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Utility of the auditory brainstem response evaluation in non-clinical drug safety evaluations ☆

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ABSTRACT

Introduction: The Food and Drug Administration (FDA) requires thorough evaluation of the potential safety hazards of all new drugs, food additives, and therapeutic devices that are intended for human use. Drugs that are otically administered (i.e., ear drops), or are known to systemically distribute to the inner ear, require additional specialized safety testing to ensure that the drug does not permanently impair auditory function.
Methods: To properly determine a drug's impact on auditory function, the FDA's Center for Drug Evaluation and Research requires the use of the Auditory Brainstem Response (ABR) evaluation. The ABR evaluation uses auditory stimuli evoked potentials to assess function by establishing minimum intensity thresholds. These thresholds can be monitored following drug treatment to determine an impact on hearing loss. This review discusses methodical considerations for conducting ABR evaluations as they apply to specialized drug safety studies. Alternative assays are discussed and compared to the utility of the ABR evaluation. Conclusions: The ABR evaluation provides reliable and sensitive measures of hearing function that are suitable for definitive drug safety evaluations or hazardous risk assessments.

1. Introduction

There are over 130 drugs or drug combinations that have a known risk liability for auditory dysfunction in humans (Seligmann, Podoshin, Ben-David, Fradis, & Goldsher, 1996). The U.S. Food and Drug Administration's (FDA's) adverse event reporting database indicates that in the last 7 years 32 drugs have required re-labeling to include side-effects related to inner ear dysfunction. Platinum-based chemotherapeutics and aminoglycoside antibiotics are predominant drug classes that have a well-characterized etiology and pattern of ototoxicity. Generally, if there are no class-specific effects on hearing function, if the new chemical entity (NCE) is not intended for the direct contact with the tympanic membrane by otic administration, or has not shown demonstrative evidence of hearing loss in preclinical studies, then most drugs will be brought through the new drug application (NDA) process without preclinical data targeting the effects of the NCE on auditory function.

Auditory testing may be required under a number of premarketing scenarios: 1) if there is clear evidence of auditory dysfunction in preclinical toxicology studies (for example, functional observational battery, detailed clinical observations, or post mortem examinations), 2) if there are adverse events reported in the early phase clinical trials, 3) if the pharmacological class has a known risk potential for ototoxicity (aminoglycosides, platinum-based chemotherapeutics), or 4) the intended route of administration of the drug is into the ear canal.

There are two regulatory guidance documents which may help to characterize the pharmacological impact of the NCE on auditory functions. The Center for Drug Evaluation and Research has concluded that auditory function must be assessed through Auditory Brainstem Response evaluations (ABR) for all drugs that are administered in or through the ear canal (U.S. Department of Health and Human Services Food and Drug Administration Center for Drug Evaluation & Research (CDER), 2008). Based on this requirement, the ABR evaluation must be used to characterize all NCEs that are functionally or structurally similar to a known class of ototoxic-inducing agent or if there is demonstrative evidence in preclinical or clinical trials that suggest impairments in auditory function. Further discussions of second-tier safety assessments of the auditory system is discussed in the follow-up studies delineated in the Core Battery section of the Safety Pharmacology Studies for Human Pharmaceuticals of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) S7A guidance document adopted by the FDA in 2001

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(International Conference On Harmonisation Of Technical Requirements For Registration Of Pharmaceuticals For Human Use, 2000).

2. Overview of auditory function (middle and inner ear)

Before the methods of conducting an ABR evaluation can be discussed, the auditory system should be briefly reviewed to allow for a better understanding of how the ABR represents the brainstem's response to sound. Sound is first received by the external ear and funneled through the external auditory canal to the tympanum, or ear drum. Sound waves interact with and cause oscillations in the tympanum which cause vibrations in the ossicular chain (the malleus, incus, and stapes). The oval window of the cochlea is covered by the stapes, which forms the footplate of the oval window that in concert with the adjacent round window, seals the fluid-filled cochlea. Inward movements from the vibrating stapes generate coordinated outward movements on the adjacent round window. This action transforms mechanical movement into the formation of an integrated fluid movement (waves) in the cochlea. This process converts one energy form to another and was characterized by von Bekesy (1970). The migrations of fluid waves through the fluid-filled cochlea generate movements of the basilar membrane which contains the inner and outer auditory hair cells. The outer hair cells are situated in rows of three to every one row of inner hair cells, and all of these hair cells have stereocilia (hair-like projections) which detect the movement of the fluid waves. The fluid waves produce a sheering-movement of the basilar membrane causing deflection of the inner and outer hair cell stereocilia, resulting in hair cell depolarization.

The outer hair cells are a rare type of cell that alters their shape following depolarization. Furthermore, the outer hair cells vary in size and length throughout the cochlea, which together the change in shape and size variation enables frequency discrimination within complex noises. The outer hair cells of the apex of the cochlea help to amply low frequency tones while the hair cells in the basal end of the cochlea amply high frequency tones. Regardless of location, the outer hair cells amplify movement of the basilar membrane which generates coordinated depolarization of the associated inner hair cell. The depolarized inner hair cells release neurotransmitters in the afferent nerve, creating an action potential that travels through higher order nuclei of the auditory pathway. This process converts mechanical air pressure wave energy from the external environment, through fluid dynamics of the inner ear, which initiates a cascade of neurochemical changes in specialized neural cells that transmit electrical signals to the brain — a process called transduction. For reference, Fig. 1 illustrates the critical structures and movement of sound through the ear as outlined in this summary.

2.1. Types of hearing loss observed following drug treatment

The ABR is a type of electroencephalographic (EEG) recording that can be used to determine functional changes that occur to hearing after drug treatments. Drug-induced hearing loss can manifest in three ways: 1) conductive, 2) sensorineural, and 3) combined conductive and sensorineural (mixed). Conductive hearing loss originates from dysfunction within the conductive structures of the external and/or middle ear (ossicles, oval window, etc.). In the context of drug safety, conductive hearing loss is generally observed following the administration of a drug or vehicle that persists in the middle ear. The presence of the drug around and against the middle ear structures produces hearing loss that recovers as the drug or vehicle is absorbed. Middle ear inflammation in response to the presence of a drug can also occur and produce recoverable conductive hearing loss much like that observed in children with acute otitis media. Sensorineural hearing loss is a permanent type of hearing loss that occurs when a drug damages the auditory hair cells or auditory nerve within the cochlea. Aminoglycoside antibiotics and platinum-based chemotherapeutics are well documented for their propensity for causing permanent sensorineural hearing loss (Schacht, Talaska, & Rybak, 2012). In some cases, a drug formulation may cause middle and inner ear damages resulting in both conductive and sensorineural mechanisms, a process considered to be of mixed origin.

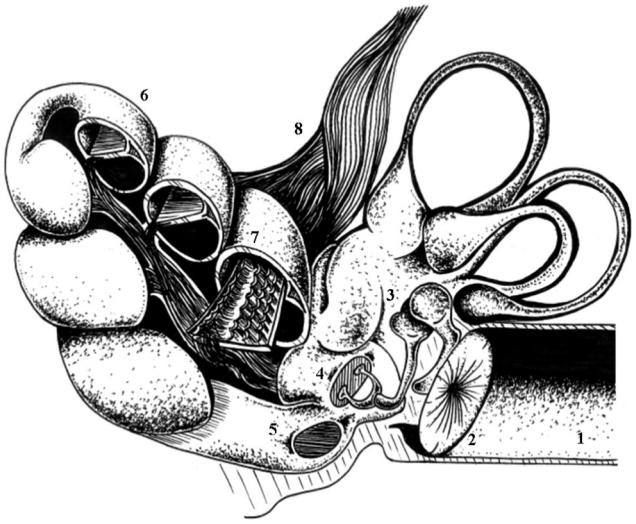

Fig. 1. Illustration showing the major structure of the middle ear and inner ear: 1) external auditory canal, 2) tympanum, 3) ossicular chain (malleus, incus, stapes), 4) oval window (with stapes footplate), 5) round window, 6) cochlea, 7) auditory hair cells, and 8) auditory nerve.

2.2. Model selection

The ABR evaluation is only as sensitive and predictive as the model used to assess otic safety of new drugs. In terms of ototoxicity, it has been well established that differential sensitivity exists between and within rodent and other common large animal laboratory species. Poirrier et al. (2010) compared the development of ototoxicity induced by kanamycin and cisplatin in both mice and guinea pigs. ABR evaluations showed a significant threshold shift in guinea pigs 2 weeks after the beginning of the ototoxic treatments, while there was no significant hearing impairment recorded in mice. Wu et al. (2001) performed a similar study comparing the sensitivity of various mouse strains and Sprague Dawley rats to kanamycin ototoxicity. ABR threshold increases were noted in both species, but rats required lower doses to produce the desired ABR threshold increases, suggesting greater sensitivity. Similar studies comparing the sensitivity of guinea pigs and rats to known ototoxins suggest that guinea pigs are the most sensitive rodent species for assessing otic drug safety (McWilliams, Chen, & Fechter, 2000; Sockalingam, Freeman, Cherny, & Sohmer, 2000). The body of ototoxicity literature suggests that the order of suitable rodent models for otic drug safety studies is guinea pig > rat > mouse.

Because of the sensitivity of the guinea pig, large animal species are not commonly used to assess otic safety. In cases where the guinea pig is contraindicated for use and a large animal species is necessary, the cat has been most commonly used in otic research. The size and structure of the cat external and middle ear is ideal for otic drug administration when compared to that of the dog and monkey. The cat has also been shown to be a sensitive model for drug ototoxicity, producing ABR threshold increases following aminoglycoside treatment (Leake & Hradek, 1988; Shepherd & Martin, 1995). The non-human primate is another suitable model for otic drug safety in terms of sensitivity to ototoxin treatment. Stebbins et al. (1981) showed a similar progression of hearing loss in guinea pigs and rhesus monkeys following administration of kanamycin supporting a conclusion of generality of ototoxic effects induced by the antibiotic. Although sensitive to ototoxins, the anatomy of the monkey external and middle ear presents a challenge for otic drug administration making it a less than ideal model when compared to the cat. Although shown to be sensitive to ototoxin

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