A Proposed Ototoxicity Monitoring Protocol Based on Specificity, Feasibility, and Early Identification

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Introduction

Ototoxicity is damage to inner ear structures resulting from exposure to an ototoxic medication (Ganesan et al., 2018). Ototoxicity damage to the cochlea is predictable across patient profiles (Ganesan et al., 2018). Ototoxicity first damages the base of the cochlea where stimulation cells for the highest frequencies are embedded (Ganesan et al., 2018). The base of the cochlea can be seen in figure 3. Establishment of an effective ototoxicity monitoring protocol can improve patient quality of life by focusing on feasibility, specificity, and early identification (Ganesan et al., 2018). Currently ototoxicity monitoring protocols exist; however, these programs have inconsistency in success (Konrad-Martin et al., 2017). A literature review was conducted to evaluate the components of current programs. This study aims to propose a protocol that embellishes early identification and intervention through implementation of the most effective, precise, and feasible components.

Affected Populations

Ototoxic medications are used to treat a wide range of medical conditions including: cancer, heart disease, renal failure, malaria, tuberculosis, and human immunodeficiency virus (Schellack, Wium, Ehlert, van Aswegen, & Gous, 2015). Platinum coordination complexes, aminoglycosides, loop diuretics, and nonsteroidal anti-inflammatory agents are among the most commonly prescribed ototoxic medications (Paken, Govender, Pillay, & Sewram, 2016). Because of the wide range of illnesses ototoxic pharmacotherapy agents treat, ototoxicity may be displayed across the lifespan (Paken, Govender, & Sewram, 2017). Severity of ototoxic symptoms is related to dosage of the ototoxic medication, frequency of treatments, cumulative medication received, and the mode of medication administration (Paken et al., 2016). Changes in hearing can arise within minutes or up to ten years after treatment (Ganesan et al., 2018; Schellack et al., 2015). Prevalence of ototoxicity steadily increases worldwide as developing countries introduce the use of ototoxic medications (Knight et al., 2017). Developing countries are challenged with treating tuberculosis, malaria, and human immunodeficiency virus (Khoza-Shangase, 2017). As these rural countries begin to combat epidemics of these conditions, medical professionals increase the prescription of ototoxic medications (Knight et al., 2017).

Current Protocol

Currently, ototoxicity monitoring protocols exist; however, these programs have inconsistency in success (Konrad-Martin et al., 2017). Current protocols use a combination of some or all of the assessments listed in the chart below (Fausti et al., 1984; Ganesan et al., 2018; Knight et al., 2017). Flaws in current protocols include, but are not limited to: baseline testing not completed, lack of structure in monitoring tests being conducted, and lack of monitored testing during treatment (Konrad-Martin et al., 2017). This would lead to inconsistent measures of threshold shifts, or lack of comparable material. Another issue is patients that never enter the monitoring program or are lost to follow-up; this typically occurs due to inconsistency in referrals (Konrad-Martin et al., 2017). Due to weakened medical status of these patients, often the extensive comprehensive monitor tests were not feasible. Other issues are related to resource restrictions. This could include both staffing restrictions as well as space and equipment limitations (Ganesan et al., 2018; Konrad-Martin et al., 2017).

Suggested Protocol

A flow chart is provided in figure 1 of the suggested protocol. The chart depicts the pros and cons of various assessment components used in monitoring ototoxicity. SRO was chosen as the primary assessment method for detecting ototoxic changes in thresholds; SRO was selected as it is a testing method that targets assessment of frequencies that ototoxicity damages first (Ganesan et al., 2018). If patients are unable to respond behaviorally for SRO assessment, DPOAEs should be used. Ototoxic changes in thresholds are detected by extended high frequency audiometry assessment, then in DPOAEs, and last in conventional PTA (Knight et al., 2017; Schellack et al., 2015). If the changes in threshold are detected during the course of treatment, steps 6 through 8a will be repeated until 10 years post treatment. If changes in thresholds do not occur, steps 7 to 8b will be completed until 10 years post treatment as ototoxicity can display delayed changes. Additionally, as highlighted in figure 1, counseling of the patient must occur early and often. The multimodal team should explain the potential for hearing loss prior to and after administration; this promotes the patient's and loved ones' development of realistic expectations should hearing loss occur (Ganesan et al., 2018; Knight et al., 2017).

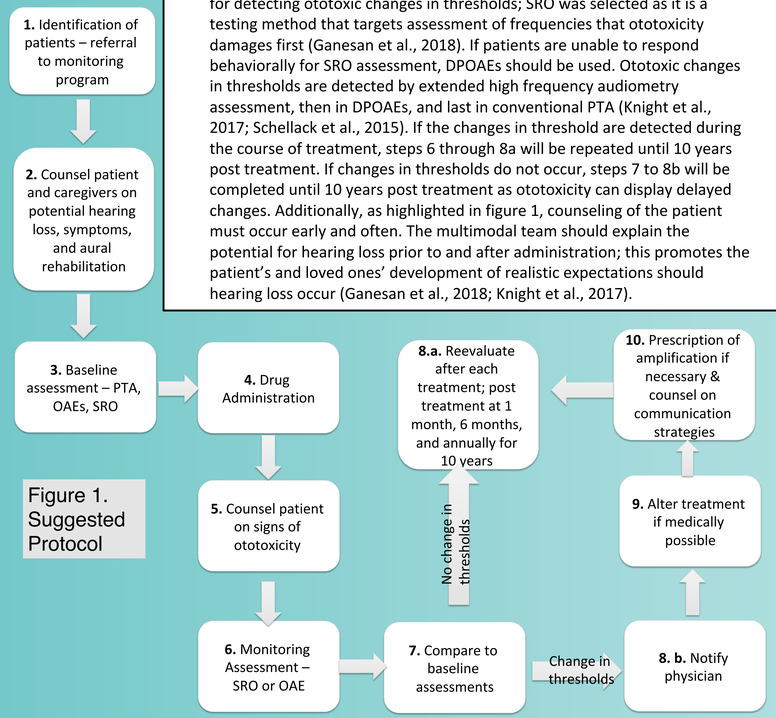

Figure 1. Suggested Protocol

Assessment Component	Definition	Pros	Cons
Pure Tone Audiometry (PTA)	Determines a patient's hearing sensitivity at various frequencies using behavioral responses (Martin & Clark, 2015).	• Simple test (Martin & Clark, 2015) • Good test-retest reliability (Martin & Clark, 2015) • Tests frequencies necessary for speech understanding	• Traditionally assesses frequency thresholds from 250 to 8,000 Hz, whereas changes in thresholds due to ototoxicity typically occur above 8,000 Hz (Martin & Clark, 2015) • Require behavioral response which is not ideal for young children, medically frail patients, or patients with cognitive disabilities (Schellack et al., 2015).
High Frequency Audiometry (HFA)	High frequency audiometry is a specialized pure tone audiometry assessment to determine hearing acuity from 9,000 to 20,000 Hz (Ganesan et al., 2018).	• Ototoxicity effects typically occur at the base of the cochlea, where high frequencies are encoded and progress toward the apical end of the cochlea where low frequencies are encoded (Fausti et al., 1984; Schellack et al., 2015) • HFA assesses the highest frequencies above 8,000 Hz, and can detect ototoxicity before it progresses to affect the frequencies necessary for speech perception (Fausti et al., 1984)	• Require behavioral response which is not ideal for young children, medically frail patients, or patients with cognitive disabilities (Schellack et al., 2015). • In order to test the extended high frequencies, a specialized audiometer is required; this would be an additional expense to a clinical setting (Ganesan et al., 2018
Sensitive Range of Ototoxicity (SRO)	SRO is unique to each patient. SRO is defined as the highest frequency with a threshold of less than or equal to 100 dB SPL and the six frequencies below, in 1/6th octave levels (Ganesan et al., 2018). A visual representation of SRO is depicted in figure 2.	• Relatively quick to assess (Ganesan et al., 2018) • SRO is efficient in identifying ototoxicity changes earlier than conventional methods, thus allowing time to alter medication dosage if deemed medically appropriate (Ganesan et al., 2018) • Testing these high frequencies has been shown to detect ototoxic threshold changes the earliest (Knight et al., 2017)	• SRO is assessed using a portable audiometer specifically designed to monitor extended high frequency thresholds for ototoxicity patients -- this would be an additional expense for clinical settings (Ganesan et al., 2018) • This is a behavioral monitoring procedure and requires a reliable behavioral response from patients (Ganesan et al., 2018) • ASHA guidelines do not advocate SRO procedures • However, ASHA does support HFA in monitoring protocols (Ganesan et al., 2018) • In order to test the extended high frequencies, a specialized audiometer is required; this would be an additional expense to a clinical setting (Ganesan et al., 2018
Distortion Product Otoacoustic Emissions (DPOAE)	A probe containing a speaker is placed in the external ear canal (Martin & Clark, 2015). A small microphone is also placed in the canal to record the emissions response from the cochlear outer hair cells (Martin & Clark, 2015). In DPOAEs two varying tones are presented and the response is recorded (Martin & Clark, 2015).	• Non-behavioral assessment method - Preferred monitoring method for young children and non-responsive adults (Ganesan et al., 2018) • Rapid, non-invasive monitoring test (Ganesan et al., 2018) • Frequency specific (Martin & Clark, 2015) • Ability to measure over a broad frequency range (Ganesan et al., 2018) • Cost effective: reveals initial ototoxic changes before it appears on pure tone assessment, therefore reducing the need for further assessment for diagnosis (Ganesan et al., 2018; Schellack et al., 2015)	• Will not work if middle ear dysfunction is present, which is common in pediatric, immuno-compromised, and head and neck oncology populations (Ganesan et al., 2018) • May not be able to detect ototoxicity in patients with preexisting hearing loss (Ganesan et al., 2018) • Measurement of extended high frequency OAEs requires specialized equipment to deliver and record acoustic signal which would be an additional cost to a clinic (Ganesan et al., 2018)

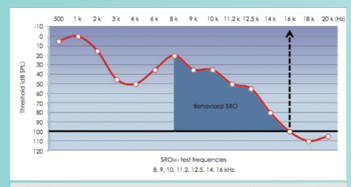

Figure 2 (Ganesan et al., 2018)

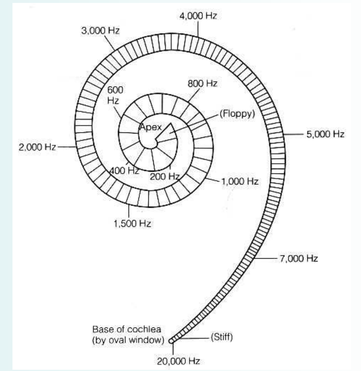

Figure 3
van Hengel, P. (2001). *Cochlea model – conceptual documentation*. Retrieved from http://www.ai.rug.nl/acg/cpsp/docs/cochleamodel.html

Discussion

Konrad-Martin (2017) suggested, "Established ototoxic monitoring programs essentially facilitate the transition from a reactive to a proactive hearing health promotion culture" (p. 2). In relation to developing countries, the need for an ototoxicity monitoring protocol is imperative as the use of ototoxic medications increase (Knight et al., 2017). However, U.S. guidelines are not feasible for application in these rural, developing countries due to resource restrictions (Konrad-Martin et al., 2017). Further research needs to be done to determine application for a feasible protocol in these developing countries. Additionally, this suggested protocol would not be feasible for patients unable to behaviorally respond who experience middle ear dysfunction. Further research should evaluate the possibility of auditory brainstem response testing for this small group.

Reference

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