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DISPOSITION AND METABOLISM OF INVESTIGATIONAL NEW DRUGS

MRI PROJECT NO. 4266-B

FINAL REPORT

By

Thomas E. Shellenberger

September 1982

(For the Period July 1, 1976 through December 31, 1979)

Supported by:

U.S. Army Medical Research and Development Command
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD-17-76-C-6059

Midwest Research Institute
Kansas City, Missouri 64110

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Antimalarials	Excretion	WR-177602·HCl WR-225448·Succinate
Pharmacokinetics	Rats	WR-172435·CH ₃ SO ₃ H Mefloquine·HCl
Drug Metabolism	Rhesus Monkey	WR-142490·HCl
Absorption	Dogs	WR-194965·H ₃ PO ₄
20. ABSTRACT (Continue on reverse side if necessary and identify by block number)		
During the 39-month experimental period, studies were undertaken to determine absorption, excretion, metabolism and pharmacokinetics in rats, dogs, or rhesus monkeys following single oral doses of ¹⁴C-labeled antimalarial chemicals. Samples including blood, excreta, and selected other tissues/organs were collected at various time intervals following dosing and analyzed for ¹⁴C content. Selected tissues and excreta were extracted and subjected to thin-layer chromatography (TLC) to determine metabolic profiles. Results were		

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20. Abstract (continued)

evaluated using pharmacokinetic models to calculate area-under-blood-curves (AUC) and excretion rates.

Methods and results were reported in detail in 11 interim reports and four annual reports:

* Annual Report No. 1, July 1977

- Interim Report No. 1 - "Absorption, Excretion, Metabolism and Pharmacokinetics of WR-177602-HCl in Rats," February 3, 1977.
- Interim Report No. 2 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on WR-172435-CH₃SO₃H in the Rhesus Monkey," (Undated).
- Interim Report No. 3 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on WR-177602-HCl in the Rhesus Monkey," April 14, 1977.
- Interim Report No. 4 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on WR-142490-HCl in the Rhesus Monkey," June 21, 1977.

* Annual Report No. 2, January 1978

- Interim Report No. 5 - "Pharmacokinetic Studies on WR-172435-CH₃SO₃H in Rhesus Monkeys," August 23, 1977.
- Interim Report No. 6 - "Preliminary Absorption, Excretion, and Pharmacokinetic Studies on WR-194965-H₃PO₄ in the Rhesus Monkey," November 15, 1977.

* Annual Report No. 3, January 1979 (Revised June 1979)

- Interim Report No. 7 - "Absorption, Excretion and Pharmacokinetic Studies on Mefloquine-HCl, WR-142490-HCl in the Rat," March 3, 1977.
- Interim Report No. 8 - "Tissue Distribution Studies on WR-172435-CH₃SO₃H in Rhesus Monkeys," May 15, 1978.
- Interim Report No. 9 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on Mefloquine-HCl, WR-142490-HCl in the Beagle Dog," May 30, 1978.

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20. Abstract (concluded)

* Annual Report No. 4, March 31, 1981

- Interim Report No. 10 - "Tissue Distribution Studies on WR-177602-HCl in Male Long-Evans Rats," October 23, 1979.
- Interim Report No. 11 - "Summary of Accomplishments and Transfer of Raw Data for Disposition, Metabolic Profile, and Pharmacokinetics of Mefloquine-HCl, WR-142490-HCl in the Monkey," July 21, 1980; Revised December 5, 1980.
- Interim Report No. 12 - "Summary of Accomplishments and Transfer of Raw Data for Preliminary Disposition Studies on ¹⁴C-WR-225448-Succinate in Monkeys and Rats," December 5, 1980.

Results obtained with WR-172435-CH₃SO₃H were presented at the 1979 annual meeting of the Society of Toxicology:

- * Hodgson, J. R., et al., "Pharmacokinetic Studies on a New Candidate Antimalarial 3-Di-n-butylamino-1-[2,6-bis(4-trifluoromethylphenyl)-4-pyridyl]propanol Methanesulfonate, WR-172435-CH₃SO₃H in Rhesus Monkeys," Toxicol. Appl. Pharmacol., 48, 148 (1979). Abstract No. 16.

PREFACE

This report was prepared at Midwest Research Institute, 425 Volker Boulevard, Kansas City, Missouri 64110, under U.S. Department of the Army, Contract No. DAMD-17-76-C-6059, MRI Project No. 4266-B, "Disposition and Metabolism of Investigational New Drugs." The work was supported by the Division of Experimental Therapeutics, Walter Reed Army Institute of Research (WRAIR), Walter Reed Army Medical Center, U.S. Army Medical Research and Development Command. Dr. Ho Chung, Department of Pharmacology, was the Contract Officer Technical Representative (COTR).

The studies initially were conducted in the Biological Sciences Division, Dr. William B. House, Director, Dr. C. C. Lee, Assistant Director, and subsequently in the Pharmacology/Toxicology Department, Dr. Florence I. Metz, Acting Director. The experimental work was supervised by Dr. John R. Hodgson, Head, Biochemical and Developmental Pharmacology Section, succeeded by Dr. Robert Short, Senior Toxicologist. The present report was prepared by Dr. Thomas E. Shellenberger, Director, Toxicology Department.

MIDWEST RESEARCH INSTITUTE



Thomas E. Shellenberger, Ph.D.
Director, Toxicology Department

Approved:



Florence I. Metz, Ph.D.
Vice President, Chemical and
Biological Sciences Group

FOREWORD

In conducting the research described in this report, the investigator(s) adhered to the "Guide for Laboratory Animal Facilities and Care," as promulgated by the Committee on the Guide for Laboratory Animal Resources, National Academy of Sciences-National Research Council.

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INTRODUCTION

Under Contract No. DAMD-17-76-C-6059, Midwest Research Institute (MRI) conducted metabolism and disposition studies of candidate antimalarial chemicals in laboratory rats, rhesus monkeys, and dogs. Experimental methods and results were reported in 12 interim reports as contained in four annual progress reports. This final report identifies each annual report and the interim reports contained therein as well as publications resulting from this contract.

REPORTS

Annual Progress Report No. 1, July 1977

Report Period: July 1, 1976 through June 30, 1977

Four studies on the metabolism and disposition of candidate anti-malarial compounds were completed during this initial contract period (July 1 through June 30, 1977). Findings and conclusions presented in the annual report included results contained in four interim reports.

- * Interim Report No. 1 - "Absorption, Excretion, Metabolism and Pharmacokinetics of DL-Threo- α -(2-Piperidyl)-2,8-Bis(Trifluoromethyl) 4-Quinolinemethanol Hydrochloride, WR-177602·HCl in Rats," February 3, 1977.
- * Interim Report No. 2 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on 3-Di-n-Butylamino-1-[2,6-Bis(4-Trifluoromethylphenyl)-4-Pyridyl]Propanol Methanesulfonate, WR-172435·CH₃SO₃H in the Rhesus Monkey," (Undated).
- * Interim Report No. 3 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on DL-Threo- α -(2-Piperidyl)-2,8-Bis(Trifluoromethyl)-4-Quinolinemethanol Hydrochloride, WR-177602·HCl in the Rhesus Monkey," April 14, 1977.
- * Interim Report No. 4 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on DL-Erythro- α -(2-Piperidyl)-2,8-Bis(Trifluoromethyl)-4-Quinolinemethanol Hydrochloride, Mefloquine·HCl, WR-142490·HCl in the Rhesus Monkey," June 21, 1977.

Annual Progress Report No. 2, January 1978

Report Period: July 1977 through December 1977

Two studies on the metabolism and disposition of candidate anti-malarial compounds were completed during the contract period of July 1, 1977 through December 31, 1977. Findings and conclusions presented in the annual report include results contained in two interim reports.

- * Interim Report No. 5 - "Pharmacokinetic Studies on 3-DI-n-Butylamino-1-[2,6-Bis(4-Trifluoromethylphenyl)-4-Pyridyl]-Propanol Methanesulfonate, WR-172435·CH₃SO₃H in Rhesus Monkeys," August 23, 1977.

- * Interim Report No. 6 - "Preliminary Absorption, Excretion, and Pharmacokinetic Studies on 4-t-Butyl-6-t-butylaminomethyl-2-(4-Chlorophenyl)Phenol Phosphate, WR-194965·H₃PO₄ in the Rhesus Monkey," November 15, 1977.

Annual Progress Report No. 3, January 1979 (Revised June 1979)
Report Period: January 1978 through December 1978

Three studies on the metabolism and disposition of candidate anti-malarial compounds were completed during this contract period (January 1, 1978 through December 31, 1978). Findings and conclusions presented in the annual report include results contained in three interim reports.

- * Interim Report No. 7 - "Absorption, Excretion and Pharmacokinetic Studies on DL-Erythro-α-(2-Piperidyl)-2,8-Bis(Trifluoromethyl)-4-Quinoline Methanol Hydrochloride, Mefloquine·HCl, WR-142490·HCl in the Rat," March 3, 1978.
- * Interim Report No. 8 - "Tissue Distribution Studies on 3-Di-n-Butylamino-1-[2,6-Bis(4-Trifluoromethylphenyl)-4-Pyridyl]-Propanol Methanesulfonate, WR-172435·CH₃SO₃H in Rhesus Monkeys," May 15, 1978.
- * Interim Report No. 9 - "Preliminary Absorption, Excretion, Metabolism and Pharmacokinetic Studies on DL-Erythro-α-(2-Piperidyl)-2,8-Bis(Trifluoromethyl)-4-Quinoline Methanol Hydrochloride, Mefloquine·HCl, WR-142490·HCl in the Beagle Dog," May 30, 1978.

Annual Progress Report No. 4, March 31, 1981
Report Period: January 1979 through December 1979

One study on the metabolism and disposition of candidate anti-malarial compounds was completed during this terminal contract period (January 1, 1979 through December 31, 1979). Findings and conclusions presented in the annual report includes results contained in one interim report.

- * Interim Report No. 10 - "Tissue Distribution Studies on Threo-α-(2-Piperidyl)-2,8-Bis(Trifluoromethyl)-4-Quinolinemethanol Hydrochloride, WR-177602·HCl in Male Long-Evans Rats," October 23, 1979.

Two additional studies were initiated but these were incomplete when the contract was terminated. Therefore the raw data were transferred to the contract officer's technical representative at Walter Reed Army Institute of Research, accompanied by brief summary interim reports.

- * Interim Report No. 11 - "Summary of Accomplishments and Transfer of Raw Data for Disposition, Metabolic Profile, and Pharmacokinetics of DL-Erythro- α -(2-Piperidyl)-2,8-Bis(Trifluoromethyl)-4-Quinolinemethanol Hydrochloride, Mefloquine·HCl, WR-142490·HCl in the Monkey," July 21, 1980; Revised December 5, 1980.
- * Interim Report No. 12 - "Summary of Accomplishments and Transfer of Raw Data for Preliminary Disposition Studies on ^{14}C -WR-225448·Succinate in Monkeys and Rats," December 5, 1980.

PUBLICATIONS/PRESENTATIONS

Hodgson, J. R., J. L. Minor, C. C. Lee, and H. Chung, "Pharmacokinetic Studies on a New Candidate Antimalarial 3-Di-n-Butylamino-1-[2,6-Bis-(4-Trifluoromethylphenyl)-4-Pyridyl]Propanol Methanesulfonate, WR-172435·CH₃SO₃H in Rhesus Monkeys," Toxicol. Appl. Pharmacol., 48, A8 (1979). Abstract No. 16.

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