Experience with High Doses of Para-Aminosalicylic Acid in the Treatment of Pulmonary Tuberculosis*

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This study was an attempt to determine whether the administration of large doses of para-aminosalicylic acid, 18 to 24 grams a day, was feasible and advantageous in the treatment of pulmonary tuberculosis. Patients for this study were not especially selected. Each one for whom antibacterial therapy was indicated and who had an odd hospital register number, between May 24, 1950 and January 1, 1951, was placed on 24 grams of PAS daily. In addition, six whose sputa showed organisms definitely resistant to streptomycin were added to the study. This made a total of 28 who were started on the proposed therapy. In six of the patients, collapse measures were added sometime during the course of treatment.

The 28 included 22 with far-advanced and six with moderately advanced pulmonary tuberculosis. All had progressive, or at least stationary lesions. Seventeen were white and 11 were negro. All were males, 12 of whom were in the third decade of life, nine in the fourth decade, two in the fifth, four in the sixth and one in the seventh. All had positive sputum, on concentration, at the beginning of therapy. PAS was given in the form of sodium salt, prepared in our pharmacy according to the method described by Lyght.† The equivalent of 6 grams of PAS was administered four times daily with food for a proposed period of 120 days.

Of the 28 begun on 24 grams of PAS, only 12 (42.8 per cent) completed the course of 120 days. However, six others were able to complete the course after the daily dose was reduced to 18 grams. This makes a total of 18 (64.2 per cent) who were able to tolerate high doses of PAS for 120 days. Almost all developed some symptom of drug toxicity, mainly anorexia, vomiting, or

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diarrhea. In most, however, the omission of the drug for a day or two was sufficient to alleviate the symptoms and permit the prompt resumption of therapy. On the other hand, in three, these symptoms were so severe as to warrant the cessation of therapy within the first month. In another, the drug had to be stopped after three weeks because of the appearance of chills, high fever (up to 105 degrees F.) and malaise after each dose administered. Thus, 14.3 per cent of our patients were unable to tolerate high doses of PAS sufficiently long to enjoy the benefits of any significant therapeutic effect.

Six other patients remained on the course for at least two months, but failed to complete the 120 days. Two of them appeared to show poor therapeutic response by the end of the third month, and a different regimen was substituted. In two others, high dosage PAS was discontinued after two and one half months in one and three months in the other, because tubercle bacilli obtained from their sputa showed well marked resistance to PAS by in vitro tests. The fifth patient left the hospital without our consent after two and one half months of therapy, and the sixth, after a similar period, suddenly refused to take all medications without offering any explanation.

Weight loss occurred in 54.2 per cent of our group, probably as a result of the gastro-intestinal dysfunction produced by the large doses of PAS, (Table I).

| TABLE I |
|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
| Weight Changes in Patients on 18-24 gms. of PAS for 2 to 4 Months |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| | LOSS IN POUNDS | | GAIN IN POUNDS | | | | | | | | |
| | Less | More | Less | More | Less | More | No Change |
| Total Number | 24 | 6 | 4 | 3 | 3 | 1 | 5 | 2 |
| Per cent | 100 | 25 | 16.7 | 12.5 | 12.5 | 4.2 | 20.8 | 8.3 |

In view of the tendency of patients on PAS to develop frequent loose stools, there was some question whether the drug was adequately absorbed and whether the increased dosage led to increased blood levels. Blood samples, therefore, were drawn at specified hours after ingestion of the drug from five patients taking 24 grams daily, and for comparison from five patients taking 12 grams daily. The results obtained, (Table II), indicate marked variation between patients on the same dose, but on the average the blood levels were higher at the third and fourth hours after ingestion in those who were taking 24 grams daily.
TABLE II

PAS Blood Levels, After Ingestion of First Morning Dose

<table>
<thead>
<tr>
<th></th>
<th>1 HOUR</th>
<th>2 HOURS</th>
<th>3 HOURS</th>
<th>4 HOURS</th>
</tr>
</thead>
<tbody>
<tr>
<td>12 grams</td>
<td>9.4</td>
<td>6.9</td>
<td>13.1</td>
<td>2.6</td>
</tr>
<tr>
<td>(3 gm. dose)</td>
<td>6.0</td>
<td>0</td>
<td>0.4</td>
<td>0.4</td>
</tr>
<tr>
<td>24 grams</td>
<td>9.2</td>
<td>7.8</td>
<td>23.0</td>
<td>11.7</td>
</tr>
<tr>
<td>(6 gm. dose)</td>
<td>0.5</td>
<td>0.3</td>
<td>9.8</td>
<td>3.5</td>
</tr>
</tbody>
</table>

The lower left figure in each box is the lowest value obtained, the upper right figure is the highest, and the center figure is the average.

A few of our patients seemed to develop streaked sputum more frequently than expected. The prothrombin level was, therefore, determined in 15. In six (40 per cent), of those tested, the level was 60 per cent or less of normal. In 10 others, not on PAS, the level was 100 per cent without exception. Probably the reduction in level in those on large doses of PAS, is due to interference with prothrombin formation, in a manner similar to the action of other salicylates, and most markedly, of dicumarol. The administration of one of the Vitamin K preparations brought a return to normal level within a few days.

The various complications encountered, and the apparently mediocre results obtained, as compared to combined therapy, made us bring the study to a halt. Thus the number of patients treated are too few to permit of anything more than an impression. Our immediate results are tabulated in Table III, and for comparison the results obtained by the British Medical Research Council in a series of 59 cases of acute progressive bilateral tuberculosis treated with 20 grams of PAS daily for a period of three months without any concomitant collapse measures, is included.

TABLE III

Immediate Results of 2-4 Months of 18-24 gms. PAS

<table>
<thead>
<tr>
<th></th>
<th>X-Ray Improvement (Per cent)</th>
<th>Sputum Conversion (Per cent)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. Cases</td>
<td>All Degrees</td>
</tr>
<tr>
<td>BMRC</td>
<td>59</td>
<td>47.5</td>
</tr>
<tr>
<td>Kennedy</td>
<td>24</td>
<td>62.5</td>
</tr>
</tbody>
</table>

In Table IV, the results obtained in the two series, six months after the start of therapy, are compared. The number diminished...
by five because three went on to receive major surgical measures during the follow-up period while two left the hospital against advice and have not been followed.

**TABLE IV**

Results of 18-24 gms. PAS, 6 Months After Beginning of Therapy

<table>
<thead>
<tr>
<th>BMRC</th>
<th>59</th>
<th>27</th>
<th>23</th>
<th>13</th>
<th>43</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kennedy</td>
<td>19</td>
<td>47</td>
<td>32</td>
<td>32</td>
<td>53</td>
</tr>
</tbody>
</table>

There are a number of competent investigators, especially among surgeons,\(^3\) who believe that previous treatment with streptomycin makes major operative procedures more hazardous and more productive of severe complications. Although we cannot agree with the above opinion,\(^4\) there is little doubt that better results are obtained if patients are turned over to the surgeons when they are still amenable to treatment with streptomycin during the operative and post-operative periods. In our group of cases, there were 10 with lesions that, at the start of treatment with PAS alone, appeared as if they would require major surgery. One of these closed his cavities and converted to negative sputum with the aid of pneumoperitoneum and phrenemphraxis. Two patients, failures of previous streptomycin therapy, failed to improve sufficiently with PAS to permit of surgical treatment. Another improved sufficiently clinically that thoracoplasty was approved at Conference, but he refused to accept the operation. The remaining six consisted of two white and four negro patients. In them, four thoracoplasties, one extra-pleural leucite plombage, and one segmental resection and partial thoracoplasty were performed. One of the thoracoplasty cases had a series of massive hemoptyses following the first-stage, and expired,—our first thoracoplasty death in more than four years. Another went AWOL before the series of stages of thoracoplasty were completed. Of the remaining four, two are now persistently negative on concentration. The resection case still has occasional positive smears. One with thoracoplasty still has a residual cavity beneath the thoracoplasty. None of these four had post-operative spreads of disease.

Another observation of interest was the not infrequent emergence of strains of bacilli resistant to PAS, during the course of therapy. In the 19 whose sputa were still positive at the conclusion of therapy, seven (39 per cent) showed bacilli resistant
to at least 10 mg. of PAS per cc. of media, in vitro. Four of these patients, however, had had prior courses of PAS in lower dosage. This increase in resistance of bacilli to PAS may interfere with the later use of combined streptomycin and PAS. Therefore, it would seem that some special consideration or indication should exist to warrant the use of PAS alone.

Acknowledgment: The PAS levels were determined by Frank Schlenker, Ph.D., Chief Biochemist at Kennedy Hospital.

SUMMARY

1) High dosages of PAS are possible in most patients able to take smaller doses, but the side-effects are more common and more troublesome.
2) Increased doses of PAS generally lead to increased blood levels of the drug, but there is marked variation from patient to patient.
3) Large doses of PAS seem to bring about decreased blood levels of prothrombin.
4) The results obtained with the use of high doses of PAS, are not impressive as compared to the use of combined therapy.
5) Use of PAS alone gives rise to strains of bacilli resistant to PAS. This may interfere with the use of combined streptomycin and PAS therapy at a later date.

RESUMEN

1) Dar altas dosis de PAS es posible en la mayoría de los pacientes capaces de tomar dosis más pequeñas, pero los efectos secundarios son más comunes y más molestos.
2) Las dosis altas de PAS generalmente conducen al aumento del nivel sanguíneo de la droga, pero hay marcadas variaciones de un paciente a otro.
3) Las grandes dosis de PAS parecen provocar una disminución del nivel de protrombina en la sangre.
4) Los resultados obtenidos por el uso de altas dosis de PAS no son convincentes, comparando con los que se obtienen por el uso de la terapia combinada.
5) El uso de PAS solo dá origen a cepas de bacilos resistentes al mismo. Esto puede interferir con el empleo posterior de estreptomicina y PAS combinados.

RESUME

1) Les doses élevées de P.A.S. peuvent être utilisées chez la plupart des malades qui sont capables de prendre des doses de moins grande importance. Mais dans ces cas, les inconvénients sont plus fréquents et plus graves.
2) D’une façon générale, l’augmentation des doses de P.A.S. a comme conséquence l’augmentation du taux sanguin de ce produit mais il existe des variations très nettes selon le malade.

3) Les fortes doses de P.A.S. semblent amener une diminution de la prothrombinémie.

4) Les résultats obtenus par l’utilisation de fortes doses de P.A.S. ne sont pas remarquables si on les compare à ceux de l’association P.A.S.-streptomycine.


REFERENCES