University of Nebraska Medical Center
BREAKTHROUGHS FOR LIFE

University of Nebraska Medical Center
DigitalCommons@UNMC

MD Theses

Special Collections

1949

Value of streptomycin in the treatment of tuberculous meningitis

Robert Leverne Cranny
University of Nebraska Medical Center

This manuscript is historical in nature and may not reflect current medical research and practice. Search PubMed for current research.

Follow this and additional works at: https://digitalcommons.unmc.edu/mdtheses

Recommended Citation

Cranny, Robert Leverne, "Value of streptomycin in the treatment of tuberculous meningitis" (1949). *MD Theses*. 1587.
https://digitalcommons.unmc.edu/mdtheses/1587

This Thesis is brought to you for free and open access by the Special Collections at DigitalCommons@UNMC. It has been accepted for inclusion in MD Theses by an authorized administrator of DigitalCommons@UNMC. For more information, please contact digitalcommons@unmc.edu.

The Value of Streptomycin in the Treatment of Tuberculous Meningitis.

Robert LeVerne Cranny

Senior Thesis

Presented to the College of Medicine

University of Nebraska

Omaha 1949

Introduction

Tuberculous Meningitis has offered a challenge to which the solution has not been forthcoming. With the advent of antibiotic therapeutics, a new agent, streptomycin, has become available for the continued effort toward the solution of this problem.

This discussion is an attempt to delineate the facts which have been discovered and to evaluate their possible clinical value.

Chemotherapy is one of the oldest fields of medical endeavor, but the chemotherapeutists of previous generations searched for remedies against disease by making extracts of higher plants. For the past two generations scientists have also been seeking antibiotic remedies from organisms in nature. They have been interested for several years in antibacterial substances which are effective against the bacillus of tuberculosis.

The ability of certain saprophytic organisms to inhibit the growth of Mycobacterium Tuberculosum has long been recognized. As far back as 1885, Cantoni obtained favorable effects from the treatment of a tuberculous patient with a culture of common bacterium. Later, Vandremer, using extracts of Aspergillus Fumigatus for the treatment of patients suffering with tuberculosis, reported satisfactory results. The recent progress made in our knowledge of antibiotic substances and their action upon various disease producing bacteria, suggested the advisability of studying the relation of some of these substances to the causative agent of tuberculosis and other related organisms.

By searching the available literature published during the last sixty years, there can be found references to at least twenty substances of microbial origin which showed some evidence of activity against the bacillus of

tuberculosis. In many instances these are truly antibiotic substances as one thinks of them today.

Among the scores of antibiotic substances known, only two have as yet reached what appears to be a stage of practical development for the parenteral treatment of systemic human diseases. These are penicillin and streptomycin.

Tuberculous meningitis is universally considered to be a fatal disease. Examples of spontaneous recovery have been reported but they are rare and complete laboratory confirmation in most of these is lacking.

In January 1944, Schatz, Bugie and Waksman reported the isolation of streptomycin. In November 1944, Schatz and Waksman demonstrated its marked bacteriostatic and bacteriocidal action against a human strain of Mycobacterium Tuberculosum in vitro. In December 1944, Feldman and Hinshaw first showed the suppressive effect of streptomycin on "the pathogenic proclivities in guinea pigs" of the human variety of Mycobacterium Tuberculosum.

It was stated in the Proceedings of the Staff Meetings by investigators at the Mayo Clinic in 1944, that, "seven antibiotic substances already have been found to be produced by soil actinomycetes, among which is streptomycin. This substance is characterized by only limit-

ed toxicity to animals, is active in vivo against a variety of bacteria but is more effective against specific organisms such as Pssudomonas Aeruginosa, Proteus Vulgaris and Mycobacterium Tuberculosum." It was further stated that "Streptomycin is an antibiotic substance well tolerated by guinea pigs and is capable under the conditions imposed of exerting a striking suppressive effect on the pathogenic proclivities in guinea pigs of the human variety of Mycobacterium Tuberculosum. The results with streptomycin are comparable to those observed previously with certain drugs of the sulfone series."

In 1945 Feldman, Hinshaw and Mann stated that, "Although capable of striking deterrent effects in combating or preventing anatomical changes due to Mycobacterium Tuberculosum, streptomycin in most instances exerted a suppressive rather than a sterilizing effect on the infective agent." Thus, bacteriostasis has been clearly demonstrated in experimentally infected guinea pigs and has subsequently been reported clinically.

Cook, Dunphy and Blake in 1945 reported "what would appear to be favorable modification of the disease" after the use of streptomycin in a one year old infant with tuberculous miningitis. There was apparent

arrest 234 days after the onset of the disease precess.

The onset of the disease is apt to be insidious with apathy, irritability, listlessness, fretfulness and loss of interest. These prodromal symptoms may last for a few days or may persist for several days or a few weeks. During this period signs of meningeal irritation are lacking and examination of the spinal fluid reveals nothing of significance. The onset may in other instances be acute with headache, stupor, and fever. Headache appears early and may be a prominent symptom. The patient presents a characteristic picture as the disease develops to more advanced stages. Somnolence is a striking feature. Convulsions may develop and stupor may in some instances supervene, deepening rapidly into coma. Meningeal signs are present with stiffness of the neck, Kernig's sign and often Brudzinski's sign. Fever is usually of a low grade (99° to 101° F.) and is irregular.

The spinal fluid is under pressure. It is usually clear, but may be misty or yellow and often develops a clot or pellicle on standing. The cells vary from fifty to five hundred and are predominantly lymphocytes. The sugar is decreased (45mg.% or below). The chlorides are moderately or greatly reduced, usually

below 650 mg.%, and constitute an important feature of the disease. The protein content may be markedly increased (up to 500 mg.%). The tubercle bacillus is found sometimes on direct smear of the spinal fluid sediment, but is more often not found.

The usual case runs a course of two to four weeks, but chronic and more prolonged cases are not uncommon.

The disease should always be suspected in a child with slight up and down fever, listlessness, somnolence, and signs of meningeal irritation, which may be very mild. If the spinal fluid chlorides are below 650 mg.% further confirmation is added but the diagnosis is not established by the low chloride content of the spinal fluid.

In many cases the problem is that of a child or adult with slight fever, with a history of listlessness, somnolence, possibly with convulsions, with signs of meningeal irritation and with an excess of lymphocytes in the spinal fluid. No tubercle bacilli are found in the spinal fluid and no evidence of tuberculosis can be found in the body. The problem in such a case is that of a lymphocytic form of meningitis of undetermined origin. Until definite evidence can be found the problem revolves itself into a consideration

of those conditions which are capable of causing meningitis with an excess of lymphocytes in the spinal fluid. This is the point at which excellent clinical judgement is needed to determine the therapeutic proceedures of choice.

There is no question but what institution of specific therapy as early as possible is highly desireable. Making a definite diagnosis may at times be exceedingly difficult if not impossible. Since the use of streptomycin is not without untoward effect, the administration of this drug should be undertaken with great care. This is especially true when dealing with the tubercle bacillus because the course of treatment is of necessity a prolonged one. However, the views on this point have altered considerably during the past year. The production of a more purified form of streptomycin has been in the main responsible for this. It is now safe to administer the drug in high dosage for a reasonable length of time (one to three months.) With this in mind, streptomycin may now be given to a patient who shows definite signs of the early stages of the disease and thus save valuable time.

From the experience which has accumulated thus far, it appears that a minimum period of three to six months

treatment is required and in some cases it will be necessary to treat patients for a longer time.

At the present time there are two accepted routes of administration of streptomycin, namely, intramuscular and intrathecal. Many clinicians prefer to use them together. In 1947, Hinshaw, Pyle and Feldman reported that of five patients whom they treated via the intramuscular route only, all five died while the four patients who received streptomycin by both routes had had no reactivation four to six months after treatment was discontinued. Recently however, uncertainty has been expressed by many workers concerning the value of intrathecal administration. Cocchi states that one "should discontinue intrathecal streptomycin after eight to fifteen days when treating children." Failure to do so may result in a "Chemical Meningitis." More recent data would indicate that intrathecal administration is of little or no value.

In order to establish certain arbitrary values for dosage it was necessary to acquire certain information. The factors of importance appeared to be (1) anatomic location of the infection, (2) weight and age, (3) various strains within a species vary considerably in their susceptibility to the drug and

there is some evidence that some cells within a single colony are more resistant than others, (4) the range of sensitivity is so great that each infecting organism should be tested before treatment and the dosage planned accordingly, (5) many strains of organisms that are susceptible to five or ten micrograms of streptomycin per cubic centimeter often acquire resistance in vivo to two hundred to five hundred of even five thousand micrograms per cubic certimeeter, (6) in the presence of blood or serum the tolerance of microorganisms to streptomycin may be increased four to eight times. It is well, therefore, to maintain in the blood a concentration of streptomycin four to eight times that necessary to inhibit completely the organisms in vitro.

In general it can be said that when o.l gram is given intramuscularly every three hours one can expect that the mean concentration in the blood over a three hour period will be two to three micrograms per cubic centimeter. When 0.2 gram is given, five to six micrograms per cubic centimeter and for 0.5 gram, nine to ten micrograms per cubic centimeter.

According to Keefer "four to six grams daily is the usual maximum tolerated dose for most patients, although as much as ten grams a day has been given to a few

patients without ill effects." The maximum dose should be used at the beginning of treatment because of the rapid development of resistant organisms when they are not eliminated and the possible "stimulating effect" of streptomycin on the growth of bacteria.

The conclusions of Fantana and Raversi contradict this sharply. They state "the small doses we have used i.e. intrathecal fifty milligrams daily, plus intramuscular fifty milligrams every three hours, have given results comparable to those obtained with larger doses.

Obviously the issue is not settled. However, most clinicians feel that the larger doses are indicated.

The incidence of toxic manifestations during or following the use of streptomycin appears to vary with the dosage. One group of workers found that the overall incidence was 20.5%. However, striking increases in reactions were noted when the daily dose exceeded one gram. (three grams....., 46%, four grams..... 60%).

It has been found that untoward reactions in their order of frequency are headache, fever, skin eruption, flushing of the skin and vertigo, alone or in various combinations. These reactions may be classified in two general groups:

Acute

1. Local reaction at the site of injection,(pain,

soreness and induration.) This varies with technique, volume and the preparation.

2. Histamine like effects (headache, flushing.)
3. Sensitization reaction (skin eruption, fever.)
4. Neurologic Disturbances (vertigo, tinnitus.)

Chronic

1. Vertigo (Later this may be compensated for, either totally or partially.)
2. Diplopia
3. Deafness
4. Hypersensitive
    a. Skin eruptions and fever
    b. Eosinophilia
    c. Neurologic disturbances (vertigo, tinnitus, deafness, parasthesia about face and extremities.)
5. Ataxia

It may be difficult to interpret the reactions that are observed in any one patient. Paine and co-workers noted that the fever in some cases may have been related chiefly to the intrathecal injection of the drug, since it subsided promptly when these injections were discontinued. Hettig and Adcock have drawn the conclusion that the aformentioned reactions probably are due to impurities retained in the preparation of streptomycin.

Symptomatic improvement is usually apparent within one or two weeks after treatment is begun. Some workers claim to have obtained more dramatic results, but substantial evidence is lacking in most of these reports. The patient experiences the return of a sense of well being, dusappearance of stupor, headache and nuchal rigidity. At the same time the fever decreases within two to three weeks and may be normal within four to eight weeks after treatment is begun. The cerebral spinal fluid improves slowly but some abnormalities persist in most patients. This is reflected by the cell count or protein content which may remain elevated or the sugar content which may remain decreased. These findings are interpreted as evidence of possible persistant infection in the patient whose meningitis has improved even though tubercle bacilli cannot be demonstrated by inoculation of a guinea pig or by culture. Reactivation of the disease may occur anytime after therapy is discontinued. Treatment is usually resumed with therapeutic value but the prognosis is poor. Internal hydrocephalus is commonly associated with the signs and symptoms of reactivation.

Reports of complete recovery over a reasonable period of time are scarce. However, Krofchik, Wissler

and Streit, and Appelbaum and Holkins have all reported such cases. Each of these patients was a child under the age of five years. These good results have been attributed to (1) early treatment, (2) pronounced sensitivity of the organism, (3) maintaining adequate concentration of the drug in the blood. Conversely the causes of failures are now generally agreed to be, (1) treatment of infections not susceptible to the action of streptomycin. (2) inadequate dosage. (3) development of resistance to streptomycin in vivo. (4) change in species of infecting organism during treatment. (5) localization of infection in an area that cannot be reached by the drug.

It is common to find certain residual signs of the disease process or of the treatment given. These usually consist of varying degrees of deafness, disturbed cerebellar function, disturbed equilibrium and mental retardation. Any, or all of these undesirable features may in time, clear either partially or completely.

A review of most statistical data reveals certain findings to be rather consistant while others are quite conflicting. There seems to be no question but what early and prolonged therapy is highly desirable. The best clinical results have coincided with a conbination of intramuscular and intrathecal administration of the

drug. However, the dosage remains equivocal. Favorable results have been obtained with both large and small dosage.

The ideal drug for the treatment of tuberculosis is not yet at hand. Streptomycin is undoubtedly the best one available at present and its use is mandatory, but it has many short comings, particularly the ease with which organisms may become resistant to it. It is doubted that the eventual mortality rate will be appreciably reduced.

B I B L I O G R A P H Y

Appelbaum, E., Halkin, C., Tuberculous Meningitis and Miliary Tuberculosis arrested with Streptomycin. J.A.M.A., Vol. 135., 153, 1947.

Alexander, H., Streptomycin in Pediatrics. J. Pediatrics. Vol. 29., 192, 1946.

American Trudeau Society. Annual report of the committee on therapy and the subcommittee on streptomycin. J.A.M.A., Vol. 135,, 641, 1947.

Anderson, D., Jewel, M., Th Absorption, excretion and toxicity of Streptomycin. New England J. Medicine. Vol 233., 485, 1945.

Barnstein, P., Streptomycin in Miliary Tuberculosis with Tuberculous Meningitis. Quart. Bull. Sea View Hosp. Vol 8., 219, 1946

Cacchi, A., Streptomycin and Tuberculous Meningitis. J.A.M.A., Vol 135., 242, 1947

Committee Bulletin. Effect of Streptomycin on Experimental Tuberculosis in Guinea Pigs. Proc. Staff Meetings Mayo Clinic. Vol 19., 593, 1944.

Committee Bulletin. Isolation of Antibiotic substances from soil Micro Organisms with special reference to Streptothrycin and Streptomycin. Proc. Staff Meetings Mayo Clinic. Vol 19k 537, 1944.

Committee Bulletin. Penicillin & Streptomycin Solutions. Proc. Staff Meetings Mayo Clinic. Vol 22., 565, 1937.

DeBakey, M., Pulaski, E., An analysis with Streptomycin therapy in United States Army Hospitals. Surgery Vol 20., 749, 1946.

Feldman, Hinshaw, Mann., Streptomycin in Experimental Tuberculosis. Vol 52., 269, 1945

Finland, M., Chemotherapy and Antibiotics. New Orleans Medical and Surgical Journal. Vol 100., 345, 1948.

Fontana, R., Streptomycin in Italy. Minerva Medicine. Vol 2., (Lancet Vol 2., 265, 1947.

Garrod, L., The Bacteriocidal action of Streptomycin. British Med. J. Vol 1., 382, 1948.

Hettig, R., Adcock, J. D., Stufies on the Toxicity of Streptomycin for Man. Science. Vol 103., 355, 1946.

Heilman, D., A Method for Estimating Concentration of Streptomycin in Body Fluids. Proc. Staff Meetings Mayo Clinic. Vol 20., 145, 1945.

Heilman, D., Heilman, R., Hinshaw, H., Nichols, D., Herrell, W., Streptomycin: Absorption, diffusion, excretion and toxicity. Amer. Med. Science. Vol 210., 576, 1945.

Hinshaw, H., Clinical Uses of Streptomycin in Medicine and Surgery. Surg. Gynec. and Obst. Vol 84., 579, 1947.

Hinshaw, H.; Feldman, Pfuetze, Streptomycin in Treatment of Clinical Tuberculosis. Amer. Rev. Tuberculosis. Vol 54., 191, 1946.

Kirshfeld, J., Buggs, C., The Present Status of Streptomycin. New York State J. Medicine. Vol 47., 1276, 1947.

Keefer, C., Streptomycin. Amer. J. Medicine. Vol 2., 419, 1947.

Krofchik, L., Tuberculous Meningitis treated with Streptomycin. J.A.M.A., Vol 132., 375, 1946.

McDermott, W., Toxicity of Streptomycin. Amer. J. Medicine. Vol 2., 491, 1947.

McDermott, W., Uses of Streptomycin. Amer. J. Medicine. Vol 4., 131, 1948.

McDermott, W., The significance of the finding of Tubercle bacilli, resistant to streptomycin in vitro in the anti-microbial therapy of tuberculosis. Bull. New York Acad. Med. Vol 24., 131, 1948.

Mekas, Truax., Streptomycin in Tuberculous Meningitis. J.A.M.A., Vol 135., 155, 1947.

Paine, T., Murray, R., Finland, M., Streptomycin in the Treatment of Meningitis. Ann. Int. Med. Vol 27., 494, 1947.

Pulaski, E., Streptomycin. Amer. J. Surg. Vol 73., 651, 1947.

Pulaski, E., Amspacker, W., Streptomycin Therapy for Certain Infections of Intestinal Origin. New England J. Med. Vol 237., 419, 1927.

Pulaski, E., Seeley, S., Further Experiences With Streptomycin Therapy in United States Army Hospitals. J. Lab. & Clin. Med. Vol 33., 1, 1948.

Rauchwerger, S., Walls, W., Streptomycin sensitivity. J.A.M.A., Vol 136., 614, 1948.

Schatz, A., Bugie, E., Wakesman, S., Streptomycin, a substance exhibiting antibiotic activity against gram-positive and gram-negative Bacteria. Proc. Soc. Exper. Biol. and Med. Vol 55., 66, 1944.

Stebbins, R., Robinson, H., A Method of Determining concentration of Streptomycin in Body Fluids. Proc. Soc. Exper. Biol. and Med. Vol 59., 255, 1945.

Wissler, Streit. Streptomycin Treatment of Tuberculous Meningitis. Praxis. Vol 36., 445, 1947. Abstracted in J.A.M.A., Vol 135., 466, 1947.