Effectiveness of Dexmedetomidine for Sedation in Auditory Brainstem Response Testing

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Abstract: Sedation is widely used for auditory brainstem response (ABR) testing for infants or young children who are unable to sleep or remain adequately quiet for testing. Because chloral hydrate is no longer readily available, dexmedetomidine has been proposed as an alternative medicinal agent to achieve moderate levels of sedation without risk of respiratory depression. The purpose of the study was to assess the effectiveness of dexmedetomidine in terms of the completeness of the audiologic data obtained in achieving moderate levels of sedation for auditory brainstem response testing. A retrospective chart review was conducted on 99 patients at Kennedy Krieger Institute. Participants were administered either chloral hydrate or dexmedetomidine prior to ABR testing. Effectiveness was defined as having obtained thresholds for click and tone burst stimuli centered at 500, 2000, and 4000 Hz for both ears. Complete audiological data were obtained on 92.2% of patients sedated with dexmedetomidine whereas complete audiological data were obtained on 91% of patients sedated with choral hydrate in a period prior to the use of dexmedetomidine. It was concluded that dexmedetomidine is as effective as chloral hydrate in producing an appropriate state for sedated auditory brainstem response testing.

Key Words: dexmedetomidine, sedation, auditory brainstem response

Acronyms: ABR = Auditory Brainstem Response; IHS = Intelligent Hearing Systems; KKI = Kennedy Krieger Institute; MRI = Magnetic Resonance Imaging

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Introduction

The auditory brainstem response (ABR) is used to delineate the auditory status of infants and children who are unwilling or unable to cooperate for developmentally appropriate behavioral test procedures or to confirm behavioral test findings obtained when a hearing loss is suspected. ABRs are bioelectric signals generated by the auditory nerve and units in the brainstem in response to auditory stimuli. The ABR is an onset response and requires neural synchrony in order to effectively record a response from electrodes which are placed on the scalp. ABR testing is a non-invasive procedure but requires the patient to remain quiet and relaxed for approximately 45 to 60 minutes. Sedation is widely used to complete ABR testing for children who are not able to sleep naturally or remain sufficiently quiet for the duration of testing (American Academy of Audiology, 2012). Infants and

older children with developmental disabilities, behavior disorder, autism, or intellectual disabilities often require sedation for successful completion of ABR testing. Using general anesthesia will achieve an adequate state for testing; however, the testing facility must arrange for anesthesiology, which may introduce delays in early identification of hearing loss. Consequently, use of sedation or general anesthesia could compromise adherence with Joint Committee on Infant Hearing Guidelines for early detection and management of hearing loss (Joint Committee on Infant Hearing, 2007). General anesthesia also introduces health risks such as respiratory and cardiac complications (Jenkins & Baker, 2003).

There are alternatives to general anesthesia for obtaining threshold-finding ABR results in infants and young children. For example, several studies have reported on the efficacy of melatonin as an alternative to sedation

for ABR testing (Guerlain et al., 2016; Marseglia et al., 2015; Schmidt, Knief, Deuster, Matulat, & am Zehnhoff-Dinnesen, 2007) and other procedures in children typically requiring the use of sedation (Marseglia et al., 2015). The efficacy of melatonin was assessed in a large sample of 250 children assessed with both click and tone burst stimuli in notched noise (Schmidt et al., 2007). Although the use of melatonin significantly reduced the need for general anesthesia by more than 80%, thresholds for a click, and three or more tone burst stimuli were only obtained in 57% of children assessed with melatonin-aided sleep (Schmidt et al., 2007). However, success rates were markedly better for children less than one year of age than for older children (Schmidt et al., 2007). More recently, use of melatonin was assessed in 56 children from 1 year to 14.5 years who were administered ABR testing with a protocol that included only thresholds for click stimuli (Guerlain et al., 2016). The click-evoked ABR was completed among 43 patients. In the patients successfully tested, the mean delay to achieving sleep was 35 minutes and the mean duration of sleep only 23 minutes (Guerlain et al., 2016).

Another alternative to sedation use for ABR testing involves using sophisticated response collection algorithms which are more robust in the presence of patient-generated motion artifact (e.g., Kalman adaptive processing; Cone & Norrix, 2015). Kalman adaptive averaging has been used to improve the signal to noise ratio in noisy recordings and has been shown to reduce the averaging time needed for resolution of ABR responses by 75% as compared to more traditional averaging techniques (Chan, Lam, Poon, & Qiu, 1995). In the presence of motoric activity, Kalman-weighted averaging coupled with in situ bio-amplifiers results in ABR threshold estimates that are 6 to 7 dB lower than when conventional ABR averaging methods are used (Cone & Norrix, 2015). It was suggested that the methodology may make it possible to test some infants in an awake state without the associated added costs and potential delays inherent with use of sedation or general anesthesia (Cone & Norrix, 2015). The effectiveness the commercial application of Kalman-weighted averaging coupled with in situ bio-amplifiers was undertaken in 103 children who were administered click and tone burst evoked ABR testing without use of sedation (Hall, 2010). It was not possible to record any interpretable ABR results on 6% of the children (Hall, 2010). Click evoked ABR thresholds were obtained on 94% of children. However, the instrumentation was less effective in obtaining thresholds for 500 Hz (24% of Ss), 1000 Hz (36% of Ss), 2000 Hz (40% of Ss), and 4000 Hz (40% of Ss) for the tone burst stimuli (Hall, 2010).

Use of conscious or moderate sedation is also an alternative to general anesthesia for achieving an adequate level of cooperation for ABR testing (Reynolds, Rogers, Medellin, Guzman, & Watcha, 2016). Dexmedetomidine has been used in recent years to achieve moderate levels of sedation for ABR and other procedures (Ambi, Joshi, Ganeshnavar, & Adarsh, 2012; Reynolds, Rogers, Medellin et al., 2016). Dexmedetomidine achieves rapid onset of sedation effects with a relatively short half-life which lends itself to non-invasive outpatient procedures such as magnetic resonance imaging (MRI) and ABR studies (Phan & Nahata, 2008). In addition, intranasal dexmedetomidine has some potentially beneficial analgesic and anxiolytic side effects which might be significant for some patients (Phan & Nahata, 2008). Use of dexmedetomidine was approved by the Food and Drug Administration for use in non-intubated adult patients in 2008 and has been used in pediatric applications for procedures which are minimally invasive off-label since that time (Shukry & Miller, 2010). It is not a controlled substance (Drug Enforcement Administration, 2017). Dexmedetomidine is an anxiolytic and sedative medication which is used in the intensive care setting for light to moderate sedation (Phan & Nahata, 2008). It is an agonist of alpha2-adrenergic receptors in certain parts of the brain and is similar to the medication clonidine, which is often prescribed in children with attention deficit hyperactivity disorder (Sallee, Connor, & Newcorn, 2013). It can provide sedative effects without risk of respiratory depression, unlike other commonly used sedatives such as propofol, fentanyl, and midazolam (Phan & Nahata, 2008). Dexmedetomidine is absorbed through the olfactory mucosa, allowing for intranasal administration (Iirola et al., 2011). Dexmedetomidine does have potential adverse side effects which include lowered blood pressure and decreased oxygen in tissues or blood (Cravero, Anderson, & Wolf, 2015). Although use of dexmedetomidine has been shown to reduce heart rate and blood pressure, vital signs remain within safe physiologic limits and no serious adverse effects have been reported (Surendar, Pandey, Saksena, Kumar, & Chandra, 2014). Intranasal dexmedetomidine produces considerably less impact upon respiration than alternative forms of sedation and is regarded as safer than chloral hydrate or other alternative drugs used to achieve conscious sedation (Cozzi, Norbedo, & Barbi, 2017). Intranasal dexmedetomidine has been used to achieve moderate levels of sedation for MRI studies (Ambi, Joshi, Ganeshnavar, & Adarsh, 2012; Zhang et al., 2016) and for electroencephalogram studies (Baier, Mendez, Kimm, Velazquez, & Schroeder, 2016) as well as auditory brainstem response measurements in children (Baier et al., 2016; Reynolds, Rogers, Capehart, Manyang, & Watcha, 2016; Reynolds, Rogers, Medellin et al., 2016).

Moderate sedation is an alternative to general anesthesia which requires less intensive medical supervision and can be undertaken outside of an operating room environment. Chloral hydrate was widely used to achieve moderate sedation for ABR studies but is no longer used for several reasons. Respiratory depression, vomiting, and paradoxical hyperactivity are potential side effects of chloral hydrate sedation (Greenberg, Faerber, & Aspinall, 1991). Complications such as vomiting, hyperactivity, or rash have been reported in 20.7% of children tested with chloral hydrate (Avlonitou et al., 2011). Additionally, chloral hydrate is often administered orally, which requires

cooperation of the patient to swallow the medication in order to ensure accurate dosing. There is also a heightened risk of respiratory compromise with the possibility of neurologic injury in patients with certain conditions (e.g., cerebral palsy, obstructive sleep apnea, hypertrophic tonsils and adenoids, and tracheostomy; Phan & Nahata, 2008). Finally, chloral hydrate is difficult to obtain, as the sole remaining pharmaceutical manufacturer in the United States has ceased production of the medication (Mason, 2014). Choral hydrate is still in use in other countries (Valenzuela et al., 2016). However, it has not been recommended for use in pediatric sedation for a number of years (Cote, Karl, Notterman, Weinberg, & McCloskey, 2000). Use of chloral hydrate is now banned in France and Italy due to evidence of carcinogenicity and genotoxicity (Cozzi et al., 2017).

In anticipation that chloral hydrate would no longer be available, a team with representatives from pediatrics, pediatric anesthesiology, nursing, and pharmacy considered available medications for moderate sedation and selected intranasal dexmedetomidine as the most suitable option for the Kennedy Krieger Institute (KKI) because of its safety profile, lack of respiratory depression effects, and ease of administration. Intranasal dexmedetomidine has been shown to achieve moderate levels of sedation in significantly less time than chloral hydrate with no occurrences of hypoxemia (Reynolds, Rogers, Medellin et al., 2016; Zhang et al., 2016). First dose success rates for intranasal dexmedetomidine have been shown to be higher than those achieved previously in patients sedated with chloral hydrate (Baier et al., 2016). The injectable formulation of dexmedetomidine is administered into the nose using an atomizer. This method of administration has been used safely in previous investigations evaluating the sedative effects of dexmedetomidine in children (Baier et al., 2016; Cravero et al., 2015; Reynolds, Rogers, Medellin et al., 2016). Onset of sedation is typically about 20 to 30 minutes and lasts 60 to 90 minutes (Reynolds, Rogers, Medellin et al., 2016).

The purpose of the present retrospective study was to compare the effectiveness of intranasal dexmedetomidine with chloral hydrate in achieving an adequate state for the auditory brainstem response testing protocol used at Kennedy Krieger Institute. Consecutive medical records were examined with no attempt made to control for subject variables. This protocol requires obtaining responses to click stimuli and tone bursts centered at 500, 2000, and 4000 Hz for both ears. The tone bursts were presented in the background of notched noise. Tympanometry and measurements of otoacoustic emissions are also performed. Few studies have investigated the effectiveness of intranasal dexmedetomidine for sedation in ABR studies (Reynolds, Rogers, Medellin et al., 2016). No studies have quantified the effectiveness of dexmedetomidine for a range of stimulus conditions, including both click stimuli and frequency specific tone burst stimuli. Previous studies investigating the efficiency of intranasal dexmedetomidine in sedation for ABR studies

have included only a single stimulus condition (Baier et al., 2016; Reynolds, Rogers, Capehart et al., 2016; Reynolds, Rogers, Medellin et al., 2016). Such data do not permit the degree, configuration, and etiology of a hearing loss to be determined. It is important that effectiveness of intranasal dexmedetomidine be evaluated for a range of stimulus conditions because the completeness of this data informs treatment decisions and the need for further evaluation and/or intervention.

Procedures

This investigation was approved by the Johns Hopkins Medicine Institutional Review Board. A retrospective chart review was conducted for patients at Kennedy Krieger Institute who underwent sedated ABR testing. Data were available for 64 patients sedated with intranasal dexmedetomidine and 35 patients sedated with chloral hydrate. The subjects in the dexmedetomidine group ranged from 6 months of age to 10 years and 7 months of age (mean age = 3.30 years). The subjects in the chloral hydrate group ranged in age from 7 months to 5 years and 11 months (mean age = 2.80 years). Sedated ABR testing is typically not performed on children younger than six months because these children are usually able to sleep without sedation for the duration of testing. The subjects typically had multiple diagnoses including speech and language delay, history of otitis media, behavior disorders, autism spectrum disorder, ADHD, global developmental delay, and hypotonia. All subjects were medically evaluated by a Kennedy Krieger Institute developmental pediatrician as well as by their own pediatrician to ensure candidacy for sedation. A sedation referral form, shown in Table 1, was completed by each child's pediatrician prior to scheduling an appointment for a sedated ABR. Because dexmedetomidine lowers heart rate and blood pressure, it is contraindicated for use in children with known bradycardia, hypotension, or other cardiac problems. When children were screened for sedation, it was decided that dexmedetomidine would not be used in children who were taking other medications that lower heart rate or blood pressure. Dosing and response to dexmedetomidine may be affected if children are prescribed other alpha-2 agonists. Guanfacine and clonidine are the two alpha-2 agonists that are commonly prescribed. Guanfacine, also known as Intuniv, is approved for treatment of attention deficit hyperactivity disorder (ADHD). Clonidine can be used for treatment of ADHD and high blood pressure. Tizanidine is also a related medication. The protocol at KKI specifies that patients discontinue these medications for 2 weeks prior to sedation, as dexmedetomidine will be more effective if patients do not have tolerance to that class of medications.

Table 1
Pre-Sedation Referral Form

Name:_____   DOB:_____

KKI#:_____   AEP DATE:_____

The above named patient has been referred for sedated AEP testing. Intranasal Dexmedetomidine will be administered.

Medical Problem List	Medications	Allergies (or sensitivities, especially to meds)	Past Surgeries

Any prior complications of anesthesia or sedation? [ ] yes [ ] no

Pertinent Past Medical History (elaborate on any Yes responses):

History of:	Yes	No	History of:	Yes	No	History of:	Yes	No
Premature birth			Obstructive sleep apnea			Congenital anomaly		
Apnea			Aspiration			Anemia		
ENT Problems			Asthma			History of transfusion		
Feeding/Swallowing problems			Other pulmonary disease			Other blood disorder		
Gastroesophageal reflux			Congenital heart disease			Seizures/epilepsy		
Frequent vomiting			Need for SBE prophylaxis			Hydrocephalus/Shunt		
Liver disease			Arrhythmia			Cerebral palsy		
Kidney disease			Other heart disease			Other neurologic problem		

Additional Info: _____

Physical Exam: Normal (N) / Abnormal (A)   Abnormal (describe)

HEENT_____   Abdomen _____

Lungs _____   Other _____

Cardiovascular_____   Weight: _____   Height: _____

I evaluated the above patient on _____ and find the patient to be in his/her usual state of health and find no contraindications to doing AEP testing under moderate sedation.

Printed Name   Provider Signature   Date/Time

_____   _____   _____

Note. AEP = Auditory Evoked Potential; ENT = Ear, Nose, and Throat; HEENT = Head, Ear, Eyes, Nose, and Throat; SBE = Subacute Bacterial Endocarditis Prophylaxis

Dexmedetomidine is administered through intranasal administration by contact with the olfactory mucosa (Iirola et al., 2011). This was achieved with use of a tuberculin syringe with an atomizer device. Guidelines promulgated by the Committee on Drugs of the American Academy of Pediatrics pertaining to dietary precautions, as well as monitoring and management of pediatric patients for conscious sedation were followed (American Academy of Pediatrics, 1992). Patients received an examination from a developmental pediatrician and a health history was taken along with a baseline weight and vital signs. Due to the possible effects of decreased blood pressure and pulse, the patients were monitored by a nurse throughout the procedure. Blood oxygen saturation was measured by continuous pulse oximetry. Blood pressure measurements were taken every 15 minutes. The available dosing of dexmedetomidine at KKI was in a concentration of 100mcg/1cc. The dosing was usually split between each nostril to decrease runoff and maximize absorptive tissue area. The ideal volume per nostril is 0.2–0.3cc and maximum recommended dose is 0.5–1cc per nostril (Barclay & Lie, 2010). When administering small doses to younger patients, it was necessary to dilute dexmedetomidine to a concentration of 50mcg/1cc to allow adequate volume for intranasal use. On the day following the appointment, a telephone call was placed to each patient's parent/guardian to inquire about recovery and any adverse effects. Based on continued evaluation of patient response intranasal dexmedetomidine at KKI, the current dosing protocol is to give 2 mcg/kg for the initial dose. Previous research provides evidence that a 2 mcg/kg dose is effective for sedation in pediatric populations (Yuen et al., 2012). If the patient is not sufficiently sedated by 25 minutes after the initial dose, an additional 1 mcg/kg dose of intranasal dexmedetomidine is given. A third dose of 1 mcg/kg is given if the patient remains awake 25 minutes after the second dose. Dosing remains individualized but this protocol has provided consistent results for the majority of our sedated auditory evoked potential and electroencephalogram procedures. The dosing for chloral hydrate was 75 mg/kg. When vomiting occurred with chloral hydrate administration, re-administration of the medication was required. In some such cases, sedation was ineffective.

After ensuring the patient had reached an adequate state for testing, ABR data were collected using an Intelligent Hearing System's (IHS) Smart Evoked Potential System. The skin was prepped using NuPrep solution and standard EEG disk electrodes were affixed to the following locations: Fpz (ground), Fz (non-inverting), A1 and A2 (inverting for ipsilateral and contralateral ear). Click stimuli and tone burst stimuli centered at 500, 2000, and 4000 Hz were presented to each ear via insert earphones. Notched noise was used for the tone burst stimuli. If any degree of hearing loss was present, testing by bone conduction was completed with the delivery of appropriate contralateral masking noise. Tympanometry and measurements of otoacoustic emissions were also performed following ABR testing.

Results

Complete audiological data was defined as having obtained thresholds for click stimuli and for tone burst stimuli centered at 500, 2000, and 4000 Hz for both the left and the right ear. Complete audiological data were obtained on 92.2% of patients sedated with dexmedetomidine. Complete audiological data were obtained on 91% of patients sedated with choral hydrate. A chi-square analysis revealed that there was no significant difference in outcome between the two forms of sedation ($\chi2$(1, N = 99) = 0.0175, p = 0.89). Complete data were obtained for at least one ear on all patients.

Table 2
Participant Demographics

Sedation Type	Effective	Not effective
Dexmedetomidine ($n = 64$)	92% ($n = 59$)	8% ($n = 5$)
Sedation Type: Chloral Hydrate ($n = 35$)	91% ($n = 32$)	9% ($n = 3$)

Most of the children required two (50%) or three doses (20%) of dexmedetomidine. Only 30% of patients sedated with a single dose. The average times before sedation were 25 minutes, 39.4 minutes, and 57.5 minutes for patients requiring 1, 2 or 3 doses of dexmedetomidine respectively.

The mean age for patients sedated with dexmedetomidine who were adequately sedated with only one dose was 3 years. The range of ages of children receiving a single dose was 6 months to 10.5 years. The mean age for those receiving more than 1 dose was 4.4 years, with a range of 9 months to 10.6 years. The mean total examination time across all participants who received dexmedetomidine was 53.1 minutes. No patients in the dexmedetomidine group required supplemental oxygen. All patients returned to baseline functioning and were discharged on the same day as the procedure. No patients receiving dexmedetomidine experienced nausea or vomiting that was either observed or reported after discharge.

Discussion

The results of this investigation indicate that intranasal dexmedetomidine is as effective as chloral hydrate in achieving moderate levels of sedation for ABR testing. No sentinel events occurred due to the use of dexmedetomidine. None of the adverse side effects associated with chloral hydrate including vomiting, hyperactivity, or respiratory depression occurred during

the use of intranasal dexmedetomidine. Intranasal dexmedetomidine was noted by all members of the team to be far easier to administer than oral chloral hydrate. Intranasal administration requires minimal cooperation from the patient. A team member or family member gently tilts the patient's head posteriorly and immobilizes the head while the nasal spray is being administered. The patient remains in this position for approximately 20 seconds and can then resume normal activities. In contrast, administration of chloral hydrate required staff to induce patients to swallow an ill-tasting medication which was for some patients difficult to achieve without uncertain amounts of the medication being spit out or vomited. This study supports previous studies suggesting that intranasal dexmedetomidine is an appropriate alternative to chloral hydrate or general anesthesia for ABR testing for most patients (Baier et al., 2016; Reynolds, Rogers, Medellin et al., 2016). The effectiveness of dexmedetomidine appears to be superior to that of alternatives such as administration of melatonin (Schmidt et al., 2007) or use of Kalman averaging (Hall, 2010) which previous studies have shown to be less effective than results achieved in the present study.

Several limitations of the present investigation were noted. The retrospective design of the investigation did not allow for variables such as patient age, the presence of health conditions, or time of testing to be controlled or systematically examined. Additionally, the participants in this investigation were limited to the patients who chose to seek care at KKI. Use of dexmedetomidine requires medical monitoring and continuous physiological monitoring with the attendant expense just as when using chloral hydrate. Further investigations should be completed to include larger sample sizes and diverse populations. As noted earlier, there are alternatives to moderate sedation or general anesthesia for obtaining threshold-finding ABR results in infants and young children. For example, several studies have reported on the efficacy of melatonin as an alternative to sedation for ABR testing with few adverse side effects (Guerlain et al., 2016; Marseglia et al., 2015; Schmidt et al., 2007). Future research comparing the effectiveness and safety of melatonin to dexmedetomidine for obtaining ABR measurements should be completed to determine if either medication is more effective. Additionally, Kalman adaptive averaging has been used to improve the signal to noise ratio in noisy recordings and has been shown to reduce the averaging time needed for resolution of ABR responses by 75% as compared to more traditional averaging techniques (Chan et al., 1995). Incorporating the use of this technology may improve the effectiveness of sedation medication by shortening the length of test time and allowing a greater amount of patient movement. Future investigations could evaluate the effectiveness of dexmedetomidine and/or other sedation medications while incorporating this signal averaging technology.

Conclusions

Measurement of ABRs is an important tool for the delineation of hearing status, as the ABR allows the auditory status of infants and children to be assessed when other methods are inappropriate or unsuccessful. Although sedation is commonly used for ABR testing, no medication has yet replaced chloral hydrate as the clinical standard since its large-scale production was ceased. The results of this study suggest that intranasal dexmedetomidine is an acceptable form of sedation for ABR testing in pediatric patients. Complete audiological data was achieved in 92% of patients. This was accomplished without any of the patients experiencing breathing difficulty, vomiting, or other sentinel effects during or after the procedure. Dexmedetomidine demonstrated similar rates of effectiveness as chloral hydrate with fewer side effects. This study contributes to the body of literature supporting the use of dexmedetomidine for clinical use in facilities performing sedated ABR measurements.

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