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Comparison of EEG analysis systems during lidocaine-induced seizure activity and administration of valproic acid in rabbits

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Based on algorithm differences between aperiodic and power spectrum analysis of the electroencephalogram (EEG), we hypothesized that the effects on the EEG of an antiepileptic drug would be equally well detected with either lidocaine-induced seizure by aperiodic analysis or by power spectrum analysis. However, the former is superior.

EEG activity was recorded in anesthetized rabbits prior to intravenous infusion of valproic acid and lidocaine and after the onset of EEG activity. Values for delta, theta, alpha, beta, and total activity, as well as edge frequency were compared within each group, and were expressed as percent change from baseline for comparison between aperiodic and power spectrum analysis. With valproic acid, EEG changes were modest and the two methods of EEG analysis were significantly different from one another for only two of the 12 comparisons. With lidocaine, the lidocaine-induced seizure activity was associated with widespread EEG changes which were better detected by aperiodic analysis than by power spectrum analysis. Comparison between the two methods of analysis indicated significant differences for theta, alpha, and beta activity and edge frequency. These results indicate that both methods of analysis may be suitable to detect modest drug-induced EEG changes, whereas aperiodic analysis is superior for detection of widespread seizure activity. (J Osaka Dent Univ 2016 ; 50 : 23-29)

Key words : Aperiodic analysis ; Power spectrum analysis ; Lidocaine ; Valproic acid

INTRODUCTION

There are numerous studies on EEG (electroencephalogram) activity during seizures, natural sleep, and administration of central nervous system (CNS)-acting drugs such as antiepileptics, antipsychotics, adrenergic agonists, and anesthetics[1-8] Two common methods of analyzing EEG activity under such conditions are power spectrum analysis and aperiodic analysis.[5-8] There are certain important differences between these two methods of EEG analysis. With power spectrum analysis, frequency information about the EEG is provided by applying high order mathematical treatment to reduce the complex analog waveforms to equivalent sine waves. Several segments of analog information taken over short time intervals are averaged to provide graphic and/or digital information for the entire time interval over which the several segments were obtained.

With aperiodic analysis, no averaging is performed and, instead, each individual waveform is detected and displayed graphically and/or digitally. That the essential natures of the information provided by these two methods of EEG analysis are dissimilar suggests that the two methods may differ with respect to utility for monitoring certain EEG patterns. For example, aperiodic analysis more easily and accurately identifies spike activity in the EEG.[9] This is true, at least in part, because it is the only technique with a built-in spike detection algorithm. Power spectrum analysis may fail to discriminate significant spike activity because the power contained in the spike activity is relatively low and is overshadowed by the low-frequency components which accompany the spike activity. On

the other hand, power spectrum analysis would provide excellent discrimination of small, high-frequency components contained in a predominantly low-frequency components.[9]

There are no studies in which the EEG was analyzed simultaneously by both power spectrum analysis and aperiodic analysis during seizures or during administration of antiepileptic drugs. Because aperiodic analysis includes a built-in spike detection algorithm whereas power spectrum analysis does not, and because with power spectrum analysis the low power contained in spike activity is overshadowed by the low -frequency components accompanying spike activity, we hypothesized that the effects on the EEG of an antiepileptic drug, valproic acid, would be detected equally well with either technique. However, detection of EEG seizure activity by aperiodic analysis would be superior to that by power spectrum analysis. Accordingly, the present study was designed to monitor EEG activity simultaneously with both power spectrum analysis and aperiodic analysis during intravenous (iv) infusion of valproic acid in doses previously reported in rabbits to achieve antiepileptic brain tissue concentrations[10] and during iv infusion of lidocaine in doses previously reported in rabbits to initiate EEG seizure activity.[11]

MATERIALS AND METHODS

Animal Preparation

All procedures were carried out under the Guidelines for Animal Research at Osaka Dental University and with the approval of the Animal Experiment Committee of Osaka Dental University (Approval number 06-04001). These guidelines were in accordance with the criteria outlined in the "Guide for the Care and Use of Laboratory Animals" prepared by the National Academy of Science. Forty-one Japanese white rabbits (JW/CSK ; Shimizu Laboratory Supplies, Kyoto, Japan) weighing 2.8-3.5 kg, were anesthetized by mask induction with sevoflurane (gradually increased from 0.5 to 3.5%, inspired) and nitrous oxide (50%, inspired) in oxygen. A tracheostomy was performed, a 3.0-4.0 mm endotracheal tube was inserted 1.5-2.0 cm into the trachea, and ventilation was controlled with a small animal respirator (Model 680, Harvard Apparatus, South Natick, MA, USA). Ventilation was adjusted to maintain PaCO2 at 32 ± 5 mmHg. Thereafter, expired carbon dioxide was measured continuously via a Capnococheck plus (BCI International, Waukesha, WI, USA) and ventilation was regulated by a servo-controller to maintain expired carbon dioxide at normocapnia.

A femoral vein was cannulated for drug administration, and a left femoral was cannulated for determination of systemic arterial blood pressure and heart rate, and to permit blood sampling for determination of blood gas tensions. Mean arterial blood pressure (MAP) was determined by electronic integration of systolic and diastolic blood pressures. An ear vein was cannulated for administration of saline and pancuronium (0.5 mg/h) to maintain muscle relaxation. Temperature was monitored by a rectal thermistor probe and maintained at 38.0 ± 0.5℃ by a heating mat (ATC-101, Unique Medical, Tokyo, Japan). The animal was then turned to the prone position and the head slightly elevated and fixed in a stereotaxic frame. A midsagittal scalp incision was made to expose the calvarium. A pair of gold cup electrodes was placed over one cerebral hemisphere, with one electrode over the frontal cortex and one over the parietal cortex. A second pair of gold cup electrodes was also placed over the contralateral cerebral hemisphere at the corresponding frontal and parietal locations. With one frontal-parietal pair of electrodes the EEG was recorded using a Lifescan Brain Activity Monitor System (Diatel Medical Technology, San Diego, CA, USA) with a bandpass of 0.5-29.9 Hz. This system uses aperiodic analysis to convert the analog EEG signal into a set of digital parameters.

Computer analysis of the EEG and expression as quantitative values was performed using a Lifescan Research program. With the second pair of frontal-parietal electrodes the EEG was recorded using an ERNIE System (Spacelabs, Redmond, WA, USA) with a bandpass of 0.5-32.0 Hz and a stop band cutoff at 30 Hz. This system uses power spectrum analysis to convert the analog EEG signal into a set of digital parameters. Computer analysis of the EEG and expression as quantitative values is included in the ERNIE System program. In half of the rabbits within each of

the two experimental groups (valproic acid or lidocaine) the right hemisphere EEG was analyzed using aperiodic analysis and the left hemisphere EEG was analyzed using power spectrum analysis. In the remaining rabbits aperiodic analysis was performed on the left hemisphere EEG and power spectrum analysis was performed on the right hemisphere EEG. Blood pressure and heart rate were continuously recorded on a strip chart recorder.

After the surgical preparation, the inspired concentration of halothane was decreased and anesthesia was maintained with fentanyl and halothane (0.7-0.9%, expired) and nitrous oxide (66%, inspired) in oxygen. Fentanyl was given as an initial dose of 16 μg /kg iv over 10 min and then as iv infusion at 0.18 μg/kg/min and was continued until the end of the study.

Experimental Period

In one group of rabbits (n = 17) the EEG and systemic values, such as blood gas tensions, and hemodynamics, were recorded at baseline (i.e., before iv infusion of valproic acid) and at 30 min and 210 min of iv infusion of valproic acid. Valproic acid was given as an initial dose of 7.5 mg/kg followed by continuous infusion at 125 μg/kg/min. In the second group of rabbits (n = 24) the EEG and systemic values were recorded at baseline (i.e., before iv infusion of lidocaine) and at the occurrence of lidocaine-induced epileptiform EEG activity. Lidocaine was given at an initial infusion rate of 4 mg/kg/min until the onset of epileptiform EEG activity. Epileptiform EEG activity was defined as high-voltage spikes with amplitude of 10-20 μV (power spectrum analysis) or power of 400 μV^2 (aperiodic analysis).[12, 13] After the onset of epileptiform EEG activity, lidocaine was continued at 1-3 mg/kg/min as needed to maintain epileptiform EEG activity until data collection was complete.

Statistical Analysis

Statistical comparisons within the two groups were made using the geometric mean,[14] Student's t-test for paired samples, and one-way repeated measures analysis of variance (ANOVA ; Sigma State, Jandel Scientific, San Rafael, CA, USA) as follows. For aperiodic analysis the Lifescan Research System was set to display EEG data at 60 sec intervals. Within each interval the data recorded were cumulative power (μV^2) within each frequency bin (delta, 0.5-3.0 Hz ; theta, 3.1-8.0 Hz ; alpha, 8.1-12.0 Hz ; and beta, 12.1-29.9 Hz), total power, and edge frequency (95%). Data were recorded for 10 min at each experimental condition. The geometric mean for each EEG parameter was calculated from the 3 min epoch with the least variability.

The ERNIE System program for power spectrum analysis updates displayed EEG data every 2 sec. Data for power spectrum parameters were collected over 18 sec intervals. Within each interval the data recorded were cumulative amplitude (μV) within each frequency bin (delta, 0-4 Hz ; theta, 4-8 Hz ; alpha, 8-13 Hz ; beta-1, 13-20 Hz ; and beta-2, 20-30 Hz), total amplitude, and edge frequency (95%). Data were recorded for 10 intervals at each experimental condition. The geometric mean for each EEG parameter was calculated for each 3 min epoch. The values generated by power spectrum analysis could not be compared statistically to the values generated by aperiodic analysis because the two systems differed with respect to their definition of bandwidth and the time interval at which EEG data was analyzed.

In order to permit statistical comparison between the two analysis systems, data at 30 min and 210 min of iv infusion of valproic acid, and data at occurrence of lidocaine-induced epileptiform EEG activity were expressed as percent change from baseline (i.e., pre-valproic acid and pre-lidocaine) values. Power spectrum analysis data for beta-1 and beta-2 frequency bins were combined to permit comparison to aperiodic analysis data for the beta frequency bin. Data in the group receiving valproic acid were analyzed first by one-way repeated measure ANOVA (baseline, 30 min, and 210 min) and then by Student's t-test for paired samples where indicated. Data in the group receiving lidocaine (baseline and lidocaine-induced epileptiform EEG activity) were analyzed using Student's t-test for paired samples. Comparison between the two methods of EEG analysis was made using Student's t-test for unpaired samples. For all data analyses, $p < 0.05$ was considered significant. Values were tabulated as mean and standard deviation.

RESULTS

Combined mean values for amplitude or power (total and in each frequency bin) and edge frequency for each of the two analysis systems prior to administration of valproic acid (group 1) or lidocaine (group 2) are presented in Table 1. In group 1, one way ANOVA indicated that aperiodic analysis detected statistically significant changes in beta power ($p = 0.015$) and edge frequency ($p = 0.016$), and power spectrum analysis detected statistically significant changes in beta amplitude ($p = 0.038$) following administration of valproic acid (Table 2). Subsequent T-tests indicated that aperiodic analysis detected statistically significant decreases in beta activity and edge frequency at both 30 min and 210 min after valproic acid as compared to pre-valproic acid values. Power spectrum analysis detected statistically significant decreases in beta activity only at 210 min after valproic acid as compared to pre-valproic acid values. The percent change from pre-valproic acid values for each EEG parameter with aperiodic analysis and power spectrum analysis are presented in Table 3. Comparison between the two analysis systems of the percent change from pre-valproic acid values indicated statis-

Table 1 Combined baseline EEG values as determined by aperiodic analysis and power spectrum analysis

	Aperiodic analysis*	Power spectrum analysis**
Delta activity	68.3 ± 42.1	57.8 ± 21.1
Theta activity	28.9 ± 24.8	23.7 ± 7.3
Alpha activity	10.4 ± 8.8	7.8 ± 6.2
Beta activity	7.4 ± 5.2	6.8 ± 2.2
Total activity	129.0 ± 60.4	60.9 ± 20.0
Edge frequency, Hz	16.2 ± 2.5	11.4 ± 3.5

EEG : Electroencephalogram, *Activity expressed as power, $\mu V^2 \cdot 10^3 \cdot min^{-1}$, **Activity expressed as amplitude, $\mu V \cdot 2\ sec^{-1}$, n = 41, Mean ± SD.

Table 2 P values resulting from comparison of geometric mean EEG values for each method of EEG analysis within the group of rabbits receiving valproic acid

	Statistical test	Aperiodic analysis	Power spectrum analysis
Delta activity	ANOVA	0.382	0.770
baseline vs 30 min	T-test	0.716	0.264
baseline vs 210 min	T-test	0.285	0.575
Theta activity	ANOVA	0.290	0.182
baseline vs 30 min	T-test	0.258	0.247
baseline vs 210 min	T-test	0.750	0.227
Alpha activity	ANOVA	0.195	0.051
baseline vs 30 min	T-test	0.353	0.385
baseline vs 210 min	T-test	0.060	0.068
Beta activity	ANOVA	0.015#	0.038#
baseline vs 30 min	T-test	0.039*	0.0724
baseline vs 210 min	T-test	0.030*	0.010*
Total activity	ANOVA	0.846	0.781
baseline vs 30 min	T-test	0.518	0.775
baseline vs 210 min	T-test	0.595	0.612
Edge frequency	ANOVA	0.016#	0.098
baseline vs 30 min	T-test	0.013*	0.055
baseline vs 210 min	T-test	0.011*	0.083

#Significant difference between baseline, 30 min, and 210 min, *Significantly different from baseline, ANOVA : Analysis of variance, n = 17.

Table 3 Percent change from baseline EEG values with aperiodic analysis compared to that with power spectrum analysis in rabbits receiving valproic acid

	30 min after valproic acid (mean percent change from pre-valproic acid)			210 min after valproic acid (mean percent change from pre-valproic acid)		
	Aperiodic analysis	Power spectrum analysis	P value	Aperiodic analysis	Power spectrum analysis	P value
Delta activity	75 ± 141	39 ± 99	0.408	126 ± 227	61 ± 181	0.482
Theta activity	233 ± 315	42 ± 97	0.032*	10 ± 105	−7 ± 90	0.678
Alpha activity	−7 ± 39	51 ± 101	0.058	−27 ± 44	−20 ± 36	0.615
Beta activity	−43 ± 43	8 ± 52	0.006*	−51 ± 37	−32 ± 32	0.228
Total activity	60 ± 137	32 ± 72	0.390	24 ± 96	59 ± 167	0.547
Edge frequency	−23 ± 23	−22 ± 39	0.932	−29 ± 30	−32 ± 46	0.844

*Significant difference between aperiodic analysis and power spectrum analysis, n = 17, Mean ± SD.

tically significant differences for theta and beta activity at 30 min after administering valproic acid.

In group 2, T-tests indicated that aperiodic analysis detected statistically significant increases in delta, theta, alpha, beta and total activity, as well as edge frequency as compared to pre-lidocaine values (Table 4). Power spectrum analysis only detected statistically significant decreases in theta activity as compared to pre-lidocaine values. The percent change from pre-lidocaine values for each EEG parameter with aperiodic analysis and power spectrum analysis are presented in Table 5. Comparison between the two analysis systems of the percent change from pre-lidocaine values indicated statistically significant differences for theta, alpha, and beta activity, as well as edge frequency during lidocaine-induced EEG seizure activity.

Table 4 P values resulting from comparison of geometric mean EEG values for each method of EEG analysis within the group of rabbits receiving lidocaine

	Statistical test	Aperiodic analysis	Power spectrum analysis
Delta activity	T-test	0.004*	0.696
Theta activity	T-test	0.001*	0.003*
Alpha activity	T-test	0.001*	0.525
Beta activity	T-test	0.001*	0.078
Total activity	T-test	0.001*	0.673
Edge frequency	T-test	0.001*	0.156

*Significant different from baseline, n = 24.

Table 5 Percent change from baseline EEG values with aperiodic analysis compared to that with power spectrum analysis in rabbits receiving lidocaine

	During lidocaine-induced seizure EEG activity		
	Aperiodic analysis	Power spectrum analysis	P value
Delta activity	16 ± 184	5 ± 93	0.76
Theta activity	168 ± 240	−43 ± 65	0.001*
Alpha activity	499 ± 434	−12 ± 132	0.001*
Beta activity	1446 ± 1042	−28 ± 83	0.001*
Total activity	129 ± 276	29 ± 106	0.063
Edge frequency	104 ± 61	−24 ± 66	0.001*

*Significant difference between aperiodic analysis and spectrum analysis, n = 24, Mean ± SD.

DISCUSSION

The combined mean values for amplitude or power (total and in each frequency bin) and edge frequency prior to administration of valproic acid or lidocaine are similar to EEG values previously reported in rabbits anesthetized with sevoflurane and nitrous oxide in oxygen.[15-18] The two way ANOVA findings in group 1, i.e., that aperiodic analysis detected changes in beta power and edge frequency (but no change in delta, theta, alpha, and total power), and that power spectrum analysis detected changes in beta amplitude (but no change in the other EEG parameters), indicate that the dose of valproic acid given here causes moderate EEG changes. There findings are similar to the previously reported EEG effects of valproic acid in anesthetized rabbits.[15, 16]

The subsequent T-test findings in group 1 indicate that aperiodic analysis detected EEG changes in two of six EEG parameters at both time periods after administration of valproic acid whereas power spectrum analysis detected EEG changes in just one of six EEG parameters at only one of two time periods after administration of valproic acid. Comparing EEG percent change from predrug values detected by aperiodic analysis against those detected by power spectrum analysis indicated that the two analytical systems detected different changes for only two of six EEG parameters (theta and beta activity) at only one of two time periods (30 min) after giving valproic acid (i.e., two of 12 comparisons). Taken together, the results of the within-group T-test and between group T-tests indicate that this dose of valproic acid causes modest EEG changes and there are modest differences between aperiodic analysis and power spectrum analysis with respect to the ability of the two analysis systems to detect valproic acid-induced EEG changes.

The findings in group 2, i.e., that aperiodic analysis detected changes in power in all frequency bins (delta, theta, alpha, and beta) and in edge frequency, whereas power spectrum analysis detected changes only in theta amplitude, indicate that the wide spread EEG changes occurring during lidocaine-induced seizure activity and clearly present on the analog EEG signal were better detected by aperiodic analysis.

That lidocaine-induced seizure activity agrees with results of previous studies where continuous infusion of lidocaine was used to produce EEG seizure activity, somatic seizures, and increased permeability of the blood-brain barrier.[12, 13]

Based on differences between power spectrum analysis and aperiodic analysis with regard to data averaging and spike detection algorithm, we advanced two hypotheses prior to undertaking our comparison of these two methods of EEG analysis. The first hypothesis was that the effects on the EEG of an anticonvulsive drug, valproic acid, would be detected equally well with either technique. This hypothesis is somewhat supported by the data from the present study. In the group receiving valproic acid, there were only a few times/conditions where there were statistically significant differences between aperiodic analysis and power spectrum analysis with respect to the drug-induced EEG changes.

Simultaneous comparison of power spectrum analysis with aperiodic analysis during administration of drugs and gases commonly used for anesthesia is needed to determine whether the results we observed with valproic acid also hold for anesthetics. If so, power spectrum analysis and aperiodic analysis may be equally effective for detection of EEG of an anticonvulsive drug. The second hypothesis was that detection of EEG seizure activity by aperiodic analysis would be superior to that by power spectrum analysis. This hypothesis is strongly supported by the data from the present study in the group receiving epileptogenic doses of lidocaine, and there were statistically significant differences between aperiodic analysis and power spectrum analysis with the majority of parameters of drug-induced EEG seizure activity. Simultaneous comparison of power spectrum analysis with aperiodic analysis during other drugs and conditions that initiate EEG seizure activity is needed to determine whether the results we observed with lidocaine also hold for other epileptogenic stimuli. If so, aperiodic analysis may be superior to power spectrum analysis for detecting EEG seizure activity in patients.

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