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Effect of Neomycin, Para-Aminosalicylic-Acid and Other Antibacterial Drugs on Serum Cholesterol Level of Man. (25188)

PAUL SAMUEL* (Introduced by Charles F. Wilkinson, Jr.)

Dept. of Medicine, N. Y. University-Bellevue Medical Center, Post-Graduate Medical School, N. Y. City

It has been reported(1-2) that oral administration of neomycin lowered serum cholesterol concentration significantly in 10 patients. In extending this study, the effect of neomycin and other antibacterial drugs upon serum lipid levels of an additional group of patients was observed.

Methods. Twenty-five patients, 14 males and 11 females, were studied in 44 experimental periods. The average age was 54.2 years (35 to 74 years). Sixteen patients were hospitalized and 9 were followed as outpatients. Clinical diagnoses were coronary artery disease (6 patients), cerebral vascular disease (8 patients), familial hypercholesterolemia (2 patients), familial hyperlipemia with coronary artery disease (1 patient), diabetes mellitus (2 patients, including one of the CVA patients). In 7 patients there was no evidence of vascular disease or disturbance of lipid metabolism. Serum cholesterol levels were determined once a week, in the fasting state, by the method of Zak *et al.*(3). Serum phospholipid determinations were carried out by the method of Simonsen *et al.*(4) and the alpha and beta cholesterol levels by the method of Langan *et al.*(5). The control serum cholesterol levels, prior to administration of the drugs, were followed during a period of 6 weeks or longer. Hospitalized patients were maintained on regular hospital diet with the exception of the 2 diabetics, and the diet of the outpatients remained relatively constant during the study. A preparation containing 70% of neomycin sulfate (Mycifradin Sulfate,®)† was given orally to 18 patients in doses of 1.5 to 2 g daily for 4 to 20 weeks. Doses of medication in this study represent the weight of Mycifradin Sulfate. Five patients were given 60 mg of neomycin intramuscularly daily for a period of 3 weeks. This amount is equivalent to or higher than the proportion of oral dose (3%) which is absorbed from the gastrointestinal tract(6). Para-aminosalicylic-acid‡ (PAS) was given orally to 4 patients in 6 experimental periods. Four were given 6 g of PAS daily for 4 to 5 weeks. Two patients received 12 g of PAS for 9 and 4 weeks respectively. Isoniazid‡ (300 mg daily) was administered orally to 3 patients for a period of 4 weeks. Phthalylsulfathiazole§ (12 g daily) oxytetracycline‖ (1 g daily), polymyxin B sulfate‖ (150 mg daily) and novobiocin§ (1 g daily) were each given orally to 2 patients for a period of 3 weeks. Dihydrostreptomycin‖ (2 g daily) and bacitracin‖ (20,000 units daily) were each administered orally to 2 patients for a period of 2 weeks.

Results. The results of oral administration of neomycin are summarized in Table I. Mean serum cholesterol levels were lowered significantly in each patient by 17 to 29% during administration of neomycin, the average for the group being 21%. Two to 3 weeks were necessary before the concentration of serum cholesterol decreased to its low point. Cholesterol levels remained low as long as

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§ Supplied by Merck Sharp and Dohme Labs.

‖ Supplied by the Pfizer Labs.

TABLE I. Effect of Neomycin and PAS on Average Serum Cholesterol Level (mg/100 cc), in 20 Patients.

Age	Sex	Diagnosis	Medication and dose	Wk on medication	Total serum cholesterol		
					Control	Medication	% fall
58	♀	CVA	Neo.* 2 g orally	20	355	273	23
55	♂	"	" 2 "	15	314	245	20
42	♂	Coronary artery disease	" 1.5 "	13	342	284	17
52	♀	Diabetes mellitus	" 2 "	10	339	269	20
48	♀	Familial hypercholesterolemia	" 1.5 "	9	513	378	26
68	♂	Coronary artery disease	" 1.5 "	8	293	232	21
42	♂	CVA	" 2 "	8	268	223	17
44	♂	Paraplegia of undetermined cause	" 2 "	8	264	210	20
68	♂	Coronary artery disease	" 1.5 "	7	274	227	17
44	♂	*Idem*	" 1.5 "	7	256	211	17
59	♀	Familial hypercholesterolemia	" 1.5 "	6	438	321	27
46	♀	CVA. Diabetes mellitus	" 2 "	6	304	251	17
41	♀	Multiple sclerosis	" 2 "	5	190	142	25
60	♀	CVA	" 2 "	5	394	281	29
61	♂	Coronary art. dis. Familial hyperlipemia	" 2 "	5	305	249	18
58	♀	No clinical disease	" 2 "	4	313	254	19
63	♂	Coronary artery disease	" 1.5 "	4	273	203	26
35	♂	Multiple sclerosis	" 2 "	4	158	120	24
52	♀	Diabetes mellitus	" 60 mg intramusc.	3	339	322	
42	♂	CVA	" 60 "	3	268	260	
44	♂	Paraplegia of undetermined cause	" 60 "	3	264	269	
46	♀	CVA. Diabetes mellitus	" 60 "	3	304	306	
35	♂	Multiple sclerosis	" 60 "	3	158	168	
61	♂	Coronary art. dis. Familial hyperlipemia	PAS 12 g orally	4	305	226	26
43	♀	Rheumatic heart disease	" 12 "	9	244	168	24
44	♂	Paraplegia of undetermined cause	" 6 "	5	264	245	
61	♂	Coronary art. dis. Familial hyperlipemia	" 6 "	4	305	299	
43	♀	Rheumatic heart disease	" 6 "	4	244	235	
51	♂	CVA	" 6 "	5	242	230	

* Neomycin.

the drug was given orally, and returned to control levels 2 to 7 weeks after administration of neomycin was discontinued (Fig. 1 and 2). In 8 patients studied the over-all average of the esterified fraction of cholesterol was 77% during the control period and 78% during administration of neomycin. The mean phospholipid concentrations remained unchanged in 1 case and decreased by an average of 24% in 6 cases during the experimental period in the 7 patients studied. In 6 patients, mean concentration of beta cholesterol decreased in 4 by an average of 9% and remained unchanged in 2.

The results of intramuscular administration of neomycin are included in Table I. In the 5 patients studied, serum cholesterol levels failed to show appreciable changes following intramuscular administration of the drug. (Fig. 1).

No significant side effects occurred in the group given neomycin. A mild, transitory diarrhea was present in 6 of the 18 patients at the initial phase of oral administration of the drug. Weight of the patients remained approximately unchanged.

Table I shows the results obtained with the use of oral PAS. At the daily dose of 6 g of PAS no significant changes in serum cholesterol concentration occurred. Increasing the daily dose of the drug to 12 g in 2 patients resulted in a reduction of average serum cholesterol concentration within 2 weeks by 24% in one and 26% in the other (Fig. 2), with a return to control levels 2 weeks after administration of PAS was discontinued. No significant side effects were noted. A mild nausea

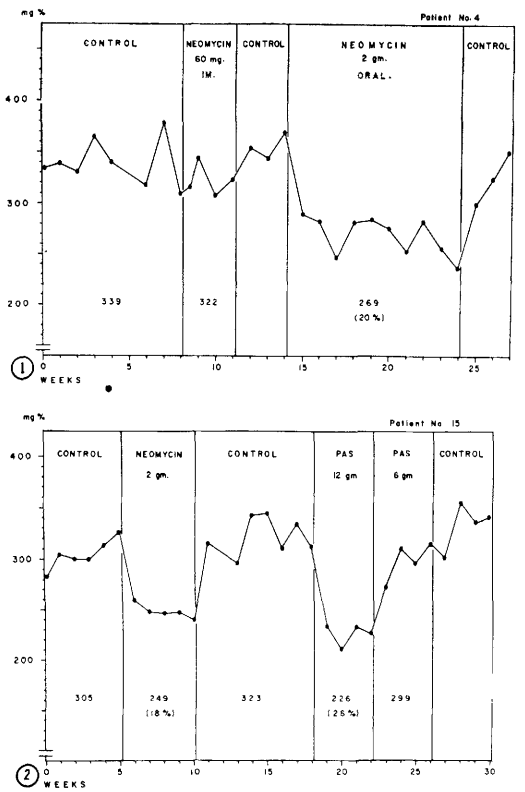

FIG. 1. Effect of intramuscular and oral neomycin on serum cholesterol concentrations.

FIG. 2. Effect of oral neomycin and PAS on serum cholesterol concentrations.

was periodically observed without appreciable changes of the patients' weight.

Oral administration of isoniazid, phthalylsulfathiazole, oxytetracycline, polymyxin B sulfate, novobiocin, dihydrostreptomycin and bacitracin failed to alter serum cholesterol levels appreciably.

Comment. It is known that approximately 97% of orally administered neomycin is eliminated unchanged in the stool and only about 3% is absorbed(6). Since intramuscular administration of 3% or more of the orally effective dose failed to alter serum cholesterol levels, it is apparent that the cholesterol lowering effect of neomycin is dependent upon its action in the gastrointestinal tract. At present the mechanism of this action is not understood. However, it is possible that the effect of neomycin is due to modification of the intestinal bacterial flora or inhibition of intestinal enzyme systems.

The mechanism of the serum cholesterol lowering action of PAS cannot be explained. Recently, Tygstrup *et al.* have also noted the serum cholesterol lowering action of this drug (7). Although PAS is readily absorbed, one cannot rule out the possibility that its action would be mediated *via* changes in the gastrointestinal tract. Studies are in progress to elucidate these problems.

Summary. 1) Neomycin was given orally to 18 patients at daily dose of 1.5 to 2 g for 4 to 20 weeks. Mean serum cholesterol levels were decreased significantly in each patient by 17 to 29%, and were maintained low for duration of administration of neomycin. Average fall for the group was 21%. Intramuscular administration of neomycin to 5 patients for 3 weeks failed to alter serum cholesterol levels. 2) Oral administration of 12 g of para-aminosalicylic-acid to 2 patients lowered serum cholesterol concentrations significantly in each, while the daily dose of 6 g had no effect on serum cholesterol levels. 3) When phthalylsulfathiazole, isoniazid, dihydrostreptomycin, oxytetracycline, polymyxin B sulfate, bacitracin and novobiocin were given orally, no appreciable changes in serum cholesterol concentration resulted.

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