THERAPEUTIC AND TOXIC EFFECTS OF STREPTOMYCIN

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Part I, Therapeutic effects on tuberculous otitis media.

In 1947, J. Holt and F. Snell were the first to report effects of streptomycin in cases of acute and chronic otitis media. Since then local application of streptomycin ear drops for chronic suppurative middle ear infection has proven effective in various cases. H. Carithers emphasizes that acute otitis media in infants caused by pseudomanas aeruginos responds favorably to the injection of 40 to 50 mg. of streptomycin every four hours for an average of one week. Also B. Senturia recommends application of a streptomycin solution of at least 0.5 per cent for the local treatment of the external ear canal infection.

As the cases in all other regions of the body in the ear the effect of streptomycin on the tubercle bacilles is more impressive and important, while other conservative and surgical treatments of tuberculosis otitis media are tiresome and thankless. Previously the course of the middle ear tuberculosis has depended greatly upon the development of the basic tuberculous affection which in most cases is a pulmonary tuberculosis. Greif and Gould were the first to achieve healing of the perforation in two cases of tuberculosis in the middle ear by the intramuscular injection of streptomycin. In another case intramuscular and local application of streptomycin led to rapid healing of the wound and of the perforated tympanic membrane after bilateral mastoidectomy. L. Titche confirms these first successes of streptomycin in a large number of cases. In 32 cases with tuberculous otitis media, involving 35 ears, healing of the perforation occurred in 18 ears, inprovement in 11 ears, in which with the perforation remaining open, the discharge ceased without recurrence during the time the patient was under observation, six ears showed no improvement. Streptomycin was applied locally by instillation into middle ear in four patients, leading to improvement in three cases and healing of the perforation in one case.

In the present paper I intend to report the results obtained by local application of streptomycin on 76 cases of tuberculous otitis media from 1948 to 1952 at Kokura Memorial Hospital, shindenba Sanatorium and Showa Hospital.

In a total of 76 cases, 36 cases or 47.3 per cent of my cases the ear trouble began with earache without any pronounced disturbance in the general condition of the patient and tubercle bacilli could be demonstrated in the direct smear of the ear pus. A single rapidly growing perforation of the ear drum was found more often than

multiple defects which has been generally emphasized as a typical figure of middle ear tuberculosis in textbooks. These were specific infiltrations of the pars mucosa shining through the outer layers of the ear drum. X-ray picuture of the mastoid cells appeared veiled even at the onset of the disease.

Hearing loss beginning at a early stage and progressing rapidly, shown to be a combined type of deafness, pointed to a tuberculosis otitis media. In some cases nerve deafness might even be more pronounced than conductive deafness, probably due to a tuberculotoxie reaction of the labyrinth. Furthermore, with the progress of necrosis of the middle ear and the ossicles impairment of sound conduction growed decidedly worse, in a few cases to extent of total deafness.

As I already stated above, in 40 cases or 52.7 per cent of my cases the tubercle bacilli could not be found, so that my diagnosis was based entirely on clinical symptoms.

To study the results obtained by local application of streptomycin, after cleaning up the ear canal and perforation on the ear drum a 10 per cent solution of streptomycin in water was inserted into the external ear canal at least twice a day over a period of weeks or months.

Table 1 shows clinical findings of the cases treated with streptomycin in the present study. From clinical findings my cases were classified into four groups.

Table 1. CASES TREATED WITH STREPTOMYCIN (76 cases)

Clinical findings	Cases	%
Group I 1) Asmall perforation on the eardrum.	22	29.0%
Group II 2) Multiple perforations on the eardrum.	15	19.7%
Group III 3) Large perforation on the eardrum with granulation tissue on the middle ear.	31	40.8%
Group IV 4) Caries on the middle ear.	8	10.5%

1) Twenty-two cases which had a small perforation on the ear drum with pus comprised 29.0 per cent of total.
2) Fifteen cases (19.7 per cent) had many perforations on the ear drum with pus.
3) Cases which had a large perforation on the ear drum with granulation tissue numbered 31 (40.8 per cent).
4) Eight cases who has caries on the middle cavity comprised 10.5 per cent of the total number.

Table 2 shows the results obtained by local application of streptomycin.

Of the group 1 of 22 cases had a small perforation on the ear drum, 15 cases or 68.2 per cent were dry in the canal and 5 cases or 22.7 per cent had decreased ear

Table 2 RESULTS OBTAINED BY STREPTOMYCIN THERAPY (76 cases)

	Group I 22	Group II 15	Group III 31	group Iv 8
1. Ear discharge				
cease	15 (68.2%)	10 (66.7%)	9 (29.0%)	2 (25.0%)
decrease	5 (22.7%)	2 (13.3%)	17 (55.0%)	2 (25.0%)
unchange	2 (9.1%)	3 (20.0%)	5 (16.0%)	4 (50.0%)
2. Hearing loss				
improvement	3 (13.60%)	3 (20.0%)	3 (9.7%)	2 (25.0%)
unchange	19 (86.4%)	12 (80.0%)	28 (90.3%)	6 (75.0%)

pus. Whereas 2 cases or 9.1 per cent were unchanged. As to hearing loss 3 cases or 13.6 per cent improved after treating with streptomycin and 19 cases or 86.4 per cent were unchanged.

Of the group 2 of 15 cases which had multiple perforations on the ear drum, 10 cases or 66.7 per cent had the completely dry ear canal and 2 cases or 13.3 per cent had decreased ear pus, whereas 3 cases or 20 per cent were unchanged. Of the same group 3 cases or 20 per cent improved hearing often treatment and 12 cases or 30 per cent were unchanged.

Of the group 3 of 31 cases which had large perforation with granulation tissue on the middle ear, 9 cases or 29 per cent had the dry ear canal and 17 cases or 55 per cent were found to have decreased ear pus whereas 5 cases or 16 per cent were unchanged. Of this group of 31 cases 3 cases or 9.7 per cent had a improvement of hearing after treatment and 28 cases or 90.3 per cent were unchanged.

Of the group 4 of 8 cases which had caries of the middle ear, 2 cases or 25 per cent had the dry ear canal and 2 cases or 25 per cent were decreased in pus whereas 4 cases or 50 per cent were unchanged. In this group these were 2 cases or 25 per cent improved hearing after treatment.

In my experience the best results in exudative tuberculosis of the middle ear were obtained by combining the local administration of strcptomycin with injection. In all cases a total of at least 60 g. of streptomycin in daily maximal doses of 24 mg. per kg. body weight was administered. In addition, the locally applied streptomycin directly might attack the tubercle bacilli in ulcerations and granulations in the mucous membrane of the middle ear cavity.

By only the local application of streptomycin I have achieved definite improvement in some cases having a small perforation on the ear drum. In these cases ear secretion ceased within one to three weeks.

case: O. S. The patient is a 23 year-old man with a cured pulmonary tuberculosis and an ear discharge in June 1947. Tubercule bacilli were found in the ear discharge.

The ear drum showed a small perforation in the pars tensa with pus. Hearing test revealed a loss of 15 db. on air conduction. Local treatment of streptomycin twice a day was begun immediately. Within 10 days the ear discharge ceased without recurrence. However, 25 per cent of cases treated with only local application of streptomycin there was a recurrence of ear discharge, partly specific and partly nospecific in nature. It could be arrested promptly by a second or third local treatment with streptomycin.

Cessation of the secretion probably paralleled a cretain degree of stabilization of the disease process. The ear drum perforations in most cases did not expand, and destruction of the ossicles ceases. In my 76 cases I found no further complications in the mastoid cells or in the endocranium.

Regarding to the hearing loss, once such a loss has manifested, the improvement of hearing in a large number of cases never occurred.

SUMMARY

Clinical studies on local application of the streptomycin on the 76 cases of tuberculous otitis media are demonstrated. In the cases with only perforation on the ear drum ear discharge ceases in about 50 per cent of cases, whereas in the cases with granulation tissue on the middle ear cavity it decreases in about 50 per cent and in the cases of the caries on the middle ear it unchanges in 50 per cent. As to the hearing, there are the cases improved after treatment in about 17 per cent.

Part II. Streptomycin poisoning in the ear.

Recently the otologist has been more interested in the toxic effects rather than in the therapentic effects of streptomycin in the ear. The specific effects of streptomycin on the vestibular labyrinth opened certain possibilities for exploration of functions of the inner ear. The problem of its clinical applicability can now be considered as solved, because we, otologists, know that loss of hearing as well as disturbances of the vestibular labyrinth to a great extent may be avoid adjusting the dosage of streptomycin to the weight of the patient. For this purpose the daily doses should not exceed 24 mg. of streptomycin per Kg. bodyweight, providing the kidneys function normally; furthermore, toxic disturbances of equilibrium and hearing present even loss frequently upon parenteral administration of dihydrostreptomycin instead of streptomycin. C. Domon, P. Kilbourne and E. King gave a total of 270 g. of dihydrostreptomycin in daily doses of 3 g. to an adult without any toxic effects.

In the present paper I describe a comparative study of the ototoxity of streptomycin and dihydrostreptomycin.

A total of 285 cases with pul monary tuberculosis, in some instances with other tuberclous lesions fell into two general groups. 1) 148 cases were treated with

streptomycin sulfate (group 1), 2) 137 cases were applied with dihydrostreptomycin sulfate (group 2). Each patient received 0.5 g. daily of either streptomycin or dihydrostreptomycin for a total for 60 days with some exception. Detailed clinical records were maintained for every cases in routine. Special note was made of sputum bacteriology, X-ray change, bronchoscopic changes and ototoxic manifestations.

To study function of the inner ear hearing and vestibular tests were done prior to therapy, one month and, two months post therapy. Hearing was checked by pure tone audiometry and vestibular responses were tested by postrotatory nystagmus. Table 3 shows the degree of patient's condition.

Table 3. A TOTAL OF THE CASES (285)

Degree of condition	Group 1 (148 cases) Streptomycin	Group 2 (137 cases) Dihydrostreptomycin
Minimal	43	45
Moderately advanced	77	62
Far advanced	28	30

Of the group 1 of 148 cases treated with streptomycin, 5 cases evedenced auditory disturbances; hearing loss with tinnitus on both ears in 3 cases and tinnitus unilaterally in 2 cases, and 6 cases had the vestibular disturbances.

Of the group 2 of 137 cases dealed with dihydrostreptomycin 4 cases had auditory disturbances; tinnitus unilaterally in 3 cases, hearing loss with tinnitus unilaterally 1 case, and 3 cases had some vertigo and vestibular disturbances (Table 4).

Table 4. POISONING OF STREPTOMYCIN AND DIHYDROSTREPTOMYCIN

	Auditory lesions	Vestibular lesions
Group 1 (148 cases) Srteptomycin	5	6
Group 2 (137 cases) Dihydrostreptomycin	4	3

It is evedent that toxic effects of streptomycin and dihydrostreptomycin are almost equal in nature.

Part III. Experimental studies streptomycin poisoning.

The problem whether the toxic effect of streptomycin on the cochleo-vestiblular system is localized in the inner ear or in the central nervous system is still under discussion. Histological studies published thus far, include reports of ganglion cells

and central nulei in several cases, which is not favourable to give a enough unstanding of the streptomycin poisoning.

It is the purpose of the present part to demonstrate histological findings of the senosory nerve, ganglion cells, the central acoustic, and vestibular nuclei on streptomycin poisoned rabbits. The rabbits comprise three series of animals dealed with different doses of streptomycin and a control group.

In addition vestibular response was recorded by positional reflex and postrotatory nystagmus.

Table 5. VFSTIBULAR FUNCTIONS AFTFR TRFATING WITH STRFPTOMYCIN

		Group 1. 8	Group 2. 5	Group 3. 10
1) Spontaneous nystagmus	present	0	3	8
	non	8	2	2
2) Head nystagmus	present	0	0	5
	non	8	5	5
3) Postrotatory nystagmus	normal	6	0	0
	dimished	2	3	0
	abolished	0	2	10

1. Vestibular functions after treating with streptomycin.

1). Group 1: Eight rabbits were treated with 100 mgs. Per kilo of streptomycin, daily, four weeks. After procedure, there was neither spontaneous nor head nystagmus and abnormal posture in all animals.

Postrotational nystagmus was present within normal in all animals except dimished in two. All animals gained weight during the experiments (Table 5).

2). Group 2: Five animals were treated with 200 mgs streptomycin per Kilo, daily, for four to five weeks, after procedure. There was spontaneous nystagmus in 3 animals.

Postrotatory nystagmus was dimished in 3 and abolished in 2 animals. There was moderate loss of body weight in all animals (Table 5).

3). Group 3: Ten animals were treated with 200 mgs per kilo twice daily, or 400 mgs per kilo, daily, until vestibular response was abolished on an average of four or five weeks. All animals lost a considerable amount of body weight (Table 5).

HISTOLOGICAL STUDIES

After examing vestibular function all animals were sacrificed under urethane anaesthesia by injection into the aorta of 500 mg. saline solution followed by 500 ml. of Wittmaak's solution. Both labyrinths were removed and fixed in formalin soon after death, decalcified, embedded in celloidin and sectioned at 20 microns. The serial sections were stained by hematoxylin and eosin. The brain was removed, paraffin blocks were made, and stained with hematoxylin eosin, Einarson's gallocyamin chrome-alum mordant and weil's myelin stain.

The histological examination of the labyrinth disturbed by streptomycin showed

changes in the sensory endings within the peripheral vestibular apparatus; The cristae and maculae display a distinct resuction of sensory epithelium. This forms a band in which numberous dark and nearly round nulei can be recognized but frequently without cellular outlines or cuticular border. The injury starts in the sensory cells, which gradually disappear, while the supporting cells swell and perhaps even multiply. Generally the cristae ampullaris and maculae utriculi show more changes than the maculae sacculi. The degeneration of sensory cells is accompanied by the loss of the sensory hairs, beginning with the loss of single hairs and then expanding over a large surface. The histological examination of the cochlear apparatus of the streptomycin-damaged animal's labyrinth shows more or less pathological changes in all animals, particularly in ihe organ of Corti.

In the severe cases, it disappeared symmetrically on either side of the entire area of the first turn. Where the organ of Corti has disappeared an ascending degeneration of afferent nerve fibers of the ganglion spirale, changes in the ganglion spirale itself, and further degeneration of the fibres leading to the eighth cranial nerve can regularly be demonstrated. The stria vascularis, situated in front of destroyed organ of Corti also exhibits marked pathological changes. The histological examination of the central nervous system of the streptomycin-damaged rabbits, shows certain pathological changes in the form of isolated glia nodules and some degeneration of ganglion cells, located in the area of the vestibular nuclei on the bottom of the fourth ventricle and in the nucleus cochlearis ventralis.

SUMMARY

Histological examinations in rabbits treated with streptomycin from 100 mgs per kilo daily to 400 mgs per kilo daily are demonstrated. In all animals which vestibular function is abolished or dimished, were found degeneration of the nerve cells, in the central vestibular and cochlear nuclei, corresponding with clinical effect on the animals.

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