Clinical Observations on Viomycin Sulphate
in the Treatment of Tuberculosis*

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Viomycin,** a new antituberculous agent was isolated independently by
Findlay et al.¹ and Bartz and his co-workers² from two actinomycete
believed to be new strains of streptomyces. Streptomyces puncteus and
Streptomyces floridiae have been proposed as the names of these new
strains. The two new strains have not been proven identical, but probably
are.

Numerous investigators including the original workers, Hobby, et al.³
Steenken and Wolinsky,⁴ and Youmans and Youmans,⁵ reported that in
vitro, viomycin had inhibitory activity against Mycobacterium tuberculosis.
It was found to be effective against streptomycin sensitive and streptomycin
resistant organisms in experimental tuberculosis in animals.

The drug was described at the Ninth Streptomycin Conference of the
Veteran's Administration⁶ in April, 1950. Following this announcement five
patients with far advanced pulmonary tuberculosis and without history
of previous antimicrobial therapy were treated with this drug. The purpose
of these early studies was to determine the antimicrobial efficacy and the
chronic toxicity of Viomycin.

These patients received 3 grams of viomycin daily for 13 weeks. In Table
I, it can be seen that proteinuria developed early in treatment in all five
patients. Despite the evidence of small losses of urine albumin in qualitative
determinations (Table I), quantitative determination revealed that from
7.2 to 26.2 grams of protein per liter was lost. Urea clearance tests showed
a diminished rate of clearance for all patients in the third month (Table
II). One patient developed uremia during the last three weeks of treatment
and died four weeks after the drug was discontinued. This patient also
had hypokalemia just prior to the onset of uremia. The urea clearance
tests of four patients showed gradual improvement with discontinuance

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This work was supported in part by a grant from the Shrine Tuberculosis and
Cancer Foundation.
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### TABLE I

**SPECIFIC GRAVITY AND ALBUMIN REPORTED IN A.M. URINE EXAMINATIONS OF FIVE PATIENTS TREATED WITH VIOMYCIN SULPHATE 3G DAILY FOR 13 WEEKS BY WEEKS OF OBSERVATION**

<table>
<thead>
<tr>
<th>Patient</th>
<th>Observation Week</th>
<th>2nd Week</th>
<th>4th Week</th>
<th>6th Week</th>
<th>8th Week</th>
<th>10th Week</th>
<th>12th Week</th>
<th>17th Week</th>
<th>21st Week</th>
<th>42nd Week</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.025</td>
<td>1.018</td>
<td>1.011</td>
<td>1.010</td>
<td>1.015</td>
<td>1.012</td>
<td>1.010</td>
<td>Died</td>
<td>Trace</td>
<td>19th Wk.</td>
</tr>
<tr>
<td></td>
<td>Neg.</td>
<td>2 +</td>
<td>2 +</td>
<td>2 +</td>
<td>1 +</td>
<td>2 +</td>
<td>Trace</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>B</td>
<td>1.018</td>
<td>1.018</td>
<td>1.012</td>
<td>1.012</td>
<td>1.010</td>
<td>1.010</td>
<td>1.010</td>
<td>1.010</td>
<td>1.011*</td>
<td>2 +</td>
</tr>
<tr>
<td></td>
<td>Neg.</td>
<td>Trace</td>
<td>2 +</td>
<td>2 +</td>
<td>1 +</td>
<td>2 +</td>
<td>Neg.</td>
<td>Trace</td>
<td>1.010</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>1.022</td>
<td>1.022</td>
<td>1.023</td>
<td>1.014</td>
<td>1.020</td>
<td>1.016</td>
<td>1.027</td>
<td>1.027</td>
<td>1.018</td>
<td>1.018</td>
</tr>
<tr>
<td>D</td>
<td>1.024</td>
<td>1.010</td>
<td>1.015</td>
<td>1.010</td>
<td>1.016</td>
<td>1.010</td>
<td>1.005</td>
<td>1.015</td>
<td>1.010</td>
<td>Neg.</td>
</tr>
<tr>
<td></td>
<td>Neg.</td>
<td>Trace</td>
<td>1 +</td>
<td>1 +</td>
<td>2 +</td>
<td>Neg.</td>
<td>Trace</td>
<td>Neg.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>E</td>
<td>1.014</td>
<td>1.013</td>
<td>1.013</td>
<td>1.009</td>
<td>1.012</td>
<td>1.010</td>
<td>1.009</td>
<td>1.008</td>
<td>1.007</td>
<td>Trace</td>
</tr>
<tr>
<td></td>
<td>Neg.</td>
<td>Neg.</td>
<td>1 +</td>
<td>2 +</td>
<td>2 +</td>
<td>1 +</td>
<td>Trace</td>
<td>Neg.</td>
<td>Trace</td>
<td></td>
</tr>
</tbody>
</table>

*Patient "B" died in the 30th week of observation.
OBSERVATIONS ON VIOMYCIN SULPHATE

of viomycin. Loss of protein in the urine ceased and no evidences of permanent renal damage occurred.

Figure 1 reveals that viomycin sulfate, 3 grams daily, caused a return of the temperature to normal in all patients, but a return of fever as soon as the drug was discontinued in four out of five patients. In Figure 2 it can be noted that after improvement in the chest roentgenograms during the first two months, spread occurred later during treatment in all but one patient.

On the basis of these studies it was concluded that 3 grams of viomycin sulfate daily had a definite antimicrobial effect, but was too toxic for widespread use in tuberculosis therapy.

Shortly after these studies Tempel reported that viomycin sulfate, 2 grams every three days, could be administered safely to patients in combination with PAS or streptomycin. On the basis of this report it was determined that a group of patients should have viomycin, 2 grams twice

The Mean Weekly Oral Temperatures of 5 Patients

TABLE II: THE RESULTS OF UREA CLEARANCE TESTS IN FIVE PATIENTS RECEIVING 3 GRAMS OF VIOMYCIN DAILY FOR 13 WEEKS

<table>
<thead>
<tr>
<th>Patient</th>
<th>12th Week Per cent</th>
<th>17th Week Per cent</th>
<th>23rd Week Per cent</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>12.5</td>
<td>7.1</td>
<td>Died</td>
</tr>
<tr>
<td>B</td>
<td>36</td>
<td>20</td>
<td>96</td>
</tr>
<tr>
<td>C</td>
<td>30</td>
<td>33</td>
<td>98.5</td>
</tr>
<tr>
<td>D</td>
<td>18.34</td>
<td>20.61</td>
<td>88</td>
</tr>
<tr>
<td>E</td>
<td>17.5</td>
<td>20.45</td>
<td>90.5</td>
</tr>
</tbody>
</table>
weekly and comparable patients should have dihydrostreptomycin in 2 gram twice weekly dosages and that both groups should have sodium PAS, 12 grams daily.

**The Group Studied**

Patients were matched roughly for equivalent types of disease and duration of illness. They ranged from 16 to 53 years of age. No diabetics and none with evidence of renal impairment were included in either group. None of these patients showed severe metabolic deterioration as a result of tuberculosis.

The group reported consists of 35 patients treated with viomycin and PAS. Seven of them had organisms resistant to 100 mcg. of streptomycin prior to selection for treatment. Four were ambulatory.

The control group consisted of 24 treated with streptomycin and PAS. One with no history of previous streptomycin treatment was reported to have organisms resistant to 100 mcg. of streptomycin shortly after treatment.

These patients were treated by whatever other methods which were applicable.

### TABLE III: THE DURATION OF OBSERVATION OF 59 PATIENTS TREATED WITH 2 GRAMS OF VIOMYCIN OR STREPTOMYCIN TWICE WEEKLY AND 12 GRAMS OF SODIUM PAS DAILY

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No. of Patients</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
</tr>
</thead>
<tbody>
<tr>
<td>Viomycin-PAS</td>
<td>35</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>5</td>
<td>3</td>
<td>26</td>
</tr>
<tr>
<td>Streptomycin-PAS</td>
<td>24</td>
<td>0</td>
<td>1</td>
<td>0</td>
<td>9</td>
<td>0</td>
<td>14</td>
</tr>
</tbody>
</table>
**Evidences of Toxicity**

**Signs of Local Toxicity:** Both viomycin sulfate and dihydrostreptomycin were dissolved in proportions of 1 gram to each 2 cc. of distilled water and given intramuscularly, 1 gram in each gluteal muscle twice weekly. Viomycin injected in this dilution caused no unusual complaints of discomfort or local reaction. Minor complaints of local soreness were equally common among both groups.

**Auditory and Vestibular Damage:** After five to six months of treatment, audiograms revealed diminished hearing in six of 23 viomycin treated patients. Three with abnormal audiograms had history of previous streptomycin treatment. The other three had losses of 30 to 60 decibels at 1,024 cycles and above.

Evidence of damage to the vestibular branch of the eighth nerve was shown by loss of response to caloric stimulation in three of 10 patients treated with viomycin. Two of them were known to have received previous...
### TABLE IV
THE RESPONSE TO VIOMYCIN OF SEVEN PATIENTS RESISTANT TO STREPTOMYCIN
Two grams Viomycin Sulfate Twice Weekly, 12 grams Sodium PAS Daily

<table>
<thead>
<tr>
<th>Patient</th>
<th>Initial Temperature</th>
<th>Temperature After One Month</th>
<th>Tendency of Weight Before Viomycin Therapy</th>
<th>Viomycin Weight</th>
<th>Weight After Two Months Viomycin Therapy</th>
<th>Tendency Before Viomycin Therapy</th>
<th>X-Ray Changes by Months</th>
<th>Prognosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>A.T.</td>
<td>100</td>
<td>98.6</td>
<td>L</td>
<td>165</td>
<td>157</td>
<td>W</td>
<td>I I I S</td>
<td>Improved</td>
</tr>
<tr>
<td>L.G.</td>
<td>98.6</td>
<td>98.6</td>
<td>S</td>
<td>89</td>
<td>91</td>
<td>W</td>
<td>S S I S</td>
<td>Improved</td>
</tr>
<tr>
<td>J.A.</td>
<td>98.6</td>
<td>98.6</td>
<td>S</td>
<td>81</td>
<td>88</td>
<td>W</td>
<td>I S I S</td>
<td>Improved</td>
</tr>
<tr>
<td>E.L.</td>
<td>98.6</td>
<td>98.6</td>
<td>S</td>
<td>116</td>
<td>117</td>
<td>S</td>
<td>S S S S</td>
<td>Improved (to surgery)</td>
</tr>
<tr>
<td>D.L.</td>
<td>98.6</td>
<td>98.6</td>
<td>S</td>
<td>91</td>
<td>98</td>
<td>W</td>
<td>I W S S</td>
<td>Improved</td>
</tr>
<tr>
<td>A.R.</td>
<td>100</td>
<td>98.6</td>
<td>S</td>
<td>92</td>
<td>99</td>
<td>W</td>
<td>I S S W</td>
<td>Improved</td>
</tr>
<tr>
<td>S.S.</td>
<td>100</td>
<td>98.6</td>
<td>S</td>
<td>120</td>
<td>123</td>
<td>W</td>
<td>S S S I</td>
<td>Improved</td>
</tr>
</tbody>
</table>

**Code:**
- **W** = Worse
- **S** = Stable
- **I** = Improved
- **L** = Losing
courses of streptomycin. In the streptomycin treated group nine of 26 tests were positive. Seven of these had no previous streptomycin treatment.

Renal Toxicity: In neither group have we observed abnormalities in the urine specific gravity, non protein nitrogen, plasma proteins, or electrolyte balance. No tendency to excrete protein in the urine has been observed. Although reports of a trace of albumin were given for four patients in the third and fourth months, they could not be confirmed on re-examination.

Allergic Sensitivity: Up to April 15, 1952, no signs of allergic sensitivity were noted in either group. About this time eight viomycin treated patients complained of angioneurotic edema, a generalized urticarial rash and
itching and burning at the site of injection. All of them experienced these symptoms within 24 hours after the injection.

All on viomycin were then changed to a new lot. No recurrence of these allergic symptoms were observed with the new lot of the drug.

Allergic sensitivity to streptomycin did not occur.

**Patients Resistant to Streptomycin**

For the seven patients initially resistant to streptomycin on starting viomycin treatment, the drug appeared clinically effective (Table IV). One improved sufficiently to have right pneumonectomy in the sixth month of treatment. Four still had organisms resistant to 100 mcg. of streptomycin after six months of viomycin treatment. The three other patients had negative cultures at this time.

**Bacterial Resistance to Viomycin**

Of 35 patients placed on viomycin, 25 had organisms sensitive to 5 mcg. of viomycin at the beginning of treatment. Nine had negative cultures of whom three had later cultures sensitive to 5 mcg. One was reported sensitive to 50 mcg. but not to 25 mcg. initially but in the third month of treatment was culture negative.

Out of 15 viomycin treated patients with five month culture reports, eight had negative cultures. Of the seven positive, six were sensitive to 5.0 mcg., and one is sensitive to 12.5 mcg. None of seven cultures positive patients became resistant to streptomycin.

**Sputum Conversion**

The sputum concentrates of streptomycin treated patients became negative more frequently in the early months of treatment and tended to remain so (Figure 3). Negative sputum concentrates were less frequent and less persistent among the viomycin treated patients (Figure 4).

Cultural results are not significant because of the large number not reported in the later months of observation.

**X-ray Improvement or Stability**

X-ray clearing of exudative lesions seemed more striking with streptomycin treatment (Figures 5 and 6). Viomycin treated patients showed definitive improvement but less frequently and less strikingly.

**Ambulatory Patients**

Four ambulatory patients receiving viomycin and PAS showed clinical improvement after six months of therapy. Three of them had moderate improvement of recent exudative spread and one showed healing of a tuberculous sinus of four years duration. Sputum was negative in all four at the beginning of treatment and remained so throughout the study.

**Clinical Improvement**

As already stated, seven patients having streptomycin resistant organisms showed clinical improvement with 2 grams of viomycin given twice weekly and 12 grams of PAS given daily (Table IV).
Staff opinions of the clinical effectiveness of viomycin rate it below streptomycin and better than PAS alone.

The influence of the drug on the systemic symptoms of tuberculosis is difficult to evaluate from this series. Fever was present initially in 11 of the viomycin treated patients. It became normal for all from two to six weeks after starting therapy. In 11 febrile streptomycin treated patients temperatures became normal in from one to four weeks. Body weight increased under treatment in both groups. There was little difference in the rate of weight gain between the two groups.

SUMMARY

1) Viomycin in doses of 2 grams twice weekly combined with 12 grams of PAS daily is of slight toxicity.

2) Tinnitus may be expected to occur. Allergic symptoms have not been a major problem. Auditory nerve damage of a serious degree is not frequent.

3) Streptomycin resistant organisms are affected by viomycin and patients having such organisms improve under intermittent viomycin treatment.

4) Bacterial resistance to viomycin did not develop to a significant degree among patients treated for six months.

5) Clinical and x-ray improvement is more striking in streptomycin-PAS treated patients, however, the effectiveness of viomycin-PAS is definite and demonstrable.

6) The clinical use of viomycin is feasible in the presence of streptomycin resistant organisms, and allergic sensitivity to streptomycin. Its use with newer antimicrobials should be explored.

RESUMEN

1) La viomicina a la dosis de dos gramos dos veces por semana combinada con 12 gramos de PAS diariamente, es de ligera toxicidad.

2) Tinnitus puede ocurrir. Los síntomas alérgicos, no han sido un problema de consideración. El daño al nervio auditivo en grado serio no es frecuente.

3) Los organismos estreptomicino-resistentes, son afectados por la viomicina y los enfermos que tienen tales organismos, mejoran bajo la tratamiento intermitente de viomicina.

4) Entre los enfermos tratados durante seis meses, no se desarrolló al viomicino-resistencia en grado significante.

5) La mejoria clínica y radiológica, es más notable en los enfermos tratados con estreptomicina-PAS; sin embargo, la efectividad de la viomicina es definida y demostrable.

6) El uso clínico de la viomicina, es practicable en presencia de organismos estreptomicino-resistentes y ante la sensibilidad alérgica la estreptomomicina. Su uso con los más recientes antibióticos, debe investigarse.

RESUME

1) La viomycine à la dose de deux grammes, deux fois par semaine, associée à 12 grammes de P.A.S. par jour est de faible toxicité.
2) Des tintements d'oreille peuvent apparaître. Il n'y à pas de problème majeur posé par des signes d'intolérance. Les atteintes graves du nerf auditif ne sont pas fréquentes.

3) La viomycine agit sur les microbes résistants à la streptomycine. Les malades porteurs de tels bacilles sont améliorés lorsqu'ils sont soumis au traitement par la viomycine.

4) Il n'apparait pas un degré important de résistance bactérienne à la viomycine chez les malades traités pendant six mois.

5) L'amélioration clinique et radiologique est plus frappante pour les malades traités par la streptomycine et le P.A.S. bien que l'action de la viomycine associée au P.A.S. est certaine et peut être démontrée.

6) L'utilisation clinique de la viomycine est efficace dans les cas où les bacilles sont streptomycino-résistants, ou lorsque les malades sont intolérants à la streptomycine. Son action devrait être étudiée en conjonction avec les nouveaux produits antimicrobiens.

REFERENCES


6 Proceedings of the 9th Streptomycin Conference (V. A.), April, 1950.