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REVERSAL OF *PLASMODIUM FALCIPARUM* RESISTANCE TO CHLOROQUINE IN PANAMANIAN *AOTUS* MONKEYS

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Abstract. An *Aotus–Plasmodium falciparum* model was used to determine if chloroquine resistance could be reversed in vivo. The putative resistance modulators tested all reverse chloroquine resistance in vitro and included verapamil, chlorpromazine, prochlorperazine, cyproheptadine, ketotifen, a tiapamil analog (Ro 11-2933), and a chlorpromazine analog (SKF 2133-A). Combinations of chloroquine plus chlorpromazine or prochlorperazine confirmed reversal of chloroquine resistance as exhibited by cures obtained in six *Aotus* monkeys infected with chloroquine-resistant *P. falciparum* (Vietnam Smith/RE strain) and rapid clearance of parasitemia, followed by recrudescence in six additional monkeys. The results indicate the following order of in vivo efficacy for reversing chloroquine resistance in *Aotus:* chlorpromazine > prochlorperazine ≫ desipramine ≫ Ro 11-2933 (tiapamil analog) > ketotifen. Cyproheptadine and verapamil were not effective in reversing chloroquine resistance and probable drug toxicity was observed with these drugs in combination with chloroquine.

Despite the widespread prevalence of drug-resistant *Plasmodium falciparum*, chloroquine remains an important drug in the treatment of malaria in many parts of the world.[1] The discovery that chloroquine resistance could be reversed in vitro by using verapamil suggested a novel approach to combination therapy and raised hopes that the clinical response to chloroquine could be restored.[2] Numerous compounds besides verapamil have now been shown to reverse chloroquine resistance in vitro,[3–6] but experience with resistance modulators plus chloroquine in vivo is limited. In various mouse malaria models, verapamil, cyproheptadine, ketotifen, and amlodipine have been shown to reverse chloroquine resistance,[5, 7–9] but primate in vivo data versus chloroquine-resistant *P. falciparum* are limited to a single observation.[10] In that study, desipramine given in combination with chloroquine cleared parasitemia in *Aotus* monkeys infected with chloroquine-resistant *P. falciparum*, but in each case the infection eventually recrudesced. In this study, we report our results with a series of resistance modulators in a Panamanian *Aotus–P. falciparum* model. The results confirm the reversal of *P. falciparum* chloroquine resistance in *Aotus* and allow for comparison of relative abilities of different compounds to reverse chloroquine resistance.

MATERIALS AND METHODS

Malaria-naive Panamanian owl monkeys (*Aotus lemurinus lemurinus*) were used as hosts for chloroquine-resistant *P. falciparum*, and previously described procedures and husbandry practices were followed.[11] The chloroquine-resistant Vietnam Smith strain was used in the initial experiments with chloroquine combined with verapamil or SKF 2133-A (a chlorpromazine analog). In subsequent studies, a recrudescent isolate from a Vietnam Smith strain–infected *Aotus* monkey treated with chloroquine was used. This strain, designated Vietnam Smith/RE, was more resistant to chloroquine as evidenced by limited effects on parasitemia in *Aotus* monkeys receiving 20 mg/kg/day of chloroquine for seven days.

Each monkey was inoculated intravenously with 5×10^6 trophozoites of the chloroquine-resistant Vietnam Smith or Vietnam Smith/RE strain of *P. falciparum*. The inoculum size produced a parasitemia of at least $5 \times 10^3/mm^3$ by the fifth day postinoculation, at which time treatment was begun. Stock solutions of water-soluble drug were prepared at appropriate concentrations and maintained at 4°C during the course of treatment. A suspension of water-insoluble drugs was prepared in 0.3% methylcellulose just

prior to use. All drugs were administered by gastric intubation in a volume of 7.0 ml, followed by a 7.0-ml rinse with either water or 0.3% methylcellulose. Chloroquine alone or in combination with the candidate resistance modulator drug was given orally for either three or seven consecutive days. In several experiments, the putative resistance modulator was given three times per day (8:00 AM, noon, and 4:00 PM) for three or seven days. A 20 mg/kg dose of chloroquine, given once a day for either three or seven days, was used as a negative control in all experiments. Administration of chloroquine in either three daily doses of 20 mg/kg or seven daily doses of 5–20 mg/kg is effective at curing infections with chloroquine-susceptible parasites in *Aotus;* however, these regimens are not effective against the Vietnam Smith or Vietnam Smith/RE strains.[10, 12]

Giemsa-stained blood smears were prepared from all animals and examined daily beginning the day after inoculation until parasitemia was cleared and for at least seven days thereafter. At that time, blood films were examined twice a week up to 100 days after treatment. Thick blood films were considered negative if no parasites were seen after examination for at least five min. Ten or less parasites on a thick blood film were recorded as < 10. Parasitemia was enumerated by the Earle-Perez technique[13] and expressed as number of parasites/mm^3. Treated animals were observed twice a day for signs of drug toxicity, as evidenced by abnormal behavior, anorexia, diarrhea, or vomiting. Necropsies were performed on all animals that died. In conducting the research described in this report, the investigators adhered to the *Guide for the Care and Use of Laboratory Animals,* as promulgated by the National Research Council.

The classification of treatment outcomes was adapted from Schmidt,[14] and the outcome of each infection was compared with untreated controls and monkeys treated with chloroquine or the resistance modulator alone. The infection was considered suppressed when parasitemia persisted throughout treatment, but was reduced to less than one-fiftieth the level of parasitemia in the control on the same day postinitiation of treatment. An infection was considered cleared if the parasitemia became negative by 12 days after the infection became patent and remained negative for seven days; clearance of parasitemia after the infection was patent for 12 days was indicative of a self-limiting infection and was not attributed to a drug affect. An infection was considered cured if the parasitemia cleared and blood films remained negative for 100 days after the end of treatment. Infections that failed to be cured by the initial treatment were subsequently treated with higher doses of resistance modulator plus chloroquine or with mefloquine. Re-treatment data were not considered in the analysis of drug efficacy because of the high rate of self-limiting infections (73%) observed in this model.[11] Clear evidence of drug efficacy can be observed through the peak phase of parasitemia, which is up to 8–11 days from initiation of patency. Parasitemia in self-limiting infections begins to decrease 8–14 days after initiation of patency.[11]

RESULTS

Experiments designed to detect the ability of verapamil to reverse chloroquine resistance in *Aotus* involved using two different treatment regimens. In the first experiments, verapamil was administered at a dose of 25 or 50 mg/kg once a day for three days with or without chloroquine (Figure 1). In *Aotus* monkeys infected with the Vietnam Smith strain, parasitemia in two animals receiving 20 mg/kg of chloroquine was not significantly affected and one died from malaria (Figure 1A). Parasitemia remained high for more than seven days subsequent to treatment with 25 mg/kg of verapamil alone (Figure 1B). Parasitemia in each monkey became negative by day 21 post-treatment; however, the rate of parasite clearance was equal to that in self-limiting Vietnam Smith infections and could not be attributed to a drug effect. A three-day dosage of 50 mg/kg of verapamil alone had no effect upon parasitemia and both monkeys died of apparent drug toxicity 4–6 days after the completion of treatment. Two animals received 25 mg/kg of verapamil plus 20 mg/kg of chloroquine (Figure 1C). Parasitemia became negative in both monkeys by day 21 post-treatment, but again at a rate similar to that seen in untreated infections. Two monkeys received 50 mg/kg of verapamil plus chloroquine and both died, one of apparent drug toxicity and the other of malaria.

In the second series of experiments with verapamil and chloroquine, the Vietnam Smith/RE strain was used and divided doses of verapamil were given to reduce the toxicity observed with higher daily doses in the first experiment. Verapamil (5 mg/kg) was given three times per day

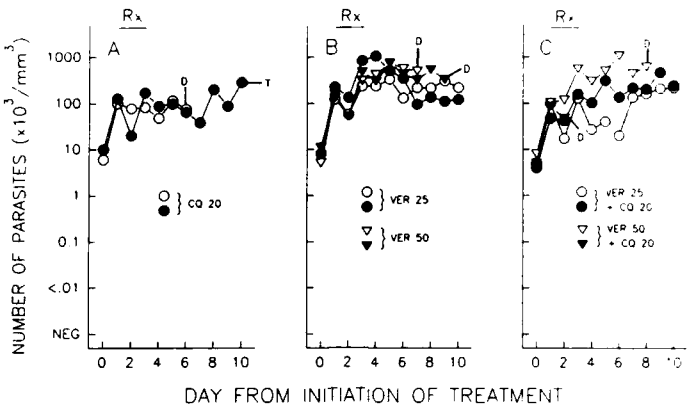

FIGURE 1. Activities of verapamil (VER) and chloroquine (CQ) in *Aotus* monkeys infected with the chloroquine-resistant Vietnam Smith strain of *Plasmodium falciparum*. VER (25 or 50 mg/kg) **(A)** and CQ (20 mg/kg) **(B)** were given alone or in combination **(C)** once a day for three days. Each curve represents parasitemia of an individual monkey. Rx = treatment period; T = monkey treated with an increased dose of VER plus CQ or with mefloquine; D = monkey died.

(8:00 AM, noon, and 4:00 PM) and chloroquine (20 mg/kg) was given once a day (8:00 AM) for three days (Figure 2). Parasitemia was not significantly affected in two monkeys given 5 mg/kg of verapamil (15 mg/kg/day) plus chloroquine or in two monkeys given chloroquine alone. No response in parasitemia was seen in monkeys administered the same doses of verapamil alone.

An analog of tiapamil (Ro 11-2933) that was previously shown to reverse chloroquine resistance in vitro[3] was tested in a modified seven-day regimen. This analog (20 mg/kg) was given three times per day for seven days and chloroquine (20 mg/kg) was administered once a day for three days (Figure 3A). Parasitemia was suppressed in both monkeys receiving the combination treatment, but it began to increase by the seventh day of treatment.

A chlorpromazine analog (SKF 2133-A) that reverses chloroquine and quinine resistance in vitro[3] was tested in combination with chloroquine in *Aotus* monkeys (Figure 3B). Parasitemia was not affected by treatment with either 5 or 10 mg/kg of SKF 2133-A plus 20 mg/kg of chloroquine given once a day for three days.

Two additional phenothiazines, chlorpromazine and prochlorperazine, were evaluated in combination with chloroquine over a seven-day treatment regimen (Figure 4). The low dose of chlorpromazine (10 mg/kg) plus chloroquine (20 mg/kg) cleared the parasitemia in four of four monkeys and cured the infection in one animal (Figure 4E). The 20 mg/kg dose of chlorpromazine plus chloroquine cleared parasitemia in four of four treated monkeys, and cured the infections in three of these (Figure 4F). The results were similar when prochlorperazine plus chloroquine was used in the same seven-day treatment regimen (Figure 4B and C). Two of two monkeys were cleared of parasitemia after receiving 10 mg/kg of prochlorperazine and 20 mg/kg of chloroquine (Figure 4B). Parasitemia in both monkeys recrudesced by day 18 post-treatment. The higher dose of prochlorperazine (20 mg/kg) plus chloroquine cleared and cured infections of the chloroquine-resistant Smith/RE strain in two monkeys (Figure 4C). No response in parasitemia was observed when chlorpromazine, prochlorperazine, or chloroquine were administered alone (Figure 4B–D).

The antihistaminic agents cyproheptadine and ketotifen were evaluated in combination with chloroquine in a seven-day treatment regimen. No significant reduction in parasitemia was seen when either cyproheptadine, ketotifen, or chloroquine were given alone (Figure 5B and D). In addition, no response was noted when cyproheptadine (10 or 20 mg/kg) plus chloroquine (20 mg/kg) were given in combination once a day for seven days (Figure 5C). One monkey died of apparent cardiac toxicity on day 3 of treatment when given 20 mg/kg of cyproheptadine plus chloroquine. A slight decrease in parasitemia in one of two monkeys was seen with 10 mg/kg of

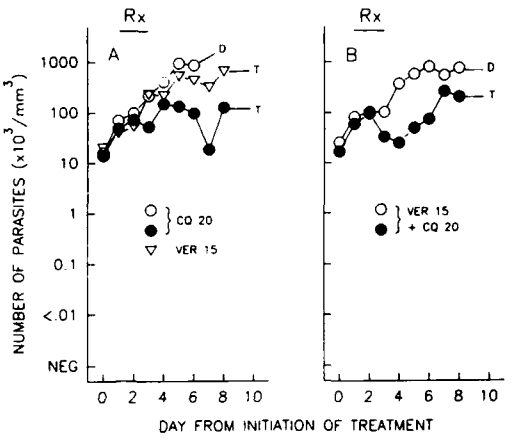

FIGURE 2. Activities of verapamil (VER) and chloroquine (CQ) in *Aotus* monkeys infected with the chloroquine-resistant Vietnam Smith/RE strain of *Plasmodium falciparum*. VER (5 mg/kg given at 8:00 AM, noon, and 4:00 PM, 15 mg/kg/day) and CQ (20 mg/kg given at 8:00 AM) were administered alone **(A)** or in combination **(B)** for three days. Each curve represents parasitemia of an individual monkey. Rx = treatment period; T = monkey treated with an increased dose of VER plus CQ or with mefloquine; D = monkey died.

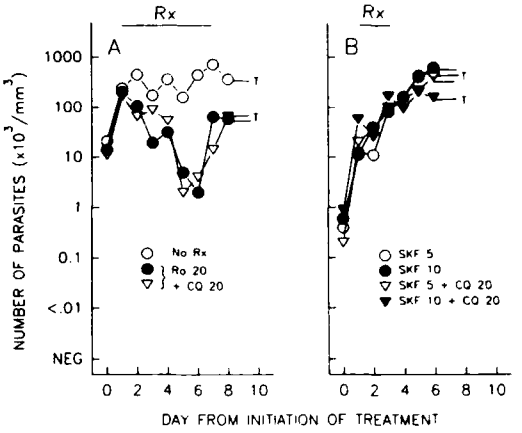

FIGURE 3. Activities of Ro 11-2933 (Ro) and SKF 2133-A (SKF) alone or in combination with chloroquine (CQ) in *Aotus* monkeys infected with the chloroquine-resistant Vietnam Smith/RE strain of *Plasmodium falciparum*. Ro (20 mg/kg) was given for seven days **(A)** and SKF (5 or 10 mg/kg) was administered for three days **(B)**; chloroquine (20 mg/kg) was given for three days in both experiments. Each curve represents parasitemia of an individual monkey. Rx = treatment period; T = monkey treated with increased dose of Ro or SKF plus CQ or with mefloquine.

ketotifen plus chloroquine, whereas suppression was observed in one of two animals receiving 20 mg/kg of ketotifen plus chloroquine. No monkeys were cleared of parasitemia or cured of infection after receiving any combination of either cyproheptadine or ketotifen plus chloroquine.

DISCUSSION

A Panamanian *Aotus* monkey–*P. falciparum* model has been used to determine if the reversal of chloroquine resistance could be confirmed in vivo with a series of resistance modulators. A previous study demonstrated that the combination of desipramine (50 mg/kg on day one and 25 mg/kg on days two and three) plus chloroquine (20 mg/kg for three days) could clear infection with the Vietnam Smith/RE strain; however, in each case parasitemia recrudesced by day fourteen post-treatment.[10] In this study, the combination of chloroquine plus chlorpromazine or prochlorperazine confirmed reversal of chloroquine resistance in *Aotus*. This effect was demonstrated by clearance of parasitemia and by cures obtained in six *Aotus* monkeys infected with the chloroquine-resistant Vietnam Smith/RE strain. Clearance of parasitemia, followed by recrudescence on days 10–21 post-treatment, was observed in six other monkeys. This represents the first report of cures in an in vivo study using resistance modulators plus chloroquine against chloroquine-resistant *P. falciparum*.

Although treatment regimens varied, the pronounced differences in treatment outcomes allow for comparison of the relative abilities of candidate resistance modulators to reverse chloroquine resistance in *Aotus*. Two phenothiazines, chlorpromazine and prochlorperazine, were the most effective at reversing resistance in the *Aotus–P. falciparum* model. Combinations of these two phenothiazines plus chloroquine resulted in the only cures obtained. An analog of chlorpromazine (SKF 21133-A) that reverses chloroquine resistance in vitro was not effective in this model. The optimal response with ketotifen and a tiapamil analog (Ro 11-2933) in combination with chloroquine was the suppression of parasitemia in *Aotus* monkeys. Verapamil and cyproheptadine, both potent reversing agents in vitro,[2,5] were not effective in reversing chloroquine resistance and probable drug toxicity was observed. It is not known why verapamil and cyproheptadine did not reverse chloroquine resistance in *Aotus* monkeys, but it could be due

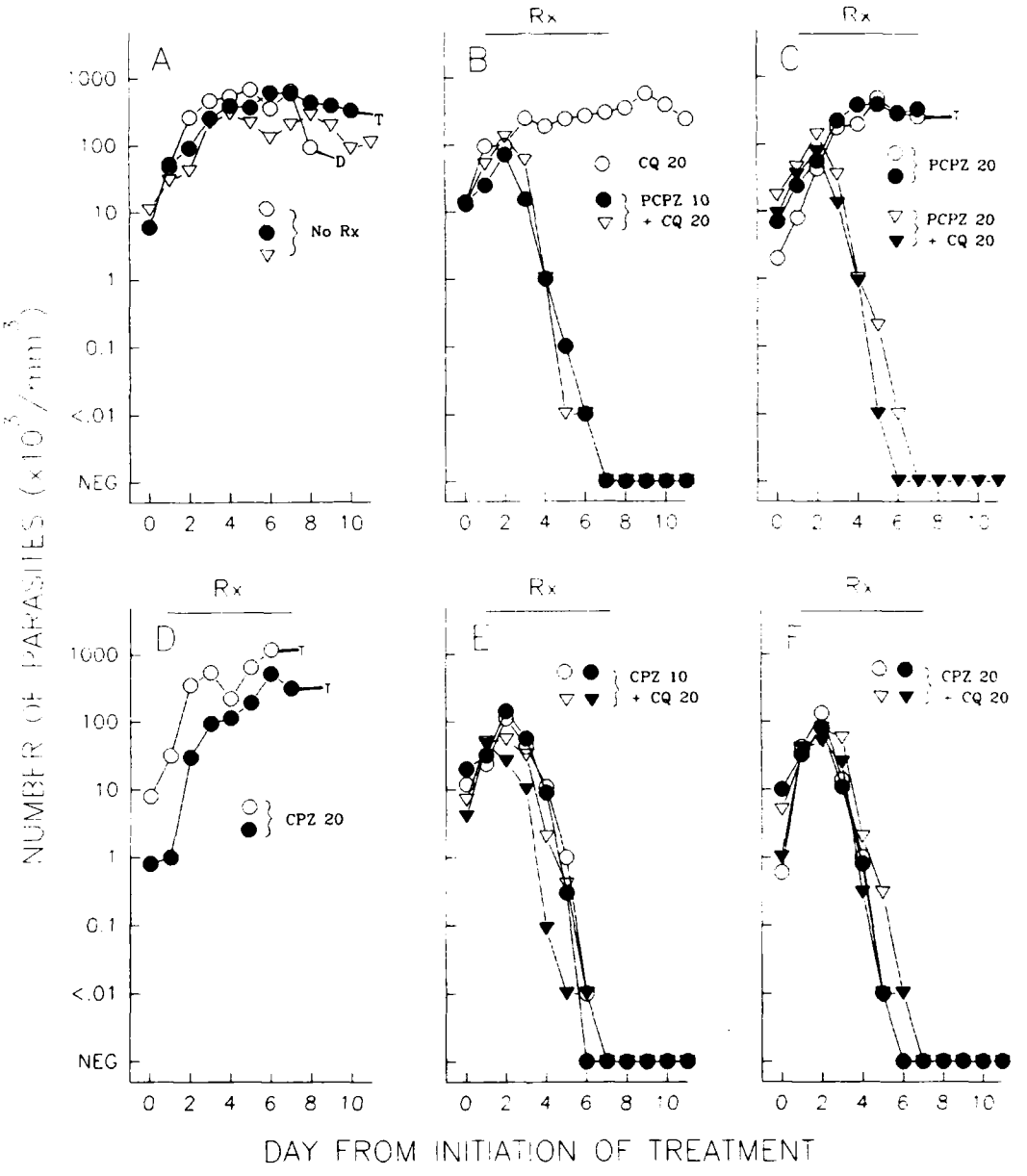

FIGURE 4. Activities of prochlorperazine (PCPZ) and chlorpromazine (CPZ) alone or in combination with chloroquine (CQ) in *Aotus* monkeys infected with the chloroquine-resistant Vietnam Smith/RE strain of *Plasmodium falciparum*. Monkeys were given 10 or 20 mg/kg of PCPZ or CPZ alone **(C and D)** or in combination with 20 mg/kg of CQ **(B, C, E, and F)** once a day for seven days. Untreated monkeys **(A)** and animals treated with CQ alone **(B)** were used as controls. Each curve represents parasitemia of an individual monkey. Rx = treatment period; T = monkey treated with an increased dose of PCPZ or CPZ plus CQ; D = monkey died.

to pharmacokinetics or drug metabolism in the host. These results and those previously published[10] indicate the following order of in vivo efficacy of reversing chloroquine resistance in the *Aotus* model: chlorpromazine > prochlorperazine ≫ desipramine ≫ Ro 11-2933 > ketotifen. These results suggest that structure-activity relationships for phenothiazines and tricyclic an-

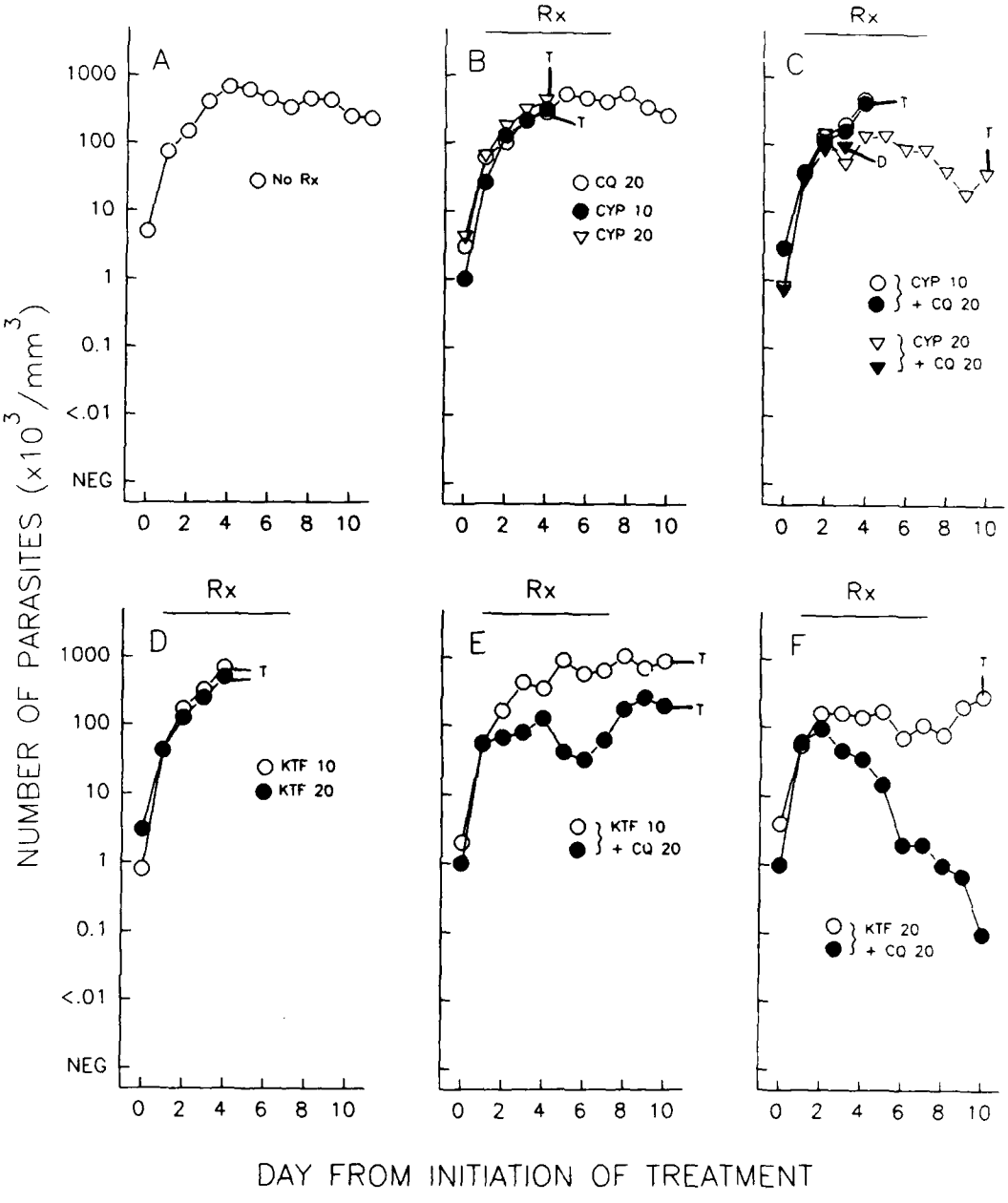

FIGURE 5. Activities of cyproheptadine (CYP) and ketotifen (KTF) alone or in combination with chloroquine (CQ) in *Aotus* monkeys infected with the chloroquine-resistant Vietnam Smith/RE strain of *Plasmodium falciparum*. Monkeys were given 10 or 20 mg/kg of CYP or KTF alone **(B and D)** or in combination with 20 mg/kg of CQ **(C, E, and F)** once a day for seven days. An untreated animal **(A)** and a monkey treated with CQ alone **(B)** were used as controls. Each curve represents parasitemia of an individual animal. Rx = treatment period; T = monkey treated with an increased dose of CYP or KTF plus CQ; D = monkey died.

tidepressants should be conducted. The goal would be to identify potent resistance modulators that lack pronounced activities as antipsychotics or antidepressants.

The results obtained in this study with antihistaminics and verapamil contrast with the reversal of chloroquine resistance demonstrated in two mouse malaria models.[5, 7, 8] In the chloro-

quine-resistant *P. yoelli* model, verapamil, cyproheptadine, and ketotifen each reverse chloroquine resistance.[5,7] Verapamil also reverses chloroquine resistance in *P. chabaudi*.[8] The contrasting results in *Aotus* and mice could be attributed to differences in the pharmacokinetics of the drug combinations, differences in the route of drug administration (oral in monkeys versus subcutaneous in mice), differences in the mechanism(s) of chloroquine resistance in *P. falciparum, P. yoelli,* and *P. chabaudi,* or to a combination of these factors. The negative results of this study with the combination of chloroquine plus cyproheptadine are similar to those observed in a clinical study conducted in Africa.[15] Therefore, in both humans and *Aotus,* the combination of chloroquine plus cyproheptadine was not effective in reversing chloroquine resistance. This lack of effect could be attributed to very low levels of cyproheptadine or cyproheptadine metabolites found in plasma following oral administration of the drug.[16]

The in vivo confirmation of the reversal of chloroquine resistance in *Aotus* reported here is encouraging and supports the possibility that eventually resistance modulators may be useful clinically for the treatment of chloroquine-resistant malaria; however, these data should not be construed as supporting immediate initiation of clinical trials with chlorpromazine, prochlorperazine, or other resistance modulators with chloroquine. Direct extrapolation of data from the *Aotus–P. falciparum* model to humans is unwarranted without determining if the pharmacokinetics of the drugs in combination are similar in both hosts. In addition, the doses of prochlorperazine used in this study are much higher than those used in humans and the doses of chlorpromazine used are close to the highest doses used in patients.

The possibility for toxic consequences with resistance modulator therapy have been suggested for the treatment of cancer and malaria.[17,18] An example of this has been shown in schizophrenic patients in Africa receiving chloroquine and chlorpromazine. Pretreatment with chloroquine markedly increases plasma levels of chlorpromazine and a major metabolite (7-hydroxychlorpromazine) in patients to potentially toxic levels and influences urinary excretion of the drug.[19,20] In this study, the results of trials with verapamil and cyproheptadine suggest that combined drug toxicity can not be excluded as a cause for deaths in several owl monkeys. The reasons for the deaths of *Aotus* monkeys 4–6 days after treatment with verapamil alone or in combination with chloroquine are unknown. A cardiac-active drug such as verapamil would be expected to produce more acute toxic effects. Clearly, thorough studies of pharmacokinetics and acute toxicology are needed with chloroquine plus resistance modulator combinations before proceeding to clinical trials.

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