

TOXIC EFFECT OF STREPTOMYCIN UPON BALANCE AND HEARING

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The curious and damaging affinity of streptomycin for the eighth-nerve system was recognized by Hinshaw and Feldman (1945) soon after its introduction into clinical practice. They found that the earlier compounds, the calcium and sulphate salts, affected mainly the vestibular part of the eighth-nerve system, causing a disturbance of balance, though it was noted that sometimes deafness also followed prolonged use of the drug owing to intoxication of the cochlear system as well.

The disturbance of balance caused by intoxication of the vestibular system was often so inconvenient and disabling that a search was made for a compound of streptomycin without these undesirable toxic effects. This led to the introduction of dihydrostreptomycin. Unfortunately this compound proved to have a selective and destructive action upon the cochlear system, causing deafness, though in large enough doses it also affected the vestibular system. It was soon found that deafness was even more inconvenient than giddiness from loss of vestibular sense, and in consequence there has been a retreat from the cochleo-toxic dihydrostreptomycin in favour of the vestibulo-toxic sulphate preparation of streptomycin, though some prefer to use a mixture of the two in what is believed to be subtoxic doses. Nevertheless, instances of disturbed equilibrium and of deafness have been reported after using the mixture.

As we have seen a number of patients crippled by streptomycin therapy, some after small doses, we feel that the time has come to reconsider the toxic properties of streptomycin, with special reference to its effect upon the vestibular system, particularly as many of our patients have been middle-aged or elderly, when the effect of a disordered vestibular system is not easily overcome.

Eighth-nerve System and Streptomycin

The eighth-nerve system consists of two sensory receptors—one for balance and the other for hearing—both of which are housed in the labyrinthine spaces of the internal ear in each temporal bone. The nerve fibres from each set of end-organs are collected within the temporal bone into two nerves—the cochlear, on which lies the spiral ganglion, and the vestibular, on which lies the ganglion of Scarpa. These two nerves leave the temporal bone together as the eighth cranial nerve and after a short course enter the brain stem, where again they separate, the vestibular fibres going to nuclei in the brain stem and cerebellum on the same side, and the cochlear to nuclei on both sides. Thence each is relayed to appropriate motor nuclei in the brain stem and spinal cord, and to higher centres in the temporal lobe.

There has been much discussion about which part of the eighth-nerve system is affected by streptomycin. Earlier workers, Hinshaw and Feldman (1945), Fowler and Glorig (1947), and Winston *et al.* (1948), favoured the nuclei in the brain stem, but more recently it has been held that the end-organs or peripheral ganglia bear the brunt of the toxic effect. Caussé (1949), Ruedi *et al.* (1951), and Hawkins and Lurie (1954) believe that the drug acts peripherally. If

sufficient streptomycin is given both central and peripheral parts of the system can be affected.

Effect of Loss of Vestibular Function

At this stage it will be convenient to consider the effect of loss of vestibular function, as this is the part of the eighth-nerve system usually affected, and the effect and process of compensation are not always fully appreciated.

Balance is governed by impulses received from the vestibular end-organs in the labyrinth. These are aided by visual impressions which often give advance information about a change in balance (for example, uphill, downhill, steps, uneven ground, etc.), while kinaesthetic impressions from the skin, muscle, and joints also aid balance. In fact, man, accustomed as he is to walking with his feet firmly on the ground and in daylight or well-lighted surroundings, is able to do much of his balancing with his eyes and his skin-muscle-joint sense, being quite unaware, except when something goes wrong with it, that he is possessed of a special balancing sense.

The effect of losing vestibular function is governed by the suddenness and degree of the failure. In its acutest form the vertigo, nystagmus, and vomiting can reduce the sufferer to a state of helpless misery. As central control is gradually established these symptoms and signs subside in the course of about three weeks, leaving a residual difficulty in balancing when up and about, and a tendency to momentary dizziness with sudden head movements. Balancing at first is not easy, and even the most adept will walk with a wide base and will need a stick for some time and will have to turn slowly. They will also have to go cautiously on uneven ground or up and down stairs and will have to avoid walking in the dark. Furthermore, they will find that all movements must be planned beforehand and executed deliberately, otherwise they will tend to overbalance. The rate of recovery depends upon the age and also upon temperament. The young make a quick recovery and can adapt themselves well to the loss of the vestibular sense, though they cannot manage if deprived of either of the other aids to balance. On the other hand, patients over 40 usually find it difficult to walk unaided after losing the vestibular sense, and some may be positively crippled. Much, however, depends upon temperament and training, and the following case record shows what a good recovery can very occasionally take place.

Mrs. A. S., aged 58, had 2 g. of streptomycin sulphate daily for 10 days for bronchiectasis. After this each vestibular labyrinth remained unresponsive to caloric stimulation, but the patient was a woman of great determination who had fought against chronic ill-health for many years; and within two months she was able to resume her household duties and go out shopping unaided.

When the loss of vestibular function is less sudden and incomplete the clinical picture is less dramatic and less obvious. Nevertheless, if it is not recognized as such it can be disabling, and we have always found that demonstrating a definite organic cause for the symptoms is the first stage in the management of disturbed vestibular function. Patients are encouraged to walk and balance, using the special head and balancing exercises devised at King's College Hospital by Cawthorne (1946) and Cooksey (1946). Most patients are able to get about again within a few weeks, though the older among them have to use one or even two sticks. The young are usually able to adapt themselves to altered conditions of balance sufficiently well to be able to get about unaided and to do most forms of work. Older patients, however, find it very difficult to readjust. If their plight is not appreciated and vigorous measures are not undertaken to get them moving again, they may well remain in bed or at any rate be chair-ridden.

For these reasons we feel that loss of vestibular function can be a serious disability and that all who use streptomycin should be fully aware of its potentially disabling properties even, at times, after a dose as small as 3 g. given in three days.

Sometimes the vestibular disturbance seems to be more than usually disabling, as the following case record shows.

Mrs. S. M., aged 26, lost vestibular function on one side only after 29 g. of streptomycin sulphate given over a month for tuberculous salpingitis. With one normally acting labyrinth she was in the same state as those patients who have one labyrinth destroyed on account of Ménière's disease. Such patients invariably respond well to balancing exercises and are able to return to an active life after a month. However, despite the fact that she was young, of a cheerful disposition, and keen to recover, she was unable to walk unaided after six weeks of balancing exercises. This we feel may well be due to damage to the central vestibular system in the brain stem as well possibly as in the labyrinth. In such an event it is likely that the normal compensating processes which are believed to be due to the tonic action of the vestibular nuclei are interfered with, thus delaying recovery.

Properties of Streptomycin

Streptomycin is prepared from *Streptomyces griseus* and is second after penicillin in the antibiotic hierarchy. It is available as the sulphate or dihydro salt and is usually given by intramuscular injection, though it can be used in addition intrathecally, injected into the pleural or peritoneal cavity, or given by inhalation. Orally it is effective only within the gastro-intestinal tract, and locally on the skin or in wounds it is apt to cause local reaction. Like penicillin it is bacteriostatic and in large doses is bactericidal, and is particularly useful in combating infections caused by *Mycobacterium tuberculosis*, *Escherichia coli*, *Pseudomonas pyocyanea*, *Proteus vulgaris*, and certain other Gram-negative organisms as well as many of the Gram-positive. It is used for tuberculous infections and, because of its action on Gram-negative organisms, for infections of the gastro-intestinal tract and the genito-urinary tract. It is also used for certain infections by Gram-positive bacteria which are resistant to penicillin, and sometimes it is given in combination with penicillin.

Unlike penicillin, which is excreted by the renal tubules, it is excreted by glomerular filtration. With each antibiotic the serum level cannot normally reach more than a certain height despite the dosage, owing to the filtering-off action of the kidney. If renal excretion is impaired then the level of the antibiotic in the serum may reach a higher level than in the normal subject. This is one reason why some cases of toxic manifestations following even a small dose of streptomycin have been reported; and is illustrated by the following cases.

Mrs. A. H., aged 65, who was suffering from pyelonephritis in her only functioning kidney, lost all vestibular function after a total dose of 3 g. of streptomycin sulphate, 1 g. being given on each of three successive days.

Mr. B. S., aged 25, had pyelitis in his only kidney, the other having been removed five years previously. He was given only 0.5 g. of streptomycin sulphate daily for one month, and at the end of this time he had lost all vestibular function.

Thus streptomycin should be given only in small doses and with great caution to patients with renal dysfunction.

It is generally believed that as much as 1 g. a day of streptomycin is well tolerated for several weeks, and the toxic effects are usually noticed only when more than 1 g. a day is given for at least a fortnight.

Glorig (1950), however, has found that intoxication is by no means uncommon with smaller doses than 1 g. a day, and this has also been our experience, as the following case shows.

Mrs. R. G., aged 72, who was suffering from recurrent bronchitis following coronary thrombosis, was given a course of injections of streptomycin sulphate, 1 g. each day. After three days she noticed some dizziness, and as this seemed to get worse the streptomycin was discontinued after five days, when 5 g. in all had been given. Despite this she was so disabled by a disturbance of balance that she could not leave her bed for over three months and then she could walk only a short way with a companion, and with the aid of a stick after a further two months. Examination revealed a severe impairment but not complete loss of response to caloric stimulation of the vestibular labyrinths, and this defect has remained unchanged for one year.

Generally the toxic effect of streptomycin on the eighth-nerve system is irreversible; though in a fortunate few some recovery of function takes place if the drug is withdrawn soon after symptoms have appeared, as the following example shows.

Mrs. T. K., aged 63, was given 1 g. of streptomycin sulphate daily for four days following resection for carcinoma of the rectum. She became very giddy and gave no response to caloric stimulation of each labyrinth. When tested four years later the right labyrinth responded normally to caloric stimulation though the left was still unresponsive.

No doubt the ability to compensate in part for loss of vestibular function has led to the belief that return of function after the drug has been stopped happens much more often than is really the case.

On the other hand, it has been suggested that vestibular function can continue to deteriorate after the withdrawal of the drug, though we do not believe that such an unfortunate state of affairs can be very common.

Progressive loss of hearing after the withdrawal of dihydrostreptomycin is also reported, and the following case shows how disturbing this can be.

A professional man aged 39 received daily 1.5 g. of dihydrostreptomycin by intramuscular injection, and 0.1 g. intrathecally for six weeks, because of tuberculous meningitis. He recovered from the infection, but lost the function of one vestibular labyrinth and some of the hearing in each ear. After the drug had been stopped the hearing continued to deteriorate for three months. A hearing-aid gave him but little assistance, and despite great efforts he was unable to keep up his profession. He became more and more depressed and finally took his own life.

Another effect of streptomycin which can be distressing, though fortunately it is reversible, is upon the skin. Skin reactions may vary from a mild dermatitis to a severe and extensive exfoliative dermatitis, and the following case is an example of this and of vestibular destruction.

P. M., a boy aged 13, developed an aching left ear after a head cold, and two days later the ear began to drip clear fluid at the rate of half a teacupful in three hours. He was admitted to hospital and given systemic penicillin pending further investigations. Two days later the ear discharge became purulent and signs of meningitis appeared. Pus from the ear grew *Ps. pyocyanea*. He was given streptomycin, 0.9 g. daily intramuscularly and 0.1 g. daily intrathecally. After 10 days the left mastoid was opened and two days later the streptomycin was stopped because of generalized exfoliative dermatitis. Within a week the dermatitis had almost entirely cleared and the cerebrospinal fluid was normal. The boy made a complete recovery except for loss of vestibular function. He soon adjusted to this, and when last seen, eight years after his illness, he had been in employment as a tractor driver for three years. Despite absence of vestibular function his disability was noticeable only when he tried to walk with his eyes closed, and he volunteered the information that he was unable to swim and in fact was afraid of the water, this of course being due to loss of visual and kinaesthetic aids upon which he had to rely for maintaining balance.

Ménière's Disease

It has been suggested that the toxic effect of streptomycin upon the vestibular system should be turned to advantage in the treatment of Ménière's disease, where the disordered vestibular system can be ablated without any harm to the hearing.

Unfortunately, streptomycin can act equally upon each vestibular system whether diseased or not, so that when Ménière's disease is unilateral and the patient is over 40, to abolish both sides of the vestibular system may well end up by the cure being worse than the disease, as the following case record shows.

Mr. W. W., aged 56, had been troubled with bouts of severe vertigo and vomiting for three years. Before each attack the slight but persistent noise in his left ear increased and the hearing in that ear was also affected. In between attacks, however, he was quite well and the hearing in the left ear was only slightly affected. A caloric test of vestibular function revealed a moderate impairment of response on the left side only. Nothing influenced the frequency and severity of the attacks, so, in view

of the good hearing on the left side, it was decided to try the effect of a course of injection of streptomycin. He was given 2 g. daily for four weeks, after which there was no evidence of any remaining vestibular function on either side. When we first saw the patient a year later he was still unable to walk at all. After a course of special balancing exercises he was just able to get about with the help of a companion and a stick, but it was an effort both for him and for his companion and he could not venture up or down stairs or beyond his own small garden; he was quite definite that if he could he would change back to his attacks and good balancing between-whiles.

There are, however, occasions when the deliberate intoxication of the vestibular system in cases of bilateral Ménière's disease is justified.

The two cases just described illustrate very well how much more disabling loss of vestibular function is in older as compared with younger persons such as the boy P. M. Ruedi (1951) and others have hoped that in Ménière's disease function in the affected labyrinth is more readily destroyed than that in the healthy labyrinth. This has not been our experience, though this is not to say that the toxic effect is always bilateral and symmetrical, and we have seen several patients in whom only one side was affected. The case of one of these, Mrs. S. M., has already been described.

Increased Incidence of Vestibular Damage

We seem to have seen more patients recently with absence of or disordered vestibular function following the administration of comparatively small quantities of streptomycin; and the Table includes all those patients listed in years since 1951 who have shown symptoms and signs of intoxication after a total dose of less than 20 g. of streptomycin.

Patients Exhibiting Toxic Effects of Streptomycin Where the Total Dose has been Less than 20 g., 1951-6

Name	Age	Daily Dose (g.)	Total Amount (g.)	Condition for which Given	Hearing	Vestibular Function
1951: Mrs. M. B. Mr. P. D.	48 62	2 1	10 11.5	Cystitis Fistula in ano	Unaffected "	R. lost L. lost. R. impaired
1952: Mrs. T. K. Mrs. H.	63 50	1 2	4 9	Resection of colon Nephrectomy	" Slight high tone loss. Both	Both lost Both slightly impaired
Mrs. L.	44	1	16	Tuberculosis in solitary kidney	Severe deafness. Both	Normal
1953: Mrs. S. M. Mr. C. W.	50 66	1 2	5 8	Renal calculi Retention of urine	Unaffected "	Both impaired L. lost. R. impaired
1954: Mr. L. D. Mr. B. S.	68 25	1 0.5	12 15	Pulmonary tuberculosis Pyelitis solitary kidney	" "	Both lost " "
1955: Mrs. P. Mrs. F. P. Mr. S. H.	63 50 41	2 1 1	11 16 12	Resection of colon Pulmonary tuberculosis Bazin's disease	" " Moderate deafness. Both	L. lost Both impaired Normal
Mrs. A. H.	65	1	10	Pyelitis	Unaffected	Both lost
1956: Mrs. A. W. Mrs. C. R. Mrs. K.	61 56 46	1 1 1	5 7 8	Arthrodesis of toe Hernia Nephrectomy	" " "	" " R. lost " "
Mrs. G. G.	47	1	14	Pulmonary tuberculosis	"	" "
Mrs. M. P.	63	2	16	Broncho-pneumonia	"	" "
Mrs. A. K. Mrs. F. S.	42 50	1 1.5	3 15	Laparotomy Perianal abscess	" "	R. impaired Both lost
Mrs. R. G.	72	1	5	Bronchitis	"	Both impaired
Mrs. J. A.	40	2	10	Nephrolithotomy	"	R. lost

We think that this increasing incidence may be due to a more general adoption of the custom of carrying out tests of sensitivity to different antibiotics on infected material. Streptomycin is usually one of the antibiotics tested, and if the infection is found to be more susceptible to streptomycin than to any other antibiotic, the clinician may decide to use it in preference to the others. Although he may be aware of the toxic effect of streptomycin upon the eighth-nerve system, we have the impression that a dose of 1 g. a day for two weeks is generally regarded as being a safe dose. Many of the infections tested for antibiotic sensitivity are particularly sensitive to streptomycin, and this applies especially to infections of the lower respiratory, the lower digestive, and the urinary tracts.

It may well be that the incidence of vestibular damage when the dosage of streptomycin does not exceed 1 g. a day for two weeks is low; but it is there, and we are finding it to be on the increase. For these reasons we believe that all clinicians should be aware of the possible consequences of the use of streptomycin even in small doses over a short period of time.

Reports that the pantothenate salts of streptomycin reduce ototoxicity have not been confirmed, but work is still continuing on the development of other preparations of the drug. Thus it seems that there is some hope that a less toxic form of streptomycin may soon appear.

For the present, however, until we are sure of this it behooves all who use streptomycin to do so as sparingly as the infection will allow, and to be prepared to withdraw it at the first symptom of ototoxicity.

Finally, if the daily dose does not exceed 0.5 g. toxic symptoms are unlikely to occur, except when there is renal insufficiency, and in such an event streptomycin should, if possible, be avoided. It is, of course, appreciated that to control certain serious infections such as tuberculosis a daily dose of 1 g. may be necessary.

Summary

The ototoxicity of streptomycin is discussed and the effect of intoxication of the vestibular part of the eighth-nerve system is described.

Though it is generally believed that toxic symptoms are unlikely to appear so long as the daily dose does not exceed 1 g., several instances are given in which intoxication occurred even though this dosage was not exceeded.

The number of cases of intoxication is on the increase, and this may be due to a wider use of streptomycin as the result of sensitivity tests.

Renal insufficiency, by permitting a high concentration of streptomycin in the blood, renders a patient unduly susceptible to the drug.

It is concluded that symptoms of intoxication are unlikely to occur so long as the daily dose of streptomycin does not exceed 0.5 g.; though it is appreciated that in serious tuberculous infections as much as 1 g. a day may be needed.

We would like to thank all our colleagues at the National Hospital for Nervous Diseases, Queen Square, the Middlesex Hospital, King's College Hospital, the London Chest Hospital, and elsewhere for referring their patients to us, and to Dr. H. M. Walker for the help he has given.

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