

Efficacy, Tolerance, and Safety of Colestipol HCL as a Hypocholesterolemic Agent in Hyperlipidemic Patients with Studies of its Effect on Gastrointestinal Absorption

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Abstract

Colestipol and muestran comparably and effectively lower serum cholesterol levels as compared with an Avicel placebo. There is no significant effect on serum triglyceride levels. There are no serious adverse effects and few nonserious side effects with either drug. There is no effect: on carotene, carbohydrate, or amino acid absorption with long-term use of either hypocholesterolemic drug (JPMA 31:241, 1981).

This study was designed to assess the efficacy, tolerance, and safety of colestipol HCL as a hypocholesterolemic agent in hyperlipidemic patients; and compare it with the effects of cholestyramine (Questran).

Review of the Literature

Hypercholesterolemia is a major risk factor for the development of atherosclerotic coronary heart disease (Keys, 1970; Primary Prevention, 1970; Arteriosclerosis, 1971). Although neither dietary nor drug intervention which reduces serum cholesterol levels has been documented to alter coronary risk many factors may contribute to this situation (CDP Research Group, 1975; Ischaemic Heart Disease, 1971). Dietary-therapy can reduce serum cholesterol by 10% to 25% at best; many of the populations studied have been older individuals followed for only modest periods of time; and most currently available hypocholesterolemic drugs appear to entail independent risk. The unequivocal delineation of atherosclerotic plaque regression in non-human primates, associated with lowering of the serum cholesterol concentration, has encouraged the continued search for an effective and tolerable pharmacologic agent to supplement dietary therapy (Cooper, 1975; Miskhel, 1977; Kuo, 1979; Gundersen, 1976); a combined pharmacologic regimen may be even more effective (Kane, 1981; Illingworth, 1981).

Colestipol, a resin sequestrant, is a high-molecular weight, insoluble, nonabsorbable, copolymer of tetraethylonepentamine and cyclohexanol, with an in vitro bile-acid binding capacity of about 1 meq cholic acid per gram (Parkinson, 1970). Cholestyramine (Questran) (Hashim, 1965) is another bile sequestrating agent which effectively lowers serum cholesterol levels.

Material and Methods

The study design was a single-blind comparison of colestipol, placebo (Avicel.) and cholestyramine (Questran), with treatment assigned on the basis of random number tables. Outpatients in the Cardiac Clinics of Grady Memorial Hospital in Atlanta, Georgia, USA, were recruited for entry into the study. After giving informed consent, patients entered, a 6-week screening (pre-randomization) period;- a history and physical examination were recorded and 12-hour post-prandial serum cholesterol, triglyceride and glucose determinations (as well as other clinical laboratory tests) were performed at 2-

week intervals by the Clinical Research Laboratory of the Upjohn Company, Kalamazoo, Michigan. Patients received placebo therapy during the pre-randomization period. Those who qualified for entry into the study were then assigned to treatment with colestipol, cholestyramine, or placebo. Clinic follow-up was at monthly intervals during the (first year and bimonthly thereafter).

Patients eligible to enter the study were men and women over age 35 (provided no possibility of pregnancy existed in the women), who had not received any lipid-influencing drugs within the preceding 3 months. Patients with hepatic or renal disease, hypothyroid patients, and those receiving steroid or anticoagulant drugs were excluded. To qualify for the study, patients had to have at least 2 serum cholesterol values in excess of 250 mg/dl during the pre-randomization period.

Because there is limited information on the effect of colestipol on human gastrointestinal absorption (Phillips, 1974; Mo, 1974), this was also studied in the three treatment groups. Both colestipol and cholestyramine are known to affect the absorption of lipid-soluble materials, but their long-term effect on carbohydrate and protein absorption has not been well studied. Colestipol does not appear to alter fat-soluble vitamin concentrations (Schwarz, 1980) or phenprocoumon absorption (Harvengt, 1973). However, cholestyramine has been shown to reduce oral digoxin bioavailability, related to the dose of cholestyramine and the proximity of time of administration of the two drugs (Brown, 1978).

Oral tolerance tests are used to study gastrointestinal absorption. These are commonly done by feeding a standard test meal and then obtaining blood levels for 1 to 3 hours following this procedure. Another method of studying gastrointestinal absorption is by collecting urine for 3 to 5 hours following a test meal to see how rapidly the substance is absorbed from the intestine, enters the circulation, and then appears in the urine. All these methods are indirect techniques; they do not have the accuracy of direct absorption methods which are more quantitative. On the other hand, these indirect absorption methods are practical for clinical use.

Simultaneous studies of carbohydrate, amino acid, and protein absorption were carried out. During the performance of these studies, an effort was made to maintain consistency; the same technique was used for each patient each time. Specimens were obtained at the 0, 7, 12, 13 and 26 month visits. The 26-month determination was made after the patient was removed from the test drug and is essentially another "baseline" determination after the cessation of therapy. The test material consisted of 25 mg gelatin mixed with 25 gm xylose, providing a uniform test meal containing protein and carbohydrate; the taste was disguised with an acceptable fruit juice (Thiel, 1963). Fasting, 1 hour and 3 hour blood levels were obtained for blood xylose and blood hydroxyproline (Roe, 1948; Prockop, 1960); fasting blood levels of carotene were also obtained (Wenger et al., 1957).

The test drug was colestipol hydrochloride, an odorless, tasteless finely granular, light yellow powder, dispensed in individual-dose 5 gram packets. The control drug was Questran (cholestyramine) powder, dispensed in 9-gram packets each containing 4 grams of cholestyramine resin. The placebo used was Avicel (microcrystalline cellulose coarse powder NF), provided in moisture proof, polyethylene-lined, individual-dose packets containing 2 grams of the white powder. This drug was given to all patients during the 6-week pre-randomization period and to the placebo group after assignment to treatment. Patients were instructed to take a single dose of medication just prior to meals 3 times daily, mixed with aqueous juices, flavored drinks, milk, or soup, allowing 2-3 minutes for hydration of the drug. Drug dosage remained constant during the study, and it was recommended to the patients that their diet remain stable throughout the study.

At each clinic visit, patients were examined and interviewed with specific questions addressing side effects of the drug, tolerance for the powder, and how many of the packets had been taken since the last visit. Body weight and blood pressure were recorded; and blood and urine specimens obtained.

Serum cholesterol, triglyceride, and glucose determinations were performed by the Clinical Research Laboratory of the Upjohn Company at each clinic visit. The following serum assays were also performed in the Clinical Research Laboratory at 1 and 3 months, then every 3 months for the first years every 4 months thereafter: bilirubin, creatinine, SGOT, alkaline phosphatase, uric acid, calcium,

phosphate, sodium, chloride, and potassium. Hematocrit, hemoglobin, white blood cell count and differential, platelet count, prothrombin time and complete urinalysis determinations were performed by the Emory University School of Clinical Research Laboratory at the same intervals. The absorption studies were analyzed in the Research Laboratory of the V.A. Medical Center (Atlanta).

Results and Discussion

Forty-two patients were enrolled in the study. There were 14 men and 26 women, and the group included 12 white and 28 black patients. There was 1 patient in the age group 30-39, 8 patients age 40-49, 17 patients age 50-59, 13 patients age 60-69, and 1 patient age 70-79.

The Avicel group consisted of 2 men and 13 women, 3 whites and 12 blacks. The colestipol group included 4 men and 6 women, 4 whites and 6 blacks; and the Questran group had 8 men and 7 women, 5 white and 10 blacks. Group composition did not differ significantly.

Mean heights and weights were comparable both for the total group and for men and women (Table 1).

Table 1

Mean Heights and Weights

<i>Medication</i>	<i>HT (Total Group)</i>	<i>WT (Total Group)</i>
Avicel Placebo	64.5	169.5
Colestipol	65.0	172.8
Questran	66.5	174.5

Fifteen patients were assigned to the placebo group, 11 to colestipol therapy, and 16 to cholestyramine therapy. Fourteen of the placebo patients completed 3 months of therapy, 9 patients 6 months of therapy, 6 patients 12 months of therapy, 4 patients 18 months of therapy, and 1 patient completed 2 years on placebo. In the colestipol group, 9 patients were followed for 3 months, 8 patients for 6 months, 4 for 12 months, 3 for 18 months, and 1 for 24 months. Thirteen of the cholestyramine patients completed 3 months of therapy, 11 completed 6 months, 8 completed 12 months, 5 completed 18 months, and 3 completed 2 years.

Analysis of overall data and of data from individual studies indicated that the maximum cholesterol-lowering effect of colestipol and cholestyramine occurred within the first 1-3 months, and was maintained (with fluctuations) during the period of continued treatment. Therefore, the most appropriate statistical method to use in comparing treatment groups was the mean percent change from the pre-treatment value. This was determined as for each patient, the average pre-treatment value and

average value during treatment were calculated, and the individual percent change calculated from the difference. Then a group percent change for the total treatment period was calculated from the individual percent change. Group averages are indicated in Tables 2 and 3.

Table II

Serum Cholesterol

<i>Medication</i>	<i>PTS</i>	<i>Mean Baseline (mg/dl)</i>	<i>Mean % Change</i>	<i>S.E.</i>
Avicel Placebo	15	278.6	-2.6	3.94
Colestipol	11	284.6	-9.5	2.53
Questran	14	306.8	-8.3	2.31

Table III

Serum Triglycerides

<i>Medication</i>	<i>PTS</i>	<i>Mean Baseline (mg/dl)</i>	<i>Mean % Change</i>	<i>S.E.</i>
Avicel Placebo	15	161.2	- 8.3	6.53
Colestipol	11	154.6	- 5.5	7.24
Questran	14	217.7	-11.4	10.01

A comparable and significant lowering of cholesterol levels was obtained with both colestipol and cholestyramine as compared with the Avicel placebo. Serum triglyceride levels were not consistently

altered.

All intercurrent medical events occurring during the study were recorded. No adverse reactions were recorded before assignment to treatment or during the placebo pre-randomization period. During treatment, 1 patient receiving Avicel placebo had an episode of bacterial endocarditis. 1 patient receiving cholestyramine had an episode of cholecystitis, and 2 patients receiving cholestyramine died, both of acute myocardial infarction. None of these events was considered drug-related.

Nonserious side effects-abdominal distress, bloating, constipation, nausea, and vomiting- were minimal in all 3 groups. No significant abnormality of the screening laboratory data was encountered.

Serum carotene levels generally parallel serumlipid levels. In this study, fasting serum carotene levels did not change significantly (Table 4);

Table IV

Fasting Serum Carotene Levels \pm S.D.

<i>Blood Specimen</i>	<i>Questran (8)</i>	<i>Avicel (9)</i>	<i>Colestipol (9)</i>	<i>Significance</i>
7 Month	122 \pm 64	177 \pm 57	101 \pm 65	N.S.
12 Month	128 \pm 51	128 \pm 71	105 \pm 52	N.S.

*Number of patients indicated in parentheses.

and there was no correlation between serum carotene and serum cholesterol levels in the simultaneous measurements in any of the three groups. Since colestipol and cholestyramine affected only cholesterol levels and not triglyceride levels, the absence of changes in serum carotene concentration is not surprising.

Carbohydrate absorption was studied by a fasting and 1 and 3 hour blood levels of xylose. The urine for xylose determination was collected at the end of 3 hours. Particularly in older patients, this technique of urine collection may not be very reliable, because of variability in the rate of glomerular filtration and urinary excretion of any test material. A new technique (Haeney et al., 1978) relates blood levels to body surface area and tends to correct for some abnormalities which might occur in older patients. Blood specimens were collected for fasting xylose levels and all subsequent specimens had this fasting level subtracted. Although xylose is not a normal constituent of blood, some chromogenic materials in blood appear to give the reaction of xylose; therefore, this value was subtracted from the subsequent xylose determinations. In most patients (Table 5),

Table V

One Hour and Three Hour Serum Xylose Levels \pm S.D.

<i>Blood Specimen</i> (29)	<i>Questran</i> % (8)	<i>Avicel</i> (9)	<i>Colestipol</i> (9)	<i>Significance</i>
7 Month				
(1 hour)	27 \pm 13	33 \pm 10	39 \pm 9	N.S.
(3 hour)	25 \pm 11	34 \pm 8	35 \pm 9	N.S.
12 Month				
(1 hour)	36 \pm 10	35 \pm 13	38 \pm 10	N.S.
(3 hour)	33 \pm 8	33 \pm 12	36 \pm 9	N.S.

*Number of patients indicated in parentheses.

a rise in xylose levels was readily detected in the 1 and 3 hour blood levels to concentrations of 25 to 35 mg/dl.

The protein mixture that was administered was primarily gelatin. The gelatin contains predominantly the aminoacid hydroxy-proline, but also contains other aminoacids. Three blood specimens: fasting, 1 hour, and 3 hour- were measured for total aminoacids (West, 1946). There was a consistent rise of the blood amino acid level from the fasting to the 1 hour determination in most patients.

Table VI

Fasting, One Hour, and Three Hour Serum Amino Acid Levels \pm S.D.

<i>Blood Specimen</i> (29)*	<i>Questran</i> (8)	<i>Avicel</i> (9)	<i>Colestipol</i> (9)	<i>Significance</i>
7 Month (Fasting)	5.0 \pm 1.1	5.0 \pm 2.2	3.7 \pm 0.7	N.S.
(1 hour)	7.7 \pm 3.7	6.4 \pm 2.1	5.3 \pm 1.6	N.S.
(3 hour)	5.2 \pm 1.3	5.3 \pm 1.8	4.1 \pm 1.1	N.S.
12 Month (Fasting)	5.1 \pm 1.4	4.5 \pm 1.5	3.8 \pm 0.8	N.S.
(1 hour)	6.7 \pm 1.9	5.5 \pm 1.5	5.1 \pm 1.5	N.S.
(3 hour)	5.8 \pm 1.9	4.8 \pm 1.5	3.8 \pm 1.2	N.S.

*Number of patients indicated in parentheses.

Table 6 shows the trend of changes in patients in the three treatment groups. Total blood amino acid determination is a simple method for studying amino acid absorption, but is very nonspecific. It does not indicate which amino acids rose after the test meal, but shows a trend which was fairly reproducible in most patients.

Hydroxy-proline is an amino acid which is liberated from gelatin. The fasting and 1 and 3 hours blood levels of hydroxy-proline were measured in most patients. Again, the urine was collected for total amino acid determination, and the change from the fasting to the 3 hours urine determination was measured; however, this is not a very reliable measurement, as the clearance of amino acids from the blood to the urine is variable. It depends upon many factors, including the state of hydration of the patient and the degree of renal impairment; therefore, the urinary hydroxy-proline determinations are not very reliable.

Blood levels of hydroxy-proline are more dependable. There was a definite rise from the fasting to the 1 and to the 3 hour blood hydroxy-proline levels. Both the free and the total hydroxy-proline measurements showed this rise. However, for the purposes of this study, we may ignore the difference between these two measurements and study only the total blood hydroxy-proline. Since there is normally a small amount of hydroxy-proline present in blood, the fasting or basal concentration was subtracted from all subsequent determinations. The 1- and the 3-hour blood levels show a rise in most patients in all three treatment groups. This rise is consistent and shows almost the same pattern as the total blood amino acid levels, but it is a more precise biochemical measurement.

Table VII

One Hour and Three Hour Serum Hydroxyproline Levels \pm S.D.

<i>Blood Specimen</i> (29)*	<i>Questran</i> (8)	<i>Avicel</i> (9)	<i>Colestipol</i> (9)	<i>Significance</i>
7 Month (1 hour)	156 \pm 108	172 \pm 103	140 \pm 48	N.S.
(3 hour)	128 \pm 52	162 \pm 69	172 \pm 50	N.S.
12 Month (1 hour)	192 \pm 122	123 \pm 62	127 \pm 42	N.S.
(3 hour)	162 \pm 135	126 \pm 73	163 \pm 42	N.S.

*Number of patients indicated in parentheses.

Table 7 shows the pattern of absorption and the lack of difference between patients receiving placebo and those receiving a cholesterol-binding drug.

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