

Alterations in brain-stem auditory evoked potentials among drug addicts

A cross-sectional study

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ABSTRACT

الأهداف: مقارنة الاختفاء المطلق، والاختفاء الغير مطلق وترددات من الطول الموجي المختلفة من إمكانات جذع الدماغ السمعية المثارة (BAEP) لمتعاطي المخدرات ومجموعة الضوابط. لتحديد الضرر العصبي في وقت مبكر من الأشخاص الذين يتعاطون أنواع مختلفة من المخدرات بحيث يحصلوا على المشورة المناسبة والتدخل في الوقت المناسب.

الطريقة: في هذه الدراسة المستعرضة قيمت BAEP's للحصول على البيانات ونظام تحليلي في 58 من متعاطي المخدرات من الذكور في الفئة العمرية من 15-45 عام، وكذلك في سن 30 المتطابقة للضوابط الصحية. حللت الاختفاء المطلق والاختفاء الغير مطلق من BAEP من خلال تطبيق طريقة واحدة ANOVA واختبار (ت). وقد أجريت الدراسة في كلية GGS الطبية، فريدكوت، بنجاب، الهند بين يوليو 2012م ومايو 2013م.

النتائج: تم العثور على الفرق في الاختفاء الذروة المطلقة والاختفاء الغير مطلق من BAEP في مجموعتين لتكون ذات دلالة إحصائية في كل الأذنين ($p < 0.05$). ومع ذلك، وجدنا فرق إحصائي في نسبة السعة في كلا الأذنين.

الخاتمة: ارتبط التسمم المزمن من المخدرات المختلفة بشكل كبير مع طول اختفاء الذروة المطلقة والاختفاء غير المطلق من BAEP لمتعاطي المخدرات مما يعكس التأثير السلبي للإدمان المخدرات على انتقال العصبية في ممرات الأعصاب السمعية المركزية.

Objective: To compare the absolute latencies, the interpeak latencies, and amplitudes of different waveforms of brainstem auditory evoked potentials (BAEP) in different drug abusers and controls, and to identify early neurological damage in persons who abuse different drugs so that proper counseling and timely intervention can be undertaken.

Methods: In this cross-sectional study, BAEP's were assessed by a data acquisition and analysis system in

58 male drug abusers in the age group of 15-45 years as well as in 30 age matched healthy controls. The absolute peak latencies and the interpeak latencies of BAEP were analyzed by applying one way ANOVA and student t-test. The study was carried out at the GGS Medical College, Faridkot, Punjab, India between July 2012 and May 2013.

Results: The difference in the absolute peak latencies and interpeak latencies of BAEP in the 2 groups was found to be statistically significant in both the ears ($p < 0.05$). However, the difference in the amplitude ratio in both the ears was found to be statistically insignificant.

Conclusion: Chronic intoxication by different drugs has been extensively associated with prolonged absolute peak latencies and interpeak latencies of BAEP in drug abusers reflecting an adverse effect of drug dependence on neural transmission in central auditory nerve pathways.

*Neurosciences 2015; Vol. 20 (3): 253-258
doi: 10.17712/nsj.2015.3.20150105*

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Received 9th February 2015. Accepted 11th May 2015.

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Evoked potentials have emerged as an important electro-diagnostic technique in recent times.¹ Brainstem auditory evoked potentials (BAEP) represent the resultant response of cortical as well as subcortical areas to auditory stimulation. The measurement of auditory evoked potentials has been considered a novel technique for assessing the neurological changes as

a result of exposure to different drugs. During BAEP studies, 5 significant waveforms are recorded within 10 ms of auditory stimulus. Wave I originates from the peripheral portion of the VIIIth cranial nerve adjacent to the cochlea while Wave II, III, IV, and V originate from the cochlear nucleus, superior olivary nucleus, lateral lemniscus, and inferior colliculi.² Commonly measured parameters for the analysis of BAEP are absolute latency, interpeak latencies (IPLs), and amplitude. The most common IPLs are I-III, which measure the conduction from the VIIIth cranial nerve across the subarachnoid space into the core of lower pons, I-V which measures the conduction from the VIII cranial nerve through pons to midbrain, and III-V, which measures the conduction from lower pons to midbrain.¹ Drug addiction is a chronic, often relapsing brain disease as it leads to changes in the structure and function of the brain.³ The most common types of drugs that people abuse fall into 4 categories: stimulants, depressants, hallucinogens, and opioids. In addition, use of prescription drugs like sedatives and tranquilizers for non-medical reasons, called prescription-drug abuse, has also increased in recent years. Though the effect of each group of drugs is different, all are harmful to the user's body, mind, and social life.⁴ Similarly, use of tobacco is a serious intentionally invited health hazard. Tobacco smoking affects both active, as well as passive smokers.⁵ Alcohol is another widely abused substance. It is believed that chronic use of alcohol leads to neurological damage including the central auditory tracts.⁶ Marijuana or Cannabis intake has been reported to affect cognitive functions such as selective attention, decrease in P300 amplitude, and decrease in performance that provides evidence for early stage sensory processing deficits in cannabis users.⁷⁻⁹ Hence, the present study was conducted to assess the functional integrity of the brainstem through assessment of central auditory pathways, even before the clinical manifestation in substance abusers.

Methods. Brainstem evoked potentials were recorded by using the Data Acquisition and Analysis System, (Neurostim [NS4], Medicaid Systems, Chandigarh, India) in a sample of 58 drug abusers, all males, in the age group of 15-45 years, as well as in 30 age-matched healthy controls. This cross-sectional study was carried out at the GGS Medical College, Faridkot, Punjab, India from July 2012 to May 2013. The 30 control subjects were recruited randomly from nearby residential areas of the institution, and the cases were taken from the patients admitted to the Drug De-addiction Center

of this tertiary health care institute of Punjab by convenient sampling. The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from each individual as per the guidelines of Helsinki.

A self-designed substance use questionnaire (Proforma) was administered to all subjects before recording of evoked potentials, which included information on type of substance abuse, family history of substance abuse, its frequency, quantity, and density of substance consumption, age at first substance abuse, total duration of substance use, and time of last use. The validity and reliability of the questionnaire were determined before administration. The tool was found to be validated and reliable as no specific problem was found in the patient history proforma during a pilot study.

The substance abusers recruited for this study included 11 alcoholics, 21 opiate addicts (heroin, morphine), 12 tobacco chewers/smokers, and 14 pharmaceutical drugs addicts (using cough syrups, pain killers, anti-emetics, and so forth). The subjects were excluded from the study if suffering from any type of posttraumatic coma, neurological diseases (multiple sclerosis, brainstem tumor, and so forth), hearing defects, and other psychiatric disorders (mood disorder, organic brain disorder, personality disorder, and neurotic disorder).

The test was explained to the subjects to ensure full cooperation, and the participants were instructed not to sleep during the procedure and the instrument was placed out of the view of the subject.

Equipment set up. Two channels were used (as per 10-20 international system of EEG electrode placement): Channel 1: A_1-C_z (active electrodes), Channel 2: A_c-C_z , Ground: F_z . The subjects were allowed to sit comfortably in a fully relaxed state and one ear was tested at a time. The skin at the point of placement of the electrodes was cleaned with spirits. Using electrode paste or conducting jelly, the recording electrodes were placed on both the ears; namely, ipsilateral (A_1), and contralateral ear (A_c), the reference electrode at vertex (C_z) and the ground electrode was placed at F_z . The brief click stimulus was delivered by shielded headphones, which is a square wave pulse of 0.1 ms duration. The low cut filter was set at 100 Hz and the high cut filter at 3000 Hz. The sweep speed was 1 ms/div and sensitivity was set at 0.5 μ v/div. The rarefaction stimulus was delivered at an intensity of 70 db; namely, above the hearing threshold. The hearing threshold was determined by Pure Tone Audiometry (PTA) for all, at the onset of recording in order to eliminate any peripheral hearing defect. Two separate trials of 2000 responses were recorded and

superimposed. Skin to electrode impedance was kept below 5 kohm.

Statistical analysis. The absolute peak latencies of waves I-V, the IPLs I-III, I-V, III-V, and amplitude ratio V/I of both the ears were measured and compared between the drug abusers group and controls and also in between the different groups of drug abusers. Values were expressed as means ± standard deviation. Means were compared by the Student t test and one-way ANOVA using the Statistical Package for Social Sciences System version 16.0 (SPSS Inc., Chicago, IL, USA). A *p*-value <0.05 was considered to be statistically significant.

Results. The study was conducted on 58 male drug abusers consuming different types of drugs in the age group of 15-45 years. Out of these, 21 were opiate abusers, 11 alcoholics, 14 prescription drug abusers, and 12 tobacco smokers. The controls were all healthy subjects in the same age group who were not dependant on any drug. Table 1 shows the difference of absolute latencies of waves of BAEP (I, II, III, IV, V) of the right ear between drug abusers and controls and these differences were statistically significant (*p*<0.05) in waves I, II, III, and V.

Table 2 shows the difference in IPLs of BAEP of the right ear between the drug abusers and controls, and it was found that the difference in interpeak latency I-III was statistically highly significant, and the difference in IPLs I-V and III-V was statistically significant. However, the difference in amplitude ratio (V/I) of the right ear between drug abusers and controls was found to be statistically insignificant.

Table 3 shows the difference in latencies of waves of BAEP of the left ear between drug abusers and controls, and it was found highly significant in waves II and III, and statistically significant in waves I and V between drug abusers and controls.

Table 4 shows the difference in IPLs (I-III, I-V, III-V) of BAEP of the left ear between drug abusers and controls, and it was found statistically significant (*p*<0.05) in all the IPLs; however, the difference of amplitude ratio (V/I) was found to be statistically insignificant (*p*>0.05) between drug abusers and controls.

In Table 5, the difference in the duration of waves and IPLs of BAEP of the right ear were compared between different groups of drug abusers and found to be statistically insignificant in waves I to V, and also in IPLs I-III and I-V except the interpeak latency III-V, which was found statistically significant.

Table 6, the mean of duration of waves and IPLs of BAEP of the left ear were compared between different

Table 1 - Comparison of absolute latencies of waves (ms) of BAEP of right ear between drug abusers (n=53) and controls (n=30).

Wave	Cases		Controls		t-value	p-value
	Mean	SD	Mean	SD		
I	1.53	0.1	1.16	0.1	3.06	0.003*
II	2.80	0.28	2.68	0.2	2.07	0.04*
III	3.66	0.27	3.78	0.17	2.20	0.03*
V	5.52	0.16	5.59	0.10	2.17	0.03*

BAEP - brainstem auditory evoked potentials, *significant (*p*<0.05)

Table 2 - Comparison of interpeak latencies (IPL) (ms) and amplitude ratio (V/I) of BAEP of the right ear between drug abusers (n=58) and controls (n=30).

IPL of right ear	Cases		Controls		t-value	p-value
	Mean	SD	Mean	SD		
I-III	2.16	0.13	2.31	0.19	4.26	0.0001**
I-V	4.01	0.3	4.15	0.24	2.19	0.03*
III-V	1.93	0.28	1.82	0.08	2.10	0.04*
V/I	171.96	245.71	159.10	146.6	0.26	0.79***

BAEP - brainstem auditory evoked potentials, *significant *p*<0.05, **highly significant *p*<0.001, ***non significant *p*>0.05

Table 3 - Comparison of absolute latencies of waves (ms) of BAEP of left ear between drug abusers (n=58) and controls (n=30).

Wave	Cases		Controls		t-value	p-value
	Mean	SD	Mean	SD		
I	1.40	0.15	1.36	0.20	3.35	0.001*
II	2.78	0.22	2.60	0.10	4.23	0.0001**
III	3.68	0.22	3.48	0.3	3.48	0.0008**
V	5.34	0.26	5.19	0.4	2.07	0.04*

BAEP - brainstem auditory evoked potentials, *significant *p*<0.05, **highly significant *p*<0.001

Table 4 - Comparison of interpeak latencies (IPL) (ms) and amplitude ratio (V/I) of BAEP of the left ear between drug abusers (n=58) and controls (n=30).

IPL of left ear	Cases		Controls		t-value	p-value
	Mean	SD	Mean	SD		
I-III	2.28	0.39	2.09	0.19	2.50	0.01*
I-V	4.13	0.44	3.93	0.31	2.20	0.03*
III-V	1.98	0.41	1.79	0.31	2.20	0.03*
V/I	161.97	265.41	179.50	139.4	0.34	0.74**

BAEP - brainstem auditory evoked potentials, *significant *p*<0.05, **non significant *p*>0.05

groups of drug abusers. It was found that the difference in duration of waves II, III, and V was statistically significant but no difference was found in waves I and IV. Also, the difference in IPLs was found to be statistically non significant.

Discussion. Drug abuse is an upcoming health problem prevalent in all societies. Unfortunately, across the globe and throughout time, drug abuse has manifested itself in one form or another; however, it

Table 5 - Comparison of absolute latencies of waves (ms) and interpeak latencies (ms) of BAEP of the right ear between different groups of drug abusers (n=58) using one way ANOVA.

Wave	Mean				F-value	P-value
	Opiates n=21	Alcohol n=11	Pharma n=14	Tobacco n=12		
I	1.58	1.51	1.51	1.46	0.285	0.836**
II	2.71	2.92	2.74	3.05	2.404	0.077**
III	3.70	3.68	3.57	3.68	0.629	0.599**
IV	4.81	4.69	4.85	4.96	1.799	0.158**
V	5.49	5.42	5.57	5.79	1.281	0.29**
I-III	2.18	2.17	2.06	2.21	0.553	0.648**
I-V	3.95	3.91	4.06	4.32	0.964	0.416**
III-V	1.78	1.82	2.06	2.44	5.826	0.002

BAEP - brainstem auditory evoked potentials, *significant $p < 0.05$, **non significant $p > 0.05$, #after post hoc test (Bonferroni Test), a significant difference was observed for inter peak latency (III-V) of the right ear between alcoholics and tobacco smokers ($p = 0.014$); and a highly significant difference was seen between opiate abusers and tobacco smokers ($p = 0.001$)

Table 6 - Comparison of absolute latencies of waves (ms) and interpeak latencies (ms) of BAEP of the left ear between different groups of drug abusers (n=58) using one way ANOVA.

Wave	Mean				F-value	P-value
	Opiates n=21	Alcohol n=11	Pharma n=14	Tobacco n=12		
I	1.430	1.40	1.54	1.48	0.413	0.744**
#II	2.74	2.73	2.69	2.32	3.317	0.027*
#III	3.67	3.99	3.78	3.76	2.824	0.047*
IV	4.76	5.00	4.74	4.68	1.406	0.251**
V	5.40	5.86	5.61	5.76	2.976	0.04*
I-III	2.23	2.59	2.24	2.28	2.392	0.079**
I-V	4.02	4.46	4.07	4.28	1.532	0.217**
III-V	1.76	1.86	1.83	2	0.782	0.509**

BAEP - brainstem auditory evoked potentials, *significant $p < 0.05$, **non significant $p > 0.05$, #After post-hoc test in the BAEP of the left ear, a significant difference was observed in wave II between opiate addicts and tobacco smokers ($p = 0.029$), and in wave III between opiate addicts and alcoholics ($p = 0.032$)

appears that drug abuse affects both the psychological and physical well being of a person. Most drugs affect the brain by interfering with the release of neurotransmitters or chemical messengers. Over time, a chemical dependency develops and their body does not function correctly without the drug. According to the National Institute on Drug Abuse, addiction occurs when a chemical dependency to a drug is combined with an overwhelming urge to use the substance.¹⁰ This brainstem auditory evoked potential study was carried out in a group of different drug abusers as it is considered to be a very useful technique to check the functional integrity of the auditory pathway, thereby assessing the neurological damage in the auditory nerve fibers. This study compared the absolute peak latencies, and IPLs of BAEP in a group of different drug abusers (n=58) compared with controls (n=30), and also between the different groups of drug abusers.

We observed that in the right ear, the peak latencies of waves I, II, III, and V; and all the IPLs were significantly prolonged in different drug abusers compared with controls. Similar findings were also observed in the left ear with the absolute latencies of all the waves of BAEP (I, II, III, V) and the IPLs (I-III, III-V, I-V) being significantly prolonged among drug abusers. This could be due to delay in conduction velocity associated with demyelination of the auditory nerve pathways as a result of chronic intoxication by different drugs. In the present study, no statistically significant difference was seen in the amplitude ratio (V/I) between drug abusers and controls. The difference of latencies between the different groups of drug abusers was also found to be statistically significant in waves II, III, V of the left ear, and a prolonged interpeak latency III-V in the right ear indicating that different drugs abused affect the auditory pathways to a different extent. These findings indicate that the conductivity of sensory impulses along the auditory nerve pathway is affected due to prolonged and chronic use of different drugs as evident by significant prolongation of absolute peak and IPLs as a result of their adverse effect on myelination of auditory nerve pathway, and also presumably may be mediated by loss of white matter. This may also indicate changes in excitability of the neural pool of these generators in the lower brainstem; namely, the medullo pontine region.

Kumar and Tandon¹¹ also found that conductivity of sensory impulses along the acoustic nerve and pons is affected in smokers as evidenced by significant prolongation of latencies of wave I and III. Nicotine and toluene present in tobacco smoke may perhaps be implicated as culprit chemicals inducing changes in BAEPs because of the affinity of nicotine and toluene

towards lipid rich tissues of the brain, prolongation of latencies of BAEPs occur as a result of their adverse effect on myelination of the sensory pathway. It has further been reported that large doses of nicotine affect the sensory motor system via its action on brainstem areas.¹²

Lal and Bhatia¹³ revealed significant prolongation of waves III ($p < 0.001$) arising from the pons, and V ($p < 0.01$) arising from the midbrain. All the IPLs (I-III, III-V, and I-V) were found to be prolonged significantly, thus, signifying an impaired conduction in the auditory nerve pathway along the lower and upper brainstem. These abnormalities may suggest demyelination or neuronal loss in the brainstem. Smith and Riechelmann⁶ recorded brainstem auditory evoked responses from 38 male patients and reported that the latency difference between the lower and upper brainstem components was positively related to the level of alcohol exposure and this adverse effect of decreased conduction velocity, presumably could be mediated by loss of white matter. Chan et al¹⁴ also found that the mean value of the I-V interval was prolonged in all the alcoholics with and without the Wernicke-Korsakoff syndrome. Patients in syndrome group showed more prolonged I-V and I-III intervals than in the group without the syndrome.¹⁴ Misra and Kalita¹ attributed the prolongation of wave V latency with alcohol to lowering of body temperature. Other authors also reported the same findings of increased absolute peak latencies and IPLs in alcohol addicts,^{15,16} and heroin abusers.¹⁷

The P300 component of the auditory evoked potentials is an indicator of attention dependent target processing. The P300 data suggest that chronic nicotine use reduces P300 amplitudes. The results are additive in subjects using both nicotine and opiates. The P300 amplitudes of methadone substituted opiate addicts were in between the 2 control groups.¹⁸ The auditory brainstem evoked response (BAER) in male drug abusers also reported a significant delay in BAER latency.^{19,20} Similar results were found in cocaine abusers, which showed increased latency and decreased amplitude of P300.^{21,22} Nitrous oxide (N₂O) abusers also showed abnormal BAEP with delayed wave V, and difficulty in recognition of waves I and III.²³ Nitrazepam abusers, a benzodiazepine derivative, also demonstrated delayed IPS's (namely, I - III, I - V, III - V).²⁴ Therefore our findings corroborate with the findings of other authors thereby reiterating the fact that any type of drug abuse could damage the auditory nerve pathways leading to long term effects on hearing.

In conclusion, it can therefore be assumed that BAEP measurement is a useful tool for evaluating the

effects of drug abuse on the auditory system as these potentials reflect the functional integrity of the sensory tract in the brainstem area, and helps in identifying the sites impaired due to neurotoxic effects of these drugs. Hence, this could help in timely intervention and counseling of drug abusers to prevent any neurological damage in the pathway and improve their quality of life. The present study can be extended to include P300 as a test of cognitive functions and also the effect of duration of exposure to different drugs on BAEP between different drug abusers and be the area of future research.

Acknowledgments. We would like to thank Mr. Baltej Singh, Assistant Professor of statistics for his help in data analysis. We would also like to thank the laboratory technicians and employees of the physiology department for their technical assistance, and above all we are grateful for the support of the patients who participated in this study

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CASE REPORTS

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