Present Status of Streptomycin In Tuberculosis

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Streptomycin has become established as a valuable weapon in the therapy of tuberculous infections. Tuberculosis is a protein disease, its symptomatology and prognosis variable. As is well known, spontaneous healing may occur without benefit of presently accepted therapeutic measures. Hence it is readily apparent that the final evaluation of any tuberculo-chemotherapeutic agent will be possible only after long and arduous experimental and clinical study.

Nearly four and one-half years have passed since streptomycin was first reported by Schatz, Bugie and Waksman.1 This antibacterial agent is produced by certain strains of the actinomycete, Streptomycin griseus. It possesses selective activity against a variety of pathogenic organisms in vitro, among them human and bovine strains of Mycobacterium tuberculosis.

Within a year following the discovery of streptomycin Feldman and Hinshaw2,3 had found that the antibiotic exhibits a unique suppressive action against tuberculous infections, both experimentally and clinically. This work has been confirmed by many other investigators. Following the early investigations at the Mayo Clinic and Mineral Springs Sanatorium, various Federal agencies in cooperation with the drug companies producing streptomycin instituted a centralized program of experimental and clinical research. As a consequence, in the past three years many hundreds of carefully selected cases of various forms of tuberculosis have been treated, and many problems inherent in the chemotherapeutic assault on tuberculosis have been clarified. But the complete role of streptomycin in the treatment of tuberculosis has yet to be determined.

Streptomycin in Experimental Tuberculosis

The antibiotic action of streptomycin in experimentally induced tuberculosis in guinea pigs has been well established.

In 1944, Feldman and Hinshaw demonstrated the effectiveness of streptomycin in vivo. In a series of extensive experiments4 they

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proved that streptomycin has the striking ability, not only to inhibit the progress of tuberculous lesions, but also to reverse the potentially fatal course of experimentally induced tuberculosis in the highly susceptible guinea pig. The drug was found to have a relatively low toxicity.

In the fall of 1944, it was felt that cautious use of streptomycin was justified in human beings. Cases selected for the first clinical trials were those in which the prognosis was considered hopeless, such as miliary and meningeal forms of tuberculosis, and nearly terminal pulmonary cases. Careful pharmacological studies for toxic manifestations were made on these patients. The encouraging clinical results obtained and the relatively low toxicity which occurred soon made it apparent that the drug could be used in patients with a more favorable prognosis. A summary of observation on 100 cases of human tuberculosis treated with streptomycin was published in November, 1946.

**Clinical Use of Streptomycin**

*Pulmonary Tuberculosis:* In the chemotherapy of pulmonary tuberculosis, it is paramount that there be an intensive evaluation of the individual case prior to commencing treatment. At present, due to the phenomenon of acquired bacterial resistance, it is felt that streptomycin cannot be expected to exhibit its suppressive action for more than one period of treatment. Caution, then, with regard to the long term management of the patient is imperative, because there may be greater need for the use of streptomycin at a future time. Experience to date indicates that the drug is not as effective in many cases of pulmonary tuberculosis as in some other forms of the disease.

The maximum therapeutic benefit of streptomycin in pulmonary tuberculosis occurs in pneumonic and early exudative lesions. There may be some degree of improvement in proliferative lesions, but the pathologic tissue changes occurring in fibrocaseous and fibrocavernous lesions are often irreversible. In minimal pulmonary tuberculosis streptomycin therapy is seldom indicated.

With some exceptions, the selection of cases to receive streptomycin is best determined by roentgenographic and clinical observation over a period of at least several weeks. Results will be more nearly comparable when there has been an adequate trial of rest with or without other therapeutic procedures. A lesion that has been progressive or has remained stationary with previous therapy may respond favorably to the retardative action of streptomycin, permitting the natural defense mechanisms of the host to accelerate the reparative processes.

The Streptomycin Committee of the Veterans Administration
reported in December 1947, the results of 223 cases of pulmonary tuberculosis treated with the drug under carefully controlled conditions. Of these 223 cases, 156 (70 per cent) were far advanced, 65 (29.1 per cent) were moderately advanced and 2 (0.9 per cent) were minimal. The patients were predominately white males, less than 30 years of age, and were selected because they had progressive or stationary lesions after two months of observation. They received a daily dose of 1.8 grams of streptomycin (0.3 grams every four hours) for 120 days. On the basis of roentgenographic changes, 85 per cent were judged as improved, 10 per cent as unchanged, and 0.5 per cent (1 case) showed progression during the period of treatment. Of 182 cavities at beginning of treatment, 47 (26 per cent) were closed or had disappeared and 67 (37 per cent) were smaller. The remainder were unchanged or larger.

In this study 195 patients were followed by serial roentgenograms for an average of 117 days after cessation of treatment. Of these 40 per cent continued to show improvement, 44 per cent remained unchanged and 16 per cent had extensions or spreads that occurred mainly within 30 days after discontinuing treatment. The authors concluded that "the case for streptomycin rests primarily on the fact that, during treatment, some degree of roentgenographic clearing occurred in 85 per cent of the lesions, of which a majority had been stable or progressive before streptomycin was instituted." They also re-emphasized the fact that streptomycin is an adjunct in the treatment of tuberculosis and superior in suitable cases to bed rest alone.

Similar results are reported by Muschenheim, McDermott, et al8 in their study of 43 patients, in which they used 3 grams of streptomycin in their early cases for 120 days and one gram daily in 10 cases for 42 days. They concluded that there was some measurable improvement in all of these 43 cases, as shown by roentgenographic clearing.

Results indicate that with the use of streptomycin the scope and frequency of surgical procedures in the treatment of pulmonary tuberculosis are definitely increased. Such procedures are frequently made possible by resolution of exudative lesions, especially in the contralateral lung, and by improving the patient's general condition.

In the selection of cases to receive streptomycin therapy it must be borne in mind that there exists a real hazard of the dissemination of drug-resistant organisms. When patients discharging such organisms leave a sanatorium against advice, they constitute a particularly dangerous public health menace. Experience to date indicates that drug-resistant tubercle bacilli
transferred to previously uninfected individuals will retain their resistance: streptomycin probably will be of no value in the treatment of these people.

Tuberculous Empyema: Streptomycin appears to have little value in the treatment of well established tuberculous empyema. Experience with the drug in this condition has thus far proved to be disappointing. It remains to be seen whether the use of streptomycin in combination with detergents and other antibacterial agents will achieve better results.

Disseminated Tuberculosis: Conclusive evidence of the efficacy of streptomycin therapy is apparent in the unprecedented clinical and objective improvement which often occurs within one to three weeks in the otherwise highly fatal forms of disseminated tuberculosis. Since there is no other known treatment capable of bringing about remission, treatment with streptomycin is mandatory in every case. It is imperative that the disease be recognized early and the maximal tolerated doses of streptomycin be employed immediately, attempting to avoid only the more serious and permanent types of toxicity. In cases of meningitis, treatment with streptomycin should be instituted whenever presumptive evidence indicates that the tubercle bacillus may be the etiological agent, without waiting for bacteriological confirmation.

In tuberculous meningitis the ultimate mortality probably will not be decreased appreciably, but the remission due to streptomycin is often remarkable in degree and may persist for many months. Lincoln and her co-workers report success in the treatment of tuberculous meningitis, using promizole, a sulfone compound, in addition to streptomycin administered intramuscularly and intrathecally. However, her series of cases is small, treatment was begun very early in the course of the disease, and insufficient time has elapsed since termination of treatment to determine whether this combination of therapeutic agents is superior to streptomycin alone.

In generalized miliary tuberculosis the probability of permanent arrest is considerably greater than in tuberculous meningitis or in disseminated tuberculosis with meningeal involvement. Miliary pulmonary lesions may show improvement after only three or four weeks of treatment, and frequently such lesions are scarcely detectable roentgenographically after eight weeks of therapy. They may be complete remission as observed clinically, bacteriologically, and roentgenologically.

Unfortunately the remission which occurs in miliary tuberculosis is not always sustained. It has been shown that streptomycin does not penetrate the substance of the brain and this may be a significant factor in cases which terminate fatally. Not uncom-
monly meningeal involvement becomes manifest when the patient with miliary tuberculosis is already receiving streptomycin intra-
muscularly in adequate doses. The meningitic process may or
may not undergo remission when intrathecal administration of
streptomycin is instituted.

When disseminated tuberculosis recurs after a streptomycin-
induced remission, a second course of treatment is beneficial
only if the infecting organisms are still predominantly sensitive
to the drug. In most cases, further treatment is of no value, or
the remission effected is less striking in degree and duration
than the original remission.

Other Forms of Tuberculosis: Ulcerative and granulomatous
lesions of the larynx and tracheobronchial tree respond to strep-
tomycin therapy with almost uniform healing. Improvement may
be noted within two weeks during therapy, and in the majority
of cases healing usually occurs within six to eight weeks. Ad-
ministration of the drug is effective by the intramuscular route
and relatively ineffective by aerosol therapy alone.

In tuberculous lesions of the oropharynx, streptomycin has
proved to be the treatment of choice. The majority of these
lesions can be expected to heal completely within two to three
months, with doses of one gram daily or less. In one case under
our observation, a lesion of the tongue proved tuberculous by
biopsy was associated with fibrocaseous pulmonary tuberculosis
and positive sputum. Healing of the lesion occurred after six
weeks of treatment with a dose of 0.5 gram of streptomycin given
intramuscularly in one injection daily.

In tuberculous enteritis streptomycin is the treatment of choice.
Cases usually respond with a marked decrease in symptoms
within two weeks.

Draining cutaneous sinuses from tuberculosis of the bone, joint,
cartilage, and lymph glands respond to streptomycin with rapid
and consistent healing. The response in this form of tuberculosis
is valuable as it affords an easily objective study of the effec-
tiveness of streptomycin. There is a tendency in a few cases for
subsequent recurrence of drainage and enlargement of lymph
glands. The Veterans Hospitals have reported that closure of
draining sinuses is accelerated by removal of pus and necrotic
material surgically.

Tuberculosis of bone and joints appear to be retarded in some
cases sufficiently to produce healing, alone or in conjunction
with orthopedic surgery. Further study is necessary to permit
conclusions as to the ultimate place of streptomycin in treat-
ment in these conditions.

Genito-urinary tuberculosis has responded to streptomycin,
chiefly by improvement in symptoms. The drug is of value as an adjunct when surgery is indicated and is the treatment of choice when surgery is impossible, as in tuberculosis of a solitary kidney, or bilateral renal tuberculosis. Its palliative effects are pronounced and prolonged in more than 50 per cent of the lesions treated. At the Veteran's Hospital at Bronx, New York, 23 out of 32 cases of tuberculosis of the genito-urinary tract were reported as improved, but the investigators draw no conclusions as to the maintenance of improved status.

In tuberculous peritonitis, the number of cases treated with streptomycin has been small, but reports indicate that the drug has a definitely favorable effect on the course of the disease. It appears that streptomycin is the treatment of choice in such cases, combined with rest and other accepted therapy.

Tuberculous pericarditis, to date, has not responded successfully to streptomycin in the great majority of cases. This may be due to failure in starting treatment sufficiently early in the course of the disease.

The response of the various forms of skin tuberculosis to streptomycin has been variable, with a tendency toward recurrence of the lesions.

Evidence accumulated thus far would indicate that streptomycin is often beneficial in tuberculous otitis media. We believe it will prove to be an important factor in the treatment of such cases, combined with other accepted therapy.

In ocular tuberculosis, the number of cases reported to date, treated by streptomycin, is too small to permit drawing any conclusions.

Administration and Dosage

For all forms of tuberculosis except meningitis, streptomycin should be given parenterally, preferably by intramuscular or deep subcutaneous injection. In tuberculous meningitis, daily intrathecal injections of 25 to 100 milligram in addition to the intramuscular administration were previously considered imperative. However, this opinion has been challenged recently by some investigators both in the United States and in Europe. Investigations carried out at Herman Kiefer Hospital in Detroit have led the group there to believe that intrathecal injection of streptomycin has no particular value and is contra-indicated because of the severe toxic manifestations which may result from this method of administration. Undoubtedly, further clinical study will determine which of these two views is correct. In any event, early diagnosis and treatment is most essential to recovery. A minimal dosage of two grams daily, given intramuscularly, for at
least three to four months is recommended at this time for this disease.

For all other forms of tuberculosis, a total dose of one gram daily for two to three months is sufficient. Some investigators are reporting good results in many cases with doses of 0.5 gram daily or less for periods of 30 to 60 days. Frequency of administration may vary from 12 to 24-hour intervals, apparently with similar results clinically. The present trend seems to be toward a single injection daily. The optimal duration of therapy will vary considerably in different cases, depending upon the time of appearance of streptomycin-resistant strains. Further investigations will undoubtedly clarify the problems of daily dosage, frequency of administration, and duration of treatment.

Toxicity: Most investigators have been impressed with the relative lack of serious toxic effects from streptomycin. The potential toxicity should not be a deterrent when indication for treatment is definite.

The three chief toxic manifestations of streptomycin are:
(1) damage to the eighth nerve resulting in vestibular disturbance, (2) renal irritation, and (3) sensitization reactions. Vestibular disturbance is noted in the large majority of patients who receive 2 or more grams daily for extended periods of time. Dizziness and ataxia may vary in severity and in time of appearance. They may occur early or late in the course of treatment. The loss or decrease of labyrinthine function can be demonstrated by caloric stimulation tests, and this loss appears to be permanent.

Fortunately most patients can compensate for vestibular dysfunction to a remarkable extent. A number of our patients, in whom there is complete loss of vestibular function as demonstrated by caloric stimulation tests, have returned to their former occupation. Middle aged and elderly patients compensate more slowly and to a less degree than younger individuals.

The danger of deafness from treatment with streptomycin is negligible. Cases in which a partial loss of hearing has been reported have occurred only when concentration of streptomycin in the blood were excessive, due either to extremely high dosage or to renal insufficiency. In such cases hearing is restored if the drug is discontinued promptly. It is interesting to note that cases of permanent deafness which have been reported have occurred only in patients with tuberculosis meningitis.

Cylindruria and low grade albuminuria occur not infrequently during treatment with streptomycin. It is now accepted that permanent renal damage referable to streptomycin has occurred only when there was evidence of renal impairment before treatment.
Sensitization reactions may occur occasionally after treatment of one to three weeks, with manifestations of chills, fever, nausea, and skin rash. In such cases the drug should be discontinued until these symptoms have subsided. Treatment may then be resumed with minute doses of 0.1 gram daily, gradually increasing the dosage over a period of two to four weeks until the desired daily dosage is reached.

Isolated cases of serious toxic effects from streptomycin have been reported by the army, navy, and Veteran's Administration, including three cases of exfoliative dermatitis, one case of agranulocytosis, and two cases of aplastic anemia in which the drug is suspected of being a factor. Fortunately such cases are rare.

The toxicity of streptomycin parallels the dosage and, to a lesser extent, the duration of treatment. Among patients receiving two grams daily for three to four months, mild to severe vestibular disturbance as determined by caloric stimulation tests, can be anticipated in 90 per cent or more. In our experience, when doses of one gram daily for similar periods are used, the toxic manifestations with reference to the vestibular mechanism are markedly reduced. Approximately one half of these patients revealed no vestibular dysfunction by caloric stimulation tests.

Bacterial Resistance: The phenomenon of bacterial resistance to streptomycin is the major limitation to the use of this drug in the treatment of tuberculosis. Evidence has accumulated to indicate that in approximately three-fourths of the cases the bacterial population is predominantly resistant after two to four months of treatment. In most cases this resistance has proved to be permanent. Studies have shown that resistance may occur as early as one month after treatment is started. The importance of this problem is obvious, since further treatment with streptomycin has proven to be ineffective when the infecting organisms are drug-resistant.

It is hoped that some method will be found to prevent or delay the occurrence of resistance. Perhaps some other anti-tuberculosis agent may be discovered which is clinically applicable and can be used alone or in combination with streptomycin to achieve this end.

SUMMARY

Streptomycin is now accepted as a valuable weapon in the treatment of tuberculosis. Like other valuable drugs, it has its assets and limitations. It can not be considered a substitute for sanatorium care and other well established measures such as collapse therapy. It is a “must” in the treatment of (1) miliary tuberculosis, (2) tuberculous meningitis, (3) ulcerative tracheobronchial tuberculosis, (4) tuberculosis of the larynx and oro-
pharynx, (5) draining cutaneous sinuses, and (6) tuberculous enteritis. In tuberculous peritonitis it is probably the treatment of choice. In genito-urinary tuberculosis its value is chiefly palliative and as an adjunct to surgery. In bone and joint tuberculosis it is helpful in some cases, both alone and in conjunction with surgery.

In pulmonary tuberculosis it is a valuable adjunct in exudative and pneumonic lesions, in combination with bed rest and collapse therapy, or resection when indicated. It must be emphasized that an understanding of the pathology of tuberculosis and of the mechanism of anti-bacterial therapy is necessary if the best possible end results are to be obtained by use of the drug. Streptomycin has proved that tuberculosis is amenable to chemotherapy. It is fervently hoped that other and even more effective agents may be discovered.

RESUMEN

Actualmente se reconoce que la estreptomicina es una arma valiosa en el tratamiento de la tuberculosis. Lo mismo que otras drogas valiosas, tiene sus ventajas y sus restricciones. No puede ser considerada como substituto de la atención sanatorial o de otras medidas bien establecidas, tales como la colapsoterapia. Es obligatorio que se le emplee en el tratamiento de (1) la tuberculosis miliar, (2) la meningitis tuberculosa, (3) la tuberculosis tráqueobronquial ulcerativa, (4) la tuberculosis de la laringe y de la faringe bucal, (5) las fistulas cutáneas y (6) la enteritis tuberculosa. En la peritonitis tuberculosa es probablemente el tratamiento preferible. En la tuberculosis genitourinaria su valor es principalmente paliativo y como coadyuvante de la intervención quirúrgica. En la tuberculosis de los huesos y las articulaciones es útil en algunos casos, tanto sola como combinada con la intervención quirúrgica.

En la tuberculosis pulmonar es un coadyuvante valioso en lesiones exudativas y neumónicas, combinada con el reposo en cama y la colapsoterapia, o la resección cuando esté indicada. Debe recalzarse que es necesario comprender la patología de la tuberculosis y el mecanismo de la terapia antibacterial para que se puedan obtener los mejores resultados posibles con el empleo de la droga. La estreptomicina ha demostrado que la tuberculosis es tractable mediante la quimioterapia. Se espera fervorosamente que se puedan descubrir otros agentes aún más eficaces.

REFERENCES