DRUG TOLERANCE STUDY OF PRIMAQUINE IN RHESUS MONKEYS

Principal Investigators : Richard E. Whitmire, LTC, VC
Prayot Tanticharoenyos, DVM
Markpol Tingpalapong, DVM, LL.B.
Pranee Hunsukjariya, B.Sc.

Associate Investigator : John W. Crum, MAJ, MSC
David E. Davidson, Jr., Col, VC*

OBJECTIVES :

1. To determine the maximum tolerated dose of primaquine in rhesus monkeys (*Macaca mulatta*).

2. To determine the nature of the toxic effects, including a determination of the organ system(s) affected by primaquine.

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 primaquine in rhesus monkeys and also to determine what organ system(s) were affected by the drug.

METHODS : This study was conducted using the primary test phase format of fixed dosages. A total of 10 rhesus monkeys were utilized. The monkeys were divided into 2 groups of 5 monkeys each. There were 4 test monkeys and one control monkey in each group. In Group I, the 4 test monkeys were given Primaquine at the level of 10 mg/kg/day for 7 days suspended in 3 ml. of 0.3% methyl cellulose. In Group II, the 4 test monkeys were given primaquine at the level of 3.16 mg/kg/day for 7 days suspended in 3 ml. of 0.3% methyl cellulose. The control monkey in each group was given 3 ml. of 0.3% methyl cellulose. The dosages remained constant in each group for the entire 7 days. All drugs were administered orally via nasogastrotube.

The duration of the study was 30 days beginning on day 1 in which blood was taken for base line data. A total of five blood specimens were taken during the course of the study : days 1, 8, 15, 22 and 29. The drug was administered on days 14 through 20 inclusively. (See Table 1). Critical clinical observations were recorded on each moneky on days 14 through 21 of the study.

The following parameters were determined on each blood specimen collected : RBC, WBC, differential, hematocrit, SGOT, SGPT, BUN, Creatinine, total protein, glucose, methemoglobin. Two blood samples were taken prior to the administration of the test drug, one blood sample was taken during the administration of the drug, and two blood samples were taken after completion of the administration of the drug (See Table 1).

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* Division of Experimental Therapeutics, WRAIR

Five monkeys were randomly selected for necropsy. Monkeys number H-89 and H-91 from Group I were necropsied while monkeys number H-96 and H-97 were necropsied from Group II. Control monkey number H-106 was also necropsied.

RESULTS : All of the test monkeys survived the administration of the primaquine. Clinical illness was not observed in any of the monkeys during the test. Laboratory analysis of blood specimens taken before, during and after administration of primaquine are recorded in Tables 1 through 7.

The SGOT/SGPT levels were elevated transiently in two test monkeys in Group I (H-89 and H-91) indicating some liver cell necrosis. All other laboratory examinations on blood and serum were within normal limits and were not significant. Post mortem lesions were minimal and not significant. Histopathologic analysis is currently being performed on tissue specimens collected at necropsy.

CONCLUSIONS : The toxic dose of primaquine for the rhesus monkey is greater than 10 mg/kg/day X 7 days as no deaths occurred during this test.

Table 1.

↓ = Blood collected

R_x = Drugs administered

O = Monkeys observed, Clinical signs recorded

* = Necropsy

Calendar day																														
	↓							↓							↓								↓							↓*
														O	O	O	O	O	O	O	O									
														R_x	R_x	R_x	R_x	R_x	R_x	R_x											
Day of study	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
	13							20							27							3							10	
								MARCH														APRIL								

Laboratory Tests Required :

SGOT
SGPT
BUN
Creatinine
Total Protein
Glucose
Methemoglobin
WBC
RBC
Differential
Hematocrit

TABLE 2. SGOT/SGPT NORMAL VALUES = 33.4 ± 8/20.3 ± 5.8 IU

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-88	10 mg	34.08/21.12	35.52/27.36	32.64/21.12	23.04/19.20	19.20/24.96
H-89	10 mg	29.76/17.76	53.76/23.04	35.52/15.84	64.32/43.20	23.04/24.96
H-90	10 mg	42.24/24.96	35.52/19.20	27.84/15.84	29.76/19.20	29.76/17.76
H-91	10 mg	32.64/19.20	35.52/23.04	24.96/19.20	64.32/49.92	29.76/27.36
H-106	Control	32.64/17.76	35.52/17.76	24.96/11.04	24.96/15.84	23.04/15.84
H-92	3.16 mg	35.52/19.20	35.52/14.40	27.84/15.84	27.84/14.40	24.96/14.40
H-94	3.16 mg	32.64/21.12	32.64/14.40	24.96/29.76	19.20/11.04	21.12/19.60
H-96	3.16 mg	42.24/21.12	38.40/23.04	32.64/19.20	27.84/17.76	27.84/19.20
H-97	3.16 mg	42.24/23.04	32.64/24.96	32.64/17.76	32.64/15.84	29.76/23.04
H-108	Control	32.64/19.20	42.24/24.96	32.64/29.76	29.76/17.76	29.76/17.76

TABLE 3. BUN/Creatinine NORMAL VALUES = 12.3 ± 1.9/1.50 ± 0.09

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-88	10 mg	20.5/1.3	24.1/1.3	20.2/1.4	22.6/1.4	16.9/1.1
H-89	10 mg	12.8/1.1	17.7/1.0	12.4/1.2	20.0/1.2	12.6/1.0
H-90	10 mg	13.9/1.1	17.7/1.1	16.1/1.3	18.8/1.3	13.8/1.0
H-91	10 mg	14.7/1.1	15.3/1.1	13.9/1.3	21.6/1.3	19.5/1.0
H-106	Control	13.9/1.2	14.7/1.4	14.4/1.3	22.2/1.2	15.6/1.2
H-92	3.16 mg	17.4/1.1	19.3/1.1	13.9/1.2	18.8/1.3	16.9/0.8
H-94	3.16 mg	12.8/1.0	17.1/0.9	13.9/1.2	17.1/1.0	13.8/0.7
H-96	3.16 mg	18.9/1.2	20.3/1.2	16.1/1.2	18.5/1.4	16.2/1.2
H-97	3.16 mg	16.8/1.4	20.3/1.2	12.4/1.1	18.8/1.4	18.9/1.3
H-108	Control	17.6/1.4	23.8/1.6	21.5/1.7	41.6/1.8	27.8/1.6

TABLE 4. TOTAL PROTEIN/GLUCOSE NORMAL VALUES = 7.20 ± 0.44/91.0 ± 14.0

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-88	10 mg	7.6/99	7.3/102	5.8/95	6.7/46	7.0/67
H-89	10 mg	7.8/107	5.5/72	6.2/75	6.6/97	7.0/84
H-90	10 mg	7.0/74	6.9/94	6.0/109	6.7/126	7.2/60
H-91	10 mg	7.6/32	7.1/84	6.2/70	6.7/46	7.0/48
H-106	Control	7.1/71	7.0/105	-/81	6.9/91	7.2/81
H-92	3.16 mg	7.1/34	6.8/54	5.9/56	6.9/54	7.3/32
H-94	3.16 mg	7.8/58	7.7/67	6.2/51	7.3/56	7.4/39
H-96	3.16 mg	6.7/35	6.8/52	5.4/97	6.4/119	6.8/74
H-97	3.16 mg	7.8/109	7.4/131	6.1/101	7.2/131	7.2/81
H-108	Control	7.4/115	7.5/100	5.9/101	6.9/88	7.0/114

TABLE 5. HEMATOCRIT/METHEMOGLOBIN NORMAL VALUES = 32-50/0.0-0.23

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-88	10 mg	43/0.23	43/0.11	40/0	40/0.12	41/0
H-89	10 mg	46/0.13	40/0.23	40/0	37/0.11	38/0
H-90	10 mg	43/0	42/0.11	40/0	40/0	39/0
H-91	10 mg	45/0.11	42/0.11	42/0	41/0	38/0
H-106	Control	42/0.23	42.5/0.23	40/0	41/0	40/0
H-92	3.16 mg	44/0.12	43/0	40/0	40/0	40/0
H-94	3.16 mg	46/0.35	44/0.11	41/-	40/0	40/0
H-96	3.16 mg	42/0	41/0.11	39/0	39/0	39/0
H-97	3.16 mg	44/0	42/0	37/0.11	39/0	39/0
H-108	Control	46/0.11	41/0	44/0.12	40/0.23	41/0

TABLE 6. RBC^{10^6}/WBC^{10^3} NORMAL VALUES = $3.1\text{-}8.6X10^6/mm^3/10.6\pm1.62X10^3/mm^3$

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-88	10 mg	6.02/7	6.64/7.7	6.13/4.3	5.69/3.6	5.15/4.2
H-89	10 mg	7.89/14.8	6.49/11.1	6.88/7.7	5.48/6.2	4.5/9
H-90	10 mg	5.82/9.7	6.63/10.2	5.81/7.4	6.84/8.3	5.07/7.3
H-91	10 mg	6.73/10.3	6.71/11.8	6.35/10.7	6.5/4.1	4.47/10.7
H-106	Control	6.87/16	6.66/7	5.29/7.5	6.14/6.6	5.5/9.7
H-92	3.16 mg	8.01/11.4	7.13/10	6.58/7.1	6.46/6.1	5.45/6.6
H-94	3.16 mg	7.24/10.5	6.75/7.9	6.89/6.1	6.91/6.7	5.31/8
H-96	3.16 mg	6.45/9.8	6.41/6.7	5.77/4.8	5.5/5.5	4.84/5.8
H-97	3.16 mg	6.74/7.7	6.90/8	5.58/5.6	7.40/5.7	4.75/6.4
H-108	Control	8.04/11.1	7.3/8.9	7.02/7.1	5.85/9.5	5.93/10

TABLE 7. DIFFERENTIAL

Normal Values = NS-37.6% L-58.8% M-1.6% E-1.8% B-0.2%

NS = Neutrophil/segmented
NB = Neutrophil/band
L = Lymphocyte
M = Monocyte
E = Eosinophil
B = Basophil

Monkey Number	Dose mg/kg	Day 1		Day 8		Day 15		Day 22		Day 29	
H-88	10 mg/kg	NS-25 NB-0 L-70	M-3 E-2 B-0	NS-48 NB-0 L-50	M-2 E-0 B-0	NS-40 NB-0 L-57	M-2 E-1 B-0	NS-33 NB-0 L-58	M-6 E-3 B-0	NS-45 NB-0 L-51	M-2 E-2 B-0
H-89	10 mg/kg	NS-59 NB-0 L-39	M-0 E-2 B-0	NS-47 NB-0 L-50	M-2 E-1 B-0	NS-48 NB-0 L-49	M-3 E-0 B-0	NS-17 NB-0 L-67	M-12 E-4 B-0	NS-38 NB-0 L-55	M-4 E-3 B-0
H-90	10 mg/kg	NS-30 NB-0 L-65	M-1 E-4 B-0	NS-24 NB-0 L-73	M-1 E-1 B-1	NS-44 NB-0 L-52	M-3 E-0 B-1	NS-21 NB-0 L-70	M-1 E-1 B-1	NS-20 NB-0 L-77	M-2 E-1 B-0
H-91	10 mg/kg	NS-21 NB-0 L-76	M-0 E-3 B-0	NS-17 NB-0 L-78	M-3 E-2 B-0	NS-32 NB-0 L-62	M-5 E-1 B-0	NS-19 NB-0 L-73	M-5 E-2 B-1	NS-28 NB-0 L-65	M-0 E-4 B-0
H-106	Control	NS-32 NB-0 L-65	M-2 E-1 B-0	NS-29 NB-0 L-66	M-1 E-4 B-0	NS-58 NB-0 L-33	M-8 E-1 B-0	NS-36 NB-0 L-57	M-5 E-2 B-0	NS-67 NB-0 L-31	M-0 E-1 B-1

TABLE 7. (continued)

Monkey Number	Dose mg/kg	Day 1		Day 8		Day 15		Day 22		Day 29	
H-92	3.16 mg/kg	NS-51 NB-0 L-48	M-0 E-1 B-0	NS-46 NB-0 L-51	M-2 E-1 B-0	NS-46 NB-0 L-50	M-3 E-1 B-0	NS-20 NB-0 L-75	M-5 E-0 B-0	NS-44 NB-0 L-53	M-2 E-1 B-0
H-94	3.16 mg/kg	NS-32 NB-0 L-64	M-1 E-3 B-0	NS-24 NB-0 L-64	M-2 E-9 B-1	NS-30 NB-0 L-65	M-2 E-3 B-0	NS-17 NB-0 L-72	M-3 E-6 B-2	NS-13 NB-0 L-77	M-3 E-5 B-2
H-96	3.16 mg/kg	NS-51 NB-0 L-47	M-1 E-1 B-0	NS-8 NB-0 L-87	M-3 E-2 B-0	NS-15 NB-0 L-78	M-5 E-1 B-1	NS-15 NB-0 L-81	M-2 E-2 B-0	NS-27 NB-0 L-68	M-4 E-1 B-0
H-97	3.16 mg/kg	NS-11 NB-0 L-86	M-2 E-1 B-0	NS-11 NB-0 L-88	M-0 E-1 B-0	NS-15 NB-0 L-80	M-1 E-4 B-0	NS-21 NB-0 L-76	M-2 E-1 B-0	NS-12 NB-0 L-85	M-3 E-0 B-0
H-108	Control	NS-29 NB-1 L-68	M-1 E-1 B-0	NS-50 NB-0 L-46	M-2 E-1 B-1	NS-35 NB-0 L-63	M-1 E-1 B-0	NS-52 NB-0 L-45	M-1 E-2 B-0	NS-43 NB-0 L-55	M-0 E-2 B-0