ORIGINAL RESEARCH

Bioimpedance in monitoring of effects of selective serotonin reuptake inhibitor treatment

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Background: Bioimpedance has been shown to be a safe technique when used in a number of biomedical applications. In this study, we used the Electro Interstitial Scan (EIS) to perform bioimpedance measurements to follow up the efficacy of selective serotonin reuptake inhibitor (SSRI) treatment in subjects diagnosed to have major depressive disorder.

Methods: We recruited 59 subjects (38 women, 21 men) aged 17–76 (mean 47) years diagnosed with major depressive disorder by psychiatric assessment at the Botkin Hospital according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV). Baseline Clinical Global Impression scores and EIS (electrical conductivity and dispersion α parameter) measurements were done before starting SSRI therapy. Treatment follow-up was undertaken using EIS bioimpedance measurements and by treatment response based on the Hamilton Depression Scale and Clinical Global Impression, every 15 days for 60 days. At day 45, we classified the patients into two groups, ie, Group 1, including treatment responders, and Group 2, including nonresponders. At day 60, patients were classified into two further groups, ie, Group 3, comprising treatment responders, and Group 4, comprising nonresponders.

Results: Comparing Group 1 and Group 2, electrical conductivity measurement of the pathway between the two forehead electrodes had a specificity of 72% and a sensitivity of 85.3% ($P < 0.0001$), with a cutoff >4.32. Comparing Group 3 and Group 4, electrical conductivity measurements in the same pathway had a specificity of 47.6% and a sensitivity of 76.3% ($P < 0.16$), with a cutoff >5.92. Comparing Group 1 and Group 2, the electrical dispersion α parameter of the pathway between the two disposable forehead electrodes had a specificity of 80% and a sensitivity of 85.2% ($P < 0.0001$) with a cutoff >0.678. Comparing Group 3 and Group 4, the electrical dispersion α parameter of the same pathway had a specificity of 100%, a sensitivity of 89.5% ($P < 0.0001$), and a cutoff >0.692.

Conclusion: Electrical conductivity measurement of the forehead pathway using EIS has a high specificity and sensitivity at day 45 when comparing treatment responders and nonresponders, but decreases at day 60. The EIS electrical dispersion α parameter of the forehead pathway has a high specificity and sensitivity at day 45 when comparing treatment responders and nonresponders, and increases at day 60. The EIS system may be a noninvasive, easily administered, low-cost technique that could be used as an adjunct to DSM-IV and Clinical Global Impression scores for monitoring of efficacy of treatment in patients with major depressive disorder.

Keywords: major depressive disorder, selective serotonin reuptake inhibitors, Electro Interstitial Scan, electrical conductivity, dispersion α parameter

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Introduction

Depression is a common illness with a high degree of morbidity and mortality.[1] It is a serious disorder that interferes with physical and mental functioning to a greater

extent than a number of other common chronic conditions, including hypertension, arthritis, and diabetes.[1] Major depression significantly affects the quality of life and productivity of the patient. Early recognition and treatment are essential to minimize the personal and societal cost associated with depression.[2] In spite of the serious consequences associated with untreated depression, most studies report that it remains largely underdiagnosed and inadequately treated.[2] Nevertheless, it is encouraging to note that if treated early and appropriately with an antidepressant, approximately 60%–70% of patients respond to the initial course of therapy.[3] People respond differently to a variety of treatments, and only Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV)[4] and Clinical Global Impression (CGI) scores[5] are considered to be reliable methods for assessing treatment response. The likelihood of response to a given medication is well known, but psychiatrists are not able to predict if therapy will be effective in an individual patient. In clinical practice, psychiatrists use the method of trial and error.[6]

Bioimpedance has been shown to be a safe technique when used in a number of biomedical applications, including for estimation of body composition,[7] impedance cardiography,[8] quantification of brain edema in neurosurgery,[9] and for detection of differences between normal, abnormal, and malignant prostate tissue.[10] In this study, we used the Electro Interstitial Scan (EIS) to perform bioimpedance measurements as follow-up of the effect of selective serotonin reuptake inhibitor (SSRI) treatment in patients diagnosed with major depressive disorder. This follow-up was performed from the conductivity and dispersion values of the pathway between two disposable electrodes placed on the forehead and compared with the results of assessment using DSM-IV questionnaire and the CGI scale.

Methods and materials

This study was approved by the ethics committee at Botkin Hospital, and adhered to the ethical principles of the Declaration of Helsinki. Each patient signed an informed consent form, and confidentiality was maintained for all participants.

Subjects

Fifty-nine subjects (38 women, 21 men) of mean age 47 (range 17–76) years were recruited from the Psychiatric Department of Botkin Hospital. Patients were excluded if they had a neurological disorder precluding ability to sign

a consent form, if in the opinion of the investigator they were clinically unsuitable candidates for the trial, and/or had any contraindications to use of the EIS system. Use of the EIS is contraindicated in the presence of an external defibrillator, skin lesions likely to come into contact with the electrodes, excessive perspiration, a cardiac pacemaker, electronic life support, any implanted electronic device, inability to remain still for three minutes, metallic pins or prostheses in the digits or joints, pregnancy from the third trimester onwards, and absence of a limb.

All 59 patients had a clinical diagnosis of major depressive disorder as scored on the Hamilton Depression[11] (Ham-D) and CGI scales. Once diagnosed, the patients were sent to the Department of Physiology at Botkin Hospital before starting antidepressant treatment, and an examination was performed using the EIS. The patients were then started on an SSRI (fluoxetine 20 mg/day), and follow-up was undertaken using both EIS bioimpedance measurements and Ham-D and/or CGI scores at 15-day intervals for 60 days. Treatment response was defined as a score of 1 or 2 on the CGI improvement scale and/or a decrease of at least 50% in Ham-D score. At day 45, patients were classified into two groups, ie, Group 1 (responders) and Group 2 (nonresponders). At day 60, patients were again classified into two groups, ie, Group 3 (responders) and Group 4 (nonresponders).

Materials

The EIS system is a programmable electromedical system comprising a USB plug and hardware including an interface box, disposable electrodes, reusable plates, and reusable cables, with software installed on a computer. The system uses bioimpedance in bipolar mode with direct current (1.28 V), and measures the electrical conductivity and dispersion α parameter in 11 pathways of the body using six electrodes placed symmetrically on the palms of the hands, soles of the feet, and on the forehead. Each pathway is recorded twice from anode to cathode and then from cathode to anode. Electrode polarization does not affect bioimpedance measurements,[12] and transmission of the current from the electrode to the hardware is performed by chronoamperometry.[13]

EIS and electrical conductivity

With direct current, the plasma membrane acts as an insulator and the current is not able to penetrate the cell, so most of the current flows around the cell and therefore in the interstitial fluid.[5] Analysis of the direct current at the cathode and anode in electrolytic solution is performed at

Table 1 Patient demographic data

	Group 1	Group 2	Group 3	Group 4	P value
n	34	25	38	21	
Age	47.1	46.8	47.8	46.3	NS
Male/female ratio	0.54	0.48	0.55	0.46	0.01
Conductivity	4.92	3.1	6.12	3.95	0.001
Dispersion	0.689	0.645	0.697	0.651	0.001
Ham-D	<50%	>50%	<50%	>50%	
CGI average	1.75	3	1.60	3	

Abbreviations: CGI, Clinical Global Impression scale; Ham-D, Hamilton Depression scale; NS, not significant.

both the anode and the cathode. The electrical conductivity is measured in μSiemens. In this study, we considered only the pathway between the two disposable frontal electrodes (Ag/Ag/Cl). The electrochemical reaction at the cathode[12] is: $2H_2O + 2e^- = H_2(gas) + 2OH^-(base)$ and at the anode[12] is: $2H_2O = O_2(gas) + 4H^+ + 4e^-(acid)$.

EIS and electrical dispersion

The cell membrane has the ability to store capacitive energy via its dielectric or insulator properties. The cell membrane is the cellular structure that makes the major contribution to the dielectric behavior of living tissue. Living tissue is considered as a dispersive medium.[13,14] Electrical dispersion is expressed by the α parameter value. In 1940, Cole introduced the first mathematical expression to describe the "depressed semicircles" found experimentally. This is known as the Cole equation, as follows:

$$Z = R_\infty + \frac{\Delta R}{1 + (j\omega\tau)^\alpha}, \qquad \Delta R = R_0 - R_\infty$$

where Z is the impedance value at frequency ω, j is the complex number $(-1)1/2$, R_∞ is the impedance at infinite

frequency, R_0 is the impedance at zero frequency, τ is the characteristic time constant, and α is a dimensionless parameter with a value between 0 and 1.[13,14]

Parameters analyzed

Statistical analysis was conducted to test for concordance between the bioimpedance measurements (electrical conductivity and electrical dispersion α parameter) and treatment responses according to Ham-D and CGI scores. A receiver-operating characteristic curve was constructed for bioimpedance measurements in the pathway of the forehead electrodes for Groups 1 and 2 at day 45, and another receiver-operating characteristic curve was constructed for bioimpedance measurements in the pathway of the forehead electrodes for Groups 3 and 4 at day 60.

Statistical analysis

Statistical analysis was performed using MedCalc software. The number of patients needed for the study was calculated to be 50 on the basis of $\alpha = 5\%$, at 80% power = F (Δ, N, variability DS), taking into account the judgment criteria Δ at approximately 50 DS (5% error). A P value of <0.005 was accepted as being statistically significant.

Results

Fifty-nine subjects were enrolled in the study and started on SSRI treatment of fluoxetine 20 mg/day.

At day 15, there were no responders to treatment, at day 30 there were six responders, at day 45 there were 34 responders (Group 1) and 25 nonresponders (Group 2), at day 60, there were 38 responders (Group 3) and 21 nonresponders (Group 4).

Electrical conductivity and electrical dispersion increased in the four groups during SSRI treatment. Demographic
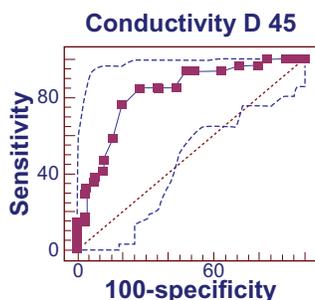
Variable	Conductivity_D_45 ConductivityD 45
Classification variable	ReponsesD_45

Sample size	59
Positive group: ReponsesD_45 = 1	34
Negative group: ReponsesD_45 = 0	25

Disease prevalence (%)	Unknown

Area under the ROC curve (AUC)	0.825
Standard error[15]	0.0568
95% confidence interval[a]	0.704 to 0.911
Z statistic	5.719
Significance level P (area = 0.5)	<0.0001

Figure 1 Comparing Group 1 (D+45 responders) and Group 2 (D+45 nonresponders), electrical conductivity measurement of the pathway between the two forehead electrodes.
Note: [a]Binomial exact.
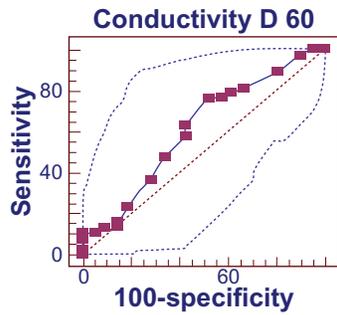
Variable	Conductivity_D_60 Conductivity D 60
Classification variable	ReponsesD_60 ReponsesD +60

Sample size	59
Positive group: ReponsesD +60= 1	38
Negative group: ReponsesD +60 = 0	21
Disease prevalence (%)	Unknown
Area under the ROC curve (AUC)	0.610
Standard error[15]	0.0798
95% confidence interval[a]	0.474 to 0.734
Z statistic	1.375
Significance level P (area = 0.5)	0.1692

Figure 2 Comparing Group 3 (D+60 responders) and Group 4 (D+60 non responders), electrical conductivity measurement of the pathway between the two forehead electrodes.
**Note:** [a]Binomial exact.

characteristics are shown in Table 1. Treatment responses were coded as 1 (response) and 0 (no response). Comparing Group 1 and Group 2, electrical conductivity measurement of the pathway between the two forehead electrodes had a specificity of 72% and sensitivity of 85.3% ($P < 0.0001$) with a cutoff >4.32 (see Figure 1). Comparing Group 3 and Group 4, the electrical conductivity of the same pathway had a specificity of 47.6% and a sensitivity of 76.3% ($P < 0.16$) with a cutoff >5.92 (see Figure 2). Comparing Group 1 and Group 2, electrical dispersion of the pathway between the two forehead electrodes had a specificity of 80% and a sensitivity of 85.2% ($P < 0.0001$) with a cutoff >0.678 (Figure 3). Comparing Group 3 and Group 4, electrical dispersion of the same pathway had a specificity of 100% and a sensitivity of 89.5% ($P < 0.0001$) with a cutoff >0.692 (Figure 4).

Discussion

People respond differently to antidepressant treatment. With some knowledge of the therapeutic modalities available, both pharmacologic and nonpharmacologic, coupled with a reasonable amount of patience on the part of both the health care provider and the patient, treatment can be highly successful in regaining an appropriate level of well-being.[16] The antidepressant properties of SSRIs are due to increased concentrations of serotonin at the synaptic cleft, enhancing serotonergic transmission and inducing downregulation of postsynaptic receptors. Although neurotransmitter reuptake inhibition is an important property of SSRIs, the temporal difference between the rapid onset of this pharmacological effect and slower symptomatic relief suggests that secondary adaptive responses may contribute to the effectiveness of SSRIs as antidepressants.[17]

Electroencephalography using disposable frontal electrodes has been investigated in the prediction of response to antidepressant therapy. Various electroencephalographic parameters have been associated with response to treatment.[18] To our knowledge, this is the first study using the bioimpedance measurement with two components, ie, conductivity
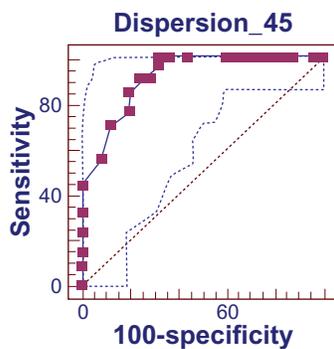
Variable	Conductivity_45 ConductivityD_45
Classification variable	ReponsesD_45

Sample size	59
Positive group: ReponsesD_45 = 1	34
Negative group: ReponsesD_45 = 0	25
Disease prevalence (%)	Unknown
Area under the ROC curve (AUC)	0.914
Standard error[15]	0.0366
95% confidence interval[a]	0.811 to 0.971
Z statistic	11.311
Significance level P (area = 0.5)	<0.0001

Figure 3 Comparing Group 1 (D+45 responders) and Group 2 (D+45 nonresponders), electrical dispersion of the pathway between the two forehead electrodes
Note: [a]Binomial exact.
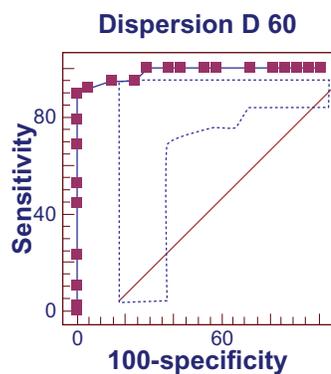
Dispersion D 60

Variable	Dispersion_D_60 Dispersion D 60	
Classification variable	Reponses_60 Reponses +60	
Sample size		59
Positive group: Reponses +60 = 1		38
Negative group: Reponses +60 = 0		21
Disease prevalence (%)		Unknown
Area under the ROC curve (AUC)		0.983
Standard error[15]		0.0117
95% confidence interval[a]		0.909 to 1.000
Z statistic		41.118
Significance level P (area = 0.5)		<0.0001

Figure 4 Comparing Group 3 (D+60 responders) and Group 4 (D+60 nonresponders), electrical dispersion of the pathway between the two forehead electrodes.
Note: [a]Binomial exact.

and dispersion, to monitor response to an antidepressant therapy. In our study, the best indicator of treatment response was the dispersion α parameter at day 60, with a specificity of 100%, a sensitivity of 89.5% ($P < 0.0001$), and a cutoff >0.692.

Ivorra et al[16] investigated the significance of the dispersion α parameter by computer simulations and demonstrated its practical importance in a rat kidney model. The simulations indicated that the dispersion width is determined by the morphology of the extracellular space and suggest that this technique could detect structural tissue changes. One explanation as to why electrical conductivity measurements increased in the forehead pathway after 45 days of SSRI treatment could be related to an increased concentration of serotonin at the synaptic cleft and an associated change in cerebral tissue blood flow. A second explanation as why the dispersion α parameter increased in the forehead pathway after 45 and 60 days of SSRI treatment could be related to changes in the morphology of the extracellular space in the cerebral tissue.

Conclusion

EIS electrical conductivity measurement in the forehead pathway showed high specificity and sensitivity at day 45 for distinguishing between responders and nonresponders to SSRI therapy. The specificity and sensitivity decreased at day 60. The EIS electrical dispersion α parameter in the forehead pathway has a high specificity and sensitivity at day 45 when comparing responders and nonresponders, and the specificity and sensitivity increase at day 60. EIS could be a low-cost noninvasive system that is easy to use in the office and may become an adjunct to DSM-IV questionnaires and Clinical Global Impression scores for monitoring the efficacy

of treatment for major depressive disorder. Longitudinal studies are now under way to confirm our findings.

Disclosure

The authors report no conflict of interest in this work.

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