Combined Para-Aminosalicylic Acid and Dietary Therapy in Long-term Control of Hypercholesterolemia and Hypertriglyceridemia (Types II\textsubscript{a} and II\textsubscript{b} Hyperlipoproteinemia)

PETER T. Kuo, M.D., WARREN C. Fan, M.D., JOHN B. Kostis, M.D., AND Kiyoshi Hayase, Ph.D.

SUMMARY The hypolipidemic effect of PAS-C-diet treatment was studied in 63 patients with Types II\textsubscript{a} and II\textsubscript{b} hyperlipoproteinemia for 6–36 months. Serum lipids and body weights of all patients were stabilized by a low cholesterol-saturated fat-refined carbohydrate diet before the initiation of an eight-week placebo-drug single-blind crossover study. During the placebo period the plasma lipids levels, mean ± sd: cholesterol 355 ± 63.5 mg\%, triglyceride 141 ± 68.7 mg\%, and LDL-cholesterol 279 ± 56.8 mg\% were lowered to 274 ± 53.1 mg\%, 98 ± 40.6 mg\%, and 209 ± 52.9 mg\%, respectively ($P < 0.001$ in each instance), with 7.5–11.0 grams of PAS-C/day given in one to three divided doses. In ten patients who have completed three years of treatment similar results were obtained. They showed no tendency to develop drug tolerance. Eight had watery diarrhea during the initial period which promptly subsided with interruption of drug therapy. Reintroduction of PAS-C in smaller dose (4.5 g/day) with gradual increment to effective dosage level was tolerated by all. No hematologic, hepatic, and ophthalmologic abnormalities were demonstrated by periodic monitoring. The hypolipidemic effect of the drug was found to be diminished by alcohol and caloric excess.

OF ALL THE HYPERLIPOPROTEINEMIC DISORDERS, Types II\textsubscript{a} and II\textsubscript{b} have been shown to confer the highest risk of developing coronary artery disease\textsuperscript{6}–\textsuperscript{8} and to be resistant to treatment.\textsuperscript{9,10} Although the beneficial effect of hypolipidemic therapy has not been conclusively determined, it is generally agreed that vigorous treatment aimed at lowering serum cholesterol and triglyceride concentrations might help to prevent or delay the occurrence of atherosclerotic complications.

In using para-aminosalicylic acid (PAS) in antituberculous therapy, a number of observers have reported on its hypcholesterolemic effect.\textsuperscript{8,11} The development of a highly purified preparation by recrystallizing the drug in vitamin C (PAS-C) has greatly improved its taste and absorption, while reducing its undesirable gastrointestinal effects of gastric irritation, diarrhea, and steatorrhea.\textsuperscript{12,13}

This report deals with the use of PAS-C in combination with diet in the attempt to: 1) achieve significant lowering of serum cholesterol and triglyceride levels in 63 patients with Type II hyperlipoproteinemia for 6–36 months, and 2) determine the side effects and acceptance of the drug by patients on a long-term basis.

Patients and Methods of Study

Patients

Patients were referred to the clinic because of resistant hypercholesterolemia with or without clinical ischemic heart or peripheral vascular disease. Affected family members of the propositi were diagnosed by screening. The age range varied from 8–63 years. Selection of primary Type II patients, with exclusion of those with secondary hypercholesterolemia, was made according to the criteria of Fredrickson and Levy.\textsuperscript{1} Sporadic Type II patients\textsuperscript{2} were included if their hypercholesterolemia failed to respond to a standard low cholesterol diet.\textsuperscript{14} To avoid the inclusion of patients with diet-induced hypercholesterolemia, lipoprotein phenotyping was performed after their plasma lipids levels were stabilized by diet.

Diet

To prepare patients for the treatment, all of them were asked to sign an informed consent before they were given instruction to go on a low cholesterol and limited saturated fat-simple carbohydrate ("therapeutic") diet\textsuperscript{15} with interruption of previous drug therapy for a minimum of four weeks. Adherence to the diet was periodically reviewed and patients were encouraged throughout the course of PAS-C treatment.

Methods

In single-blind crossover study, PAS-C and placebo administration were alternated with each successive patient entering the trial to form two groups. Thirty-three patients from two study groups who have completed the placebo period of the initial single-blind study and went on to take the drug for six or more months were included in this evaluation. Three baseline plasma lipid-lipoprotein determinations were made before the patient started to receive placebo or drug and at bi-weekly intervals afterward for four weeks. On starting PAS-C, each patient received complete physical and ophthalmologic examinations and a battery of laboratory tests (electrocardiogram, chest X-ray, urinalysis, and hematologic and biochemical studies). All blood, physical and ophthalmologic examinations were repeated two weeks later and at three-month intervals throughout the trial, while brief physical examination and plasma lipid-lipoprotein analyses were made at monthly intervals. Depending on the size of
the patient, initial dosages of the drug, ranging from 4.5-7.5 g/day were prescribed to be taken as 3-5 tablets three times a day with or immediately after meals to minimize the gastrointestinal reactions. In a number of patients, dosage of the drug was gradually increased according to their tolerance to a maximum of 11 g/day for more optimal control of their blood lipid levels. The majority of adults were maintained on 8-9 g/day dosages, while most of the children, 12 or younger, were kept on 5-6 g daily dose. Each patient was requested to count the number of remaining pills at each visit to check on the actual amount used.

Fasting serum cholesterol and triglyceride levels were measured with automated procedures standardized by the Center for Disease Control, U.S. Public Health Service. Low density lipoprotein (LDL) cholesterol was calculated as the difference between total plasma cholesterol concentration and that in high density plus very low density lipoproteins. Statistical analysis of the differences between plasma lipid levels obtained before and at various intervals after the start of drug therapy was evaluated by paired t-test.

Results

The pertinent clinical data of this series of patients are summarized in table 1. There is a preponderance of Type IIa over Type IIb lipoprotein abnormality (47 versus 16), after lipid metabolism of these patients was stabilized on the "therapeutic diet." Many of them have corneal arcus, tendinous xanthomata, and clinical atherosclerosis. Three patients continued to consume moderate amounts of alcohol (beer) with periodic interruptions.

Single-blind Crossover Study

The baseline pre-diet serum lipid values of these patients and their serum lipid levels while they were receiving placebo and PAS-C are shown in table 2 for evaluation and comparison. The "therapeutic diet," containing no added polyunsaturated oil, was effective only in lowering their serum triglyceride levels but not in their cholesterol and LDL-cholesterol concentrations. Despite considerable individual variability in response to PAS-C, the drug was effective in lowering the mean serum cholesterol, triglyceride, and LDL lipoprotein-cholesterol to significant degrees, \( P < 0.001 \) in each category (table 2). In general, patients with high serum cholesterol levels (> 400 mg%) were resistant to treatment and would require higher than average drug dosage to achieve significant hypolipidemic effect.

The hypolipidemic effect observed after drug administration could not be attributed to weight loss secondary to a possible drug-induced gastrointestinal disturbance, since the mean weight change of this group from the placebo period amounted to only \(-0.2 \text{ kg}\) at the end of four weeks of drug treatment.

Alcohol Effect

Alcohol drinking can apparently counteract the hypolipidemic effect of PAS-C. The data obtained from three patients are presented in figure 1. Each charted point (exclusive of large symbols denoting mean values) represents the mean of three or more serum cholesterol, triglyceride, and LDL-cholesterol observations made on each patient at different periods during the course of study.

Frequency of Drug Administration

Each of the 12 randomly selected patients, ranging from 11-58 years of age receiving 5-11 g of PAS-C/day, was asked to take his total daily drug in three divided doses, and then in two and one daily dosages. Each method of drug administration was continued for three months. Table 3 shows that the hypolipidemic effect of PAS-C was unaltered by changing the frequency of drug administration.

Long-Term Effects of PAS-C

In 63 patients the drug administration has been continued for six months to three years beyond the initial single-blind crossover trial period. Except for special conditions, pill count check indicated a consistent 85-95% drug utilization in all patients. The degree of mean serum cholesterol reduction approximated closely that observed during the initial period. The serum triglyceride response, however, was relatively less significant statistically than that of cholesterol (table 4), although the percentage reduction of the two serum lipid fractions was quite similar. At the end of the

<table>
<thead>
<tr>
<th>TABLE 1. Summary of Clinical Data of Patients Studied</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total number: 63</td>
</tr>
<tr>
<td>(male/female): 40/23</td>
</tr>
<tr>
<td>Age (years): 8 - 63</td>
</tr>
<tr>
<td>Ht (in)/Wt (lb): 43-75/80-220</td>
</tr>
<tr>
<td>Daily cocktail or beer: 3</td>
</tr>
<tr>
<td>Clinical data:</td>
</tr>
<tr>
<td>Corneal arcus: 15</td>
</tr>
<tr>
<td>Tendinous xanthomata: 21</td>
</tr>
<tr>
<td>Coronary heart disease: 24</td>
</tr>
<tr>
<td>Carotid and/or peripheral vascular disease: 11</td>
</tr>
<tr>
<td>Lipoprotein phenotypes:</td>
</tr>
<tr>
<td>( \Pi_a ): 47</td>
</tr>
<tr>
<td>( \Pi_b ): 16</td>
</tr>
</tbody>
</table>

| FIGURE 1 Interaction between PAS-C and alcohol: effect on serum lipids. Each small symbol represents the mean of three or more serum cholesterol, triglyceride, and LDL-cholesterol measurements made on each patient during different periods of study: \( \circ \), before PAS-C; \( \times \), while on PAS-C; \( \bullet \), PAS-C + alcohol. Large symbols \( O, X \), \( \bullet \) represent the mean of each group of small symbols. |
third year of drug treatment, the mean serum triglyceride of ten patients changed from the initial value of 147 ± 63.1 mg/100 ml to 91 ± 32.1 mg/100 ml, a decrease of 56 mg/100 ml, \( P < 0.025 \). The mean weight change of these ten patients was 1.8 kg as compared with that of the pretreatment placebo period.

**Early and Late Side Effects**

Side effects of PAS-C were primarily limited to the gastrointestinal system. Four patients developed watery diarrhoea during the early phase of drug administration; while in four others diarrhoea occurred suddenly with the onset of a nonspecific intestinal disturbance. In all instances, acute symptoms subsided within two to three days after interruption of drug therapy.

Reintroduction of the drug at 4.5 g/day with a gradual increment to higher dosages was well tolerated by all patients who suffered diarrhoea. Fourteen patients complained of epigastric discomfort or of loose bowel movements for one–two days during the course of their treatment. Microscopic examinations and chemical analyses for stool fat made randomly and during the height of diarrhoea failed to demonstrate significant steatorrhea in eight patients.

For better supervision of drug intake by children and for convenience of some adults, the entire daily dose was dissolved in water and given on an once-a-day schedule without provoking gastrointestinal symptoms or resulting loss of drug efficacy. Hematological and biochemical findings were unchanged throughout the prolonged period of drug administration. PAS-C also did not produce any detectable adverse effect upon the eyes, heart, and kidneys.

**Discussion**

The frequency of Type II hyperlipoproteinemia (primary hypercholesterolemia) has been shown to range between 0.5–1.0% of live births on neonatal cord blood screening.19

The number is swollen by the inclusion of “sporadic” cases. A close association of this type of hyperlipidemia with early development of coronary artery disease has been well documented by a number of well-conceived studies. The need of altering the abnormal lipid metabolism with the assumption that it may retard progression of atherosclerosis is generally recognized.

Currently, therapy favors the use of anion exchange resins7,21 in this condition despite their minimal serum triglyceride lowering effect. Since these are water insoluble powders, they must be taken in rather large quantities. This study confirms and extends the report of Barter et al.20 that

**Table 2. Single-blind Crossover Study: Serum Cholesterol, Triglyceride, and LDL-Cholesterol During Placebo and PAS-C* Periods in 63 Patients**

<table>
<thead>
<tr>
<th>Serum lipids</th>
<th>Baseline before diet (3–4 wk)</th>
<th>Placebo (4 wk)</th>
<th>( \Delta ) and ( P )</th>
<th>Placebo (4 wk)</th>
<th>PAS-C* (4 wk)</th>
<th>( \Delta ) (%) and ( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total cholesterol</td>
<td>373 ± 59.5</td>
<td>355 ± 63.5</td>
<td>–18</td>
<td>355 ± 63.5</td>
<td>274 ± 53.1</td>
<td>–81 (22.8)</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>181 ± 81.2</td>
<td>141 ± 68.7</td>
<td>–40</td>
<td>141 ± 68.7</td>
<td>98 ± 46.0</td>
<td>–43 (30.5)</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>287 ± 58.2</td>
<td>279 ± 56.8</td>
<td>–8</td>
<td>279 ± 56.8</td>
<td>209 ± 52.9</td>
<td>–70 (25.1)</td>
</tr>
</tbody>
</table>

Values given are mean ± standard deviation in mg %. *PAS-C = para-aminosalicylic acid, recrystallized in vitamin C. NS = nonsignificant.

**Table 3. Frequency of PAS-C Administration: Effect on Serum Lipids in 12 Patients**

<table>
<thead>
<tr>
<th>Serum lipids</th>
<th>Values observed with 3-way administration of daily dosage*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Three daily</td>
</tr>
<tr>
<td>Cholesterol</td>
<td>249 ± 38.6</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>97 ± 39.4</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>186 ± 43.9</td>
</tr>
</tbody>
</table>

Values given are mean and standard deviation of mg %. *PAS-C = para-aminosalicylic acid, recrystallized in vitamin C.
PAS-C tablets are relatively easy to administer and the drug is safe and effective in lowering serum cholesterol and triglyceride in hypercholesterolemic (Types IIa and IIb) patients.

Among the more significant information we have obtained are the absence of serious side effects and the maintenance of effectiveness following a prolonged period of drug administration. In addition, the importance of combining dietary control to complement drug therapy is emphasized by the demonstration of serum lipid elevation, especially triglyceride, following the minor relaxations in the dietary-regimen resulting in mild weight gain in some of our patients in the third year of their treatment. Lastly, the potent hyperlipidemic effect of alcohol in nullifying the hypolipidemic action of the drug has been demonstrated in each drinking period in three alcohol (beer) users.

PAS-C may exert multiple modes of action to accomplish serum lipid depression. In isolated rat and monkey liver cell preparations, the drug has been found to suppress hepatic cholesterol and triglyceride synthesis from acetate, pyruvate and glucose. It is safe to assume that ascorbic acid used in the preparation of PAS-C has little or no contribution to the pharmacological activity of the drug, since its vitamin C content was found to be too small for chemical detection.

References

26. Ziporin ZZ: Chemistry Division, Research and Development Division, Fitzsimons General Hospital, Denver, Colorado: Biochemical Analysis of PAS-C to Hellwig Inc., 1962. (Copy of report available from author)
Combined para-aminosalicylic acid and dietary therapy in long-term control of hypercholesterolemia and hypertriglyceridemia (Types IIa and IIb hyperlipoproteinemia).
P T Kuo, W C Fan, J B Kostis and K Hayase

Circulation. 1976;53:338-341
doi: 10.1161/01.CIR.53.2.338

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 1976 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/53/2/338

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org//subscriptions/