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Review

Monitoring Ototoxicity through Otoacoustic Emissions. Present, COVID-19, and Future Related Insights

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ABSTRACT

The administration of certain drugs is directly related to inner ear damage. Due to the potential of these elements and their usage, more extensive monitoring of adverse effects should be implemented. That is why, baseline evaluation for ototoxicity must be adequately extensive and should embrace conventional PTA thresholds, HFA, immittance measurements, speech audiometry in quiet and in noise, and assessment of OAEs. Health care specialists have reasonably quested other test modalities for ototoxic monitoring, in their effort to eliminate behavioral – subjective testing and even more establishing further improvements in test efficacy. To iterate, drug induced ototoxicities typically are initially presented as OHC dysfunction, and the exact correlation between present OAEs and functional OHCs is fairly well demonstrated. This study provides recent evidence regarding OAEs' strategic advantages as a part of an ototoxicity monitoring program, as they can detect earlier ototoxic induced thresholds shifts, do not need patient's own cooperation and are substantially easy to perform and quick. This fact is particularly crucial during present COVID-19 pandemic where ototoxic agents such as chloroquine and hydroxychloroquine are routinely administered in many patients who may be too sick and haggard to perform adequately enough in conventional PTA or similar, behavioral based exams.

Keywords: *Ototoxicity; OAEs; DPOAEs; TEOAEs; Ototoxicity monitoring; COVID-19.*

INTRODUCTION

Otoacoustic emissions (OAEs) represent sounds computed in the outer ear, normally from 0 to 20 dB, that reflect normal function of the Outer Hair Cells (OHCs) inside the cochlea.[1] OAEs are generated by the energy derived of OHCs' displacement that is transmitted from the inner ear through the middle part, oscillating the tympanic membrane, and distributing outwards into the outer part.[1]

OAEs are routinely used in the field of current everyday practice for many applications; from newborn hearing screening to establishing diagnosis of the various audio-vestibular pathologies. Nevertheless, OAEs are not a test of hearing. As stated previously, they merely represent a scale of healthy OHC function.[1]

Two types of OAEs are utilized for every day clinical usage, Transient Evoked OAEs (TEOAEs) and Distortion Product OAEs (DPOAEs). TEOAEs are produced after very short (transient) sounds, like clicks and tone bursts, generated at a magnitude of 80 dB SPL. TEOAEs reflect cochlear (OHC) health and are typically measured over the frequency range of 500 up to about 5500 Hz with the current clinical equipment available.[1] DPOAEs are induced with volumes of pairs of pure tone frequencies, stated as f2 and f1, that are tightly seperated and exhibited at the same instant, at intermediate intensities, most often at 55 and 65 dB SPL respectively.[1,2] DPOAEs can be clinically measured during every day clinical practice across from 500 up to 10KHz (and nowadays can reach up to 14KHz, with the aid of ultra-high frequency DPOAEs (UHF DPOAEs), which start becoming commercially available).[1,2]

OTOTOXIC AGENTS

Certain drug administrations cause impairment to the Hair Cells (HC) of the cochlear and vestibular apparatus in a dose-dependent way and

are known as 'ototoxic'. Such ototoxic agents mainly include loop diuretics, especially when administered at high doses, anti-cancer drugs (such as cisplatin and carboplatin), non-steroid anti-inflammatory drugs (and salicylates), vancomycin, quinine, chloroquine, hydroxychloroquine, macrolides, and aminoglycoside antibiotics.[3,4]

By far, the most often utilized ototoxic medications are the platinum deratives, loop diuretics, non-steroidal anti-inflammatory substances and aminoglycosides.[4]

MAIN OTOTOXIC DRUGS' RELATED MECHANISMS AFFECTING OUTER HAIR CELLS

Due to their contingency on healthy OHC metabolism, OAEs are extremely dependent on the mildest OHC change of function.[4] The majority of injuries to the cochlea initially influence the OHCs. Drug related vascular, hypoxic, or metabolic deficits will be concomitantly accompanied by diminished OAE magnitude.[4] That is why when middle ear is within normal limits, OAE deficits signalize primal and persuasive proof of cochlear and more specifically OHC dysfunction.

Regarding platinum derivatives, such anticancer inorganic compounds are a crucial part of the current arsenal against a plethora of neoplasms.[4] HCs and spiral ganglion neuronic bodies are particularly prone to death and those located at the basal cochlear turn show greater degeneration than those located at the apical turn.[4] Such constructive modifications are directly correlated with shifts in hearing sensitivity starting at higher frequencies and moving to lower ones. In addition, cisplatin damages the stria vascularis causing depression of the Endocochlear Potential (EP) and thus directly affecting the functional status of cochlear cells.[4,5]

Aminoglycosides are even today the drug of choice for TBC and heavy bacterial infections. Aminoglycosides (which among others include neomycin, kanamycin, gentamicin, and amikacin) act directly upon the cochlear hair cells, damaging initially the OHCs, then the inner hair cells, with a base to apex directional gradient.[4]

Loop diuretics are routinely utilized to alter the constitution along with the amount of body fluids to manage diseases like increased blood pressure, congestive heart failure, renal dysfunction, liver disease, and nephrotic syndromes.[4] The most frequently used substances include bumetanide, furosemide, and ethacrynic acid.[4] Their molecular action involves the discharge of sodium from the marginal cells into the intrastrial space thus creating loss of volume of strial marginal cells, edema of strial intermediate cells and extracellular swelling of the intrastrial space. These alterations disrupt the endocohlear potential, which is crucial for the production of normal intensity voltage from the HCs.[4]

Non-steroidal anti-inflammatory drugs (NSAIDs) and salicylates are utilized as analgesic antipyretics, anti-coagulative, anti-inflammatory substances, and in the prophylaxis of heart failure, vascular thrombosis, and colorectal cancer.[4] Salicylates typically reversibly prevent the transportations of anions across cell membranes, a fact that can inhibit OHCs' electromotility, adversely affecting the cochlear amplifier and thereby contributing to their ototoxic effect. Moreover, the mechano-sensory function of the OHCs, may be also compromised by high-dose NSAIDs along with minor alterations in the stereocilia of HCs leading to a reduction of the OAE amplitude in general.[4]

Finally, chloroquine and hydroxychloroquine, as prophylactic treatment against COVID-19 infection, can also induce ototoxicity sensitive to OAEs screening. They can directly and indirectly affect OHCs' function with mechanisms analyzed later on the paper.

TARGETS OF OTOTOXICITY MONITORING

Searching for potential ototoxicity is mainly useful for 2 reasons. This lies on the fact that the term "ototoxicity monitoring" expresses not only the principle of early identification, but also that of early intervention.[4] The first purpose encompasses the idea of primal diagnosis of thresholds shifts most likely related to a specific agent administration. Should such threshold shifts be detected early, further changes in the drug dosage or different management options, perhaps involving less ototoxic drugs, may be taken into account.[4] The second purpose refers to proper management should severe hearing deficit has already taken place. Sadly, this induced auditory deficit may be more than often inevitable even after meticulous ototoxicity monitoring, as the ultimate goal remains the effective management of the major, probably life threatening, disease itself via the prescribed drug therapy.[4]

In this case, when typical threshold shifts do occur, especially such shifts which have managed to reach the speech frequencies, the rationale behind ototoxicity monitoring focuses on the rehabilitation of an auditory deficit that cannot be managed medically. Priorities are then re-established to help the patient along with his/her relatives to efficiently communicate, particularly as hearing loss advances.[4,5] Such type of interventions can endorse among others counseling, communication plans of action, hearing aids along with other assistive listening devices.[4,5]

UP TO DATE OPTIONS FOR OTOTOXICITY MONITORING

Currently, ototoxicity monitoring targets undoubtedly peripheral auditory function. 3 main approaches regarding monitoring for ototoxicity are fairly well established: the basic Pure tone Audiologic Assessment (PTA) from 125Hz to 8KHz, High Frequency Audiometry (HFA) that reaches up to 20KHz, and the various types of OAEs measurements.[4] All these measurements differ in utility, reliability, purpose and applicability to particular patient populations. They can be utilized together or apart depending on the clinical purpose, available equipment and specific patient considerations.

Regardless of the potential protocol, ototoxicity monitoring needs an initial baseline measurement for future referrals. Every baseline screening should be completed before any potential ototoxic agent administration, so that future findings can be ideally compared to the most well-defined basis. Taken into account the high prevalence of pre-existing hearing loss in the general population, particularly (but not exclusively) affecting the elders, the absence of a baseline testing prior to drug administration makes it considerably harder to demonstrate a clear connection between a pre-existing and a drug induced threshold shift.

The initial assessment must encompass every measurement which may be taken into account in follow up testing, even when only one test is decided to serve as the future follow-up monitoring. If an alteration does take place on the follow-up screening, thorough testing will be utilized then, to evaluate whether the shift is attributed to the medication, or elsewhere like middle ear infection, that is typically found in such patient populations.[4,6]

That is why, baseline evaluation must be adequately extensive and should embrace conventional PTA thresholds, HFA, immittance measurements, speech audiometry in quiet and in noise, and assessment of OAEs.

OAES VERSUS CONVENTIONAL AND HIGH FREQUENCY AUDIOMETRY

The primal effects of ototoxic medications seem to target the OHCs tonotopically situated at the base of the cochlea.[4] Ototoxic threshold changes at the beginning tend to appear involving a narrow sweep of frequencies next to the most superior frequencies perceived by each patient. The majority of threshold shifts are found to take place within one octave of the highest detected frequency in every patient.[4] This range is proved to be specific for every patient and closely related to his' / her's hearing status and conformation.

The basic PTA assessment, conventionally limited to frequencies up to 8KHz, regrettably, does not allow the sooner possible discovery of such ototoxic induced shifts. Nevertheless, during the follow up process, besides monitoring for threshold shifts, it is crucial for evaluating the patient's capability to understand speech for communication purposes under everyday conditions. Typically, defining both air and bone conduction thresholds along with immittance measurements and acoustic reflexes, can easily exclude a middle ear pathology and evaluate the most crucial frequencies for speech comprehension.[4]

HFA ranging up to 16-20kHz permits earlier detection of ototoxic effects that initially tend to take place basalward, such as aminoglycoside and cisplatin related ototoxic deficits.[4,5] These losses can be detected sooner with regards to those detected with the conventional PTA.[4]

Hesitance to widely adopt HFA for many years was due to clinicians' concern for wide intrasubject variability of threshold values above 8KHz, partly attributed to the potential presence of standing waves in the outer canal beyond its resonant frequency.[4] When the instruments became more accurate, thresholds beyond 8KHz could be adequately determined with acceptable variations, thus proving HFA's efficacy for early ototoxicity detection.[4,7]

Unfortunately, HFA is not always a viable option for every patient. A lot of people suffering from hearing loss beyond 8KHz may not exhibit detectable thresholds at high frequencies making pre and post treatments comparisons almost impossible.[4] The elderly are the main candidates for such exclusion. Moreover, any pre-existing type of hearing loss may also decrease the usefulness of HFA, as the most common losses are sloping high-frequency types. In such patients, thresholds are presumed to continue rolling off towards the uppermost frequency range of hearing. Also, even purely noise induced hearing losses may present themselves with considerable high-frequency involvement.[4]

DPOAEs on the other hand, have long been considered as a way to objectively detect changes in hearing status and evolving into a critical part in hearing monitor programs for subjects prone to ototoxic and noise induced hearing loss.[4-6]

CLINICAL ADVANTAGES OF OAE

Health care specialists have reasonably quested other test modalities for ototoxic monitoring, in their effort to eliminate behavioral – subjective testing and even more establishing further improvements in test efficacy.[4] To iterate, drug induced ototoxicities typically are initially presented as OHC dysfunction, and the exact correlation between present OAEs and functional OHCs is fairly well demonstrated.[4,5] OAEs are considered as a relatively simple, straight forward technique. Test time is particularly brief. Usually it takes up to 2 minutes per ear for testing frequencies up to 10KHz. Even more, little training and scientific background from the examiner's is required. They are fairly objective, unaffected by patient's attention, cognition and cooperation. They are independent of age, as they can even be detected straight after birth. Ear specific measurements can be easily obtained along with frequency specific data for adequate individual frequencies.[8] The most important fact though is that OAEs' thresholds tend to alter before auditory thresholds in the typical frequency range, but not before HFA thresholds shifts where OAEs cannot be measured or acquired.[4,5,8] In a study regarding ototoxicity monitoring in toddlers receiving cisplatin compounds, HFA typically revealed ototoxic shifts sooner than DPOAEs, although both HFA and DPOAES thresholds degraded prior to those in the conventional frequency range.[4,9] Moreover, these testings can be more easily utilized in patients too sick and haggarded to perform adequately enough in conventional PTA or similar, behavioral based exams.[6] The bottom line is that, OAEs may provide strategic advantages as a part of an ototoxicity monitoring program, as they can detect earlier ototoxic induced thresholds shifts, they do not need patient's cooperation and are substantially quick.[4]

TEOAES VERSUS DPOAES

Because of their widespread clinical availability as well as their ability to test OHC function at higher frequencies compared with standard transient-evoked OAEs, DPOAE testing is a key component in ototoxicity monitoring programs. This relies mainly on the fact that, with the current equipment available, DPOAEs measurements can reach higher frequency range compared to TEOAEs, thus becoming more responsive to the cochlear tonotopic frequency areas disrupted at the beginning.[6] So, from a practical – clinical perspective, DPOAEs detect ototoxic changes earlier than TEOAEs.

Moreover DPOAEs can typically be elicited in the existence of more intense threshold shifts than TEOAEs, providing more eligible patients with OAE monitoring.[4] Interestingly enough, it has been reported that when a threshold shift occurred in the high frequencies domain of HFA, a concomitant DPOAE shift at 8 kHz and below followed, yet a lot of further investigation is needed for this potential correlation.[4]

CLINICALLY MEANINGFUL SHIFTS IN DPOAES' LEVEL

The standard monitoring approach with DPOAEs for ototoxicity is to take a baseline, ideally pre-exposure DPOAE measurement and then repeat the measurement during subsequent monitoring appointments to determine whether an alarming alteration in cochlear function, has occurred. If the difference between the baseline and monitoring measurements exceeds expected test retest deviations, then further testing is recommended.[3,10]

Adult DPOAE test retest deviations estimates can be found in several published studies, although they vary among studies and even within clinical populations.[6] In a homeostatic reference population, 90% reference limits for DPOAE shifts should yield a 10% total false referral rate, with 5% falling below the lower limit and 5% falling above

the upper limit of the reference interval. Clinical application of a reference interval with upper and lower reference limits implicitly assumes that either a large negative or positive value of the DPOAE level shift is clinically alarming. This approach is preferable in the case of DPOAE shifts because it can be generally assumed that either a DPOAE level degradation or an enhancement may indicate cochlear damage worthy of follow-up. DPOAE level enhancement has been indeed observed in serial monitoring following exposure to noise or ototoxic drugs, particularly at frequencies below the damaged region identified by PTA.[6] Enhancement below the "*audiometric edge*" of the presumed damage is also consistent with animal models of ototoxic exposures.[6] Hypothesis for generating enhancements involves reduced activity of the medial olivocochlear system and/or removal of contributions from additional "*basal sources*".[6] In addition, DPOAEs arise from at least two generator mechanisms, nonlinear distortion and linear reflection, which interact constructively or destructively depending on their phase relationship.[6] Some enhancements do occur when damage alters the contributions from these sources and thus their interaction in the ear canal.

SCREENING FOR OTOTOXICITY DURING COVID-19 PANDEMIC

Patients receiving chloroquine and hydroxychloroquine, as prophylactic agent against COVID-19 infection, should be also monitored periodically for ototoxicity.[11] Possible mechanisms of chloroquine and hydroxychloroquine ototoxicity include: (i) damage to the stria vascularis (ii) microcirculatory ischaemia; and (iii) injury to the cochlear melanocytes with induced degenerative alterations in the stria vascularis.[11-14] Typically initially the deficit involves the OHCs in the cochlear basal turn, then progressing to the apical turn.[12-14] Further damage can also take place in the immediately associated neural structures.[11-14]

High frequency hearing loss, tinnitus and dizziness are the most common manifestations reported due to chloroquine and hydroxychloroquine toxicity.[11-14] Although such kind of damage is usually irreversible, some authors have reported that when adequate intervention is established, early termination of the drug administration may reverse the inner ear breakdown.[11]

In such a case OAEs provide strategic advantages as a part of an ototoxicity monitoring program because, not only they can detect earlier ototoxic induced thresholds shifts but also, they do not mandate patient's own cooperation as they are very easy to administer. This fact is particularly crucial in cases of Covid-19 patients who may be too exhausted to perform adequately enough in conventional ototoxicity screening with PTA or similar, behavioral based tests.

THE FUTURE OF OTOTOXIC MONITORING WITH OAES

Interestingly enough, DPOAEs are recently proved to be sensitive biomarkers of exposure to ototoxic materials such as industrial solvents.[15] They are found to be particularly useful for the early detection of ototoxicity in such populations.[15]

Moreover, methods for optimizing the sensitivity of DPOAEs, across more frequencies with less test time are being explored by many researchers.[6] DPOAEs are found to be repeatable over time both at lower frequencies (less than 8KHz) and higher frequencies (up to 16KHz) in healthy, normal-hearing subjects.[7] Current experimental evidence suggests that such repeatability of DPOAEs measurements with high-frequency stimuli also exists in those patients' population exposed to ototoxic agents. In such a case OAEs not only may detect an imminent threshold shift, but also eventually precede the improvement of cochlear status before behavioral threshold recovers in the high frequency range that could only be assessed in the past with HFA. After the emergence of UHF-DPOAEs in the frequency range of 9-16KHz, hearing changes preceding ototoxic induced hearing loss in these frequencies could be identified at early stages, before the cochlear deficit affects lower frequencies.

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