

## DRUG TOLERANCE STUDY OF WR225448 IN RHESUS MONKEYS

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### OBJECTIVES :

1. To determine the maximum tolerated dose of WR 225448 in Rhesus Monkeys (*Macaca Mulatta* ).
2. To determine the nature of the toxic effects, including a determination of the organ system(s) affected by WR225448.

**BACKGROUND :** While certain chemical compounds are known to have excellent schizonticidal activity, they are, at the same time, toxic to the host. WR225448 was tested for toxicity in Rhesus monkeys last year at the level of 10 mg/kg/day X 7 days in order to determine the maximum tolerated dose. Four monkeys were given the 10 mg/kg dose for 7 consecutive days and one monkey served as a Control and was given only the vehicle, methyl cellulose. All 4 monkeys died prior to the completion of the test. Preliminary necropsy results plus laboratory data on liver serum enzymes indicated that the liver was the target organ. (1)

This test was run in order to determine the toxic effects of WR225448 at a reduced dosage level.

**METHODS :** This study was conducted using the primary test phase format of fixed dosage. Five rhesus monkeys were used in the test. Four monkeys were given 3.16 mg/kg/day for 7 consecutive days by nasogastrotube suspended in 3 ml. methyl cellulose. One monkey served as a control and was given only 3 ml. of 0.3% methyl cellulose. The dosage remained constant for the entire test.

The duration of the test was 30 days. Blood was collected for laboratory analysis on 5 occasions during the test; on days 1 and 8 (before administration of the test drug), day 15 (during administration of the test drug) and days 22 and 29 (following administration of the test drug). The drug was administered on days 14 through 20 inclusively (see Table 1). Critical clinical observations were recorded on each monkey 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 and methemoglobin.

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Two monkeys were selected for necropsy (H-99 and H-101)

**RESULTS :** All of the test monkeys survived the administration of the test drug WR225448. Clinical illness was not observed in any monkey during the test. Results of laboratory tests on blood specimens taken at various points during the study are recorded in Tables 2 through 7.

No significant values for any of the laboratory tests were noted during the test. Some of the blood glucose levels were depressed but this can be partially explained by the fact that the specimens were collected in the early morning and before the monkeys had been fed. The blood urea nitrogen levels were slightly elevated over normal values but not significantly. The creatinine levels were well within normal limits.

Post mortem examination of the two monkeys that were necropsied revealed no significant gross lesions. Histopathologic examination of the tissues are currently being performed.

**CONCLUSIONS :** Based on the results of last year's test (1) and the results of this study, the toxic dose of WR225448 for rhesus monkeys is at a point between 3.16 mg/kg and 10.0 mg/kg per day.

**REFERENCE :**

1. Whitmire, Richard E., et al., AFRIMS Annual Report, pp. 356-358, 1978-1979.

TABLE 1.

- ↓ = Blood collected
- R<sub>x</sub> = Drugs administered
- 0 = Monkeys observed, Clinical signs recorded
- \* = Necropsy

Calendar day	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
Day of Study	13						20								27						3								10	

MARCH

APRIL

Laboratory Tests Required :

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

NORMAL VALUES =  $33.4 \pm 8/20.3 \pm 5.8$  IU

SGOT/SGPT

TABLE 2.

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-98	3.16 mg	46.08/21.12	38.40/21.12	32.64/19.20	32.64/17.76	29.76/14.40
H-99	3.16 mg	46.08/23.04	35.52/21.12	32.64/24.96	42.24/21.12	32.64/34.56
H-100	3.16 mg	35.52/14.40	29.76/21.12	23.04/17.76	24.96/17.76	32.64/21.12
H-101	3.16 mg	49.92/15.84	35.52/37.44	29.76/19.20	38.40/19.20	32.64/19.20
H-110	Control	42.24/19.20	38.40/21.12	32.64/27.36	27.84/23.04	29.76/24.96

TABLE 3.

BUN/Creatinine

NORMAL VALUES =  $12.3 \pm 1.9/1.50 \pm 0.09$ 

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-98	3.16 mg	14.7/1.1	17.7/1.1	13.4/1.4	17.4/1.4	13.8/1.5
H-99	3.16 mg	18.9/1.1	21.6/1.1	12.9/1.1	18.8/1.5	18.9/1.3
H-100	3.16 mg	19.9/1.1	22.3/1.3	18.4/1.3	26.4/1.4	18.2/1.3
H-101	3.16 mg	18.9/1.3	17.1/1.1	12.9/1.2	21.9/1.5	15.6/1.2
H-110	Control	18.0/1.2	21.6/1.4	19.6/1.5	21.9/1.6	16.9/1.4

TABLE 4. TOTAL PROTEIN/GLUCOSE NORMAL VALUES =  $7.2 \pm 0.44/91.0 \pm 14.0$

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-98	3.16 mg	7.7/110	7.3/88	6.4/133	6.8/81	7.2/65
H-99	3.16 mg	7.4/67	7.4/78	6.1/53	7.3/99	7.4/73
H-100	3.16 mg	6.7/67	6.4/81	4.6/95	6.8/79	7.2/78
H-101	3.16 mg	7.1/57	7.4/75	6.0/70	7.2/62	7.5/70
H-110	Control	7.3/103	7.7/111	6.8/131	7.4/99	7.8/108

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-98	3.16 mg	45/0	41/0.11	42/0	34/0	38/0
H-99	3.16 mg	43/0.12	39.5/0.23	40/0.12	38/0	37/0
H-100	3.16 mg	42/0.23	41/0.11	42/0	40/0	41/0
H-101	3.16 mg	42.5/0.11	42/0	41/0	35/0	38/0
H-110	Control	46/0.23	45.5/0	46/0.12	45/0	45/0

TABLE 6.  $RBC^{10^{-6}}/WBC^{10^{-6}}$  NORMAL VALUES =  $3.1-8.6 \times 10^6/mm^3 / 10.6 \pm 1.62 \times 10^3/mm^3$

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-98	3.16 mg	6.47/12.6	7.15/9.5	6.61/9.7	4.92/8.4	4.25/10.7
H-99	3.16 mg	6.34/11.1	6.02/8.5	5.83/4.8	5.04/6.7	4.14/10.2
H-100	3.16 mg	5.81/7.0	6.18/6.0	6.34/4.9	5.41/7.0	5.86/5.1
H-101	3.16 mg	5.5/12.4	6.75/9.7	5.81/7.8	4.81/6.9	4.65/9.0
H-110	Control	7.46/9.4	7.76/10.4	7.36/8.8	6.49/13.7	7.26/9.4

NS = Neutrophil/segmented  
 NB = Neutrophil/band  
 L = Lymphocyte

M = Monocyte  
 E = Eosinophil  
 B = Basophil

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

TABLE 7. DIFFERENTIAL

Monkey Number	Dose mg/kg	Day 1	Day 8	Day 15	Day 22	Day 29
H-98	3.16 mg	NS-55	NS-34	NS-37	NS-44	NS-53
		NB-0	NB-0	NB-0	NB-0	NB-0
		L-44	L-65	L-62	L-49	L-44
H-99	3.16 mg	NS-26	NS-18	NS-21	NS-28	NS-24
		NB-0	NB-0	NB-0	NB-0	NB-0
		L-58	L-68	L-58	L-68	L-74
H-100	3.16 mg	NS-34	NS-36	NS-20	NS-26	NS-16
		NB-0	NB-0	NB-0	NB-0	NB-0
		L-59	L-56	L-77	L-68	L-81
H-101	3.16 mg	NS-33	NS-42	NS-54	NS-38	NS-36
		NB-0	NB-0	NB-0	NB-0	NB-0
		L-57	L-53	L-45	L-57	L-57
H-110	Control	NS-20	NS-28	NS-21	NS-52	NS-24
		NB-0	NB-0	NB-0	NB-0	NB-1
		L-76	L-70	L-74	L-41	L-69