Journal of Pharmacological and Toxicological Methods 74 (2015) 53–74

Contents lists available at ScienceDirect

Journal of Pharmacological and Toxicological Methods

journal homepage: www.elsevier.com/locate/jpharmtox

Review

The failure to detect drug-induced sensory loss in standard preclinical studies☆

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ARTICLE INFO

Article history:
Received 11 April 2015
Received in revised form 12 May 2015
Accepted 27 May 2015
Available online 2 June 2015

Keywords:
Drug safety
Auditory function
Ageusia
Anosmia
Ototoxicity
Drug-induced sensory loss
Risk assessment
Method
Treatment adherence
Quality of life

ABSTRACT

Over the years a number of drugs have been approved for human use with limited signs of toxicity noted during preclinical risk assessment study designs but then show adverse events in compliant patients taking the drugs as prescribed within the first few years on the market. Loss or impairments in sensory systems, such as hearing, vision, taste, and smell have been reported to the FDA or have been described in the literature appearing in peer-reviewed scientific journals within the first five years of widespread use. This review highlights the interactive cross-modal compensation within sensory systems that can occur that reduces the likelihood of identifying these losses in less sentient animals used in standard preclinical toxicology and safety protocols. We provide some historical and experimental evidence to substantiate these sensory effects in and highlight the critical importance of detailed training of technicians on basic ethological, species-specific behaviors of all purpose-bred laboratory animals used in these study designs. We propose that the time, effort and cost of training technicians to be better able to identify and document very subtle changes in behavior will serve to increase the likelihood of early detection of biomarkers predictive of drug-induced sensory loss within current standard regulatory preclinical research protocols.

Contents

☆ The authors have no conflicts of interest to declare. All contributors assisted in the literature review, consolidation and preparation of the manuscript. All data discussed in this manuscript was funded by MPI Research.

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http://dx.doi.org/10.1016/j.vascn.2015.05.011
1056-8719/

1. Introduction

The focus of this review is on the assessment of sensory systems in preclinical safety and toxicology programs conducted prior to the first dose in man. We intend to show the mutual integration of organ tissues and sensory pathways that may predict losses within one sensory domain by the direct toxic effects of drugs in a complimentary organ or sensory domain, highlight some of the current methodologies used to assess changes in sensory function, and describe how best to utilize the current study design parameters to identify markers of sensory loss that could be used to initiate a conversation regarding additional study protocols with more directed focus.

The American Conference of Governmental Industrial Hygienist (ACGIH, 2001) report of 2001 has listed 450 exogenous neurotoxic chemicals and chemical mixtures which may pose a risk to sensory functions. In his review of a prior report, Anger (1990) reported that 121 chemicals listed in the ACGIH report were associated with visual disturbances and 135 chemicals listed were associated with equilibrium disorders.

Smell, or olfaction, is the perception of odor by the nose. Taste, or gustation, is the perception of salty, sweet, sour, or bitter by the tongue. Flavor is the combination of taste, smell, and trigeminal sensations (Maheswaran et al., 2014; Cullen & Leopold, 1999). Sensory trigeminal stimulation (pain, tactile, and temperature) plays a major contributory role throughout the eating process. The chemosensory functions of taste and smell play a vital role in measures of the hedonics of taste and olfaction (McBurney & Collings, 1984) and the general sense of "quality of life". The perception of flavor is derived from cross-model interactions of both olfactory and gustatory neural pathways (see below). Flavor is critically linked to palatability of foods and beverages, the selection of nutrients essential to maintain a good life, and warning of toxic vapors, fire, and spoiled foodstuffs (Maheswaran et al., 2014). The majority of feeding dysfunctions are caused by impairments of smell rather than taste.

Taste or gustatory dysfunctions can be classified as quantitative or qualitative disorders. Quantitative disorders include ageusia (a total loss of taste), hypogeusia (a decreased sense of taste), and hypergeusia (a sharpened or heightened sense of taste), while qualitative disorders of dysgeusia (an unpleasant perception of a tastant, like metallic) or phantogeusia (a perception of taste that occurs in the absence of food or drink) are also reported.

The most common cause of olfactory dysfunction (anosmia) includes allergic rhinitis, chronic rhinosinusitis and upper respiratory infections (Malaty & Malaty, 2013). Systemic conditions such as diabetes mellitus, pernicious anemia, Sjogren's syndrome and Crohn's disease are also known contributors to patient complaints of gustatory dysfunction (Mann, 2002). Any condition that results in a compromised chemosensation environment of the tongue, saliva, oral mucosa and associated integrated pathways results in altered taste perception at any age.

Drug-induced taste disorders were found to be the most common etiology among patients visiting a taste clinic (Hamada, Endo, & Tomita, 2002). In a recent study by Coa and associates (Coa et al., 2015) approximately 40% of 1199 cancer patients undergoing active treatment experienced decreased appetite and 67% of them reported at least one chemosensory alteration. Almost 19% of the patients in the Coa et al. study reported increased sensitivities to metallic tastes, 23% reported increased sensitivity to smells like cleaning solvents, 22% had increased sensitivities to perfumes and 11% reported increased sensitivities to the smell of cooking food.

Drugs in every major pharmacological category can impair both taste and smell functions and do so more commonly than presently appreciated (Galina Elterman, Mallampati, Kay, & Urman, 2014; Doty & Bromley, 2004; Henkin, 1994). Table 1 shows a brief list of drugs reported to induce changes in taste (ageusia, dysgeusia, or parageusia) and/or smell (anosmia, dysnosmia) which includes antibiotics, neurologic medications (antiparkinsonian, CNS stimulants, migraine medications, and muscle relaxants), cardiac (antihypertensives, diuretics, statins, antiarrhythmics), endocrine (most thyroid medications), psychotropics (most tricyclic antidepressants, some antipsychotics, anxiolytics, mood stabilizers, and hypnotics), as well as some over-the-counter medications (antihistamines, bronchodilators, anti-inflammatories, smoking cessation aids, and antifungals).

Details of the clinical findings in the IND-enabling studies associated with each of the drugs listed in Table 1 are not available to open peer review, even as part of a post-hoc review of NDA approval documentation available through the U.S. FDA. It is not known at present if clinical findings like "inappetence" or "decreased food consumption" were reported or reviewed as part of the approval process. In the case of Viagra™, the NDA approval documentation available does not suggest any visual or auditory losses in the preclinical studies reviewed in the documents. Had clinical findings been reported during the conduct of the IND-enabling toxicology studies, it is not known whether the Study Director accepted the findings as a significant event 1) that may have affected the quality or integrity of the study, 2) that were potential signs of toxicity or sensory loss, or 3) that only occurred at the maximal tolerated dose of the NCE that provided plasma NCE concentrations that were several fold higher than the therapeutic targeted concentrations in humans based on standard equivalent surface area dosage conversion factors.

Impairments usually affect sensory function at a molecular level causing two major behavioral changes: 1) loss of acuity (i.e., hypogeusia and hyposmia) and/or distortions of function (i.e., dysgeusia and dysosmia). These changes can impair appetite and food intake, produce a significant decline in self-rated "quality of life" and can instigate a lack of compliance or adherence to medical treatments that strains the doctor–patient relationship. It has been estimated that 5% of the general population exhibit a functional anosmia (Welge-Lüssen, Dörig, Wolfensberger, Krone, & Hummel, 2011) and an even higher percentage of patients have taste disorders. These drug-induced taste disorders are common among older persons and are a major factor in feeding, eating disorders, and the maintenance of body weight control. They also contribute to significantly lower scores in self-evaluations of "quality of life" (Patel & Pinto, 2014). While somewhat dismissed by many practitioners as a minor inconvenience, these sensory losses play a critical role in the control of food intake, regulation of meal size, and modulation of the general sense of pleasure that can then lead to difficulty in homeostatic control of glucose levels, especially in diabetic patients.

Besides adverse events associated with olfaction and gustation, 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; Ryan & Sachin, 2014; O'Conner & Mastaglia, 2014). Drug-induced ototoxicity has been recognized since the 1800s, when it was learned that quinine and acetylsalicylic acid provoked dizziness, tinnitus, and hearing loss (Wrześniok, Buszman, & Matusiński, 2003). In 2001, Palomar Garcia et al. conducted a comprehensive literature review through 10 years of peer-reviewed publications to investigate the prevalence of drug-induced ototoxicity. In this literature search, they found 414 published articles by limiting the scope only to the cross-reference term "clinical ototoxicity". Unfortunately, this restrictive term did not include articles related to preclinical screening or animal-based studies and underestimates the number of