maternal SLE, 2 miscarriages, 2 fetal loss, 1 congenital cardiac heart block, and 18 healthy newborns.
- Parke (1996): 16 exposures throughout pregnancy to high dosage of chloroquine due to maternal SLE. No congenital anomalies, or eye injuries were noticed in the newborns in follow-up.
- Phillips-Howard et al (1998): 9 miscarriages (7.6%) and 2 newborns with congenital anomalies (1.7%), out of 118 first trimester exposures to chloroquine and proguanil, for prevention.
- Sowunmi et al (1998): 22 newborns exposed due to maternal malaria (5 of which in the first trimester).
 - Klinger et al (2001), TIS Motherisk Program: 21 exposures to high dosage of chloroquine or hydroxychloroquine over long periods during pregnancy (on an average of 7 months). The offspring did not show eye anomalies.

Prospective cohort studies with external controls

- McGready et al (2002): 246 exposures to quinine and 130 to chloroquine in the first trimester. Spontaneous abortions following exposure to quinine: 22.9%; to chloroquine: 18.3%. Stillbirth rate did not increase, and there was no increase in low neonatal weight or congenital anomalies, in comparison with the rest of the population.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 7 healthy newborns exposed to chloroquine and 2 healthy newborns exposed to hydroxychloroquine in the first 16 weeks.
- Wolfe and Cordero (1985): 169 newborns exposed to chloroquine throughout pregnancy, and 454 controls. Two newborns with congenital anomalies (tetralogy of Fallot, and congenital hypothyroidism) out of the exposed, vs. 4 out of the controls: RR = 1.3 (CI 95%: 0.3-7.3).

Conclusions: Chloroquine and hydroxychloroquine are considered drugs of choice for chemoprophylaxis (CDC 1988 and 1990) and in the treatment of malaria (Anonymous 1983, Subramanian et al 1992). Regarding their use in pregnancy as antirheumatic in the treatment of SLE, when particularly high and constant dosage is required, their harmlessness is not fully proved. Hart and Naunton (1964), as well as Martz and Naunton (1964), and Paufique and Magnard (1969) recorded various eye and ear injuries, appearing to be similar to toxic adverse effects caused in adult humans (Tanenbaum and Tuffanelli 1980) and in some species of laboratory animals (**Udalova** 1967, Dencker et al 1975).

Primaquine – P01BA03

Patented in 1946.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: There are no studies relevant to the use of primaquine in human pregnancy. See chloroquine for its pharmacological analogy.

P01BB – Biguanides

Proguanil – P01BB01

This is an antagonist of folic acid. Patented in 1948.

Case reports

- WHO (1995) in Aguilera (2004): 3 congenital defects were reported in offspring exposed to proguanil at preventive doses in the first trimester.

Prospective cohort studies without controls

- Phillips-Howard et al (1998): of 118 first trimester preventive exposures to chloroquine and proguanil, 9 miscarriages (7.6%), and 2 newborns with congenital anomalies (1.7%).

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 1 healthy newborn exposed in the first 16 weeks.

Conclusions: One single study does not suggest risk increase in congenital anomalies be associated with the use of proguanil in pregnancy. In consideration of the gravity of malaria in pregnancy, chemoprophylaxis is recommended in all fertile women traveling in malaria endemic areas (CDC 1990, WHO 1990). WGZ considers it a drug of choice in pregnancy for the prevention of malaria. It is anyway recommended to also administer 4-5 mg of folic acid.

P01BC – Methanolquinoline

Quinine – P01BC01

This drug is available since the 1930s.

Review

- Nishimura and Tanimura (1976): intake of quinine as abortifacient (1-4 g/day, a dose ranging from 3 to 13 times therapeutic use) has been reviewed, and 21 first trimester exposed newborns showed different defects.
- Schardein (2002): 45 cases of malformations were recorded in literature, most of which occurred up to the beginning of the 1960s. Half of them described ear injuries with or without hypoplasia of the acoustic nerve, the remaining concerning a variety of malformations not having a specific pattern. Most of the described cases had been exposed to high doses (up to 30 g) as abortifacient, whereas the usual therapeutic dosage was of 5-10 mg/kg.

Studies on cases without controls

- Robinson et al (1963): 200 children with congenital deafness, 2 of whom exposed to therapeutic dosage in pregnancy.

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 35 first trimester exposures, 2 newborns had major defects, 1 expected. RR = 2.0 (CI 95%: 0.2-7.2).

Prospective cohort studies with external controls

- McGready et al (2002): miscarriage rate in 246 first trimester exposures to quinine was of 22.9%, and in 130 exposures to chloroquine was of 18.3%. No increase in stillbirth, or low neonatal weight and congenital malformation was noticed, in comparison with the rest of the population.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: of 104 exposures in the first 16 weeks, 2 newborns had congenital anomalies. ARR = 0.4 (CI 95%: 0.1-1.7).

Feto-neonatal effects: thrombocytopenic purpura in mother and offspring (Mauer et al 1957), jaundice caused by hemolysis due to G6PD deficiency (Glass et al 1973).

Conclusions: A large number of clinical cases described in the past have sufficiently proved the association between high dosage of quinine used as abortifacient and the auditory apparatus. Therapeutic administration may cause side effects, but the risk – although not quantifiable – is probably not high.

Mefloquine – P01BC02

This agent has a long half-life. Patented in 1977.

Cohort studies without controls

- Balocco and Bonati (1992): 11 healthy newborns exposed in the first trimester to prevent malaria.
- Bricaire et al (1991), Vanhauwere et al (1998), Roche International Spontaneous Reporting System: of 476 newborns exposed in the first trimester, 24 showed congenital anomalies. 8 out of 181 newborns exposed in periconception period had congenital anomalies.
- Phillips-Howard et al (1998): of 99 first trimester exposures for prevention, 9 miscarriages and no newborn with congenital anomalies. 30 miscarriages and 16 newborns with congenital anomalies out of 331

exposures reported in the Roche Database. Some of the data are shared with the study by Vanhauwere et al (1998).

- Elefant et al (1991), TIS Paris: of 150 exposures to mefloquine, 43 were VIP for reasons other than medical, 24 miscarriages, 86 healthy newborns and 7 newborns had congenital anomalies (thanatophoric dwarfism; trisomy 13; trisomy 21; lagocephaly with hypotonia; hydrocephaly; DIV with facial dysmorphism and IUGR; beside multiple hypo-agenesis of limbs, and agenesis of the sacrum in a miscarriage of 8 weeks).
- Smoak et al (1997), US Army: 72 women soldiers were exposed in pregnancy during the expedition in Somalia. The outcome was unknown for 19 of them, 17 VIP for other than medical reasons, 12 miscarriages, 1 vesicular mol, and 23 healthy newborns. No impairment in psychomotor development was uncovered 13 of the children, at 1 year of age.
- Steketee et al (1996): 14 healthy newborns exposed in the first trimester for malarial prophylaxis.

Prospective cohort studies with internal controls

- Nosten et al (1999): in a study carried out in Thailand 208 exposures to mefloquine and 656 to quinine were monitored, along with 909 controls exposed to other drugs in the prevention of malaria. 2,470 non-exposed controls were surveyed. There was an increase in the risk of stillbirths among the offspring exposed to mefloquine, vs. those exposed to quinine (OR = 3.5; CI 95%: 1.6-7.6), vs. exposures to other antimalarials (OR = 5.1; CI 95%: 2.0-13.1) and vs. controls (OR = 3.5; CI 95%: 1.6-7.6). There was no increase in abortion, low neonatal weight, neurological retardation and congenital anomalies.

Feto-neonatal effects: No obstetric complications, or feto/neonatal toxicity were detected in third trimester exposures (Colignon et al 1989, Nosten et al 1990).

Conclusions: The studies we were able to find in literature do not suggest a risk increase in congenital anomalies. Teratogenic outcomes observed in laboratory animals result from the use of much higher doses than those used for humans (records provided by manufacturer for registration, not available in database). In consideration of the gravity of malaria in pregnancy, chemoprophylaxis is recommended to all fertile women traveling in malaria endemic areas (CDC 1990, WHO 1990).

P01BD – Diaminopyrimidines

Pyrimethamine – P01BD51

This is an antagonist of folic acid (dihydrofolate reductase inhibitor) Patented in 1950.

Case report

- Harpey et al (1983): 1 newborn exposed to chloroquine and pyrimethamine 10 days prior to conception and 45 days afterwards, and to dapsone (on the 10th, 20th, 30th day after conception), showed schisis of abdominal wall and thorax.

Cohort studies without controls

- Scholer (1983): 67 first trimester exposures to pyrimethamine + disulfadoxine. 66 healthy newborns, 1 with pyloric stenosis and hydrocele.

One of the healthy newborns had been inadvertently exposed to overdose of the drug for 7 days in the early 4 weeks of pregnancy.

- Phillips-Howard et al (1998): 19 healthy newborns exposed to pyrimethamine + sulfadoxine for prevention, collected by means of questionnaires. Of 153 first trimester exposures collected by Roche Database, 4 miscarriages (2.6%), 12 newborns with congenital anomalies (7.8%).

Prospective cohort studies with internal controls

- Morley et al (1964): 210 exposures and 212 controls. Monthly administration in pregnancy for prevention in endemic areas. No congenital anomalies, or adverse effects in the offspring.
- Hengst (1972): 64 first trimester exposures for toxoplasmosis and in periods following an association of sulfamerazine + sulfatolamide. 56 healthy newborns, 6 stillbirths (5 of which pre-term), and 1 newborn with Down syndrome. In 136 previous pregnancies the same women not exposed to any drugs had 99 miscarriages, 8 pre-term stillbirths, 3 neonatal deaths, 12 healthy newborns and 1 newborn with birth defect.
 - Heinonen et al (1977), CPP: 2 healthy newborns exposed in the first 16 weeks.

Feto-neonatal effects: No adverse effects in exposures after the first trimester (Roberts 1970, Terregna 1983).

Conclusions: The studies we were able to find in literature do not suggest a risk increase in congenital anomalies, nevertheless possible associations between risk and antifolics action, in specific malformations, were not studied. It appears reasonable to associate 4-5 mg/die of folic acid in the treatment with pyrimethamine.

P02 – Anthelmintics

P02CA – Benzoamine Derivatives

Mebendazole - P02CA01

Patented in 1969.

Case report

- Zutel et al (1977): 1 newborn exposed in the first month of pregnancy with multiple malformations (CNS, ears, heart and limbs related).

Cohort studies without controls

- Saigent (1979), Ortho manufacturer: 112 exposed newborns, 1 with congenital anomaly (one finger shorter in one of the hands).

Retrospective cohort studies with internal controls

- Rosa (1993), Michigan MSS: of 64 first trimester exposures, 4 newborns had major defects, 3 expected. RR = 1.3 (CI 95%: 0.4-3.4).

Prospective cohort studies with internal controls

- de Silva et al (1999): 407 first trimester exposures, 5,275 second trimester exposures. 1,737 controls. 97 newborns with congenital anomalies out of the exposures vs. 26 controls: OR = 1.2 (CI 95%: 0.8-1.9). 10 newborns with congenital anomalies out of 407 first trimester exposures: OR = 1.7 (CI 95%: 0.8-3.6)

- Diav-Citrin et al (2003), TIS Israel: of 150 first trimester exposures, 5 newborns had congenital anomalies vs. 3 out of 175 controls. RR = 1.9 (CI 95%: 0.5-8.0).

Conclusions: The studies we were able to find in literature do not suggest a risk increase in congenital anomalies.

Albendazole – P02CA03

Only 5 % of the administered dose is absorbed in the intestine. It is available in Italy since 1990.

Cohort studies without controls

- Horton (1993): 10 healthy newborns inadvertently exposed in the first trimester to high doses.

Feto-neonatal effects: No adverse feto/neonatal effects in exposures after the first trimester (Torcesse and Hdges 2000).

Conclusions: We have been unable to find enough information about the use of Albendazole, and it is not possible to draw any conclusion. In case of exposure, the following are useful arguments for professional advice: poor intestinal absorption and analogy with Mebendazole, which has been thoroughly studied.

P02CC – Tetrahydropyrimidine Derivatives

Pyrantel – P02CC01

Its intestinal absorption is of 15%. Patented in 1964.

We have been unable to locate references on possible human reproductive effects of this agent.

- Conway et al (1970) Owaki et al (1971 a and b), Clark et al (1992): nonteratogenic in horses, dogs, rats and rabbits.

Conclusions: There are no specific studies in literature, relevant to the use of pyrantel in human pregnancy. The sole possible evaluation is therefore based on its poor systemic absorption and on laboratory animals' studies, which have not uncovered any teratogenic activity (records provided by manufacturer for registration, not available in database).

Pyrvinium – P02CX01

Its main characteristic is to be hardly absorbed in the intestine (Smith et al 1976). Patented in 1950.

Prospective cohort studies with internal controls

- Heinonen et al (1977), CPP: 7 healthy newborns exposed in the early 16 weeks.

Conclusions: There are no specific studies in literature, relevant to the use of pyrantel in human pregnancy. The sole possible evaluation is therefore based on its poor systemic absorption and on laboratory animals' studies, which have not uncovered any teratogenic activity (records provided by manufacturer for registration, not available in database). FASS considers it a drug of choice in pregnancy.

P02DA – Salicylic Acid Derivatives

Niclosamide – P02DA01

This drug is poorly absorbed by intestine. Patented in 1956.

We have been unable to locate references on possible human reproductive effects of this agent, or have we found any similar studies on laboratory animals.

Conclusions: There are no specific studies in literature, relevant to the use of pyrantel in human pregnancy. The sole possible evaluation is therefore based on its poor systemic absorption and on laboratory animals' studies, which have not uncovered any teratogenic activity (records provided by manufacturer for registration, not available in database).

