Combined Para-Aminosalicylic Acid and Dietary Therapy in Long-term Control of Hypercholesterolemia and Hypertriglyceridemia (Types IIa and IIb Hyperlipoproteinemia)

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SUMMARY The hypolipidemic effect of PAS-C-diet treatment was studied in 63 patients with Types IIa and IIb, 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 HYPERLIPROTEINEMIC DISORDERS, Types IIa and IIb have been shown to confer the highest risk of developing coronary artery disease and to be resistant to treatment. 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 hypercholesterolemic effect. 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.

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. Sporadic Type II patients were included if their hypercholesterolemia failed to respond to a standard low cholesterol diet. 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 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. Sixty-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 procedures9, 10 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.1, 11 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 xanthoma, 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,"12 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,13 since the mean weight change of this group from the placebo period amounted to only -0.2 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

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**Table 1. Summary of Clinical Data of Patients Studied**

<table>
<thead>
<tr>
<th>Total number</th>
<th>63</th>
</tr>
</thead>
<tbody>
<tr>
<td>(male/female)</td>
<td>40/23</td>
</tr>
<tr>
<td>Age (years)</td>
<td>8–63</td>
</tr>
<tr>
<td>Ht (in)/Wt (lb)</td>
<td>43–75/80–220</td>
</tr>
<tr>
<td>Daily cocktail or beer</td>
<td>3</td>
</tr>
</tbody>
</table>

**Clinical data**

- Corneal arcus: 15
- Tendinous xanthoma: 21
- Coronary heart disease: 24
- Carotid and/or peripheral vascular disease: 11
- Lipoprotein phenotypes: IIa: 47, IIb: 16

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**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. •, before PAS-C; x, while on PAS-C; ○, PAS-C + alcohol. Large symbols O, X, • 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 di-
arrhea during the early phase of drug administration; while
in four others diarrhea occurred suddenly with the onset of a
nonspecific intestinal disturbance. In all instances, acute
symptoms subsided within two to three days after interrup-
tion of drug therapy.

Reintroduction of the drug at 4.5 g/day with a gradual in-
crement to higher dosages was well tolerated by all patients
who suffered diarrhea. Fourteen patients complained of
epigastric discomfort or of loose bowel movements for one–two
days during the course of their treatment. Micro-
scopic examinations and chemical analyses for stool fat
made randomly and during the height of diarrhea 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 dis-
solved in soda and given on a 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 ad-
ministration. 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.20

The number is swollen by the inclusion of “sporadic” cases.21
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.22 The
need of altering the abnormal lipid metabolism with the
assumption that it may retard progression of atherosclerosis
generally recognized.

Currently, therapy favors the use of anion exchange
resins,23 in this condition despite their minimal serum
triglyceride elevating 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.24 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>Δ and P</th>
<th>Placebo (4 wk)</th>
<th>PAS-C* (4 wk)</th>
<th>Δ (%) 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 P</td>
<td>141 ± 68.7</td>
<td>98 ± 40.6</td>
<td>-43 (30.5)</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>287 ± 58.2</td>
<td>279 ± 56.8</td>
<td>-8 NS</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.

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

<table>
<thead>
<tr>
<th>Serum lipids</th>
<th>Three daily</th>
<th>Twice daily</th>
<th>Once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cholesterol</td>
<td>249 ± 38.6</td>
<td>247 ± 38.4</td>
<td>243 ± 40.7</td>
</tr>
<tr>
<td>Triglyceride</td>
<td>97 ± 39.4</td>
<td>94 ± 37.8</td>
<td>94 ± 39.9</td>
</tr>
<tr>
<td>LDL-Cholesterol</td>
<td>186 ± 43.9</td>
<td>186 ± 46.0</td>
<td>181 ± 47.7</td>
</tr>
</tbody>
</table>

Values given are mean ± standard deviation of mg %. No significant changes observed between different methods of administration.

Table 4. Long-Term Serum Lipid Changes with PAS-C* Therapy

<table>
<thead>
<tr>
<th>Placebo period</th>
<th>Total cholesterol</th>
<th>Triglyceride</th>
<th>LDL-cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>At 6 months therapy (N = 63)</td>
<td>Placebo 355 ± 63.5</td>
<td>141 ± 68.7</td>
<td>279 ± 56.8</td>
</tr>
<tr>
<td>6 Months</td>
<td>Difference (%) = -81 (22.8)</td>
<td>-37 (26.2)</td>
<td>-70 (25.1)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 12 months therapy (N = 52)</td>
<td>Placebo 358 ± 65.0</td>
<td>148 ± 69.5</td>
<td>282 ± 57.5</td>
</tr>
<tr>
<td>12 Months</td>
<td>Difference (%) = -89 (24.9)</td>
<td>-36 (24.3)</td>
<td>-82 (29.1)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.005</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 18 months therapy (N = 44)</td>
<td>Placebo 359 ± 67.5</td>
<td>155 ± 71.4</td>
<td>281 ± 57.8</td>
</tr>
<tr>
<td>18 Months</td>
<td>Difference (%) = -89 (24.8)</td>
<td>-38 (24.5)</td>
<td>-79 (28.1)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.005</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 24 months therapy (N = 33)</td>
<td>Placebo 364 ± 73.5</td>
<td>157 ± 70.3</td>
<td>288 ± 63.6</td>
</tr>
<tr>
<td>24 Months</td>
<td>Difference (%) = -104 (28.6)</td>
<td>-45 (28.7)</td>
<td>-91 (31.8)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.005</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 30 months therapy (N = 15)</td>
<td>Placebo 372 ± 68.8</td>
<td>134 ± 54.9</td>
<td>293 ± 67.5</td>
</tr>
<tr>
<td>30 Months</td>
<td>Difference (%) = -112 (30.1)</td>
<td>-51 (38.1)</td>
<td>-95 (32.4)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.010</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>At 36 months therapy (N = 10)</td>
<td>Placebo 378 ± 56.3</td>
<td>147 ± 63.1</td>
<td>292 ± 62.4</td>
</tr>
<tr>
<td>36 Months</td>
<td>Difference (%) = -118 (31.2)</td>
<td>-50 (38.1)</td>
<td>-97 (33.2)</td>
</tr>
<tr>
<td>P</td>
<td>&lt; 0.001</td>
<td>&lt; 0.025</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Values given represent means ± standard deviation in 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.\textsuperscript{24, 25} 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.\textsuperscript{26}

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26. Zipprin 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)
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