PROCEEDINGS OF THE SOCIETY FOR EXPERIMENTAL BIOLOGY AND MEDICINE 147, 694-697 (1974)

Colestipol Therapy of Hyperlipidemia in Man[1] (38419)

BERNARD A. SACHS AND LILA WOLFMAN

Department of Medicine, Montefiore Hospital and Medical Center, Bronx, New York 10467 and Department of Medicine, Albert Einstein College of Medicine, Bronx, New York 10461; and Lipid Metabolism Laboratory, Department of Medicine, Montefiore Hospital and Medical Center, Bronx, New York 10467

Effective lowering of plasma cholesterol levels has been achieved safely by compounds which sequester bile acids. The first of these to be used on a large scale has been cholestyramine (1), which is not absorbed significantly from the gastrointestinal tract and is free of toxic side effects. The disadvantages are related to the bulk and granularity of the product and the need for taking the medication in relation to meals. A new synthetic bile acid sequestering resin, colestipol, recently has become available for study. Colestipol is a high-molecular-weight soluble copolymer of tetraethylenepentamine and epichlorohydrin. It has the advantages of palatability and better patient acceptability. The present study reports the effects of colestipol on the plasma cholesterol, triglycerides, and phospholipids in a group of patients with hyperlipoproteinemia randomly placed in the placebo or treatment groups or directly assigned to drug.

Materials and Methods. The subjects were 25 patients with familial disorders of lipid metabolism of which 22 were type II and three were type IV phenotype (Fredrickson classification) (2). Seventeen of the 25 patients were randomly assigned into a placebo group of seven and a drug group of ten. The additional eight patients were assigned directly to a drug therapy group. Blood was drawn by venipuncture at biweekly intervals during a 6-week placebo (microcrystalline cellulose) period, and during the first 4 weeks of the active drug treatment period. Thereafter, colestipol administration was continued and blood samples obtained at 4-week intervals. Subjects were advised to maintain their usual diet. Colestipol was supplied in 5-g packets and the subjects were instructed to take the resin in at least 6 oz of a suitable liquid (juice, soup, carbonated beverage) directly before meals. Venipuncture was done in the 12- to 14-hr postabsorptive state and analyzed for lipids and lipoproteins. Complete blood counts, prothrombin time, fasting blood sugar, creatinine, serum glutamic oxalacetic transaminase, calcium, phosphorus, alkaline phosphatase, total bilirubin, sodium, potassium, chlorides, uric acid, and urinalysis were done biweekly during the initial placebo period and at 1, 3, 6, 12, 16, 20, and 24 mo thereafter.

Total cholesterol was analyzed by the method of Abell *et al.* (3). Serum lipid phosphorus was determined by the Fiske–SubbaRow procedure on plasma extracted with Bloor's reagent (4). Serum triglycerides were done by the Van Handel modification of the procedure of Van Handel and Zilversmit (5). Both paper (6) and agarose gel (7) electrophoresis were performed for lipoprotein phenotyping. Blood counts and urinalyses were done by routine methods. The other blood chemistry analyses were done in the laboratories of The Upjohn Co. in Kalamazoo, MI.

Results. Cholesterol. For the 10 randomly assigned patients, the average cholesterol value during the placebo control period was 303 mg/dl and decreased to a level of 238 mg/dl (-21%, $P < 0.001$) after 2 weeks on colestipol. After 4 weeks, the average cholesterol level was 244 mg/dl and remained significantly depressed throughout the first year. During the second year, there was a gradual increase in the depressed cholesterol level so that the average fall by the end of the year in a group of patients that continued 2 years was -11%, $P > 0.05$. There were no significant changes in cholesterol level in the group of seven patients that remained on placebo (Fig. 1).

[1] Supported in part by a grant from The Upjohn Company, Kalamazoo, MI.

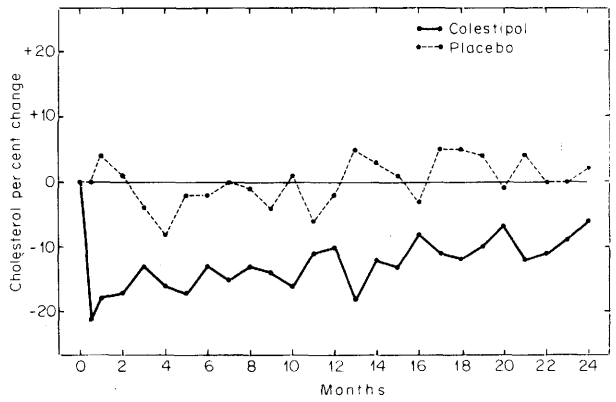

FIG. 1. Percent changes in plasma cholesterol concentrations in randomly selected patients with hyperlipoproteinemia taking cholestipol or placebo for a period of 24 mo.

The cholesterol concentration for the total group of 18 colestipol-treated subjects averaged 356 mg/dl during the placebo period and decreased to 279 mg/dl, −22%, $P < 0.001$ after taking the resin for 2 weeks. The cholesterol level remained significantly depressed at the end of 1 year, 305 mg/dl, −17%, $0.001 < P < 0.01$. The average fall for the entire 12-mo treatment period was −19% (Fig. 2).

Phospholipids. The average placebo period phospholipid level was 303 mg/dl and promptly fell to an average value of 275 mg/dl (−9%, $0.001 < P < 0.05$) after 2 weeks of colestipol. Thereafter, the phospholipid values remained approximately at this level for the rest of the study, varying between 265 and 286 mg/dl and also varying in the significance of the falls (from $0.001 < P < 0.01$ to not significant). There were no significant changes in the phospholipid values in the group of patients that remained on placebo.

In the total group of treated patients, the phospholipids level fell from an average control value of 326 to 292 mg/dl at 2 weeks (−10%, $P < 0.001$). The phospholipid concentration remained approximately at this level for the remainder of the year.

Triglycerides. There were no significant changes in plasma triglyceride levels as a result of colestipol administration. Neither the early apparent fall nor the later apparent rise in triglyceride concentration were statistically significant (Fig. 3).

Discussion. Colestipol has been shown to have an *in vitro* bile acid binding capacity of approximately 1 mequiv cholic acid/g of tissue (8). Its action is similar to that of cholestyramine and DEAE Sephadex (9). The material sequesters bile acids in the intestinal tract and enhances the fecal excretion of bile acids. This results in an increased rate of hepatic and intestinal sterol synthesis, diminished absorption of cholesterol, and diminished transfer of cholesterol from intestinal wall to lymph. These sequesterins stimulate the hepatic conversion from cholesterol to bile acids and, if hepatic cholesterol biosynthesis is increased insufficiently to compensate for this increased cholesterol catabolism, hepatic cholesterol pools may be decreased (10). Thus, plasma cholesterol concentrations may be reduced since liver and plasma cholesterol are in equilibrium (11). Although reduction of plasma

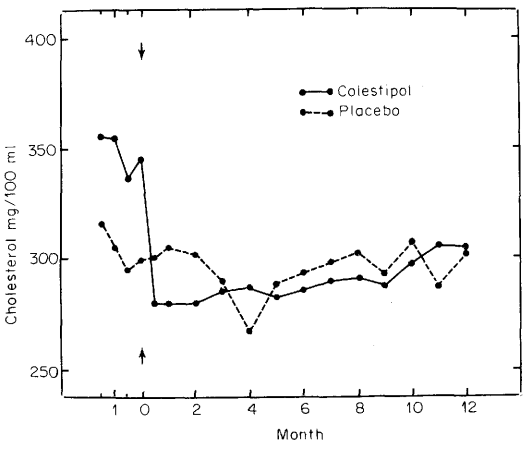

FIG. 2. Changes in plasma cholesterol concentrations in patients with hyperlipoproteinemia taking colestipol (18 subjects) or placebo (seven subjects).

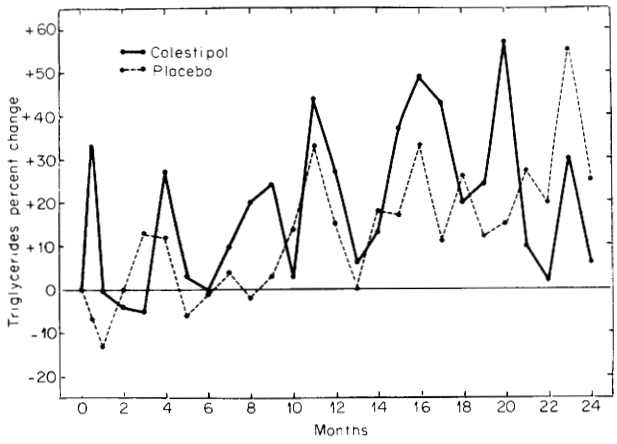

FIG. 3. Percent changes in plasma triglyceride concentrations in hyperlipoproteinemic subjects taking colestipol or placebo.

cholesterol level may not necessarily represent a reduction in tissue pools of cholesterol, the recently reported study using colestipol in conjunction with a low-cholesterol low-saturated-fat diet resulted in a notable reduction in xanthoma size (12). This suggests that tissue pools as well as plasma pools may be reduced. Bile acid sequestrants have also been shown to decrease the half-life of labeled β-lipoprotein and improve the depressed catabolism of β-lipoprotein of patients with type II hyperlipoproteinemia (13). These mechanisms appear particularly suitable for the treatment of type II, which is characterized by elevated plasma cholesterol levels and normal or slightly elevated triglyceride concentrations.

Colestipol has been shown to inhibit hypercholesterolemia induced by cholesterol feeding in cockerels and to markedly reduce lipids in normolipemic dogs (8). Recent initial studies in man have shown reductions in serum cholesterol levels of -20% (8), -19% (12), -14% (14), -16% (15), and -17% (16). The results of our more prolonged present study are similar, with an average reduction in cholesterol level of -19%. Of interest is the increase in the depressed cholesterol levels during the second year of the study, which we attribute to less rigid drug adherence. In a comparison of the effects of cholesterol on familial and nonfamilial hyper-β-lipoproteinemia, colestipol appeared to have a delayed hypocholesterolemic response in the familial group as compared to the prompt fall seen in the nonfamilial group (15). However, the study included few patients and was short in duration.

Side effects were minimal and necessitated cessation of therapy in only one patient (not included in this study) because constipation led to aggravation of preexisting hemorrhoids. The most common side effect was constipation in eight subjects. Dryness of the skin occurred in two and one patient each complained of either bleeding hemorrhoids, diarrhea, subjective dizziness, choking sensation, itching and tearing of the eyes, or increased angina. However, the relationship of these symptoms to the medication is not definite. During the placebo period, two patients complained of abdominal bloating, one complained of abdominal cramps, and one of mild diarrhea. The only disadvantages observed during the administration of colestipol have been in its bulk 5-g packets instead of pills or capsules, the necessity for mixing with a suitable liquid (juice, soup, carbonated beverage, etc.), and the wait for a few minutes for the hygroscopic water-insoluble beads to swell and soften prior to ingestion. However, the material is virtually odorless and tasteless, and patients have been willing to take the colestipol over long periods of time.

Summary. Colestipol, a bile acid–sequestrant anion exchange resin, was given in doses of 15 g/day to 18 patients with familial hyperlipoproteinemia, and its effect compared to seven patients with this disorder treated with placebo. No alterations in diet were made. The colestipol significantly lowered plasma cholesterol and

phospholipid levels and produced little alteration in triglyceride concentration. The resin had good patient acceptability and appeared to be an effective addition to methods available for the treatment of hyperlipoproteinemia, particularly type II.

We are grateful to Lynn Schwarz for technical assistance and to Harriet Bresnick for assistance in preparation of the manuscript.

1. Hashim, S. A., and Van Itallie, T. B., J. Amer. Med. Ass. **192,** 289 (1965).

2. Fredrickson, D. S., Levy, R. I., and Lees, R. S., New Engl. J. Med. **276,** 32, 94, 148, 215, 273 (1967).

3. Abell, L. L., Levy, B. B., Brodie, B. B., and Kendall, F. E., J. Biol. Chem. **195,** 357 (1952).

4. Fiske, B. H., and SubbaRow, Y., J. Biol. Chem. **66,** 375 (1925).

5. Van Handel, E., Clin. Chem. **7,** 249 (1961).

6. Sachs, B. A., Cady, P., and Ross, G., Amer. J. Med. **17,** 662 (1954).

7. Elevitch, F. R., and Austin, D. G., Analytical Chemists, Inc., Palo Alto, CA (1970).

8. Parkinson, T. M., Gundersen, K., and Nelson, N. A., Atherosclerosis **11,** 531 (1970).

9. Parkinson, T. M., J. Lipid Res. **8,** 24 (1967).

10. Moore, R. B., Crane, C. A., and Frantz, I. D., Jr., J. Clin. Invest. **47,** 1664 (1968).

11. Chobanian, A. V., and Hollander, W., J. Clin. Invest. **41,** 1732 (1962).

12. Glueck, C. J., Ford, S., Jr., Scheel, D., and Steiner, P., J. Amer. Med. Ass. **222,** 676 (1972).

13. Langer, T., Strober, W., and Levy, R. I., J. Clin. Invest. **48,** 49a (1969).

14. Ryan, R. E., and Jain, A., J. Clin. Pharmacol. **12,** 268 (1972).

15. Nye, E. R., and Hunter, J. D., N. Z. Med. J. **76,** 482 (1972).

16. Sachs, B. A., and Wolfman, L., N.Y. State J. Med. **73,** 1068 (1973).

Received June 27, 1974. P.S.E.B.M., 1974, Vol. 147.