CHAPTER 17

Evaluation of Drug Resistance in Man

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A. Introduction

Drug resistance in malaria can be defined as the “ability of a parasite strain to survive and/or multiply despite the administration and absorption of a drug given in doses equal to or higher than those usually recommended but within the limits of tolerance of the subject” (WHO 1967). Although this definition could logically be applied to include all plasmodial stages, it has generally been restricted to describe the drug susceptibility of asexual blood forms, presumably because this stage in the life cycle of the parasite produces the acute clinical symptoms observed during the course of a malaria infection. Resistance of asexual blood forms to drugs has been reported in all species of human plasmodia. However, because of the appearance of chloroquine-resistant infections of falciparum malaria about 2 decades ago, attention has been focused on developing procedures for assessing the response of Plasmodium falciparum to chloroquine and other antimalarial drugs.

B. Evaluation of Drug Resistance In Vivo

I. Resistance to Chloroquine

The efficacy of a drug against falciparum infections has been determined traditionally by observing whether the level of parasites in the blood stream changes after drug administration and, if clearance occurs, by noting whether there is a subsequent recrudescence of parasitaemia. Soon after the emergence of chloroquine-resistant strains of P. falciparum, it became obvious that resistance to chloroquine varied from a level at which the drug had no apparent effect on the course of the infection to one at which the infection responded to treatment but was associated with a recrudescence of parasites 3–4 weeks after treatment. In an effort to standardise the spectrum of response observed in chloroquine-resistant strains of P. falciparum, an arbitrary system to grade the level of chloroquine resistance was proposed in 1967 (WHO 1967) and slightly modified in 1973 (WHO 1973).

1. Procedure for Grading Level of Resistance

The WHO Field Test (WHO 1973) consists of the administration of 25 mg chloroquine base/kg body wt. over a period of 3 days and a follow-up observation period of 7 days (“standard test”) or 28 days (“extended test”) to determine the response of parasites to treatment. As the “standard test” will not detect the presence of low levels of chloroquine resistance, its use should be restricted to circumstances where
reinfection is likely within 2 or 3 weeks after drug administration or where it is impossible to carry out follow-up examinations over a period of 4 weeks after treatment with chloroquine. The “alternative test,” consisting of the administration of a single dose of 10 mg chloroquine/kg body wt., is sometimes used where treatment cannot be given for 3 days or where a single dose of chloroquine has been accepted as the standard form of treatment.

The procedure involves the following steps:

1. Thick and thin blood films are collected from a patient suspected of having falciparum malaria and examined for the presence of asexual forms of P. falciparum.
2. Patients who have taken antimalarial drugs recently, who are severely ill or vomiting, or who have excessively high levels of parasitaemia, mixed species infection or only gametocytes of P. falciparum, are excluded from the test.
3. Urine specimens are collected from suitable patients who are willing to participate in the test and examined for the presence of chloroquine and, if possible, for other antimalarials. Patients who are shown to have drugs in their urine are excluded from the test.
4. A record should be kept of the duration of symptoms during the current episode of malaria, the number of previous fever episodes during the past 6 months and the probable location where the infection was acquired. Such information may be helpful in assessing the possible role of immunity in influencing the outcome of the test and in identifying the location of chloroquine-resistant strains of P. falciparum.
5. Uncoated chloroquine tablets, conforming to International Pharmacopoeia standards, are administered once on each of three successive days starting on day 0.10 mg chloroquine base on day 0, 10 mg chloroquine base on day 1, and 5 mg chloroquine base on day 2. Individuals who vomit after drug administration should not be used for the test. This risk can be minimised by swallowing the tablets after a light meal.
6. Individuals should be seen daily for 7 days after drug administration. The clinical condition of the patient always takes precedence over the conduct of the test and, if necessary, the clinical attack of malaria should be aborted by the use of alternative drugs such as quinine. Thick and thin blood films should be made each day to determine the concentration of asexual parasites of P. falciparum. Thick films are considered negative when careful examination of 100 fields (about 0.1 μl) shows no evidence of asexual parasites. Absorption of chloroquine should be confirmed by examining urine specimens for the presence of the drug 1–3 days after the beginning of treatment.
7. In the “extended test,” individuals whose asexual parasitaemia cleared by the end of 7 days are followed up for an additional 21 days. Blood films are examined at least once a week to monitor any recurrence of asexual parasites during this period.

2. Interpretation of Tests (see Chap. 16, Fig. 1, p. 424)

1. Absence of asexual parasites by day 6 and 7 after the start of treatment indicates that the infection is either sensitive or resistant at the R1 level to the drug. A sensitive (S) response can only be distinguished from an R1 level of resistance (delayed recrudescence) by the 28-day observation period of the “extended test,” providing there is no opportunity for the individual to be bitten by infected mosquitoes dur-