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The Intravenous Administration of a High Concentration of Para-Aminosalicylic Acid (PAS)

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INTRODUCTION

Eleven years have passed since Lehmann reported on paraaminosalicylic acid (PAS), and it has been accepted firmly as a useful therapeutic agent in the treatment of tuberculosis, but the effect of the oral administration of 10 Gm. of PAS per day is considerably inferior in comparison to that of the injection of 1 Gm. of streptomycin per day. Even with this dose, PAS causes loss of appetite in a significant number of patients, and for this reason, it is difficult to increase the dose.

Consequently, the parenteral administration of PAS has become an important problem. Along this line in foreign reports, the present authors find Fisher, Roberts and Hinshaw, Paraf, Löwenstein and Rockstroh, Paraf, Lowenstein and Rockstroh, Paraf, who attempted the subcutaneous administration, and Regli and Stäubli, Paraf, Bogen, Paraf, Barkley, Paraf, Tulon and Pellerat, Paraf, Hinshaw and others, Paraf, who attempted the intravenous administration. Every method attempted by those investigators was merely the injection of large volume of 2 to 3 per cent solution which may be impractical in the therapy of chronic tuberculosis.

Early in 1951, an attempt was made in this laboratory to establish a practicable method of the intravenous administration of a high concentration of PAS and it was confirmed that 4 Gm. of PAS could be given intravenously in 10 per cent solution without causing any considerable reactions by employing a sterile powder of sodium salt of PAS which was highly purified by some cooperating pharmaceutical companies, and was dissolved in distilled water at use. The results were compiled, and reported at The Commemorative Lecture on the Tenth Anniversary of the Foundation of the Tuberculosis Research Institute, Kyoto University on June 16, 1951. Reports were successively submitted to The Annual Reports of the Tuberculosis Research Institute, Kyoto University, Vol. 3, Shindan-To-Chiryo, Shinryo-No-Jissai, Reports of the Tuberculosis Research Institute, Kyoto University, Vol. 2, No. 3 and various other publications.

About the same time, reports by Nakamura, Kanda, Shinoi, Nakao,
Tomizawa\textsuperscript{17} and Fujita\textsuperscript{18} on the intravenous administration of a high concentration of PAS began to appear in this country, but in foreign countries almost no report is available on this subject up to the present day.

The present authors have continued with the study, and now with to properly arrange the results in order to ask for criticism by the readers concerned.

**Comparison of the Transitions of the Concentrations of PAS in the Blood After the Oral Administration with Those After the Intravenous Administration.**

The progressive changes of the concentrations of PAS in the blood obtained after administration of 4 Gm. of the drug in a human body at a time by the oral route was compared with those obtained by the intravenous route. For the quantitative determination, the method of Klyne and Newhouse\textsuperscript{19} was employed.

(1) **Concentrations of PAS in the Blood After Intravenous Administration.**

The successive transitions of the concentrations of PAS in the blood after intravenous administration of 4 Gm. of the drug are shown in Fig. 1. Although individual variations according to such as the body weight were noted, the peak concentrations which indicated 12 mg. to 29.5 mg. per dl. were obtained 30 minutes after the administration. The concentrations then gradually decreased as follows: 6.5 mg. to 19.5 mg. per dl. after 1 hour, 5 mg. to 12 mg. per dl. after 2 hours, 4 mg. to 10 mg. per dl. after 4 hours, 2 mg. to 6.25 mg. per dl. after 6 hours and 0.2 mg. to 2 mg. per dl. 8 hours after the administration.

(II) **Concentrations of PAS in the Blood After Oral Administration.**

Fig. 2 shows the successive transitions of the concentrations of PAS in the blood after oral administration. As may be seen the concentrations were 6 mg. to 8 mg. per dl. after 30 minutes, 10 mg. to 12.5 mg. per dl. after 1 hour, 5 mg.
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to 9 mg. per dl. after 2 hours, 1.75 mg. to 4.5 mg. per dl. after 4 hours, 1 mg. to 2 mg. per dl. after 6 hours and 0.5 mg. to 1 mg. per dl. 8 hours after the administration. In short, the peak values were found 1 hour after the oral administration and a gradual descent of the values followed, however, a measurable concentration did not disappear even after 8 hours.

(III) Comparison of the Concentrations of PAS in the Blood After the Intravenous Administration with Those After the Oral Administration in the Same Individual.

Comparison of the blood PAS concentrations following the administration by intravenous route with those by oral route in the same individual is shown in Fig. 3, 4 and 5. In Fig. 3 and 5, the variation between the concentrations by those two routes was remarkable, and not only after 30 minutes but even 6 hours after the administration, the concentrations obtained by using the intravenous route were higher than those obtained by using the oral route. Particularly in Fig. 3, the concentrations obtained by intravenous administration were higher even after 8 hours. In Fig. 4, the variation between the concentrations following the intravenous administration and those following the oral administration was not remarkable throughout the experiments except after 30 minutes, but the former was slightly higher even after 8 hours.
As may be seen from the results of the experiments the peak concentrations of PAS in the blood obtained after the administration of 4 Gm. of the drug by the intravenous route are markedly higher than those by the oral route, however, the concentrations obtained by using intravenous route are almost equal to those obtained by using oral route 8 hours after the administration.

(IV) Transitions of the Quantity of the Bacteriostatic Substance in the Blood After the Administration of PAS by Oral Route and by Intravenous Route.

Although in the preceding experiments the blood concentrations of PAS were measured by quantitative chemical analysis, it is questionable whether all the substances reacted as PAS had possessed bacteriostatic activity. It is feared that the PAS derivatives which lost some of their bacteriostatic activity by chemical changes in the living body also reacted together as PAS, while it may be more important for clinicians to know the quantity of bacteriostatic substance in the body than to know the quantity of the substances which merely present a definite chemical reaction.

The serum of the PAS administered subjects was obtained at different intervals ; Kirchner's medium which contains the serum in the concentration of 90 per cent was prepared ; the growth of human type tubercle bacilli cultured in this medium was observed ; and the durations of the bacteriostatic activity following oral administration and those following intravenous administration were compared.

This method was originally established by Naito and Shioda at this laboratory.

Materials and Methods

(1) Serum

The sera were separated routinely from the blood drawn 4, 5, 6, 7 and 8 hours after the administration of 4 Gm. of PAS by intravenous route and by oral route.

(2) Culture Medium

A modified Kirchner's synthetic medium was employed in this study. The composition was as follows : Disodium phosphate, 3.0 gm. ; Monopotassium phosphate, 4.0 gm. ; Magnesium sulfate, 0.6 gm. ; Sodium citrate, 2.5 gm. ; Asparagine, 5.0 gm. ; Glycerin 23.0 ml ; and Distilled water 100.0 ml. (The volume of distilled water was only one-tenth of that used in standard Kirchner's medium.) The pH was adjusted to 6.7 or 6.8. One part of this modified Kirchner's medium was added to nine parts of the above described serum and was sterilized for
60 minutes at 55°C water bath prior to using.

(3) Inoculum

Aoyama-B strain and Frankfurt strain of tubercle bacilli cultured in the Sauton's medium for 3 to 4 weeks were employed. In preparing the suspension of tubercle bacilli, one loop of the bacilli was transferred to 6.0 ml. of Kirchner’s medium containing several small glass-beads; after 3 to 4 weeks either 2.0 ml. of physiological saline solution or 2.0 ml. of Kirchner’s synthetic medium was added to this subculture; this was shaken for 5 minutes to break up the aggregates of the bacilli into smaller clumps and even single bacilli; after allowing to remain for 20 minutes, 1.0 ml. of the supernatant was transfused into another sterile test tube, and 4.0 ml. of physiological saline solution or Kirchner’s synthetic medium was, then, added. The preparation of the suspension of bacilli was completed by shaking the tube again. For inoculation, 1 drop of this suspension was added to each culture tube.

(4) Determination

The bacteriostatic activity was determined by observing the existence and the degree of the colonies in the bottoms of the culture tubes, comparing them with the controls. The minimum inhibitory concentration was considered as being the point where no macroscopic evidence of growth was found.

Results

The durations of the bacteriostatic activity following intravenous and oral administration of 4 Gm. of PAS at several hours interval were determined in 4 subjects by employing above stated method.

As may be seen in Table 1, the bacteriostatic activity was demonstrated 5 hours after the oral administration of PAS, but it had disappeared after 6 hours. Following intravenous administration, it was maintained up to 6 hours and disappeared at the 8 hour point.

In Table 2, the activity remained up to 5 hours after PAS orally, and disappeared after 6 hours. Measurable activity remained up to 7 hours, and disappeared 8 hours after intravenous administration.

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Hours After Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 Gm. (PAS)</td>
<td>Oral</td>
<td>4</td>
</tr>
<tr>
<td></td>
<td>Intravenous</td>
<td>-</td>
</tr>
</tbody>
</table>
Table 2 : (male, 58 kg.)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Hours After Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>4 Gm. (PAS)</td>
<td>Oral</td>
<td>−#</td>
</tr>
<tr>
<td>4 Gm. (PAS)</td>
<td>Intravenous</td>
<td>−</td>
</tr>
</tbody>
</table>

Table 3 : (male, 60 kg.)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Hours After Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>4 Gm. (PAS)</td>
<td>Oral</td>
<td>−#</td>
</tr>
<tr>
<td>4 Gm. (PAS)</td>
<td>Intravenous</td>
<td>−</td>
</tr>
</tbody>
</table>

Table 4 : (female, 45 kg.)

<table>
<thead>
<tr>
<th>Dose</th>
<th>Route</th>
<th>Hours After Administration</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>4</td>
</tr>
<tr>
<td>4 Gm. (PAS)</td>
<td>Oral</td>
<td>−#</td>
</tr>
<tr>
<td>4 Gm. (PAS)</td>
<td>Intravenous</td>
<td>−</td>
</tr>
</tbody>
</table>

# + : Macroscopic evidence of growth was found
− : No evidence

In Table 3, the activity remained up to 5 hours, and disappeared 6 hours after either intravenous or oral administration of PAS.

In Table 4, the same result as in Table 3 was obtained.

From these results, it was believed that the duration of bacteriostatic activity of the serum following administration of PAS by the intravenous route was longer than or, at least, equal to that by the oral route.

The Therapeutic Effect of PAS Given Intravenously in Tuberculous Patients

When this study was planned, it had been described in foreign reports that injection of a large volume of PAS in 2 to 3 per cent solution over long period of time was only the method of administering the drug intravenously without causing general or local toxic reactions. However, the present authors thought that the biological action of a chemically unstable substance such as PAS might be considerably influenced by its purity. The authors therefore, requested some pharmaceutical companies to prepare a highly purified sterile power of PAS.
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enclosed in ampuls which may be used by dissolving in distilled water immediately before administration. From the results of this study, it was confirmed that 4 Gm. of PAS in 10 per cent solution (40cc.) can be given intravenously by ordinary methods.

(I) The Method of Intravenous Administration of Sodium PAS.

Powder of sodium PAS (in sterile ampules) dissolved in distilled water in 10 per cent solution was injected into the antecubital vein. Special attention was paid to the time required for the injection which might influence the appearance of the toxic reaction. In a dose of 4 Gm., sodium PAS was slowly administered in 10 per cent solution, requiring more than 10 minutes for the administration.

(II) Dosage.

A single dose of 4 Gm. of PAS was administered two or three times daily.

(III) Period of Injection.

Sixteen patients were treated for period of 3 weeks to 1 month and 7 patients were treated for 2 to 3 weeks.

(IV) Selection of Patients.

Most cases were selected from in-patients of the Tuberculosis Research Institute, Kyoto University. The majority of the patients had chronic cavitary tuberculosis and a few patients had intestinal tuberculosis.

(V) Clinical Results.

The clinical results which were based upon the essential points of "The Plan of the Japanese Welfare Ministry's Antituberculous Therapy Research Committee" were gathered. All 23 cases were recorded together. The clinical results obtained one month after administration of oral PAS which were gathered in accordance with the above-mentioned plan were shown in Table 6, to be discussed in comparison with those after administration of intravenous PAS. Brief explanations are described as follows.

(1) Fever

PAS given orally was considerably effective, but that given intravenously showed more effectiveness. The temperatures in 80 per cent of 14 feverish patients treated with intravenous PAS and 38 per cent of 16 patients treated with oral PAS were reduced remarkable or slightly. The results indicate evidently that intravenous administration of PAS is more effective than oral administration. The elevated temperatures in patients treated with intravenous
PAS fell markedly within a few days and the majority returned to nearly normal level within 10 days, while the temperature elevations in the group given PAS orally returned to normal level between 3 weeks and 30 days. The reduction of fever caused by intravenous PAS may be compared with that obtained by employing streptomycin. Two of the three patients with unchanged high fevers died soon after.

(2) Appetite

As described in the introduction, the most important aim of the intravenous administration of PAS attempted in this study is related to this clause. As shown in Table 5, improvements were observed in 10 of the 16 patients with loss of appetite, and in comparison with the case in Table 6, intravenous administration is superior to oral administration. As may be seen in Table 7, 12 of the 13 patients treated with both intravenous and oral PAS separately, mentioned that their appetites during the intravenous PAS treatment were better than those during oral PAS treatment. This result may prove that PAS given by the intravenous route disturbs appetite less than that by the oral route, but, on the other hand, the improvement in appetite following PAS intravenously may be due to the remarkable reduction of fever.

(3) Body-Weight

Three patients showed increase in weight. Reduction of fever and increase of appetite may naturally cause weight increase but it seem to be inappropriate to discuss weight increase since the treatment was of a duration of only approximately one month.

(4) Sedimentation Rate of the Erythrocytes

Marked improvement occurred in 3 patients.

(5) Cough

Out of 12 patients, 50 per cent showed improvement. There was little difference between the results obtained by PAS administered intravenously and those by oral administration of PAS.

(6) Expectoration

Decrease of the amount of sputum was observed in 7 patients. In a great part of the patients, the effect of PAS appeared within a few days after intravenous administration, keeping pace with above described improvement in cough. As the amount of sputum decreased, the color of sputum turned from yellow to yellowish white. There was no marked difference between the results following administration of oral PAS and those following administration of intravenous PAS.
In 7 patients (39 per cent), favorable results were obtained. No remarkable difference was seen between the effect of intravenous administration of PAS and that of oral administration.

(8) Roentgenographic Evaluation

Slight improvement was demonstrated in 3 cases. This poor result might be due to the short periods of treatment and a large number of chronic cavitary cases.

(9) Chronic Diarrhea

In 4 of 6 patients with chronic diarrhea which was believed to be due to intestinal tuberculosis, improvements were obtained. Marked improvement in a patient whose diarrhea had continued for over a year was included. The results may indicate that intravenous PAS is effective in the treatment of intestinal tuberculosis. The superiority of intravenous administration of PAS to oral administration is evidenced by comparing Tables 5 and 6. Most of these improvements appeared within several days after start of treatment.

<table>
<thead>
<tr>
<th></th>
<th>Improved</th>
<th>Unchanged</th>
<th>Became Worse</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>markedly</td>
<td>always</td>
<td>abnormal</td>
<td>markedly</td>
</tr>
<tr>
<td></td>
<td>slightly</td>
<td>normal</td>
<td>slightly</td>
<td></td>
</tr>
<tr>
<td>Temperature</td>
<td>5</td>
<td>9</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Appetite</td>
<td>3</td>
<td>3</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>Body Weight</td>
<td>3</td>
<td>0</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>E. S. R.</td>
<td>3</td>
<td>5</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>0</td>
<td>11</td>
<td>6</td>
<td>0</td>
</tr>
<tr>
<td>Expectoration</td>
<td>1</td>
<td>4</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Tubercle Bacilli</td>
<td>4</td>
<td>5</td>
<td>10</td>
<td>1</td>
</tr>
<tr>
<td>Roentgenographic Appearance</td>
<td>0</td>
<td>0</td>
<td>17</td>
<td>1</td>
</tr>
<tr>
<td>Chronic Diarrhea</td>
<td>3</td>
<td>17</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

(VI) Toxic Reaction.

Toxic reactions encountered in intravenous administration of PAS were local vascular pain, nausea, vomiting, headache, sensation of ill-being, tinnitus, dizziness and others. Most of them appeared during the injection.

In regards to the factors of those toxic reactions, the first problem may be
Table 6: Clinical results obtained by oral PAS (26 cases)

<table>
<thead>
<tr>
<th></th>
<th>Improved markedly</th>
<th>Improved slightly</th>
<th>Unchanged always normal</th>
<th>Unchanged always abnormal</th>
<th>Became Worse slightly</th>
<th>Became Worse markedly</th>
<th>Uncertain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Temperature</td>
<td>3</td>
<td>3</td>
<td>10</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Appetite</td>
<td>0</td>
<td>6</td>
<td>3</td>
<td>16</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Body Weight</td>
<td>2</td>
<td>5</td>
<td>1</td>
<td>12</td>
<td>1</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>E. S. R.</td>
<td>3</td>
<td>6</td>
<td>2</td>
<td>15</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Cough</td>
<td>1</td>
<td>7</td>
<td>10</td>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Expectoration</td>
<td>0</td>
<td>8</td>
<td>2</td>
<td>15</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Tubercle Bacilli</td>
<td>7</td>
<td>2</td>
<td>3</td>
<td>14</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Roentgenographic Appearance</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>26</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Chronic Diarrhea</td>
<td>0</td>
<td>1</td>
<td>21</td>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Table 7: Comparison between effect of intravenous PAS and that of oral PAS on appetites

<table>
<thead>
<tr>
<th>Intravenous administration was more effective in</th>
<th>Neither intravenous nor oral administration was effective in</th>
<th>Oral administration was more effective in</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 cases</td>
<td>1 case</td>
<td>0</td>
</tr>
</tbody>
</table>

the individual variation. Probably any quality of PAS can produce the reactions in a few patients who have abnormal sensitivities to the drug.

The second problem may be the quality of manufactured PAS. The sterile powder of PAS in ampules may be the safest and most suitable, if it is dissolved in distilled water at use. The solution of PAS may be colored by long-standing, and this colored solution cannot be employed. Injection of the colored solution may cause the toxic reactions immediately.

Third, the time required for injection is important. In case that the toxic reactions occur without above-mentioned factors, it may be due to the time spent for injection. The injection should be given as slowly as possible in order to prevent the reactions. Ten minutes should be required for the injection of 4 Gm. of PAS in 10 per cent solution (40 cc.).

Thrombophlebitis, hematuria, albuminuria, hemorrhagic phenomenon and hepatic disturbance were not observed.

(1) The peak concentrations of PAS in the blood after the intravenous administration is naturally higher than those after oral administration, and moreover, the concentrations obtained by PAS intravenously and orally are equal even 8 hours after the administrations.

(2) The bacteriostatic substance in the blood following PAS administered
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Intravenously remains longer than those following PAS administered orally.

(3) PAS can be given intravenously in 40 cc. of 10 per cent solution.

(4) Clinical effect of PAS given intravenously is more marked than that of PAS given orally.

(5) Intravenous administration of PAS will not cause any considerable toxic reaction, if the injection is given over a period of longer than 10 minutes.

(Notice: The PAS employed on the present study was supplied by Tanabe Seiyaku, Takeda Yakko, Daiichi Seiyaku, Fujisawa Yakko and Sumitomo Kagaku.)

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