References

- 1 Walker MD, Alexander E, Hunt WE, *et al*. Evaluation of BCNU or radiotherapy in the treatment of anaplastic gliomas. *J Neurosurg* 1978;49:333-43.
- 2 Bloom HJG. Combined modality therapy for intracranial tumours. *Cancer* 1975;35:111-20.
- 3 Salazar OM, Rubin P, Feldstein ML, Pryzkiello R. High dose radiation therapy in the treatment of malignant gliomas. Final report. *Int J Radiat Oncol Biol Phys* 1979;5:1733-40.
- 4 Catterall M, Bloom JG, Ash DV. Fast neutrons compared with megavoltage x rays in the treatment of patients with supratentorial glioblastoma: a controlled pilot study. *Int J Radiat Oncol Biol Phys* 1980;6:261-6.
- 5 Order SE. The history and progress of serologic immunotherapy and radio-diagnosis. *Radiology* 1976;118:219-23.
- 6 Carrasquillo JA, Krohn KA, Beaumier P, *et al*. Diagnosis of and therapy for solid tumors with radiolabelled antibodies and immune fragments. *Cancer Treat Rep* 1984;68:317-28.
- 7 Hammersmith Oncology Group and Imperial Cancer Research Fund. Antibody-guided irradiation of malignant lesions: three cases illustrating a new method of treatment. *Lancet* 1984;i:1441-4.
- 8 Fabricant RN, De Larco JE, Todaro GJ. Nerve growth factor receptors on human melanoma cells in culture. *Proc Natl Acad Sci USA* 1977;74:565-70.
- 9 Parker PJ, Young S, Gullick WJ, Mayes CLV, Bennett P, Waterfield MD. Monoclonal antibodies against the human epidermal growth factor receptor from A431 cells: isolation, characterisation and use in the purification of active EGF receptor. *J Biol Chem* (in press).
- 10 Fraker PJ, Speck JC. Protein and cell membrane iodination with a sparingly soluble chloramide, 1,3,4,5-tetrachloro-5,6-diphenylglycouril. *Biochem Biophys Res Commun* 1978;80:849-57.
- 11 Lansdorp PM, Astaldi GCB, Oosterhof F, Janssen MC, Zeijlemaker WP. Immunoperoxidase procedures to detect monoclonal antibodies against cell surface antigens. Quantitation of binding and staining of individual cells. *J Immunol Methods* 1980;39:393-405.
- 12 Epenetos AA, Canti G, Taylor-Papadimitriou J, Curbing M, Bodmer WF. Use of two epithelium-specific monoclonal antibodies for diagnosis of malignancy in serous effusions. *Lancet* 1982;ii:1004-6.
- 13 Snyder WS, Ford MR, Warner GG. *Estimates of specific absorbed fractions for photon sources uniformly distributed in various organs of a heterogeneous phantom*. New York: Society of Nuclear Medicine, 1978:5-67. (Medical Internal Radiation Dose (MIRD) pamphlet 5.)
- 14 Chen H-SG, Gross JF. Intra-arterial infusion of anticancer drugs: theoretical aspects of drug delivery and review of responses. *Cancer Treat Rep* 1980;64:31-40.
- 15 Libermann TA, Razon N, Barta AD, Yarden Y, Schlessinger J, Soreg H. Expression of epidermal growth factor receptors in human brain tumours. *Cancer Res* 1984;44:753-60.
- 16 Downward DJ, Yarden Y, Mayers E, *et al*. Close similarity of epidermal growth factor receptor and v-erb-B oncogene protein sequences. *Nature* 1984;307:521-7.
- 17 Hakomori S, Koscielau J, Bloch H, Jeanloch RW. Immunologic relationship between blood group substances and a fucose containing glycolipid of human adenocarcinoma. *J Immunol* 1967;93:31-3.

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Safety of chloroquine in chemosuppression of malaria during pregnancy

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Abstract

A cohort of 169 births to women who were exposed throughout pregnancy to chloroquine 300 mg base once a week for chemosuppression of malaria was studied. The birth defects in this cohort were compared with those in a control group of 454 births to women who were not exposed to chloroquine, most of whom lived in non-malarious areas. The proportion of birth defects in the exposed group was not significantly different from that in the control group. This observation must be considered within the limitations of the study, which could detect only a strong teratogenic effect. It could not exclude risks lower than a 5-7-fold increase in the incidence of birth defects when chloroquine was used.

Women using chloroquine during pregnancy for chemosuppression of malaria can be reassured that it is not a strong teratogen, but if it is to be used the risk of developing malaria should be balanced against the lack of data to determine whether it carries a low teratogenic risk.

Introduction

Chloroquine is the antimalarial chemosuppressive drug of choice for non-immune travellers to and residents in malarious

areas free of chloroquine resistance.¹⁻³ In areas where *Plasmodium falciparum* is resistant to chloroquine the Centers for Disease Control recommend that chloroquine with pyrimethamine and sulfadoxine (Fansidar) should be used.² Concern about the potential teratogenic effects of chloroquine exists because of a few case reports.⁴⁻⁶ This has led some physicians to advise pregnant women not to take chloroquine or indeed any antimalarial drug even in areas where chemosuppression of malaria is highly recommended. The World Health Organisation and the Centers for Disease Control have reported that chloroquine has not been found to affect the fetus adversely when used in the recommended doses for malarial prophylaxis.^{1,2} This conclusion was based on case reports and the absence of studies showing teratogenicity.

We report the experiences of a cohort of women who used chloroquine for chemosuppression of malaria during pregnancy. No previous study such as this one has been reported.

Subjects and methods

From 1969 medical officers at the health units of United States embassies and consulates were requested to report births to staff of the foreign service and their dependants to the Office of Medical Services of the United States Department of State. The standard form used included date and place of birth, birth weight, illnesses of the mother during pregnancy, and a list of drugs taken and dates of administration during pregnancy. Birth defects, perinatal complications, and deaths during the neonatal period were also reported. Fetal wastage was not usually reported and was not considered in this study. Paternal and maternal ages were not reported. Minor anomalies were defined as features that did not have any clinical, surgical, or cosmetic importance—for example, isolated partial syndactyly of the second and third toes. Heart murmurs without evidence of congenital heart disease were not considered to be birth defects.

A total of 643 live births were reported among these subjects from 1969 to 1978. In 189 instances an antimalarial drug was used during pregnancy. In 169 cases the women used chloroquine in the recommended dose of 300 mg base once a week throughout pregnancy. The 20 other women used pyrimethamine, proguanil, or an unspecified antimalarial drug and were excluded from the analysis. The

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control group consisted of the 454 live births to the women who were not exposed to antimalarial drugs during pregnancy, most of whom lived in non-malarious countries.

We compared the number of birth defects observed in the infants exposed to chloroquine with that in the control infants, using Fisher's exact test.

Results

The group exposed to chloroquine consisted of 94 male and 75 female infants; the control group consisted of 227 of each sex. Although the group exposed to chloroquine contained more male infants, this was not significant ($p=0.212$).

Two infants in the exposed group had birth defects—namely, tetralogy of Fallot and congenital hypothyroidism—as did four in the control group—namely, microcephaly, congenital heart disease (unspecified), clubfoot, and hamartoma. Thus the proportion of infants with birth defects was not significantly greater in the exposed group than the controls, 2 (1.2%) compared with 4 (0.9%). The relative risk was 1.34 with a 95% confidence limit of 0.25-7.3 ($p=0.52$).

Discussion

The reporting of birth defects in the subjects of this study was about 1%, which is lower than that in surveillance programmes of birth defects.⁷ The incidence observed could have been due to underreporting of birth defects or a lower incidence of birth defects in the study group, or both. We believe that underreporting was the most likely, but we do not have a feasible method to verify this assumption. Regardless of the reason lower incidences of birth defects tend to reduce the likelihood of finding an association if one should exist.

The size of the sample must also be considered in the interpretation of the results. This study could exclude with 80% certainty a 5.7-fold or higher risk of birth defects, given a baseline rate of birth defects of 1%. Thus any risk lower than 5.7-fold may or may not have been detected. If we had considered specific birth defects such as oral clefts—which in metropolitan Atlanta occur in 1.6/1000 live births⁷—we could have detected risks related to chloroquine only if cases of oral cleft increased 15-fold. A study to determine whether chloroquine causes a modest increase in the risk of oral cleft—for example, a twofold risk—would require a sample of 11 535 pregnant women exposed to the drug and the same number of controls, or 23 070 pregnant women. To obtain such numbers of subjects, which would enable the exclusion of low grade teratogenicity of chloroquine as malarial prophylaxis, would require a worldwide cooperative standardised mechanism of reporting, and this is beyond our means.

Our results refer to the chloroquine dose normally used for malarial prophylaxis. Doses of 100 mg base daily or 300 mg base twice weekly are recommended by some authorities in highly malarious areas. Higher doses have also been used for long term treatment of collagen diseases.⁴

Malarial infection poses a serious threat to all non-immune people, particularly pregnant women and their fetuses in malarious areas.^{3,8} Malaria may cause abortion, premature labour, maternal anaemia, and congenital infection. A pregnant woman with acute malaria requires treatment with higher doses of chloroquine or other antimalarial drugs than are needed for prophylaxis. In areas where the malaria parasites are sensitive to chloroquine most authorities recommend chloroquine or a related 4-aminoquinoline drug alone for malarial prophylaxis. In areas where strains of *P falciparum* are resistant to chloroquine, chloroquine combined with pyrimethamine and sulfa-

doxine (Fansidar) is the prophylaxis recommended by the Centres for Disease Control.² For those allergic to sulfadoxine an alternative drug is pyrimethamine and dapsone (Maloprim).

Retinal damage and other defects have been reported when chloroquine is given in higher doses than those recommended for malarial prophylaxis^{4,5} (unpublished document WHO/MAL 79.906). Hart and Naunton's report on a woman with discoid lupus who took 300 mg base daily during four pregnancies is often cited as evidence of the teratogenic effect of chloroquine.⁶ One of these pregnancies resulted in a spontaneous abortion; the three others were full term, and each resulted in a child with a congenital defect—one with left sided hemihypertrophy and neonatal convulsions and two with congenital severe bilateral cochleovestibular paresis and retinal pigmentary changes similar to the defects seen in adults who have used chloroquine in very high doses. In another report a woman living in tropical Africa had taken a daily dose of 200 or 300 mg base chloroquine for malarial prophylaxis over three years and throughout two pregnancies. Both of her children were later found to have retinal degeneration, and in the absence of other possible causes the authors considered it to be highly probable that the chloroquine taken by the mother during pregnancy was responsible for the retinal lesions.⁹ The report did not state whether the children had lived in Africa, where they might have taken large daily doses of chloroquine. In these reported cases the doses of chloroquine taken by the mothers for several years and throughout pregnancy greatly exceeded those that most malaria experts recommend for suppression of malaria. Unfortunately, in all published comments and references to these two papers this aspect of excessive dosage and duration of treatment has been completely neglected.

Lindquist and Ullberg showed that chloroquine administered intravenously to pregnant mice crosses the placenta and accumulates in the eyes of the fetus at both early and late stages of development.¹⁰ A high accumulation was also observed in the inner ear during late development. Although these effects have not been reported in man, they are theoretically possible. It would be worth while to investigate a cohort of infants, such as those we studied, for evidence of retinal toxicity. Loss of hearing, possibly attributable to intrauterine effects of chloroquine, could be studied by audiometry. The infants in this study were not followed up to test for any possible late development of retinal or auditory problems.

Until more data are available pregnant women should discuss with their physicians the risk of contracting malaria when visiting or residing in an endemic area. Our data suggest that chloroquine in the recommended prophylactic doses is not a strong teratogen and that its proved antimalarial benefits outweigh any possible risk of low grade teratogenicity.

References

- 1 Bruce-Chwatt LJ, ed. *Chemotherapy of malaria*. 2nd ed. Geneva: WHO, 1981.
- 2 Centers for Disease Control. Prevention of malaria in travellers, 1982. *MMWR* 1982;31(No 15):1-28S.
- 3 Bruce-Chwatt LJ. Malaria and pregnancy. *Br Med J* 1983;286:1457-8.
- 4 Bartholomew LE, Rynes RI. Use of antimalarial drugs in rheumatoid arthritis: guidelines for ocular safety. *IM: Internal Medicine for the Specialist* 1982;3:66-70.
- 5 Rees RB, Maibach HI. Chloroquine: a review of reactions and dermatologic indications. *Arch Dermatol* 1963;88:96-105.
- 6 Hart CW, Naunton RF. The ototoxicity of chloroquine phosphate. *Arch Otolaryngol* 1964;80:407-12.
- 7 Centers for Disease Control. *Congenital malformations surveillance report*. Atlanta: Centers for Disease Control, 1980.
- 8 Lewis RB, Lauersen NH, Birnbaum S. Malaria associated with pregnancy. *Obstet Gynecol* 1973;42:696-700.
- 9 Paufigue L, Magnard P. Retinal degeneration in 2 children following preventive antimalarial treatment of mother during pregnancy. *Bull Soc Ophthalmol Fr* 1969;69:466-7.
- 10 Lindquist NG, Ullberg S. The melanin affinity of chloroquine and chlorpromazine studied by whole body autoradiography. *Acta Pharmacol Toxicol (Copenh)* 1972;31(suppl 2):1-31.

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