DISEASES of the CHEST

VOL. XVIII  DECEMBER 1950  NUMBER 6

Tibione: Laboratory and Clinical Studies*

J. DWIGHT DAVIS, M.D., F.C.C.P., SOLOMON NETZER, M.D., F.C.C.P.,†
JOSEPH A. SCHWARTZ, M.D., F.C.C.P. and
ERIC H. PATTISON, M.D.

Van Nuys, California

Tibione has been described as one of the new potent specific therapeutic agents against M. tuberculosis. This statement is based upon reports from the German literature and a single observation by competent American physicians, who feel that the drug has merit, but needs further investigation before affirming or denying its chemotherapeutic value.

The chemical is a ring compound, thiosemicarbazone which was synthesized by Behnisch and Schmidt¹ for the Bayer Company, and investigated clinically by Domagk² and other German workers. Among the German workers, the therapeutic indications were summarized by Mertens and Bunge.³ Fresh pulmonary infiltrations and spreads responded best. There was evidence of healing in ulcerative lesions of the oral cavity and larynx. Improvement was noted in tuberculosis of the gastro-intestinal tract and lymph nodes. The drug was found to be ineffective in miliary tuberculosis, tuberculous meningitis, and idiopathic pleural effusion. In all of the papers which were reviewed by us from the German literature, no notation was made of toxicity, other than in a minor degree. Results of therapy were based on varying sized daily doses from 12 mgm. to 300 mgm. and in which the drug was given for varying periods of time up to nine months.

*Presented before the Los Angeles County Trudeau Society, May 23, 1950.
†Chief, Tuberculosis Service, San Fernando Veterans Administration Hospital, San Fernando, California.

From the Pulmonary Disease Service of the Birmingham Veterans Administration Hospital, Van Nuys, California, and San Fernando Veterans Administration Hospital, San Fernando, California.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

Copyright, 1950, by the American College of Chest Physicians
In 1949, Drs. H. Corwin Hinshaw and Walsh McDermott reviewed the results in 10 German institutions of two thousand patients who had received thiosemicarbazone therapy. Their recommendation, as a result of this study, was that a prompt and thorough series of experimental and clinical trials to be held in the United States. Several hospitals were designated by the Eighth Streptomycin Conference of the Veterans Administration, held in Atlanta, Georgia, in November 1949, to test the toxicity and to determine if resistance of M. tuberculosis develops to tibione.

The veterans hospitals of Birmingham and San Fernando were two of the hospitals so designated and 42 patients were treated here by the oral administration of tibione. The following report is based on therapy for 120 days.

Of the 42 patients treated, 29 had streptomycin resistant tubercle bacilli and this group received 200 mgms. of tibione daily. In the remaining 13 patients, the organisms were still sensitive to streptomycin and the patients therefore received 1 gram of streptomycin plus 200 mgms. of tibione daily. Most of the patients of this study belonged to the older age group and were selected because they had chronic disease and would be apt to have persistent positive sputum.

**Method of Administration**

Tibione was administered for the first week in 50 mgm. daily doses, second week 100 mgm. daily doses (50 mgm. twice daily, at breakfast and supper), and 200 mgm. from the third week on (100 mgm. twice daily, at breakfast and supper). The treatment was continued for 120 days.

**Toxic Manifestations**

**Gastro-Intestinal Disturbances:** Of the 29 patients receiving tibione alone, 10 had nausea and anorexia. Five had vomiting enough to temporarily discontinue the drug, and then went on uneventfully to finish the course.

One patient had persistent vomiting, starting with the smallest dose, 50 mgms. daily. This toxic manifestation persisted with all doses. The patient became so ill that the drug was permanently discontinued at the beginning of the fourth week.

Among the 13 patients who received streptomycin and tibione, six had nausea and anorexia. Two of these cases also had vomiting severe enough to temporarily discontinue tibione for one week. These two patients were able to return to a full dosage schedule without further gastro-intestinal disturbance.

Of the eight patients in whom vomiting occurred, this symptom developed during the third week in six, or when they were first
placed on the full 200 mgm. dose of tibione. The one mentioned above developed persistent vomiting with 50 mgms. of tibione. The eighth case developed persistent vomiting on the third week, and on restarting, could only tolerate 100 mgms.

Vertigo: Vertigo, as expected, was only present in those patients receiving combined therapy. Six of the 13 patients had severe vertigo, beginning in the third week in two, and in the seventh to the tenth weeks in the remaining four.

This vertigo was so severe and serious that it was thought advisable to discontinue permanently the streptomycin in three patients. The cold caloric test in these three patients was diminished in one, and normal in two.

The fact that so many patients in this small series had to have the streptomycin discontinued, seemingly points to an enhanced toxicity of streptomycin when used with tibione. However, the average age of this group was 48 years. It has been recognized that older persons under streptomycin therapy develop vestibular changes more rapidly and severely than younger patients.

Dermatitis: In only five patients of the entire 42 was dermatitis noted. In three, it was a mild transient macular rash which disappeared spontaneously in two to four weeks following its appearance. It caused no discomfort.

In two patients, the rash was persistent. In each case, the lesion was an exfoliative dermatitis which occurred in one on the 21st day, and in the other at the completion of his course of therapy. The drug had to be stopped in the former case. There was no concomitant eosinophilia. One patient was on combined streptomycin and tibione therapy and the other received tibione alone.

The first patient who was receiving combined therapy noted at the end of the third week a severe rapidly-spreading generalized erythematous macular rash. It appeared first over the chest and abdomen and spread rapidly over the back, arms, legs, and some to the face. This rash had somewhat the appearance of that produced by streptomycin. The streptomycin was withdrawn, but the rash continued as previously. The patient was then replaced on streptomycin and tibione was discontinued. The rash disappeared in one week, leaving only a dry, scaly skin. After two weeks, during which the patient was receiving only streptomycin, 1 gram daily, a 50 mgm. tablet of tibione was given. Within two hours a re-crudescence of the erythematous macular rash occurred.

Laboratory Observations

The patients while observed had frequent blood, urine, and liver function tests at regular intervals. Among the liver function tests, the cephalin flocculation and thymol turbidity tests remained
normal throughout the course of therapy in 41 patients. One had a transitory rise in thymol turbidity to 6 units. The bromsulfalein absorption test showed abnormal findings in one instance in each of five patients. In these five patients, an icteric index was found normal at the time of the abnormal bromsulfalein absorption. Jaundice was not observed in any of the 42 persons studied.

At the Veterans Administration Hospital, Minneapolis, Minn., Dr. A. Falk had eight instances where there was a bromsulfalein retention. He did liver biopsies on five of them and found fatty infiltration in the liver specimens.

In analyzing the blood changes during therapy, in 17 patients, the hemoglobin and red blood count showed a slight reduction. In all but three instances, the reduction could be explained to be within the limits of laboratory error. In the three cases mentioned, the red blood count was reduced approximately by a million red blood cells per cu. mm. There was comparable lowering of the hemoglobin in these cases. In the first mentioned, transfusions were required to counteract the severe anemia.

At the Ninth Streptomycin Conference, the Veterans Administration Hospital, Livermore, California, reported that in their cases who developed anemia while being treated with tibione, they performed sternal marrow punctures. Hypoplasia of the marrow was demonstrated in these specimens.

The white blood counts remained appreciably unchanged. In one instance, the total count remained the same, but in the differential count, there was a drop in granulocytes from 67 to 37 per cent. There were two instances of transitory eosinophilia of 7 and 14 per cent.

Symptomatic Changes

Without giving leading questions, the patients were interviewed frequently. Nineteen of the 42 noted a decrease in cough. In 10, the reduction occurred in those receiving tibione alone. In nine of the 13 patients under combined therapy, a notable decrease in cough occurred. In most of them, the decrease occurred during the third week.

Sputum decrease was present in 19 of the 42 patients. The change occurred during the third week. In most of them the character of the sputum changed, becoming less purulent.

Also, of the 42 patients treated, 18 on tibione alone became concentrate negative. Besides the above consistent changes during therapy there were sporadic changes of the concentrates and cultures from positive to negative.

Changes in weight of the patients were equivocal. There were
no great changes. As many gained as lost weight. A sense of
well-being was noted in six of the 14 patients on tibione therapy
alone. The time of appearance was in the third week in all cases.
In the combined therapy group, five noted a sense of well-being
which was noted in the first and second weeks, similar to that
noted with streptomycin. Two had draining fistulae-in-ano which
showed clearing by the sixth week on tibione alone. One fistula
cleared by the third week of combined therapy.

Analyzing the x-ray changes after 120 days of therapy, of the
29 patients receiving tibione alone, two had the treatment stopped
early so that they cannot be included. Of the 27 remaining, nine
improved, 16 showed no change, and two became worse. Inasmuch
as these observations were on patients with chronic disease one
would expect the x-ray changes to be relatively minimal. Amongst
the patients receiving combined therapy seven improved, six re-
mained unchanged, and one became worse. Reduction in the size
of cavity when present, occurred in three patients, and was in-
creased in one. The improvement with treatment was greater
when combined therapy was used.

The second purpose for undertaking the problem was deter-
mining if resistance of M. tuberculosis developed towards tibione
during therapy. A procedure for adequately testing the sensitivity
of M. tuberculosis toward tibione was developed at Birmingham
Veterans Administration Hospital, which was reported at the Ninth
Streptomycin Conference and will be published. In 11 patients,
whose sputum cultures remained positive throughout the course
of therapy, the organisms were sensitive to tibione before therapy
and resistance began to appear in the fourth week of treatment.

With regard to blood levels of tibione, the determination is
made colorimetrically as described by Dr. Hendricks of the Food
and Drug Commission. The test gives quantitative results. The
same method is used for urine determinations.

Tibione is a cumulative drug, yet it has a definite renal thresh-
old level, as 60 to 65 per cent of all the drug is excreted unchanged
in the urine in 24 hours. After three days of ingestion, three hours
after the last dose while the patient is receiving 100 mgms. daily,
Dr. Hendricks found the blood level to be 2.6 mcgms. and with
200 mgms. daily it was 2.77 mcgms./ml.

Because of the comparable blood levels, at the Ninth Strepto-
mycin Conference, a recommendation was made to reduce the
daily dose of tibione to 100 mgms. This reduction of dosage may
also reduce the toxicity. Further studies are now in progress to
determine if the toxicity is reduced and also if 100 mgms. of tibione
is therapeutically as effective as the 200 mgm. daily dose.
CONCLUSIONS

1) Tibione is a drug of moderate toxicity.

2) The greatest toxic manifestations are gastro-intestinal disturbances which develop primarily during the third week and generally persist only a short time.

3) Other complications are dermatitis, anemia, and impaired hepatic function.

4) A decrease in cough and sputum, and a sense of well-being occur with tibione.

5) Tibione is a chemotherapeutic agent capable of conversion of the sputum.

6) X-ray film improvement after 120 days of tibione therapy has been noted. The improvement is not as marked as with streptomycin for a comparable period.

7) There has been demonstrated an acquired resistance of M. tuberculosis toward tibione.

8) Tibione should be administered only where adequate laboratory facilities are available so that frequent laboratory tests can be made.

CONCLUSIONES

1) La tibiona es una droga de moderada toxicidad.

2) Las manifestaciones tóxicas más importantes son desarreglos gastro-intestinales que aparecen principalmente durante la tercera semana y que, por lo general, sólo persisten por un corto tiempo.

3) Otras complicaciones son: dermatitis, anemia y deterioro de la función hepática.

4) Disminuyen la tos y el esputo y ocurre una sensación de bienestar cuando se administra la tibiona.

5) La tibiona es un agente quimioterapéutico que es capaz de convertir el esputo.

6) Se ha observado mejoria en la película radiográfica después de 120 días de tratamiento con tibiona. Esta mejoria no es tan notable como la que causa la estreptomicina en un período comparable.

7) Se ha demostrado que el M. tuberculosis adquiere resistencia a la tibiona.

8) Sólo debe administrarse la tibiona cuando existen adecuadas facilidades de laboratorio para que puedan hacerse frecuentes análisis.
REFERENCES


