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MAIN ARTICLE

Effects of thiocolchicoside, a commonly used myorelaxant, on the acoustic reflex

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Abstract

Objective: To determine whether thiocolchicoside, a commonly used myorelaxant, may impair the acoustic reflex.

Methods: Forty-two patients scheduled to receive thiocolchicoside treatment for different reasons were enrolled in the study. Acoustic reflex thresholds at 500, 1000, 2000 and 4000 Hz were determined and analysed statistically pre-treatment and on the 5th day of treatment.

Results: Increases were observed in the mean acoustic reflex thresholds on the 5th day of treatment compared to pre-treatment, at all frequencies, except right contralateral thresholds at 500 and 2000 Hz. These increases were statistically significant for right ipsilateral thresholds at 2000 and 4000 Hz, left ipsilateral thresholds at 500, 1000, 2000 and 4000 Hz, and left contralateral thresholds at 2000 and 4000 Hz ($p \leq 0.05$), but not at other frequencies ($p > 0.05$).

Conclusion: Muscle relaxant drugs, especially those affecting the central nervous system, may weaken the stapedial muscle so that the ability of noise to cause acoustic trauma may become evident. For this reason, physicians should advise their patients to avoid loud noises when muscle relaxant therapy is prescribed.

Key words: Reflex, Acoustic; Acoustic Trauma; Centrally Acting Muscle Relaxants

Introduction

The acoustic reflex is the most important protective mechanism against acoustic trauma to the cochlea. The stapedial muscle, one of the two muscles in the middle ear, responds to acoustic stimuli. In healthy people, this muscle usually contracts reflexively in response to acoustic stimuli over the 70–90 dB hearing threshold. This contraction increases the stiffness of the ossicular chain and tympanic membrane, thereby attenuating sounds less than approximately 2 kHz. Increases in the stiffness of the ossicular chain and tympanic membrane can be shown by tympanometry.

Contractions of the stapedial muscle as a result of acoustic stimuli occur bilaterally. Acoustic energy causes neuronal electrical stimuli at the cochlear nerves and these stimuli are transmitted to the ventral cochlear nucleus, trapezoid body, medial superior olivary body and medial part of the motor nucleus of the facial nerve.[1] The stapedial nerve, which arises from the facial nerve, causes contractions of the stapedial muscle. This reflexive arch provides an opportunity to evaluate the VIIth and VIIIth cranial nerves and brainstem upon which the reflexive arch exists.

Noise is described as sound that is above a certain intensity which can be harmful to hearing. Socially, it is described as unwanted sound.[2] The acoustic reflex is the only known mechanism to protect the cochlea from damage due to noise. Some previously investigated factors that may impair this reflexive response include neuromuscular diseases (e.g. myasthenia gravis, amyotrophic lateral sclerosis), chemicals (e.g. paints, paint thinners, solvents), drugs and alcohol abuse.[3]

Muscle relaxant drugs can affect the acoustic reflex arch and stapes muscle because of their central neurological effects. Thiocolchicoside, which is often used in orthopaedic, traumatic and rheumatological disorders, is a muscle relaxant drug that acts on the central nervous system.[4] It influences the inhibitory glycine

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and γ-aminobutyric acid type A receptors, and its muscle relaxant effects are provided without sedative effects.[5] It also has strong analgesic and anti-inflammatory effects.[6]

This study investigated the effects of thiocolchicoside on the threshold of the acoustic reflex and examined whether susceptibility to acoustic trauma is caused indirectly by the administration of this drug.

Materials and methods

This prospective study, approved by the ethical review board of our institute, was conducted at our institute between January 2013 and December 2013. Patients prescribed thiocolchicoside for various reasons in our neurosurgery and physical therapy rehabilitation clinics were enrolled in the study.

Patients were evaluated in the otolaryngology department by an ENT physician prior to thiocolchicoside treatment. Patients with normal otoscopic examination findings and no hearing problems were included in the study after providing a signed consent form. All patients' pure tone averages were in the normal ranges (as per American National Standards Institute) and the patients had normal middle-ear pressures (±50 daPa) typical of a type A tympanogram. Acoustic reflex thresholds at 500, 1000, 2000 and 4000 Hz were obtained for all patients.

Hearing measurements and tympanometry were respectively carried out using the Interacoustics AC-40 audiometer (Interacoustics, Assens, Denmark) and Amplaid A766 middle-ear analyser (Amplifon, Milan, Italy). Devices were calibrated annually by the manufacturers.

The patients employed in the study were prescribed thiocolchicoside (Thiospa 8 mg tablet; Eczacıbaşı, Levent, Istanbul) twice a day, orally, for 5–7 days. Tympanometry and acoustic reflex tests were carried out before treatment and on the 5th day of therapy. Acoustic reflex thresholds at 500, 1000, 2000 and 4000 Hz were determined as ipsilateral and contralateral. Pre-treatment acoustic reflex thresholds were compared with thresholds at the 5th day of treatment.

Statistical data were analysed using SPSS 17.0 software (SPSS Statistics for Windows, version 17.0; SPSS, Chicago, Illinois, USA). The Wilcoxon signed rank test was used to compare the change in acoustic reflex threshold between pre-treatment and the 5th day of treatment. A p-value of 0.05 or lower was considered statistically significant.

Results

Forty-two patients (5 females and 37 males), aged 20–48 years (mean, 35 years), were included in the study. The pure tone averages and tympanogram findings were within normal ranges (as per American National Standards Institute) for all patients.

The acoustic reflex thresholds for both ears were determined at the desired frequencies pre-treatment and on the 5th day of treatment, and their means were calculated (Table I). Increases in acoustic reflex thresholds were observed on the 5th day of treatment when compared to pre-treatment, except for the right contralateral thresholds at 500 and 2000 Hz. These increases were statistically significant for the right ipsilateral thresholds at 2000 and 4000 Hz, the left ipsilateral thresholds at 500, 1000, 2000 and 4000 Hz, and the left contralateral thresholds at 2000 and 4000 Hz ($p \leq 0.05$); other increases were not significant ($p > 0.05$). Statistically significant increases ranged from 1.22 dB to 3.41 dB.

Discussion

The acoustic reflex is recognised as a protective mechanism against acoustic trauma to the cochlea. Disruption of this mechanism by different causes may increase susceptibility to acoustic trauma. Previous literature has reported that anaesthetics,[7] ethyl alcohol[8] and solvents[9] can increase sensitivity to acoustic trauma by suppressing the acoustic reflex. However, no studies have investigated the potential effects of thiocolchicoside, which is frequently used for its muscle relaxant effect. This possibility is particularly important for individuals who work in noisy environments.

A study published in 1967 mentioned that drugs may impair the acoustic reflex and increase susceptibility to acoustic trauma; the authors confirmed the suppressive effects of alcohol and pentobarbital.[10] Another study, published in 1977, showed that alcohol increased the acoustic reflex threshold by about 11 dB above the normal values at 100 minutes from intake, but values returned to normal by 200 minutes.[11] In 1978, researchers reported that increases in blood alcohol levels to 0.09–0.15 per cent decreased the protective effect of the acoustic reflex.[12]

A recent study investigated the effects of alprazolam, an anxiolytic drug, on the acoustic reflex by comparing the acoustic reflex thresholds prior to and following medication.[13] There was a statistically significant increase only for the left ipsilateral and contralateral thresholds. Consequently, the authors concluded that the evidence was insufficient to confirm an effect of alprazolam on the acoustic reflex.

- **Thiocolchicoside, a commonly used myorelaxant, may have a deteriorating effect on acoustic reflexes**
- **In this study, the deterioration was not clinically significant because of small differences in the results (1.22–3.41 dB)**
- **Extra precautions may only be necessary for those who work in noisy environments, to prevent occupational hearing loss**

Apart from alcohol, the most intensively investigated agents that have effects on the acoustic reflex are anaesthetic drugs. Some authors have suggested that

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TABLE I
MEAN ACOUSTIC REFLEX THRESHOLDS PRE-TREATMENT AND ON 5TH DAY OF TREATMENT

Frequency (Hz)	Mean thresholds pre-treatment (dB)	Alteration direction	Mean thresholds on 5th day of treatment (dB)	Threshold gap	p^*
Right ipsilateral					
– 500	92.92	<	93.41	0.49	0.48
– 1000	96.09	<	97.31	1.22	0.30
– 2000	93.17	<	94.87	1.7	0.02
– 4000	93.41	<	94.63	1.22	0.05
Right contralateral					
– 500	99.02	>	98.78	−0.24	0.94
– 1000	97.80	<	100.00	2.2	0.08
– 2000	98.29	>	97.80	−0.49	0.75
– 4000	101.21	<	103.17	1.96	0.26
Left ipsilateral					
– 500	91.95	<	93.65	1.7	0.05
– 1000	94.88	<	97.31	2.43	0.04
– 2000	92.68	<	96.09	3.41	0.005
– 4000	92.92	<	95.85	2.93	0.008
Left contralateral					
– 500	97.31	<	98.04	0.73	0.65
– 1000	97.56	<	99.02	1.46	0.31
– 2000	95.12	<	97.56	2.44	0.01
– 4000	99.75	<	102.43	2.68	0.04

*p-values ≤ 0.05 are statistically significant.

tympanometry could be carried out in newborns and babies under general anaesthesia because of a lack of co-operation.[14] However, these authors also stated that this procedure could yield faulty results under general anaesthesia because of the suppressive effects of anaesthetics. They confirmed that the acoustic reflex could not be observed when thiobutabarbital, propanidid and diazepam were used, whereas the acoustic reflex was observed when ketamine hydrochloride and alphaxalone-alphadolone acetate were used. A study published in 2005 showed that muscle relaxants (atracurium, cisatracurium and suxamethonium), which are anaesthesia components, had a suppressive effect on the acoustic reflex in all cases.[15] Curare has been reported to suppress the acoustic reflex by deteriorating stapedial muscle contractions, but has no effect on the reflexive arch.[16]

Solvents used in the paint and adhesive industry are also suggested to increase the harmful effects of noise by suppressing the acoustic reflex.[17] The effects of toluene on the acoustic reflex were investigated in rats under anaesthesia.[18] According to that study, toluene suppressed the acoustic reflex in anaesthetised rats. Toluene has both anticholinergic and anti-glutamatergic effects, and it also inhibits voltage-dependent calcium (Ca^{2+}) channels. Acetylcholine and glutamate play an important role in the afferent and efferent systems of the auditory pathway. The same study also showed that isoflurane, another solvent used in general anaesthesia, has a similar effect to that of toluene.[18]

Some studies have emphasised that the acoustic reflex may be deteriorated in neuromuscular diseases such as myasthenia gravis, amyotrophic lateral sclerosis and myotonic dystrophy.[19,20] Many studies have investigated the effects of central nervous system depressants such as alcohol and anaesthetic drugs on the acoustic reflex; however, no studies in the English-language literature have investigated the effects of oral forms of muscle relaxants commonly used to treat orthopaedic, traumatic and rheumatological disorders.

Our study confirmed that thiocolchicoside increased the acoustic reflex threshold on the 5th day of treatment when compared to the pre-treatment state, except for the right contralateral thresholds at 500 and 2000 Hz. However, the clinical significance of this increase in the acoustic reflex threshold is uncertain.

These increases in the acoustic reflex thresholds were never higher than 3.41 dB for each frequency, but the findings nevertheless indicate that thiocolchicoside treatment may deteriorate the acoustic reflex. The statistically significant increases observed in the present study, especially in the left ipsilateral and contralateral thresholds and at the high frequencies (2000–4000 Hz), show that thiocolchicoside has a minimal effect on the acoustic reflex. These findings are in line with the results of Ozturk *et al.*[13] Further extensive investigations are required to provide results with greater objectivity.

The absence of similar studies in the English-language literature precluded a comparison of our data with other studies. However, many published studies confirm that muscle relaxants used in general anaesthesia have suppressive effects on the central nervous system and may suppress the acoustic reflex.[13–16] Therefore, muscle relaxant drugs, especially those affecting the central nervous system, could be anticipated to weaken the stapedial muscle. However, this weakening effect was not significant clinically in the

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present study because of small differences in the acoustic reflex threshold between measurements pre-treatment and on the 5th day of treatment. Hence, extra precautions may only be necessary for those who work in noisy environments, in order to prevent occupational hearing loss.

References

1 Akyıldız N, ed. *Diseases and Microsurgery of Ear*, volume 1 [in Turkish] Ankara: Bilimsel Tıp Yayınevi, 1998
2 Akyıldız N, ed. *Diseases and Microsurgery of Ear*, volume 2 [in Turkish] Ankara: Bilimsel Tıp Yayınevi, 1998
3 Şahin F. Effects of ethyl alcohol on acoustic reflex and trauma [in Turkish] *Fırat Tıp Dergisi* 2010;**15**:79–82
4 Artusi M, Nicoli S, Colombo P, Bettini R, Sacchi A, Santi P. Effect of chemical enhancers and iontophoresis on thiocolchicoside permeation across rabbit and human skin in vitro. *J Pharm Sci* 2004;**93**:2431–8
5 Patat A, Klein MJ. Effects of acute and repeated doses of two muscle relaxants chlormezanone and thiocolchicoside, on vigilance and psychomotor performance of healthy volunteers. *Hum Psychopharmacol Clin Exp* 1991;**6**:285–92
6 Janbroers JM. Review of the toxicology, pharmacodynamics and pharmacokinetics of thiocolchicoside, a GABA-agonist muscle relaxant with anti-inflammatory and analgesic actions. *Acta Ther* 1987;**13**:221–7
7 Borg E, Moller A. Effect of central depressants on the acoustic middle ear reflex in rabbit. A method for quantitative measurements of drug effect on the CNS. *Acta Physiol Scand* 1975; **94**:327–38
8 Robinette MS, Alper RR, Brey HR. The effect of alcohol on the acoustic Reflex Relaxation Index. *J Aud Res* 1981;**21**:159–65
9 Venet T, Rumeau C, Campo P, Rieger B, Thomas A, Cour C. Neuronal circuits involved in the middle-ear acoustic reflex. *Toxicol Sci* 2011;**119**:146–55
10 Borg E, Moller AR. Effect of ethyl alcohol and pentobarbital sodium on the acoustic middle ear reflex in man. *Acta Otolaryngol* 1967;**64**:415–26
11 Cohill EN, Greenberg HJ. Effects of ethyl alcohol on the acoustic reflex threshold. *J Am Audiol Soc* 1977;**2**:121–3
12 Robinette MS, Brey RH. Influence of alcohol on the acoustic reflex and temporary threshold shift. *Arch Otolaryngol* 1978; **104**:31–7
13 Ozturk M, Ila K, Erdogan S, Polat A, Topdag M. The effect of alprazolam on acoustic stapedius reflex thresholds in healthy volunteers. *Indian J Otolaryngol Head Neck Surg* 2014;**66**: 347–51
14 Farkas Z. Acoustic reflex and general anaesthesia. *Scand Audiol Suppl* 1983;**17**:43–6
15 Ciardo A, Garavello W, Leva M, Graziano B, Gaini RM. Reversed ipsilateral acoustic reflex: a study on subjects treated with muscle relaxants. *Ear Hear* 2005;**26**:96–103
16 Ruth RA, Arora NS, Gal TJ. Stapedius reflex in curarized subjects: an index of neuromuscular weakness. *J Appl Physiol Respir Environ Exerc Physiol* 1982;**52**:416–20
17 Kemaloğlu YK, Tutar H. Noise induced hearing loss and acoustic trauma [in Turkish]. *Turkiye Klinikleri J ENT - Special Topics* 2013;**6**:44–54
18 Campo P, Venet T, Thomas A, Cour C, Castel B, Nunge H *et al*. Inhaled toluene can modulate the effects of anesthetics on the middle-ear acoustic reflex. *Neurotoxicol Teratol* 2013;**35**:1–6
19 Yamane M, Nomura Y. Analysis of stapedial reflex in neuromuscular diseases. *ORL J Otorhinolaryngol Relat Spec* 1984; **46**:84–96
20 Shimizu T, Hayashida T, Hayashi H, Kato S, Tanabe H. Stapedial reflex in amyotrophic lateral sclerosis. *J Neurol Neurosurg Psychiatry* 1996;**60**:544–8

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