"Gatalone" in the Treatment of Pulmonary Tuberculosis*

EUGENE J. DES AUTELS, M.D., F.C.C.P., KARL H. PFUETZE, M.D., F.C.C.P.
JAMES R. ZVETINA, M.S., CHARLOTTE A. COLWELL, Ph.D.
ADELINE R. HESS, M.S., and CLIFTON J. WOODS, M.S.

Hines, Illinois

Soon after a new compound d-glucuronolactone isonicotinyl hydrazone ("Gatalone"; INH-G) was synthesized by Passedouet et al1 and independently by Sah,2 the drug was reported to be highly active against tubercle bacilli and to be much less toxic than isoniazid on a weight for weight basis.1, 3, 4, 5, 6 Early reports of its effectiveness in human tuberculosis seemed to justify further clinical trials.

This study was primarily planned to investigate the potential toxicity and anti-tuberculous activity of "Gatalone"** in the treatment of pulmonary tuberculosis. Simultaneously, the Bacteriology Section of the Research Service of this hospital undertook a study of the bacteriologic aspects including the emergence of bacterial resistance to the drug, cross resistance with isoniazid, and plasma concentrations of the drug.7

At the time this study was started, the authors were convinced isoniazid should not be given alone. Consequently, they did not randomize and concurrently treat a comparable group of patients with isoniazid alone.

Clinical Material

Eleven patients with pulmonary tuberculosis were selected for this study (Table I). All were male veterans ranging from 27 to 57 years of age. Eight of the 11 were less than 40 years of age. Six were white and five were Negro. Their weights ranged from 116 to 149 pounds (52.7 to 67.7 Kg.) at the start of treatment.

Before treatment, the chest roentgenograms of all cases were interpreted as consistent with a considerable component of exudative infiltration which was considered likely to respond to effective anti-tuberculous chemotherapy. The disease was far advanced in nine cases and moderately advanced in two. The lesions were bilateral in six and unilateral in five. Cavities were present in all. The diameter of the cavities were one centimeter in two and ranged from three to seven centimeters in nine.

The known duration of symptoms, before beginning treatment was less than six months in eight cases, nine months in one, and one year or more

---

*From the Tuberculosis and Research Services, Veterans Administration Hospital, Hines, Illinois.
**Generously supplied by Barnes-Hind, Inc., San Francisco, California.
in two. No patient had previously received antimicrobial therapy for tuberculosis. None received any form of collapse therapy during the period of this study.

Treatment regimen: All patients were started on 400 mgms. of “Gatalone” four times daily by mouth and were continued on treatment for at least six months. However, the dosage was reduced to 1200 mgms. daily in two during the fifth (No. 3) and third (No. 11) months of treatment because of severe (No. 3) and moderate (No. 11) peripheral neuropathy. The dosage of 1600 mgms. of “Gatalone” contained the equivalent of approximately 732 mgms. of isoniazid, or 10.6 to 13.9 mgms. of isoniazid per kilogram of body weight daily.

Results of Treatment

Clinical response. Lessening of cough and expectoration, defervescence of fever, gain in weight and improvement of general condition was noted in all patients (Fig. 1). However, relapse of symptoms occurred during the fifth (No. 7) and sixth (No. 8) months of therapy in two cases. Cough was absent in two cases (No. 2 and No. 10) before treatment, disappeared in four, diminished to slight in three, and improved then worsened when relapse occurred in two (No. 7 and No. 8). The average quantity of expectoration diminished by two-thirds, but two patients (No. 7 and No. 8) again raised larger amounts upon relapse. Temperatures were between 100 and 103 degrees before treatment in nine cases, and subsided to normal in all (usually within two months); however, fever recurred in the two that relapsed. Two were afebrile before treatment and remained so. All gained weight ranging from five to 38 pounds (average 23.6 pounds).

Roentgenographic changes. At the end of six months of treatment x-ray films revealed marked improvement in three cases (Fig. 2), moderate im-

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Age</th>
<th>Race</th>
<th>Dur. of Symptoms</th>
<th>General Condition</th>
<th>Stage of Disease</th>
<th>Cavity Size (Cm.)</th>
<th>Distrib. of Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>36</td>
<td>W.</td>
<td>2 Yrs.</td>
<td>Fair</td>
<td>F.A.</td>
<td>L: 6.0</td>
<td>Unilat.</td>
</tr>
<tr>
<td>2</td>
<td>27</td>
<td>N.</td>
<td>Recent</td>
<td>Good</td>
<td>M.A.</td>
<td>L: 1.0</td>
<td>Unilat.</td>
</tr>
<tr>
<td>3</td>
<td>44</td>
<td>N.</td>
<td>2 Wks.</td>
<td>Fair</td>
<td>F.A.</td>
<td>L: 1.0</td>
<td>Unilat.</td>
</tr>
<tr>
<td>4</td>
<td>57</td>
<td>W.</td>
<td>1 Yr.</td>
<td>Fair</td>
<td>F.A.</td>
<td>L: 7.0</td>
<td>Bilat.</td>
</tr>
<tr>
<td>5</td>
<td>47</td>
<td>W.</td>
<td>2 Mos.</td>
<td>Fair</td>
<td>F.A.</td>
<td>L: 3.0</td>
<td>Bilat.</td>
</tr>
<tr>
<td>6</td>
<td>36</td>
<td>W.</td>
<td>5 Mos.</td>
<td>Poor</td>
<td>F.A.</td>
<td>L: 6.0</td>
<td>Bilat.</td>
</tr>
<tr>
<td>7</td>
<td>33</td>
<td>N.</td>
<td>3 Mos.</td>
<td>Fair</td>
<td>F.A.</td>
<td>R: 3.0</td>
<td>Bilat.</td>
</tr>
<tr>
<td>8</td>
<td>29</td>
<td>W.</td>
<td>Recent</td>
<td>Fair</td>
<td>F.A.</td>
<td>R: 3.0</td>
<td>Unilat.</td>
</tr>
<tr>
<td>9</td>
<td>33</td>
<td>N.</td>
<td>1 Mo.</td>
<td>Fair</td>
<td>F.A.</td>
<td>R: 4.0</td>
<td>Unilat.</td>
</tr>
<tr>
<td>10</td>
<td>34</td>
<td>W.</td>
<td>6 Mos.</td>
<td>Good</td>
<td>M.A.</td>
<td>R: 3.0</td>
<td>Bilat.</td>
</tr>
<tr>
<td>11</td>
<td>39</td>
<td>N.</td>
<td>9 Mos.</td>
<td>Fair</td>
<td>F.A.</td>
<td>L: 5.0</td>
<td>Bilat.</td>
</tr>
</tbody>
</table>
provement in three, slight improvement in three, and worsening in two (No. 7 and No. 8) at the fifth and sixth months respectively (Fig. 3). CAVities were present in all cases before treatment but were lost to view in two cases (both one centimeter in diameter before treatment), reduced in size in four, remained unchanged in three, became larger in one (No. 7) and, in the remaining case (No. 5) the cavity became filled ("blocked").

Bacteriologic response. At the end of six months of treatment, repeated examinations of 24 hour sputum concentrates by smear failed to reveal tubercle bacilli in five of 11 cases. However, only three (Nos. 2, 5, 10) were negative by culture (three consecutive negative cultures), or a conversion rate of 27.3 per cent.

In summary, improvement in general conditions, decrease of cough and expectoration, defervescence of fever and gain in weight was reminiscent of improvement seen in patients who received isoniazid alone as their original course of anti-tuberculous chemotherapy. Moderate and marked roentgenographic improvement was observed in six of the 11 cases (54.5 per cent) and sputum conversion rate was 27.3 per cent. Two patients (No. 7 and No. 8) suffered clinical, roentgenologic and bacteriologic relapse.

Toxicity of Gatalone

Seven patients (63.6 per cent) complained of numbness and tingling of their hands and feet, usually late in the second month of therapy. These symptoms were mild in five cases, and were controlled by the administration of 300 to 450 mg. of vitamin B-6 daily. In two, moderate (No. 11) and severe (No. 3) symptoms were not controlled by vitamin B-6 until the dosage of "Gatalone" was reduced to 1200 mg. daily.

Four patients developed slight rash. There was no evidence of toxicity attributable to the renal, hepatic or hemopoietic system. Treatment was not discontinued because of drug toxicity in any case.

Summary of Clinical Results in Eleven Cases of Pulmonary Tuberculosis

At the end of six months of treatment with "Gatalone"

<table>
<thead>
<tr>
<th>CASE NUMBER</th>
<th>TEMP</th>
<th>WEIGHT</th>
<th>SPUTUM</th>
<th>SYMPTOMS AT START</th>
<th>BACTERIOLOGIC CONVERSION</th>
<th>PERIPHERAL NEUTROPHIL</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>8</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>9</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>11</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Figure 1
Discussion

This study was undertaken for the purpose of investigating the antituberculous effect and potential toxicity of "Gatalone." When comparing the effectiveness and toxicity of this drug with that of isoniazid, one must recall that approximately 45.76 per cent of the molecular weight of "Gatalone" is accounted for by the isoniazid portion of its chemical structure.7 Other material factors are the comparative dosages per kilogram of body weight and the duration of treatment (or time period) at the time comparisons are made. There are valid objections to comparing our "Gatalone"-treated cases with those treated with isoniazid alone by other investigators at different times. Undoubtedly, there were differences in criteria for selection of cases, background factors, host factors, etc. Interpretations of serial roentgenograms and other elements may differ with different observers at the same time and the same observer at different times. However, when this study was started, the authors were convinced that isoniazid should not be used alone, and purposely refrained from randomizing and concurrently treating a comparable group of patients with isoniazid. Many informative reports concerning drug therapy of tuberculosis have likewise drawn comparisons between series of patients who were treated differently at different times by the same investigators, as well as at the same or different times by different investigators. Obviously, the comparison of results would be more valid were the patients selected according to strict criteria, randomized, and concurrently treated on the different drug regimens under comparison.

At the start of treatment, weights of the 11 patients ranged from 52.7 to 67.7 kilograms. The dosage of "Gatalone" was 1600 mgms. daily containing the equivalent of 732 mgms. of isoniazid, or 10.8 to 13.9 mgms.

FIGURE 2—Case 2: (E. A.) Marked roentgenographic improvement at the end of six months of treatment with INH-G.
per kilogram of body weight. Since all patients gained weight there was some corresponding reduction in the dosage per kilogram of body weight during treatment.

Substantial (moderate and marked) roentgenographic improvement was observed in six of 11 patients (54.5 per cent) by the end of six months of treatment with “Gatalone.” Within limits imposed by the small number of cases treated, this compares reasonably well with the incidence of substantial roentgenographic improvement reported in cases treated with 150 and 300 mgms. of isoniazid daily for five to eight months (38.0 per cent), 8 28 weeks (50.6 per cent), 9 28 weeks (43.1 per cent), 10 and in patients who completed six months of treatment on a dosage of 5.0 mgms. of isoniazid per kilogram of body weight daily (55.1 per cent). 14 (See Table II). Mount and his associates (USPHS Cooperative Study) 9, 10 found no statistically significant difference in the frequency of substantial roentgenographic improvement, whether isoniazid was given alone or in combination with 12.0 grams of PAS daily, or with one gram of streptomycin twice weekly. Mount and Ferebee 11, 12 again reported no statistically significant difference in the frequency of substantial roentgenographic improvement at 20 weeks 11 or at 32 weeks 12 between patients who received 3.0 and 10.0 mgms. of isoniazid per kilogram of body weight daily in combination with 12.0 gms. of PAS daily, or 1.0 gm. of streptomycin twice weekly; or when 10.0 mgms. of isoniazid per kg. of body weight was given concurrently with streptomycin plus PAS.

Thus, in the above reports and in this small series of “Gatalone”-treated cases there was little indication that higher dosages of isoniazid as such or in the form of “Gatalone,” were more effective than 300 mgms. of isoniazid daily (in terms of substantial roentgenographic improvement); or that “Gatalone” had chemotherapeutic value aside from its content of isoniazid.

Since the dosage of “Gatalone” administered (1600 to 1200 mgms.) contained the equivalent of 732 to 549 mgms. of isoniazid, and since 150 mgms. of isoniazid seemed to be approximately as effective as higher dosages in the usual case of tuberculosis, 8, 9, 10, 11, 12 the authors could neither confirm

<table>
<thead>
<tr>
<th>Reference</th>
<th>Drug</th>
<th>Daily Dosage</th>
<th>Substantial X-ray Improvement Per Cent</th>
<th>Time-Period of Evaluation</th>
</tr>
</thead>
<tbody>
<tr>
<td>V.A. SM Conf.*</td>
<td>INH</td>
<td>150 and 300 mgms.</td>
<td>38.0</td>
<td>5-8 Mos.</td>
</tr>
<tr>
<td>Mount et al</td>
<td>INH</td>
<td>150-300 mgms.</td>
<td>50.6</td>
<td>28 Wks.</td>
</tr>
<tr>
<td>Mount et al</td>
<td>INH</td>
<td>150-300 mgms.</td>
<td>43.1</td>
<td>28 Wks.</td>
</tr>
<tr>
<td>Deuschle et al</td>
<td>INH</td>
<td>5 mg./Kg. body weight</td>
<td>55.1</td>
<td>6 Mos.</td>
</tr>
<tr>
<td>Present Authors</td>
<td>INH-G</td>
<td>1600 Mgms.*</td>
<td>54.5</td>
<td>6 Mos.</td>
</tr>
</tbody>
</table>

*Equivalent to 10.8 to 13.9 mgms. of isoniazid per kilogram of body weight daily.
nor deny the claim that weight for weight "Gatalone" was as effective as isoniazid. Concurrent treatment of two comparable groups of patients with 150 mgms. of "Gatalone" and with 150 mgms. of isoniazid might shed more light upon this point. In-vitro studies did not confirm the claim of equal effectiveness of the two drugs on a weight for weight basis but rather indicated that the activity of "Gatalone" depended primarily upon its content of isoniazid.7

Peripheral neuropathy developed in six of the 11 patients (54.5 per cent) by the third month and in seven (63.6 per cent) by the end of four months of treatment with 1600 mgms. of "Gatalone" daily (containing the equivalent of 10.8 to 13.9 mgms. of isoniazid per kilogram of body weight). Ferebee and Mount11 reported peripheral neuropathy appeared in 3.4 per cent of a large group of patients who received 10 mgms. of isoniazid per kilogram of body weight daily for 12 weeks or longer. Deuschle et al11 saw no instance of neuropathy among 32 patients who received five mgms. of isoniazid per kilogram of body weight daily for one year. Biehl et al14, 15 noted evidence of peripheral neuropathy in 8 per cent, 18 per cent, and 44 per cent of their patients who received six to 10, 11 to 15, and 16 to 24 mgms. of isoniazid per kilogram of body weight daily. Hughes et al,16 and Biehl and his associates14, 15 found the incidence of peripheral neuritis was higher among those who excreted more free isoniazid and less acetylated isoniazid, especially among those who excreted substantial amounts of another unidentified breakdown product of isoniazid. They also found that the acetylated form of isoniazid was essentially inactive against tubercle bacilli. Demoen et al17 reported that INH-G was largely excreted as such or as free INH, and that only a small fraction was excreted in acetylated form. The relatively high incidence of peripheral neuropathy

FIGURE 3—Case 8: (J. G.) Moderate roentgenographic worsening at the end of six months of treatment with INH-G.
Vol. XXIX  "GATALONE" IN PULMONARY TUBERCULOSIS 363

among our patients may be explained on the basis of much less acetylation (detoxification) of INH-G due to the possible blocking action of D-glucuronolactone. Among our patients treated with 1600 mgms. of INH-G daily (containing the equivalent of 10.8 to 13.9 mgms. of INH per kilogram of body weight), the incidence of peripheral neuropathy was actually higher (63.6 per cent) than the incidence reported by others (18 per cent) among patients treated on a dosage of 11 to 15 mgms. of INH per kilogram of body weight daily. However, the element of chance is relatively high in our small series of cases.

The authors believe "Gatalone" should be tried at lower dosages containing the equivalent of three to five mgms. of isoniazid (approximately six to 10 mgms. of "Gatalone") per kilogram of body weight daily. This dosage of "Gatalone" may contain sufficient isoniazid to be approximately as effective as higher dosages in the treatment of the usual case of pulmonary tuberculosis; and the incidence of toxicity might be considerably reduced. As is presently the general impression with isoniazid, it would seem consistent to recommend that, if possible, "Gatalone" should be used in combination with other anti-tuberculous drugs rather than alone.

If INH-G is predominately excreted in active forms INH-G and free isoniazid, rather than in the inactive acetylated form as is INH, it would seem desirable to investigate the possibility that INH-G may be more effective than INH in the treatment of renal and urologic tuberculosis.

SUMMARY

Eleven patients with pulmonary tuberculosis were treated with high dosages of "Gatalone" (usually 1600 mgms. daily) for a period of six months or longer.

At the end of six months of treatment symptomatic response was very favorable and substantial roentgenographic improvement was observed in six cases (54.5 per cent). The incidence of cavity closure was 27.3 per cent and the sputum conversion rate on three or more consecutive cultures was also 27.3 per cent.

Findings attributed to peripheral neuropathy appeared in seven patients (63.6 per cent). Whereas, weight for weight "Gatalone" may be less toxic than isoniazid, results in this small series suggest that isoniazid given in the form of "Gatalone" is no less toxic than isoniazid per se on a therapeutic dosage basis.

There was no indication that the higher dosages of isoniazid given in the form of "Gatalone" were more effective than 300 mgms. of isoniazid daily in the usual case of pulmonary tuberculosis; nor that "Gatalone" had chemotherapy virtue aside from its content of isoniazid.

SUMARIO

Once pacientes con tuberculosis pulmonar fueron tratados con altas dosis de "Gatalone." La dosis generalmente administrada fue de 1600 miligramos por día por un período de no menos de seis meses.

Al cabo de seis meses de tratamiento, la respuesta sintomática fue muy favorable y se notó una mejoría sintomatológica y radiográfica en seis de
los casos (54.5%). También se observó el colapso de las cavidades en 27.3% de los casos. La desaparición de bacilos en tres o más cultivos fue observada en 27.3% de los casos.

En siete pacientes (63.6%) se observaron trastornos neuropáticos periféricos. Aunque "Gatalone" es quizás menos tóxica que la isoniazida en iguales dosis, los resultados obtenidos en esta pequeña serie nos hace creer que la isoniazida administrada en la forma de "Gatalone" no es menos tóxica que la isoniazida propia, si se compara desde el punto de vista de dosis.

No se puede concluir que la "Gatalone" en las dosis administradas fue más efectiva que 300 mgs. de isoniazida par día en los casos corrientes de tuberculosis pulmonar, ni tampoco se ha podido cerciorar que "Gatalone" tiene poderes terapéuticos otros que los debido a su contenido en isoniazida.

RESUME

Onze malades atteints de tuberculose pulmonaire furent traités par de hautes doses de "gatalone" (généralement 1.600 mmgr. par jour) pendant une période de six mois ou davantage.

A la fin de ces six mois, les symptômes s'améliorèrent beaucoup et des progrès radiologiques marqués furent observés dans six cas (54.5%). La fréquence de la fermeture des cavités fut de 27.3% et le pourcentage de négativations des crachats sur trois cultures ou davantage fut également de 27.3%.

Des constatations attribuées à une atteinte nerveuse périphérique apparurent chez 7 malades (63.6%). Bien qu'à poids égal, le "gatalone" peut être moins toxique que l'isoniazide, les résultats que les auteurs ont obtenus dans leur petite série font penser que l'isoniazide donné sous forme de "gatalone" n'est pas moins toxique que l'isoniazide lui-même si on tient compte d'unités pondérales équivalentes.

Les auteurs n'ont pas eu l'occasion de remarquer que de plus hautes doses d'isoniazide données sous forme de gatalone seraient plus efficaces que les 300 mmgr. d'isoniazide quotidiennement administrés dans les cas habituels de tuberculose pulmonaire. Ils n'ont pas noté non plus que le "gatalone" ait une vertu chimiothérapeutique propre en dehors de celle de l'isoniazide qu'il renferme.

ZUSAMMENFASSUNG

11 Patienten wurden mit hohen Dosierungen von "Gatalon" (gewöhnlich 1600 mgr täglich) während eines Zeitraumes von sechs Monaten und länger behandelt.

Am Ende der sechs Behandlungsmonate war der symptomatische Erfolg sehr günstig, und in 6 Fällen (54.5%) wurde eine greifbare röntgenologische Besserung beobachtet. Zum Kavernenschluss kam es in 27,3% der Fälle, und die Sputum-Konversion betrug nach drei oder mehr aufeinanderfolgenden Kulturen ebenfalls 27,3%.

Befunde, die der peripheren Neuropathie zuzuschreiben waren, traten bei 7 Patienten (63,6%) auf. Demgegenüber mag eine der Isoniaziddosierung entsprechende Medikation von "Gatalon" weniger toxisch sein als reines Isoniazid. Die Ergebnisse dieser kleinen Versuchsreihe lassen
vermuten, dass Isoniazid, in Form von "Gatalon" verabreicht, nicht weniger toxisch ist als Isoniazid in therapeutischer Dosierung.

Es zeigte sich, dass die höhere Dosierung des Isoniazid im "Gatalon" nicht wirksamer war als die tägliche Gabe von 300 mgr Isoniazid, die bei der gewöhnlichen Lungentuberkulose erforderlich ist; ausserdem zeigte sich, dass die Wirksamkeit des "Gatalon" lediglich auf seinem Isoniazid-Anteil beruht.

REFERENCES


