Ototoxicity In Cats Following Toxic Doses Of Streptomycin

T. Manford McGee
OTOTOXICITY IN CATS FOLLOWING TOXIC DOSES OF STREPTOMYCIN

T. Manford McGee, M.D.

The toxic effects of streptomycin sulfate in patients on long-term therapy have been observed by many clinical investigators. The toxic effect usually is centered around a dysfunction of the vestibular mechanism, and is manifested by ataxia and vertigo\textsuperscript{1,3,4}. Many patients receiving large doses have experienced temporary hearing loss and a few have sustained permanent partial deafness\textsuperscript{1}. A number of investigators have subjected animals to toxic doses of streptomycin, but their observations conflict as to the site of the organic lesion. Causse,\textsuperscript{5} Hawkins\textsuperscript{6} and Berg\textsuperscript{7} have described degenerative changes in the vestibular sense organ and organ of Corti. Christensen et al.,\textsuperscript{8} and Winston et al.,\textsuperscript{9} on the other hand, concluded that the organic changes were in the vestibular neural pathways.

A controlled study was designed to further clarify the site of the toxic effects of streptomycin and relate the lesions to alterations in vestibular and auditory functions. Pathological studies of the inner ears have been completed in some of these animals, and the organic changes in the sense organs can be correlated with the functional alterations.

The experimental group consisted of 7 healthy adult cats. Each cat had one ear surgically destroyed. Following recovery from this procedure, base-line vestibular tests and audiograms were made. In the test of vestibular function the animals were placed on a rotating table with the head over the axis of rotation of the table, turned at the rate of 1 turn per second for 10 seconds, and abruptly stopped. The duration of post-rotational nystagmus was determined for turning to both right and left. This test, carried out in the horizontal plane of the head, indicates the functional state of the crista of the horizontal canal.

Base-line cochlear function was evaluated by obtaining a series of reproducible audiograms for each animal before, during and following treatment with streptomycin. These were done utilizing conditioned response techniques\textsuperscript{10} by which the animals are trained to avoid shock by moving forward in a rotary cage in response to auditory stimuli. Because the objective of the experiment was to study toxic effects, the dosage and duration of administration varied considerably in the different animals, with the functional tests serving as a monitoring method for determining the state of toxicity. The animals were injected intramuscularly with streptomycin sulfate (Squibb) in doses varying for the different animals from 25 mg. per kilogram to 200 mg. per kilogram per day in two equally divided doses. When the desired toxic effects had been obtained the animals were kept for one year, sacrificed by intra-vital perfusion, and the ears and brains prepared for pathological study.

Results: Four of the 7 animals experienced a permanent high tone hearing loss at the completion of treatment. Six cats exhibited a loss of post-rotary nystagmus, but in 3 of these there was partial return (Table 1). Ataxia developed simultaneously with the loss of post-rotary nystagmus. The animals tended to fall to one side, and walked

\textsuperscript{*}Division of Otolaryngology
with a wide base, or refused to walk at all. They could not be persuaded to jump and had peculiar searching movements of the head. The ataxia was severe for 2-3 weeks, after which there was gradual improvement, but even at the end of one year the gait had not returned to normal. All animals demonstrated a weight loss while receiving the drug.

The findings in two representative animals will be presented:

Cat 3 received 75 mg. per kilogram of the drug for 29 days. Post-rotary nystagmus for turning both to the right and left was lost on the 30th day. Partial recovery on turning to the right was noted on the 82nd day after the drug was stopped (Fig. I.). There was a temporary high frequency deafness, but the auditory thresholds were normal after several weeks (Fig. II.). The cat was killed one year after drug administration and the cochlea was found to be normal (Fig. III.). There was near-total loss of hair cells of the cristae of all three semi-circular canals and the utricle and saccule. These pathological findings were consistent with the ataxia and loss of post-rotary nystagmus.

Cat 7 received 200 mg. per kilogram per day of streptomycin and lost post-rotary nystagmus on the 11th day of treatment (Fig. IV.). The drug was administered for 28 days. A high tone hearing loss appeared on the 20th day and remained during the 1 year observation period (Fig. V.). Ataxia was severe, and remained so until the animal was sacrificed. Histological examination revealed almost total loss of hair cells in the basal 7 mm of the cochlea and partial loss in the 12-17 mm region (Figs. VI & VII.). The sensory epithelium of the cristae and maculae was severely degenerated throughout with no hair cells remaining. (Fig. VIII.).

Summary: Toxic doses of streptomycin sulfate damage first the sensory epithelium of the vestibular labyrinth (i.e. cristae and maculae) and if administration of the drug is continued the organ of Corti is also affected. The first order neurones of the vestibular and cochlear systems do not appear to be affected directly by the drug.

Studies of the higher pathways in the brain have not yet been completed. The persistent severe ataxia manifested by some of the animals leads us to wonder if
Ototoxicity Following Streptomycin

Cat 3. Post-rotary nystagmus in seconds is plotted as a function of time in days after the onset of streptomycin treatment. Dosage: 75 mgm per kilogram per day for 29 days.

Figure 1

Cat 3. Audiograms taken immediately after streptomycin treatment revealed a high tone loss. After 3 weeks the hearing had returned to normal and remained so.

Figure 2
Cat 3. Graphic reconstruction of the cochlea, showing normal numbers of hair cells (black dots) throughout.

Cat 7. Received 200 mgm per kilogram per day for 28 days. There was no recovery of post-rotary nystagmus during the one year observation period.
Ototoxicity Following Streptomycin

Figure 5
Cat 7. A high tone hearing loss persisted for 1 year after streptomycin treatment.

Figure 6
Cat 7. Graphic reconstruction showing complete absence of hair cells in the lower basal turn and a partial loss in the 12-17 mm region.

Figure 7
Cat 7. Organ of Corti, from the 16 mm region (see arrow, Fig. 7) "I" indicates normal inner hair cells, "O" the normal first outer hair cell, "M" the location of missing outer hair cells, and "H" the flattened Hensen's cells with granular cytoplasm.
there may not be some brain changes. On the other hand, it may be that cats compensate for vestibular losses less well than humans because of the relatively greater importance, for them, of the vestibulo-spinal pathways; i. e., the neck reflexes are better developed in the cat. This may account for the fact that cats have a permanent head tilt after destruction of the labyrinth, and peculiar, rolling, searching movements of the head following destruction of the labyrinth with streptomycin (not true of humans). The experiment has shown that streptomycin sulfate has a direct toxic effect on the vestibular and cochlear sense organ. Because the measurable functional deficits are consistent in magnitude with the degenerative changes in the sense organ, it is doubtful that there is also a direct toxic effect on the brain. Studies are now in progress to determine whether or not the drug also has some effects on the central nervous system.

REFERENCES


Ototoxicity Following Streptomycin


