TRANSIENT HEARING LOSS FOLLOWING ADMINISTRATION OF FUROSEMIDE — A STUDY CONDUCTED ON GUINEA PIGS

MOHAN KAMESWARAN,* MOHAN VISWANATHAN,*
M. KANNAPPA REDDY,* MUTHULAKSHMI BHARATHY* AND
S. KAMESWARAN*

Introduction

Furosemide is a new and potent diuretic which has become very popular with physicians in the management of oedema, especially in patients with severe cardiac decompensation (e.g. Pulmonary oedema due to its substantial antihypertensive effectiveness). This study was undertaken following reports of sensorineural hearing loss in the human beings with poor kidney function, the very patient treated with these diuretics and experimental induction of deafness in guinea pigs following administrations of either Furosemide or Ethacrynic acid — another new diuretic very closely related to Furosemide in its pharmacological properties.

Chemistry

Furosemide is a monosulfamoyl anthranilic acid derivative which has greater diuretic efficacy than chlorothiazide.

The carboxyl group is a common feature amongst two diuretics — Furosemide and Ethacrynic acid, both of which have been credited with similar mechanism of action and a similar effect on hearing — namely inducing a sensorineural disturbance in hearing.

Recent Trends in the Field

Impairment of hearing, transient and permanent has been reported by several groups of workers (V. K. G. Pillay *et al.*, (1969) Becker and Schneider (1966) and one histopathological study of the temporal bone following ethacrynic acid therapy has also been published but all these studies lack precision and present a complex picture. In most cases the hearing loss could have been contributed by one or more of several factors like electrolyte imbalance, hepatic coma, other oto-toxic drugs, etc.

• Departments of Oto-Rhino-Laryngology **and** Pharmacology, Madras Medical College, Madras.

More recently Cedric A. Quick, Arndt, J. Duvall and others (1970) have done substantial work in this field. They inject Ethacrynic acid intra-venously into guinea pigs and reported loss *of* hearing in animals receiving high doses within 4-6 minutes and in most animals the hearing did not return within the time of sacrifice which was by 5-6 hours. Electron microscopic study of the cochlea revealed morphological changes confined to the striavascularis and outer hair cells. There was atrophy of the intermediate cells and less damage to the marginal cells. The basal cells, spiral ligament and spiral prominences were ultrastructurally normal. With administration of horseradish peroxidase, the pathway of this foreign protein could be traced into the intercellular spaces between the marginal and intermediate cells, after egress from the vessel, to be picked up by the intermediate cells which are the primary target of damage by ethacrynic acid. Bearing these recent advancements in mind, the oto-toxicity of the diuretic, furosemide was investigated in guinea pigs.

Methodology

The jugular veins in guinea pig was exposed with a small incision and furoaemide was injected intravenously into the animal in doses varying from 10 mg--220 mg/kg body weight. Hearing was tested by frequent assessment of preyer's reflex and the animal was also tested for any gross vestibular damage.

The animals were divided into the following groups: Group A—-treated with 50 mg/kg body weight... 20 animals. Group B —40 animals — treated with furosemide dose ranging from 10-22(1 mg/kg weight to study the dose-response relationship. Group C — 15 animals treated with 25 mg/kg of furosemide from 7 days to study the effect on hearing of chronically treated guinea pigs, and any possibility of cumulative -toxicity.

Results

In group A of the animals treated with 5 0 mg/kg weight, all the animals became clinically deaf, as indicated by the absence- of preyer's reflex from within 5 minutes to 10 minutes and regained their hearing from within 30 minutes to 1 hour with the majority of the animals recovering in 45 minutes.

In group B an attempt to find a dose response relationship showed that was no strict dose-response relationship and there was a lot of difference in individual response pattern obviously due to individual variations.

It was again observed in group B that most animals, with the exception of animals with very high doses (180-220) regained hearing within 30-75 minutes and even animals treated with very high doses 180-220 mg/kg regained their hearing within 2-3 hours. Thus any possibility of permanent damage to hearing

Was completely eliminated. Hearing loss was observed from 60 mg/kg onwards and this hearing loss was only transient even with doses 200 times the normal human dose. While regaining the hearing, it was observed that hearing returned in stages. In doses below 60 mg/kg no deafness could be clinically found.

In group C — animals with chronic treatment of Furosemide in dose of 25 mg/kg for 1 week — it was observed that there was no cumulative toxicity leading to hearing loss either transient or permanent.

Discussion

The above results leave no doubt that the loss of hearing after administration of Furosemide is purely of a transient nature. While it is not clear what exactly is responsible for this transient deafness direct toxicity to the VIII nerve in the nature of Streptomycin toxicity is ruled out because of the very short duration of deafness and absence of vestibular signs. Whether the toxicity is due to an action on the cochlea similar to its renal action is an interesting probability worth investigating into. Further, any tissue damage being the cause of deafness may also be savely ruled out in view of the transient nature of the ototoxicity. Again chronic treatment of guinea pigs with sub-toxic doses of the drug does not result in any deafness either transient or permanent, thereby eliminating the possibility of cumulative toxicity.

Results are also awaited of a study of the Electron Microscopic patterns in the cochlea during the time of this transient loss of hearing.

Summary

Furosemide has been reported to cause sensori-neural hearing loss in guinea pigs as well as humans. In this study conducted on guinea pigs the following important features were observed.

1. Furosemide causes hearing loss in guinea pigs above doses of 50 mg/kg.

2. The hearing lossistransient and unlike the reported toxicity of ethacrynic acid rarely persists for any duration longer than li hour.

3. In most of the animals the hearing returned within 30-60 minutes and it was observed that hearing returned gradually in stages.

4. Attempts to establish a dose — response relationship revealed a great degree of individual variation in response to standard dose. However the loss of hearing was definitely of a longer duration at higher doses of the drug.

5. Chronic treatment of animals with a smaller dose failed to produce any cumulative ototoxicity.

6. In our experiments there was no evidence of any vestibular damage of any nature.

7. While recovering, the animals seemed to recover hearing in stages.

REFERENCES

1. Pillay, V. K. G., Schwarty$_5$ F. D. and aimi, K., *et al.*, "Transient and permanent deafness following treatment with ethacrynic Acid 'in renal failure—*Lancet* 1, 1977 to 79, 1969.
2. Quick, C. A. and Duvall, A. J., 'Early changes in the oochlear duct from ethacrynic acid—an Electronmicroscopic evaluation '—*Laryngoscopy,* 954, 80$_3$ 1970.
3. Schneider, W. J. and Becker, E. C, ' Acute transient hearing loss after ethacrynic acid therapy' *Archives of Internal Medicine,* 715, 117, 1966.