Contribution of Distortion Product Otoacoustic Emissions (DPOAEs) to the study of aminoglycoside induced ototoxicity

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ABSTRACT: Objectives: The ototoxic effects of aminoglycosides, such as gentamicin and amikacin, are well-established. Otoacoustic emissions have been reported to be more sensitive in early detection of hearing loss than other methods, such as the conventional pure tone audiometry. This study aimed to investigate the ability of the Distortion Product Otoacoustic Emissions (DPOAEs) to detect early changes of the cochlear activity following administration of aminoglycosides.

Materials and method: This is a prospective experimental study. Eight rabbits were included in the study. Three of the subjects were injected intramuscularly with amikacin and another three with gentamicin. One rabbit from each group was injected with a combination of aminoglycoside and furosemide. All the animals were subjected to DPOAEs every two days since the beginning of the experiment for 14 days. Two animals were used as a control group.

Results: Differences in the time of detection of changes of cochlear function were noticed between the animals that received gentamicin, gentamicin and furosemide, amikacin or amikacin and furosemide. The control animals did not present changes of cochlear function over the 14 days of the experiment.

Conclusions: DPOAEs are objective, noninvasive and rapid measures used to determine cochlear function. As a method it has the ability to detect abnormal cochlear activity in early stages when hearing impairment caused by ototoxic drugs, such as aminoglycosides has not been established.

Key Words: Otoacoustic emissions, Ototoxicity, Aminoglycosides, Amikacin, Gentamicin, Loop diuretics, Hearing loss.

INTRODUCTION

Aminoglycosides and loop diuretics are ototoxic drugs that can cause neurosensory deafness.¹² The following groups of patients have a greater risk of presenting hearing loss: (a) patients with hearing loss before the administration of any drug, (b) patients treated with more than one ototoxic drugs and (c) patients who suffer from renal failure.¹

The administration of any kind of aminoglycosides can provoke disturbances of the vestibular and auditory systems.¹³⁴ Studies that have been conducted both on humans and animals, show progressive accumulation of the drugs in the endolymph and perilymph. The accumulation of aminoglycosides is mainly observed when the administered doses are high.¹⁴ Patients with high aminoglycoside plasma concentrations for a long period of time experience the ototoxic effects with a fall of the hearing thresholds at the higher frequencies, tinnitus and vertigo attacks.

Ototoxic injury can be irreversible in many cases. It is induced by the destruction of a great number of auditory cells that are sensitive to the effect of the aminoglycosides.¹ Studies that have been conducted on guinea pigs, following the administration of large doses of gentamicin, revealed degeneration of type I cells of the vestibular system and conversion of isolated sensory cells to giant cells.⁵⁶ Similar studies that monitored the effects of gentamicin and tobramycin administration showed degeneration of the organ of Corti.⁷⁸ The damage of the cochlea starts at the base of the cochlea and if the administration of the drugs is continued, the damage can advance towards the top
of the cochlea. Although aminoglycosides can harm both the vestibular and the auditory system each drug harms mainly a different part. Streptomycin and gentamicin affect in most cases the vestibular system whereas amikacin, kanamicin and neomycin affect the hair cells.

Loop diuretics inhibit the reabsorption of potassium, sodium and chlorine through the ascending limb of Henle’s loop. These diuretics act through inhibiting the sodium-potassium pump. Furosemide is a very effective diuretic of Henle’s loop. Its ototoxicity was observed since the early days of clinical use of this drug. Recent studies showed that ototoxicity due to furosemide is caused by oedema in the stria vascularis. Furosemide also damages the mechanism of ion transduction in the hair cells of the cochlea.

The aim of this prospective experimental study is to investigate the ability of Distortion Product Otoacoustic Emissions to detect the ototoxic effects of aminoglycosides administered alone or in combination with furosemide, by demonstrating at early stages changes of cochlear activity.

**MATERIALS AND METHOD**

Ethics and Veterinary Authorities approval were obtained. Eight one-month-old, New Zealand type rabbits, weighting 450-650 grams, were subjected to intramuscular injection of aminoglycosides for 14 days and were studied prospectively with Distortion Product Otoacoustic Emissions. A baseline examination with DPOEs (GSI 60, Grason Stadler, USA) of the cochlear activity of the animals was obtained from all animals. Abnormal cochlear activity would be an exclusion criterion.

Six rabbits were divided into two groups of three members each. The remaining two were used as the control group. Three animals were injected intramus-
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Particularly with 15 mg/kg/24h of amikacin. The dosage, approved for veterinary therapeutic purposes is 8-16 mg/kg/24h for intramuscular use. Another three animals were injected intramuscularly with 5 mg/kg/24h of gentamicin. The dosage approved for veterinary purposes, is 5-8 mg/kg/24h for intramuscular use. The rabbits of the control group were not given any medication. The medications were administered every twelve hours and the intervention lasted fourteen days. Furosemide (2 mg/kg/24h intramuscularly) was administered in combination with the aminoglycoside to one member of each of the two study groups. These animals were chosen randomly.

The cochlear activity of all rabbits was examined every two days with DPOAEs. The measurements were conducted in a soundproof cabin and the animals were not anesthetized in order to avoid side-effects (Figures 1, 2). The 2f1/f2 (65/55 Hz) protocol for the DPOAEs was used.

**RESULTS**

The effect of gentamicin on the hair cells appears to be less than that of amikacin. The changes are greater for those animals that received a combination of aminoglycoside and furosemide. Disturbance of the cochlear activity was noticed on the fifth day for the rabbits that received amikacin alone or in combination with furosemide. The first recorded reduction of cochlear activity of the rabbits that received gentamicin was noticed on the seventh day since the beginning of the experiment.

The intensity of the DPOAEs, recorded from the beginning of aminoglycoside administration until the 14th day is presented in Table 1. The DPOAEs recorded on the sixth day of administration of amikacin and

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**Figure 1.** DPOAEs of the rabbit which received amikacin and furosemide (6th day after the beginning of the experiment)

**Figure 2.** Recording of DPOAEs in a Faraday Chamber.
furosemide to one of the rabbits are presented in Figure 1. No changes in the cochlear activity were found for the animals in the control group. No vestibular disturbances were observed during the experiment. The small number of animals in each group does not permit statistical analysis of these initial results.

**DISCUSSION**

Audiologic monitoring for ototoxicity detection has become increasingly necessary and complicated. The number of known ototoxic substances is increasing. Numerous factors should be taken into consideration to determine the degree of risk for a patient. The only way to ensure that no patients with ototoxic hearing loss are missed is to provide testing of all patients with any possible risk factors. The selection of monitoring tools is not straightforward. The number of audiologic tests available for the detection of ototoxicity has increased but the relative sensitivity and specificity of each test are not well established.

The purpose of this study was to examine the ability of the DPOAEs to detect the ototoxic effects of aminoglycosides at early stages. Rabbits were used for convenience reasons since they were easier to manipulate during measurements and it was easier to estimate the exact drug dosage comparing to other animals. DPOAEs have been used for the study of hearing loss on rabbits by other researchers too.

DPOAEs were used since they are appropriate to detect early cochlear activity changes. The responses to the stimuli may vary. Although the adjustments should be individualized, in practice this was not possible since the animals were rabbits. The only data available in rabbits is the range of the hearing frequencies. To overcome this we compared the frequencies and the intensity of the distortion product of every measurement with those which were taken prior to the administration.

Ototoxic injuries caused by drugs such as the aminoglycosides\textsuperscript{17,18}, the loop diuretics\textsuperscript{19} and the antineoplastic substances\textsuperscript{20} are very important for the patient’s quality of life, especially when they are administered to children. The rational use of these drugs is based on better insight of the time and mechanisms of ototoxicity. This knowledge underlies the implementation of standardized administration protocols\textsuperscript{26,27}.

Recent studies conducted on both men\textsuperscript{18} and guinea pigs\textsuperscript{21} have shown the importance of the otoacoustic emissions for the early detection of ototoxic effects of the aminoglycosides and antineoplastic drugs. Most ototoxic drugs impair the outer hair cells. Therefore DPOAEs can contribute to the early detection of their ototoxic effects. DPOAEs have the capacity to detect the ototoxic effects of aminoglycosides administered alone or in combination with loop diuretics. The above is shown by a study conducted on guinea pigs\textsuperscript{21} Changes of the cochlear activity were detected at high frequencies. It is believed that DPOAEs are superior to Transient Evoked Otoacoustic Emissions\textsuperscript{4,18,20}. Transient Otoacoustic Emissions are detected when the ear is stimulated by signals, such as transient clicks. The advantage of DPOAEs is that they are specific indicators of cochlear function and able to differentiate between retrocochlear lesions and sensorineural hearing loss.

Until recently, most of the studies focused on the action of salicylates which reduce the automatic and the temporary otoacoustic emissions\textsuperscript{22,23,24}. Most of the evidence regarding cochlear impairment following ototoxic drug administration comes from studies with other methods, such as evoked potentials and pure tone audiometry. Limited research is available regarding recording of cochlear activity changes with DPOAEs for the monitoring of ototoxic effects\textsuperscript{4,18,20}.

More research is needed in order to determine the correlation between the changes in cochlear activity and hearing thresholds changes in serial audiometry\textsuperscript{25,26,27,28,29,30}.

**Figure 3.** The fit of the probe.
ΠΕΡΙΛΗΨΗ:
Σκοπός: Η ωτοτοξική δράση φαρμάκων όπως οι αμινογλυκοσίδες και τα διουρητικά της αγκύλης είναι γνωστή. Οι ωτοακουστικές εκπομπές εμφανίζουν μεγαλύτερη ευαισθησία στην ανίχνευση μεταβολών της κοχλιακής λειτουργίας σε σύγκριση με άλλες μεθόδους εξέτασης όπως το τονικό ακουόγραμμα. Σκοπός της παρούσας μελέτης είναι η διερεύνηση των δυνατών ωτοακουστικών εκπομπών προϊόντων παραμόρφωσης για να ανιχνεύσουν πρώιμες μεταβολές της κοχλιακής λειτουργίας κατά τη χορήγηση αμινογλυκοσίδων.

Υλικά και Μέθοδος: Προοπτική πειραματική μελέτη. Οκτώ ανήλικα κουνέλια τύπου Νέας Ζηλανδίας μελετήθηκαν. Σε τρία από αυτά χορηγήθηκε ενδομυϊκά αμικασίνη και σε άλλα τρία γενταμικίνη. Σε ένα πειραματόζωο από κάθε ομάδα χορηγήθηκε συνδυασμός αμινογλυκοσίδης και φουροσεμίδης, μετά από τυχαία επιλογή ενός ζώου. Τα υπόλοιπα δύο κουνέλια χρησιμοποιήθηκαν ως ομάδα ελέγχου. Η χορήγηση των ωτοακουστικών φαρμάκων έγινε επί 14 ημέρες και ανά δύο ημέρες καταγράφονταν η κοχλιακή δραστηριότητα των ζώων με την μέθοδο των ωτοακουστικών εκπομπών προϊόντων παραμόρφωσης.

Αποτελέσματα: Οι διαδοχικές εξετάσεις κατέδειξαν το διαφορετικό χρόνο εμφάνισης μεταβολής της κοχλιακής δραστηριότητας για κάθε αμινογλυκοσίδη, μόνη της ή σε συνδυασμού με φουροσεμίδη. Στην ομάδα ελέγχου δεν παρατηρήθηκαν μεταβολές της κοχλιακής λειτουργίας των πειραματών.

Συμπέρασμα: Οι διαδοχικές εξετάσεις κατέδειξαν το διαφορετικό χρόνο εμφάνισης μεταβολής της κοχλιακής δραστηριότητας για κάθε αμινογλυκοσίδη, μόνη της ή σε συνδυασμού με φουροσεμίδη. Στην ομάδα ελέγχου δεν παρατηρήθηκαν μεταβολές της κοχλιακής λειτουργίας των πειραματών.

Αποδεικνύεται η εκπληκτική δύναμη των ωτοακουστικών εκπομπών προϊόντων παραμόρφωσης στη μελέτη της ωτοτοξικής δράσης των αμινογλυκοσιδών και των διουρητικών της αγκύλης.

Λέξεις Κλειδιά: Ωτοακουστικές εκπομπές, Ωτοτοξική δράση, Αμινογλυκοσίδες, Αμικασίνη, Γενταμικίνη, Διουρητικά της αγκύλης, Βαρηκοΐα.

REFERENCES


