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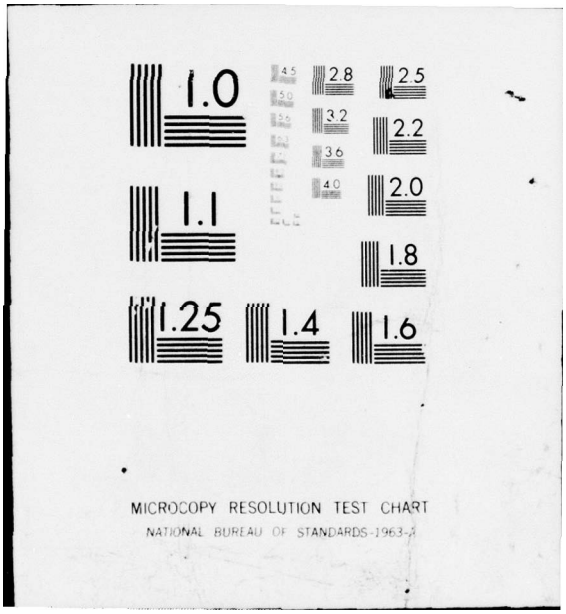
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REPORT NUMBER 1

(12)

Phase I Clinical Testing Antimalarial Drugs

Annual Report

Richard C. Reba, M.D.

Date August 1977

Supported by

U.S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Washington, D.C. 20314

Contract No. DAMD 17-75-C-5036

BIO-MED, Inc.
110 Irving Street, N.W.
Washington, D.C. 20010

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The report includes work performed under Contract DAMD 17-75-C-5036 from February 1975 through the first contract year. Two drugs have been subjected to Phase I clinical testing; Mefloquine and WR 184,806-H_3PO_4, another quinoline methanol.

A chronic safety and tolerance study of mefloquine has been initiated, in which 50 subjects will receive 500 mg mefloquine or placebo

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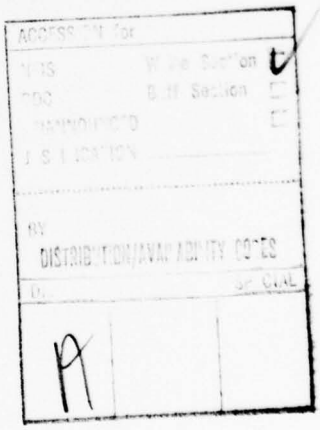
20. Abstract (Continued)

weekly for 52 weeks. Clinical, ophthalmologic, hematologic and biochemical monitoring are performed serially. During the initial weeks of study compliance has been excellent and no adverse reactions have been observed. Studies are also approved to determine the top tolerated single oral dose of mefloquine and the safety and tolerance of mefloquine when administration of a single "therapeutic" oral dose level is repeated seven days after the first adminstration.

The first administration of WR 184,806-H_3PO_4 to humans has been accomplished. Using double-blind rising dose levels, single oral doses were well tolerated to the 1000 mg level; six subjects receiving 1200 to 1400 mg all developed intolerance manifested by combinations of lightheadedness with associated difficulties such as concentrating and focusing, headache, nausea, insomia, and unusual dreams. In all subjects the symptoms were non-incapacitating and of less than 24 hours duration. Multiple oral doses were then tested administering drug or placebo every eight hours for 72 hours (9 doses). Intolerance manifestations were similar to those observed in the single dose study and occurred at the 3600 mg total dose level (400 mg/individual dose).

It is concluded that the expanded studies of mefloquine are of value and should be continued. WR 184,806·H_3PO_4 is well tolerated and intolerance is manifested only by non-incapacitating symptoms. Pharmacokinetic studies are indicated as a prelude to Phase II studies.



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Phase I Clinical Testing Antimalarial Drugs

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BIO-MED, Inc.
110 Irving Street, N.W.
Washington, D.C. 20010

SUMMARY

BIO-MED, Inc. initiated Phase I clinical testing of antimalarial drugs from February 1975 through the initial contract year. These drugs were developed by the antimalarial drug program of the U.S. Army Medical Research and Development Command. Testing was performed at the Washington Hospital Center in Washington, D.C. under Contract DAMD 17-75-C-5036. A chronic safety and tolerance study of mefloquine was started in September 1975. The study includes weekly administration of 500 mg of drug or placebo to 50 healthy subjects for a 52-week duration. No adverse reactions have been detected during the initial study months and compliance is excellent. If the drug is well tolerated throughout the study interval it is anticipated that clinical trials for mefloquine used as a prophylactic agent may be considered.

Another quinoline methanol, WR 184,806·H_3PO_4 has been administered to human subjects in short term safety and tolerance studies. Single and multiple oral doses were tested using double-blind rising dose levels. Single oral doses were well tolerated up to the 1000 mg dose level: all 6 subjects receiving 1200 to 1400 mg of drug as a single oral dose had combinations of light-headedness with associated difficulties such as concentrating and focusing, headache, nausea, insomnia, and unusual dreams. The symptoms were mild and of less than 24 hours duration in all subjects. Multiple dose studies consisted of 9 doses of drug or placebo administered every 8 hours for a total of 72 hours. Intolerance occurred at the 400 mg individual or 3600 mg total dose level with symptoms similar to those following single dose administration. No physical or laboratory abnormalities were associated with the administration of WR 184,806·H_3PO_4.

Single oral doses of mefloquine in Phase II studies have not been universally effective in parasite eradication. The safety and tolerance of repeating a "curative" single dose 7 days after the 1st dose is being tested. Additionally, a protocol has been designed, processed, and approved for implementation to determine the top tolerated single oral dose of mefloquine. This protocol should be implemented early in the next contract year.

Extension of Phase I clinical testing of mefloquine is warranted to permit further application in Phase II and Phase III testing. WR 184,806·H_3PO_4 studies demonstrated tolerance at dose levels which may be adequate for clinical purposes. Intolerance is manifested by temporary non-incapacitating symptomatology without associated physical or laboratory abnormalities attributed to the drug.

FOREWORD

Under terms of the contract, Phase I clinical testing of antimalarial drugs was performed at the Washington Hospital Center. All protocols were processed by the contractor's Organizational Review and Human Subject (Human Use) committees prior to submission to the Washington Hospital Center Research Committee.

All protocols were processed and approved by the Washington Hospital Center prior to implementation. The Washington Hospital Center is approved for performance of clinical research by the Department of Health, Education, and Welfare. (DHEW Assurance No. GO 180)

TABLE OF CONTENTS

OBJECTIVES

General: To initiate Phase I Clinical Testing of antimalarial drugs at the Washington Hospital Center using methodology providing maximum protection for the health and welfare of participating subjects.

Specific:

1. To establish as project approving and monitoring components, BIO-MED Organizational Review and Human Use Committees. The Washington Hospital Center processing agencies for clinical research will also be used.

2. To initiate a chronic safety and tolerance study of mefloquine, a quinoline methanol with demonstrated efficacy for prevention and therapy of multi-drug resistant P. malaria. The study includes weekly administration of 500 mg drug or placebo for 52 weeks to 50 subjects.

3. To perform short term safety and tolerance testing of WR 184,806·H_3PO_4, a quinoline methanol with some physical and biologic characteristics observed in pre-clinical trials which suggest potential advantages as compared with previously tested quinoline methanols.

4. To determine the top tolerated single oral dose of mefloquine.

5. To determine the safety and tolerance of repeating administration of a "curative" single oral dose of mefloquine 7 days after the first administration.

METHODS AND RESULTS

1. Organizational Review and Human Use Committees: BIO-MED established an Organizational Review Committee including physicians qualified in research and clinical medicine who are not officers or employees of BIO-MED. This eliminates a potential element of bias in reviewing protocols. The committee evaluates protocols for scientific merit and risk to the subject as well as refining methodology as appropriate.

   Following approval by the Organizational Review Committee the protocol is presented to the Human Use Committee which is comprised of lay individuals with an interest in clinical research and protection of the human subjects. Most members have participated as study subjects and many are graduate students in local universities. This committee is free standing, elects its own officers, and serves the vital function of a non-medical committee in assuring the civil

rights of the subjects are protected. In addition to assuring minimum discomfort and risk to subjects, the committee has on occasion recommended protocol modifications of a scientific nature which have been adopted.

After approval by the Human Use Committee, each protocol is submitted to the Research Committee of the Washington Hospital Center and is processed through the governing bodies. The Washington Hospital Center is approved by DHEW for performance of Clinical Research.

The process has resulted in extraordinary attention to the comfort and protection of subjects as a Human Use Committee member monitors each study "on-site" providing suggestions to improve compliance as well as subject comfort.

Overall, the project processing procedure with its multiple review and approval components has provided thorough consideration and benefit versus risk factors and has not been unduly cumbersome.

2. Mefloquine -- 52 Week Study:
This double-blind study was designed to provide five groups of 10 subjects each including drug administered and control subjects. Each subject will receive a single 500 mg oral dose of drug or placebo weekly for 52 weeks. The first group entered study in September 1975 and at this time three groups (30 subjects) are in study. The duration of the study requires careful selection of subjects since motivation must persist to maintain an acceptably low dropout rate. Comprehensive medical evaluation is performed serially. No changes attributable to drug administration have been noted in any subject.

3. Short Term Safety and Tolerance, WR 184,806·H_3PO_4:
The studies were initiated April 1975 using a single oral dose, double-blind, rising dose level method. The drug was well tolerated up to the 1000 mg dose level: all six subjects receiving 1200 to 1400 mg drug manifested combinations of light-headedness with associated difficulties concentrating and focusing, headache, nausea, insomnia, and unusual dreams. The symptoms were mild and of less than 24 hours duration. No other changes attributed to drug were observed. The complete report for submission to the technical monitor is in preparation. The Study Summary is presented in the following pages:

BIO - MED, Inc.

Tel: (202) 882-0977

Research Facility: George Hyman Research Building • 110 Irving Street, N. W. • Washington, D.C. 20010

Mailing Address: 1295 Lavall Drive • Gambrills, Maryland 21054

EXPERIMENT NO. 2: WR 184,806·H_3PO_4

SHORT TERM DOSAGE SAFETY AND TOLERANCE

RISING SINGLE DOSE LEVELS

STUDY SUMMARY

INTRODUCTION:

The study was performed to determine the short term dosage safety and tolerance of WR 184,806·H_3PO_4 administered orally to human subjects. A total of 12 study intervals were used to administer drug or placebo to 45 subjects.

SUBJECTS:

Recruitment:

Subjects were healthy males aged 21 to 45 years weighing between 50-100 kg. They were recruited from the Washington, D.C. metropolitan area and were hired as temporary employees.

Screening:

Candidates for employment underwent qualifying examinations to obtain the subjects for study. The initial evaluation included a complete history and physical examination, chest x-ray, electrocardiogram and the following tests: urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, Na^+, K^+, Cl^-, CO_2, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin. Laboratory tests were performed in duplicate by National Health Laboratories, Inc. using standard methods. Chest x-rays were performed in the Department of Radiology at the Washington Hospital Center. Electrocardiograms were performed by trained personnel using a Cambridge VS-4 portable electrocardiograph machine. Urinalyses were performed by physician investigators in the research unit laboratory using standard methods.

Informed Consent:

Qualified candidates were presented with a complete explanation of the background and rational for the study as well as procedures to be used. Candidates were interviewed as a group and individually. At individual interviews it was ascertained the candidate understood the study and personal risk factors. Qualified candidates were asked to read and permitted to sign the consent statement.

Exp. 2: Study Summary (Cont.)
Rising Single Dose Levels

Human Use Committee:

This free standing committee composed of community members and of similar age and occupation to the human subject group must give approval for each study prior to implementation. A member of the human use committee participated in the consent interviews and made frequent visits to the research unit to monitor the study and assure the subjects' health and welfare were given primary consideration. Each subject clearly understood that he could terminate his participation in the study at any time.

HOUSING:

Subjects were housed on the clinical research unit of the Washington Hospital Center, utilizing semi-private rooms with modern facilities. A lounge area was available which contained television, reading materials, games, chairs, and desks. Subjects, supervised by the investigating team, were allowed to use the tennis courts, swimming pool and recreational facilities of the Washington Hospital Center. A choice of meals was made available to each of the subjects by the Food Service Department at the Washington Hospital Center. Each subject underwent serial physical examinations in the unit examining room and special tests were performed in specialty areas within the hospital.

METHODS:

Drug administration:

Drug lots used, dosing schedules, number of subjects in each study period and incremental increases in doses are on file. 16 subjects received drug and 13 placebo.

Clinical and laboratory evaluations:

Serial comprehensive medical evaluation including physical, biochemical, hematologic and phototoxicity testing was performed on all subjects. Special tests were performed in selected groups at 1000 to 1400 mgm dose levels as follows: orthostatic tolerance, audiometry and electronystagmography. At the 1400 mgm dose detailed ophthalmologic examinations were performed before and after dosing.

RESULTS:

Symptoms and physical findings:

The onset, duration and description of symptoms and physical findings on all subjects are on file. No symptoms or findings suggestive of intolerance to WR 184,806·H_3PO_4 were observed below the 1000 mgm dose. Two of the 4 subjects receiving 1000 mgm had transient symptoms subsequently attributed to dosing: one was lightheaded for one minute and the other complained of temporary mild lightheadedness and nausea. The four subjects receiving 1200 mgm and the two receiving 1400 mgm all had symptom

patterns suggestive of intolerance including combinations of lightheadedness with associated difficulties concentrating and focusing, headache, nausea, insomnia and unusual dreams. In all subjects the symptoms were mild and of less than twenty-four hours duration.

Physical examinations:

Two abnormalities were noted initially after dosing. One subject had a poison oak rash which was not considered drug related. The other subject had a temporary decrease in amplitude of accommodation which was possibly but not probably drug related.

Laboratory tests:

There were no significant alterations in these tests attributed to drug ingestion.

Urinalyses - There were no significant alterations in urine protein or changes in urinary sediment attributed to drug ingestion.

Electrocardiography and phototoxicity testing - No electrocardiographic changes attributable to drug ingestion were observed. Phototoxicity was not produced under conditions of the study.

Special tests:

Orthostatic Tolerance:

Tests for orthostatic tolerance were performed on 10 subjects. Only one subject demonstrated orthostatic intolerance following oral administration of 1000 mgm of the drug. This subject did not have symptoms. It was concluded that non-rotational vertigo following administration of WR 184,806·H_3PO_4 in this study was not associated with orthostatic intolerance.

Audiometry and Electronystagmography (ENG):

One subject who ingested 1000 mgm of the drug had a mild unilateral sensorineural hearing loss. All other subjects had normal audiograms.

ENG analysis revealed a normally functioning vestibular mechanism for each subject with the following three exceptions: Subject No. 39 revealed a positional nystagmus probably related to vestibulogenic drug exposure immediately prior to study; repeat ENG 4 weeks later was normal. Subject No. 33 had a 22 percent decrease in left vestibular response suggestive of peripheral pathology. ENG was normal when repeated. The decreased vestibular response was not considered drug related since it was unilateral. Finally, subject number 10Bd vomited following cold water irrigation; his ENG was normal. There was no evidence under conditions of the study that WR 184,806·H_3PO_4 affected the vestibular mechanism.

Exp. 2: Study Summary (Cont.)
Rising Single Dose Levels

Ophthalmologic evaluation:

Tests were performed on subjects receiving 1400 mgm of WR 184,806·H_3PO_4. Subject Number 10Ba complained of blurred vision when reading. The only abnormality was a decrease in the amplitude of accommodation. This persisted for two days and returned to normal within a week. The presence of a small refractive astigmatism tended to exaggerate his symptomatology. The temporary change in accommodative reserve was possibly drug related.

CONCLUSION:

It was concluded that intolerance to single dose administration of WR 184,806·H_3PO_4 was manifested by lightheadedness and associated symptoms without detected objective change. Intolerance was marginal at the 1000 mgm and definite at the 1200 mgm dose level. Symptomatology was mild to moderate, most noticeable at 1400 mgm, and of less than twenty-four hours duration in all subjects.

3. Short Term Safety and Tolerance, WR 184,806·H_3PO_4: (Cont.)

Following completion of the single oral dose study, a multiple oral dose study was initiated. A double-blind, rising dose level was used with drug or placebo administered every eight hours for nine doses. Symptoms of light-headedness and tremulousness, mild and temporary occurred after the sixth administration of the 400 mg dose of drug in both subjects receiving a total dose of 3600 mg. The study was completed October 1975. The Study Summary is presented in the following pages:

BIO - MED, Inc.

Tel: (202) 882-0977

Research Facility: George Hyman Research Building • 110 Irving Street, N. W. • Washington, D.C. 20010

Mailing Address: 1295 Lavall Drive • Gambrills, Maryland 21054

EXPERIMENT NO. 2: WR 184,806·H_3PO_4
SHORT TERM DOSAGE SAFETY AND TOLERANCE
MULTIPLE DOSE LEVELS

STUDY SUMMARY

INTRODUCTION:

In single dose studies previously reported, no intolerance to WR 184,806·H_3PO_4 was observed below the 1000 mg dose level. At higher dose levels, lightheadedness with associated difficulties concentrating and focusing, headache, nausea and sleep disturbances occurred. There were no associated objective findings and the symptoms were of less than twenty-four hours duration. This study was performed to determine the short term safety and tolerance of WR 184,806·H_3PO_4 administered orally in multiple doses. A total of eight study levels were used to administer drug or placebo to 29 subjects.

SUBJECTS:

The subjects were recruited from the Washington, D.C. metropolitan area and were hired as temporary employees. Advertisements in university newspapers provided initial contacts with potential subjects. This method plus positive recommendations by participating subjects to their classmates enlarged the candidate pool. Approximately 80% of the subjects were university students with superior motivation, understanding and compliance.

Screening:

Candidates for employment underwent qualifying examinations to obtain the subjects for study. The initial evaluation included a complete history and physical examination, chest x-ray, electrocardiogram and the following tests: urinalysis, white blood cell and differential count, red blood cell count, hemoglobin, hematocrit, MCV, MCH, MCHC, platelet count, glucose, BUN, creatinine, Na^+, K^+, Cl^-, CO_2, uric acid, total protein, albumin, globulin, calcium, phosphate, cholesterol, triglycerides, alkaline phosphatase, SGOT, SGPT, LDH, total bilirubin and G6PD. Laboratory tests were performed in duplicate by National Health Laboratories, Inc. using standard methods. Chest x-rays were performed in the Department of Radiology at the Washington Hospital Center. Electrocardiograms were performed by trained personnel using a Cambridge

VS-4 portable electrocardiographic machine. Urinalyses were performed by physician investigators in the research unit laboratory using standard methods.

Informed Consent:

Qualified candidates were presented with a complete explanation of the background and rationale for the study as well as procedures to be used. Candidates were interviewed in a group and individually. At individual interviews it was ascertained that the candidate understood the study and personal risk factors. Qualified candidates were asked to read and permitted to sign the consent statement.

Human Use Committee:

This free standing committee composed of community members and of similar age and occupation to the human subject group must give approval for each study prior to implementation. A member of the Human Use Committee participated in the consent interviews and made frequent visits to the research unit to monitor the study and assure the subjects' health and welfare were given primary consideration. Each subject clearly understood that he could terminate his participation in the study at any time.

HOUSING:

Subjects were housed on the Clinical Research Unit of the Washington Hospital Center, utilizing semi-private rooms with modern facilities. A lounge area was available which contained television, reading materials, games, chairs and desks. Subjects, supervised by the investigating team, were allowed to use the tennis courts, swimming pool and recreational faciltites at the Washignton Hospital Center. A choice of meals was made available to each of the subjects by the Food Service Department at the Washington Hospital Center. Each subject underwent serial physical examinations in the unit examing room and specialty areas within the hospital.

METHODS:

The dosing schedule and number of subjects in each study period are on file. Sixteen subjects received drug and 13 placebo.

Clinical and laboratory evaluations:

Serial comprehensive medical evaluation including physical, biochemical, hematologic and phototoxicity testing was performed on all subjects.

Exp. 2: Study Summary (Cont.)
Multiple Dose Levels

RESULTS:

Symptoms and physical findings:

The onset, duration and description of symptoms and physical findings on all subjects are on file. Mild symptoms of transient diarrhea, constipation, lethargy, flushing and disturbing dreams occurred in both control and subjects receiving drug. Two subjects, receiving 3600 mg drug (1200 mg daily for 3 days) complained of vague tremulousness and lightheadedness similar to that observed when 1200-1400 mgs of WR 184,806·H_3PO_4 were administered as a single dose in a previous study. Two other subjects receiving 600 and 750 mg of drug daily experienced sleep disturbances. In all subjects the above noted symptoms were mild, temporary and without associated physical or laboratory abnormalities.

Physical Examination:

One subject receiving 3000 mg drug developed a maculopapular rash 10 days after completion of drug administration which was also associated with the subject's use of a commercial soap for the first time. The rash disappeared upon discontinuation of use of the soap and was considered a soap precipitated contact dermatitis by the consulting dermatologist.

Mild sunburn in 2 subjects and swimming pool chemical conjunctivitis in one subject were not considered drug related.

Laboratory tests:

Eighty-three percent of the subjects had at least one hematologic or biochemical abnormality. Abnormalities were distributed with equal frequency amongst subjects administered drug and placebo. No deviations were ascribed to drug ingestion.

Ten subjects had abnormal urinalyses, 6 of these received drug. Glycosuria (1+) with a normal blood sugar was detected on days 2 and 4 in one subject receiving 900 mg of drug. Intermittent trace proteinuria was detected in one subject receiving drug as well as one who received placebo. Increased numbers of red and white cells in the urinary sediment in control and drug administered subjects demonstrated no pattern and are not considered study related. No subject had cylindruria. No electrocardiographic changes attributable to drug ingestion were observed. Phototoxicity was not produced under conditions of this study.

Exp. 2: Study Summary (Cont.)
Multiple Dose Levels

CONCLUSION:

Possible intolerance to multiple doses of WR 184,806·H_3PO_4 was detected. Some subjects receiving drug, as well as controls, experienced flushing, vivid dreams and other symptoms considered potentially drug related in the previous single dose study. Tremulousness and lightheadedness occurred on the last day of dosing in two subjects receiving 3600 mg total dose. The late onset of these symptoms and similarity to symptoms of intolerance at 1200 and 1400 mg single dose levels suggests they may be drug related. Gastrointestinal symptoms occurred in the control subjects as well as those receiving drug. In the latter, the symptoms did not persist or increase in severity with continued drug administration. No physical or laboratory abnormalities were ascribed to drug ingestion.

4. Top Tolerated Single Oral Dose Mefloquine:
This protocol has been processed and approved for implementation. Scheduled to initiate study February 1976.

5. Mefloquine:
Safety and tolerance single oral dose repeated 7 days after first administration. This double-blinded, rising dose level study was initiated December 9, 1975. Any report at this time would be premature.

CONCLUSIONS:

The accomplishments of the first contract year may be enumerated as follows:

1. The Organizational Review Committee and the Human Use Committee are performing in a superior manner. The Human Use Committee members, by providing continuous monitoring during studies, has performed a significant service in the areas of subject protection, understanding, and compliance. The Washington Hospital Center participation has been productive and not obstructive. The close liaison with the Walter Reed scientists increases efficiency and productivity.

2. The 52-week mefloquine study is well underway. The careful selection of subjects and subject management during the study should assure a low dropout rate.

3. WR 184,806·H_3PO_4 is a promising compound both because of an acceptable top tolerated dose and intolerance manifested by temporary, non-incapacitating symptoms without associated clinical abnormalities.

4. The application of mefloquine in Phase II clinical trials threatened to outstrip needed Phase I testing. This threat is being eliminated by the Phase I testing being performed through this contract.

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