Hypocholesterolemic Effect of Rifampin in the Monkey (*M. fasicularis*) (35542)

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Rifampin, (Rifadin) a new antimicrobial agent introduced for the treatment of tuberculosis and other infections, is a semisynthetic antibiotic of orange-red color with molecular weight of 822.97. It has a macrolide-like ring structure and is the 3-(4-methyl piperazinyl iminomethyl) derivative of Rifamycin SV (1, 2).

In the course of chronic toxicity studies conducted in this laboratory it was noted that the oral administration of rifampin to the *M. fasicularis* monkey resulted in marked reductions of the serum cholesterol levels. These results are presented below.

Materials and Methods. A total of 48 cynomolgus (*Macaca fasicularis*) monkeys, males 3.21 ± 0.65 kg and females 2.62 ± 0.5 kg, were used. The monkeys were caged individually in an air-conditioned environment for approximately 90 days during which time they were stabilized to diet,[1] feed schedule, body weight, handling and dosing procedures; and a minimum of 3 blood samples were collected to establish base line hematologic and clinical chemistry values. The monkeys were grouped and divided equally by sex for administration of single daily oral doses of 40, 80, and 110–120 mg/kg of rifampin which was suspended daily in 10% aqueous gum acacia at a concentration of 80 mg/ml. Acacia vehicle and isoniazid (25 mg/kg/day) for tuberculosis prophylaxis were administered to controls. In addition, control and treated monkeys were given Tang[2] (5.0 ml) to increase the palatability of oral dosage forms.

[1] Purina Monkey Chow, Ralston Purina, Checkerboard Square, St. Louis, Missouri.

[2] Tang, General Foods Corporation, White Plains, New York.

Prior to drug administration, fasting blood samples were withdrawn from the femoral vein or artery at periodic intervals to determine the mean total serum cholesterol levels by the methods of Levine and Zak (3) with the Technicon AutoAnalyzer (4). Treatment groups 2 and 3 were initially administered dosage levels of 40 and 80 mg/kg, respectively, whereas group 4 animals were started at 110 mg/kg and raised to 120 mg/kg after approximately 60 consecutive days of treatment. Gastroenteric disturbances, characterized by vomiting, moderate anorexia, and intermittently loose and firm feces, were observed in several animals on the high dosage level during the initial 2 weeks of treatment. Drug administration was withdrawn on 5 males from the high dosage level for a 5-day period because of these adverse effects. Aside from these initial effects, rifampin was generally well tolerated at all dosage levels during the 180-day period.

Discussion. The results obtained from periodic determination of serum cholesterol levels in cynomolgus monkeys prior to, and during, the period of rifampin treatment are presented in Table I. The data indicate that marked reductions occurred in the serum cholesterol levels after oral administration of rifampin. An analysis of variance showed that percentage changes in cholesterol levels in all treatment groups were significantly different at the 95% level from the control group at all measurement intervals after treatment. Furthermore, there was no significant difference between groups that would suggest a dose–response relationship. Decreases in cholesterol levels of control monkeys were attributed to cyclic or hormonal influences. This influence was also reflected in treatment

TABLE I. Average Percentage Changes in Cholesterol Levels in Cynomolgus Monkeys After Oral Administration of Rifampin.

	Sampling period									
(weeks):	2		4		8		12		26	
Treatment	Male	Female	Male	Female	Male	Female	Male	Female	Male	Female
None (174 ± 35)[a]	—11.9	—16.0 (—13.9)[b]	—17.8	—26.1 (—21.7)	—18.5	—23.2 (—20.8)	—14.3	—26.7 (—20.5)	—4.9	—9.3 (—7.1)
40 mg/kg (154 ± 26)	—31.9	—45.2 (—38.5)	—40.1	—53.5 (—46.8)	—40.7	—50.7 (—45.7)	—43.6	—57.1 (—50.4)	—20.3	—41.2 (—30.8)
80 mg/kg (160 ± 40)	—44.5	—46.7 (—45.6)	—36.4	—47.9 (—42.7)	—46.7	—54.9 (—50.8)	—43.2	—49.3 (—46.3)	—28.5	—35.7 (—32.1)
110–120 mg/kg (162 ± 36)	—32.8	—53.8 (—43.4)	—51.7	—65.0 (—58.3)	—49.6	—56.9 (—53.2)	—50.7	—68.5 (—59.6)	—43.8	—45.5 (—44.7)

[a] Mean cholesterol levels (av of 3 pretreatment levels mg/100 ml).
[b] Group average change (%) in cholesterol levels.

group cholesterol levels as shown by the apparent increase in levels at the 26-week sampling period.

Lowering of serum cholesterol levels has been reported after oral administration of polyene macrolide antifungal antibiotics (5) and the nonantibiotic *N*-methyl neomycin (6). It was suggested that these might exert their effects on cholesterol lowering by preventing absorption–resorption of cholesterol (5) or by complexing with bile acids (6).

In contrast to the polyene antifungal antibiotics, rifampin is readily absorbed from the gastrointestinal tract. In addition, rifampin was shown to have an enterohepatic circulation and choleretic activity (7). It is of interest to speculate whether the choleretic activity of rifampin or complexing with bile acids might be bases for the hypocholesterolemic effect observed in the cynomolgus monkey after oral administration of rifampin.

Summary. The oral administration of rifampin to cynomolgus monkeys at dosage levels of 40, 80, and 110–120 mg/kg for 180 consecutive days resulted in marked lowering of serum cholesterol levels. Choleretic activity or complexing with bile acids by rifampin may be a mechanism(s) for the observed hypocholesterolemic effect.

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