

Drug Tolerance Study of WR 225448 in Rhesus Monkeys

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OBJECTIVES

1. To determine the maximum tolerated dose of selected antimalarial compounds.
2. To characterize the nature of the toxic effects, including a determination of organ systems affected.

BACKGROUND : While certain chemical compounds are known to have excellent schizonticidal activity, they are, at the same time, toxic to the host. The purpose of this study was to determine the toxic dose of WR 225448 and also to determine what organ system(s) were affected by the drug.

METHODS : This study was accomplished in two phases

1. Secondary Test Phase (Graduated Dosage Study)

The candidate compound was administered orally to each of 2 rhesus monkeys using the method described by Davidson, *et al.* (1975)(1). This test phase was accomplished in March 1978 and final results are awaiting the histopathological examination of the tissues collected at necropsy.

2 Primary Test Phase (Fixed Dosage Study)

Following completion of the secondary test, a primary test, or fixed dosage study, was initiated in June 1979. Four monkeys were given the maximum tolerated dose as determined in the secondary test phase which for WR 225448 was 10.0 mg/kg. body weight/day. One monkey was included as a control and only the vehicle, methyl cellulose, was administered to it.

Blood was collected once a week from each monkey beginning 14 days prior to the administration of the test drug (WR 225448) and the following laboratory tests performed: RBC, WBC, Differential, Hematocrit, SGOT, SGPT, BUN, Total Serum Protein, Bolld glucose, and Creatinine.

Additional blood specimens were collected and the above listed laboratory tests performed on three more days during the course of the study as indicated in Table I.

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The dosage of WR 225448 remained 10 mg/kg. body weight throughout the study. Monkeys that died during the study were necropsied immediately and tissues from all organ systems collected for histopathological examination.

RESULTS : Four rhesus monkeys, #G406, G392, G411, and H-4 were given 10 mg/kg. body weight beginning on 18 June 1979. Monkey #G397 served as a control.

Monkey #G406 died on 23 June 1979 after receiving five doses of WR 225448. Monkey #G392 died on 24 June 1979 after six doses of the drug, Monkey #G411 died on 27 June 1979, 3 days after the last dose. Monkey #H-4 died on 28 June 1979, 4 days following the last dose of WR 225448. The control monkey, #G397, was euthanized and necropsied on 5 July 1979.

All four test monkeys died before the scheduled completion date of the study, suggesting that the 10 mg/kg. body weight dose exceeds the maximum tolerated dose originally determined by the secondary test phase. Complete necropsies were performed on all the monkeys. Based on gross necropsy observations and laboratory tests performed the liver appears to be the target organ. (See Table II). Final results of this study are awaiting completion of histopathologic examination of the tissues.

REFERENCE :

1. Davidson, D.E., et al.: Evaluating New Antimalarial Drugs Against Trophozoite Induced *Plasmodium cynomolgi* Malaria in Rhesus Monkeys, Am, J. Trop. Med. Hyg., (1976): 26-33.

Table II. Liver Enzyme Levels

Monkey Number	SGOT/SGPT				
	Day -14	Day -17	Day +1	Day +8	Day +15
G 392	34/25	34/28	46/42	**/	
G 406	34/20	34/28	46/34	**/	
G 411	34/22	40/20	50/30	1460/1800	**/
H-4	20/17	20/17	30/22	800/1340	**/
G 397*	37/25	34/25	46/14	40/28	40/54

* Control
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G 406 - Died Day +5
 G 392 - Died Day +6
 G 411 - Died Day +9
 H-4 - Died Day +10