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Triazolam Tolerability During Auditory Brainstem Evoked Potential in Children: Potential Effect on the Cardio-Respiratory Functions

Hayder M Alkuraishy[1], Ali I Al-Gareeb[1], Marta C Monterio[2]

[1]Assist Professor in Department of clinical Pharmacology and therapeutic, Medical Faculty College of Medicine, Al-Mustansiriya University, Baghdad, Iraq.
[2]Pharmaceutical Science Post-Graduation Program, Neuroscience and Cell Biology, Post-graduate Program Health Science Institute, Federal University of Pará/UFPA, Belém, Brazil

Abstract

Triazolam is a member of benzodiazepine class that has central depressant effect and used as sedative for insomnia since; it possesses sedative, amnestic, anxiolytic and anti-convulsant effects. Therefore, the aim of the present study was assessment the effect of triazolam on cardio-respiratory vital signs during auditory brainstem response (ABR) test in children screened for hearing loss. Randomized selection of 60 children with age ranged between 1-5 years and body weight range from 10-21kg, the children have no history of any acute or chronic somatic or psychological diseases and not take any medication during this study. The children were divided into two groups, 30 children in each group, Group A: Received triazolam 0.015 mg/Kg (n=30), Group B: Received triazolam 0.030 mg/Kg (n=30). All participants in the current study undergo measurement of blood pressure (by using blood pressure monitor device) in a supine position on the right arm, in addition to measure pulse rate, oxygen saturation (by using oxymeter device) and respiratory rate in supine position before and after of the sedation induced by triazolam along 120 minute, the duration of study last four weeks. Triazolam at a dose of 0.015 mg/Kg produced sedation time that last for 36.44 ± 5.62 minutes whereas at a dose of 0.030 mg/Kg produced sedation time that last for 40.45 ± 4.79 minutes which differ significantly p=0.004. All vital signs were not significantly differed between low and high dose of triazolam except partial oxygen saturation (PaO_2) (%) which was high in low dose of triazolam and low in high dose of triazolam p=0.001. Conclusion: Triazolam is safe sedative drug for induction of hypnosis during ABR test with minimal effect on cardio-respiratory functions.

Keywords: Triazolam, ABR, sedation, Vital signs.

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Introduction

Preoperative anxiety and fear is associated with inauspicious outcomes including high requirement of analgesic agents, extended post-operative care and negative psychological effects thus; premedication is required [1]. Benzodiazepines are mainly used as oral medications to avoid other painful routes and have potent sedative, muscle relaxant and hypnotic effects [2].

Triazolam is a member of benzodiazepine class that has central depressant effect and used as sedative for insomnia since; it possess sedative, amnestic, anxiolytic and anti-convulsant effects [3]. Triazolam is short acting benzodiazepine with rapid onset of action thus; it used as adjuvant during anesthesia for short medical procedures and reduction of anxiety during MRI [4]. This drug is associated with risk of rebound insomnia, tolerance and dependence during long term uses

Triazolam activates GABA-A receptor that augment the binding of GABA to GABA receptors causing hyperpolarization and opening of cl-channel lead to neuronal inhibition , this effect is antagonized by the effect of flumazenil (GABA antagonist) [5]. The amazing safety of triazolam is that in the increases of cl- channel opening frequency not duration as in barbiturates additionally; triazolam effect depends on the pre-synaptic GABA releases when it low triazolam not produced any effect on contrary barbiturates activates GABA receptors even when GABA concentration is low [6].

Triazolam produced minor effect on the neural electrical activity, it produced little effect on auditory evoked potential and sleep waves thus; triazolam is safe during brain activity recordings [7].

The auditory brainstem response ABR is an important test that used for evaluation of neuro-physiological

responses along the auditory pathway depending on sound stimuli that generate action potentials which conducted along the eighth nerve, brain stem and then to the brain, thus; in many countries, the newborn ABR test is consistently done for early detection of any hearing problems and preventing further effects on speech and language developments [8].

ABR test is usually done while the subject is sleep or completely relaxes to prevent any exogenous effect on the response recording since; ABR test required sedation in infants, young children and in mental retarded patients to obtain accurate results [9].

Therefore the aim of the present study was assessment the effect of triazolam on cardio-respiratory vital signs during ABR test in children screened for hearing loss.

Materials and Methods

Study site: The study was conducted in Department of Clinical Pharmacology, College of Medicine, Al-Mustansiriya University in cooperation with ENT unite in Al-Yarmook teaching hospital.

Subjects: Randomized selection of 60 children with age ranged between 1-5 years and body weight range from 10-21kg the children have no history of any acute or chronic somatic or psychological diseases and not take any medication during this study.

Study design: The children were divided into two groups, 30 children in each group

Group A: Received triazolam 0.015 mg/Kg orally (n=30)

Group B: Received triazolam 0.030mg/Kg orally (n=30)

The duration of study last four weeks

All participants in the current study undergo measurement of blood pressure (by using blood pressure monitor device) in a supine position on the right arm, in addition to measure pulse rate, oxygen saturation (by using oxymeter device) and respiratory rate in supine position before and after of the sedation induced by triazolam along 120 minute. This study was approved by the specific Scientific Jury and Ethical Committee in the medical board college of medicine, Al-Mustansiriya, all of enrolled participants gave informed verbal consent for their participations in this study.

The children were prepared by give their parents the following instructions:

- Weak up the child early and don't let him sleep until the test.
- Simple breakfast should be taken, avoid drinking through the last 3 hour before the test.
- Mother combined is preferred for help.
- Bring additional cloth for the child if possible.

Before sedation, patients screening should be done for

- Patients age and weight
- Drug allergies and sensitivities
- Blood pressure
- Heart, kidney, and liver problems
- Neuromuscular disorders (such as: muscular dystrophy)
- Medication and herbal supplements taken

Triazolam tablets 0.125 mg (Halcon, Pfizer, medicine mexico.com) were purchased from private pharmacy, the tablet was dissolved in 5ml distilled water then each ml contains 0.025 mg of triazolam this solution given orally according to the body weight thirty minute prior to the ABR test.

The sedation level was assessed by Ramsy sedation scale [10] and all vital signs were assessed before and after sedation.

Statistical Analysis

Data were analyzed using Statistical Package for the Social Sciences (SPSS version 21, IBM New York Corp). Data of the present study were presented as mean ± SD and proportions; paired student t test was used to determine the significance of differences regarding P value less than 0.05 is significant.

Results

Triazolam at a dose of 0.015 mg/Kg produced sedation time that last for 36.44 ± 5.62 minutes whereas at a dose of 0.030 mg/Kg produced sedation time that last for 40.45 ± 4.79 minutes which differ significantly $p = 0.004$. Additionally, the number of children that complete ABR test with low dose of triazolam was 66.67% while those who completed ABR test with high dose of triazolam was 93.33% $p = 0.009$.

Furthermore, all vital signs were not significantly differed between low and high dose of triazolam except PaO_2 (%) which was high in low dose of triazolam and low in high dose of triazolam $p = 0.001$ (Table 1).

In the present study, high dose of triazolam produced minimal reduction in systolic and diastolic blood pressure compared to the low dose of triazolam $p > 0.05$ (Figure 1).

Triazolam produced minimal reductions in the heart rate at a dose of 0.015 mg/kg while triazolam at a dose of 0.030 mg/kg showed sequential reduction in heart rate but not significant as compared with low dose of triazolam $p > 0.05$ (Figure 2).

Moreover, triazolam at 0.015mg/kg and 0.030 mg/kg produced little effect on the respiratory rate during ABR test $p > 0.05$ (Figure 3).

Table 1. *Differential dose dependent effects of triazolam on the sedation time and vital signs during ABR test.*

Variables	Trizolam 0.015 mg/Kg (n=30)	Trizolam 0.030 mg/Kg (n=30)	p
Sedation time (min)	36.44 ± 5.62	40.45 ± 4.79	0.004*
Complete ABR(n)	20 (66.67%)	28 (93.33%)	0.009*
SBP (mmHg)	102.44 ± 2.33	100.35 ± 2.66	>0.05
DBP (mmHg)	68.23 ± 4.62	66.59 ± 4.87	>0.05
HR(beat/min)	98.66 ± 5.88	94.74 ± 5.63	>0.05
RR (min)	23.41 ± 1.66	23.55 ± 1.37	>0.05
PaO2 (%)	96.93 ± 2.53	90.44 ± 3.62	0.001*

Data are expressed as mean ± SD; *p <0.01; ABR: auditory brainstem response; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; RR: respiratory rate; PaO2: partial oxygen saturation.

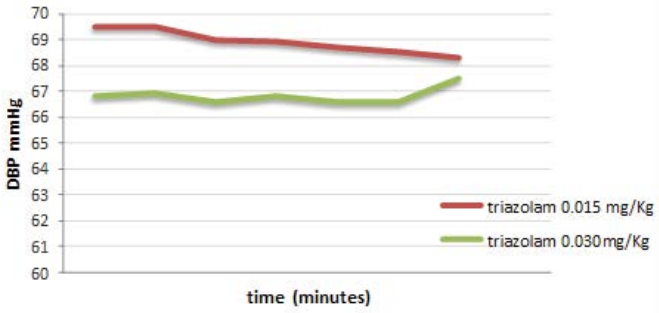

Figure 1. *Effect of low and high dose of triazolam on diastolic blood pressure during ABR test.*

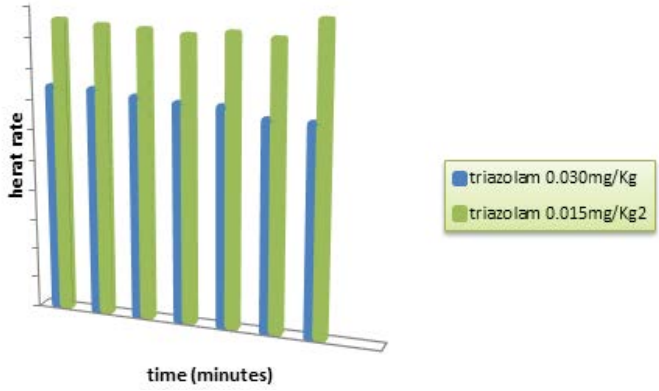

Figure 2: *Effect of low and high dose of triazolam on heart rate during ABR test*

Furthermore, triazolam at a dose of 0.030mg/kg produced significant reduction in PaO_2 % P < 0.01 compared to the low dose of triazolam 0.015mg/kg (Figure 4).

Discussion

The study illustrated dose dependent effect of triazolam in the induction of sedation and hypnosis in the children that are elected for ABR test, high dose of triazolam showed more significant effect in the initiation of hypnosis. Previously, diazepam administration was used as sedative agent during auditory brainstem evoked response since; it was not affect ABR amplitudes but significantly prolongs wave V interval [11] and this sedative effect can be reversed by administration of benzodiazepine antagonist, thus

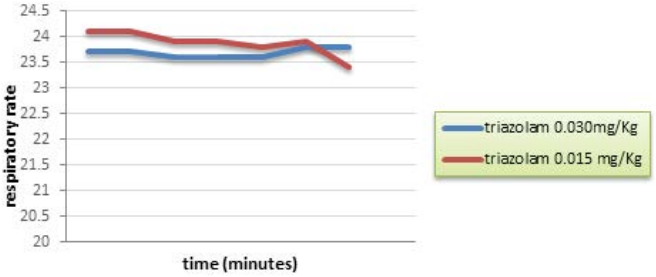

Figure 3: *Effect of low and high dose of triazolam on the respiratory rate during ABR test*

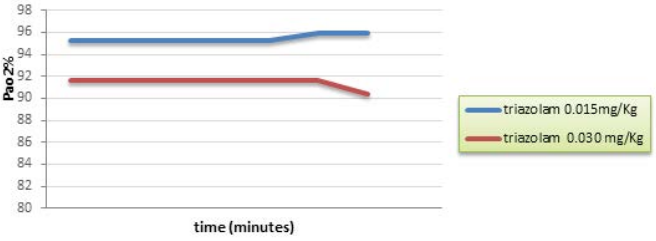

Figure 4: *Effect of low and high dose of triazolam on PaO2 % during ABR test*

benzodiazepine is more preferred than general anesthetic agents during ABR recording since; general anesthetic agent affects ABR wave and temporal precision response at brainstem neurons, while Morizot et al , research revealed an adaptation effect of alprozolam on auditory pathway [12] thus; benzodiazepine effect on ABR recording is a drug selective in view of the fact that ;GABA receptors at auditory pathway illustrated an unexpected reaction due to differences in GABA-A subunits [13]. Triazolam bind to benzodiazepine receptors that enhance the effect of GABA on GABA receptors led to neuronal membrane hyperpolarization, [14]. Indeed, triazolam compact the excitatory postsynaptic potential at hippocampal area that participating for its sedative effect [15]. The sedative effect of triazolam may be related to the orexine cells in the perifornical area of the hypothalamus via activation of GABA receptors and inhibition of histaminergic receptors [16]. In addition, triazolam activates BZ1 receptor (for induction of sedation) and BZ_2 (for induction of anxiolytic effect), also Z-compounds that are non-bezodiazepine like zolpidem only activate BZ1 receptor, since; GABA-A is consist of three main subunits called alpha, beta and gamma which regarded as binding site for different CNS depressant drugs, triazolam binds to alpha subunit of GABA-A receptor that trigger the opening of inhibitory chloride channel so; triazolam is unable for opening of inhibitory chloride channel directly [17]. Thus, triazolam produced significant sedative effect useful for sedation and hypnosis during ABR test. In the present study; no significant changes were showed on children systolic blood pressure between high and low dose of triazolam, during and after sedation, since; neither low nor high dose of triazolam during sedation showed any effects on systolic blood pressure at the present study doses [18]. On the other hand, our study showed that triazolam showed insignificant reduction of heart rate since; sympathetic activity is regulated by GABA ergic neurons

thus; triazolam potentiate the inhibitory effect of GABA on the sympathetic outflow [19], additionally Zahner and Lidp study, confirmed that administration of diazepam for induction of minor sedative effect lead to augmentation and provoking of GABAergic-inhibitory post-synaptic currents (IPSCs) at hypothalamus causing significant attenuation of sympathetic outflow in a dose dependent manner and consequently; reduced cardiac excitability and heart rate [20], recently; Yeganeh et al., research revealed that activation of GABA-A receptor via diazepam lead to preservation of cardiac function and heart rate through inhibition of vasopressin release which has a positive dromotropic and chronotropic effects [21]. This effect was not showed in our study may be due to small sample size or short term effect of triazolam may have little effect on sympathetic inhibition. During ABR testing there was insignificant effect of triazolam on children respiratory rate, in view of the fact that triazolam is GABA agonist and glutamatergic NMDA receptor antagonist thus; it modulates respiratory center sensitivity and respiratory drive during sedation [22]. Similarly, diazepam also modulate respiratory function during ABR sedation due to activation of GABA receptors that causing respiratory failure but only at higher doses [23], for that reason both of α_1 and α_2 of GABA-A receptors mediated the changes of the two phases of the respiratory cycle (inspiration and expiration), so; α_1-GABAA receptors activation causes shortening of expiration, while activation of α_2-GABAA receptors shorten the inspiration duration which may lead to respiratory depression [24]. Moreover, human and animal researches showed minimal effect of benzodiazepine on respiratory function during sleep and wakefulness, but respiratory depression have been documented during benzodiazepine therapy that depend on its dose and rout of administration since it rare but may occurred, also benzodiazepine lead to tachypnea due to depression on the neural circuits that organize the respiratory cycle [25] so; intravenous administration of benzodiazepine led to shortening of inspiration and expiration time through inhibition of bulbar neurons, since breathing behavior is vagally mediated that is controlled by central GABA-A activity which regulate duration of inspiration and initiation of expiration [26]. Therefore, diazepam shortens the inspiratory time due to peripheral muscle relaxant effect and central activation of α-2 subunit of GABA-A receptor [27]. Interestingly, diazepam is efficient agent against apnea in human during non-REM sleep, since; midazolam reduced the episodes of apnea in Rett syndrome thus; clonazepam and triazolam are of value in management of idiopathic sleep apnea [28]. On contrast, Chen et al. study showed that uses of diazepam in patients with chronic obstructive airway disease may lead to dangerous respiratory failure so; non-benzodiazepine may be safer in treatment of insomnia in those patients [29] while; Gallos et al. study recently reported that activation of α-5 subunit of GABA-A receptor at airway smooth muscle significantly reverse bronchospasm induced by chloral hydrate via modulation of bronchial calcium and bradykinin releases [30]. Low PaO_2 indicates low oxygenation and hypoxemia, normally PaO_2 level is from 75-100 mm Hg, PaO_2 lower than 60 mm Hg oxygen supplementation is indicated since; below 26 mmHg leading to the death [31]. In the present study significant changes were revealed in children oxygen partial pressure (PaO_2) between high and low dose of triazolam during ABR testing, PaO_2 was significantly decreased in high dose of triazolam since, Henao-Guerrero and Ricco study showed that administration of diazepam 0.2 mg/kg alone or in combination with propofol or ketamine lead to significant reduction in PaO_2 and other cardio-respiratory parameters so; 100% oxygen supplementation is recommended [32].The mechanism of triazolam in the reduction of PaO_2 is related to respiratory depression induced by GABA activation, activation of alpha or gamma subunit of GABA-A receptor causing influx of chloride channel and then inhibitory hyperpolarization at respiratory centre that lead to reduction in the initiation of action potential, this effect was mainly seen with intravenous administration but orally administrated of diazepam or chloral hydrate cause less inhibition due to low density of binding site at respiratory centre [33]. So, all of those studies are in agreement with our results because we used appropriate doses of triazolam orally that caused mild reduction in PaO_2 but not hypoxia.

Conclusion

Triazolam is safe sedative drug for induction of hypnosis during ABR test with minimal effect on cardio-respiratory functions since it minimally affects heart rate, respiratory rate and PaO_2 in a dose dependent manner thus; low triazolam dose is effective as large dose with substantial low side effects.

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Correspondence to:

Hayder M. Alkuraishy,
Assist Professor,
Faculty of Medicine,
Department of clinical Pharmacology and therapeutic,
Al-Mustansiriya University, Baghdad.
Iraq
E-mail: Hayderm36@Yahoo.com