Influence of Anesthetic Drugs and Concurrent Psychiatric Medication on Seizure Adequacy During Electroconvulsive Therapy

Bogata D. Bundy, MD; Walter Hewer, MD; Franz-Josef Andres, MD; Peter Gass, MD; and Alexander Sartorius, MD, PhD

Objective: Electroconvulsive therapy (ECT) is performed under anesthesia and muscle relaxation. Only well-generalized seizures seem to have the high "adequacy" or "quality" that have been claimed to reflect positive predictive power for the outcome of an ECT course. The induction of well-generalized seizures can be potentially influenced by several variables. One major variable is concurrent medication including anesthetic drugs, since most anesthetic drugs are potent anticonvulsives. We hypothesized a negative influence of anesthetics and benzodiazepines but a positive effect of antidepressants and antipsychotics concurrently applied during ECT on seizure adequacy.

Method: We included inpatients (n = 41) with a *DSM-IV*–diagnosed major depressive episode treated with ECT (411 ECT sessions) during a period of 20 months (May 2005 to December 2006) in an open label and noncontrolled study. A repeated measurement regression analysis was performed with 8 seizure adequacy parameters as dependent variables. We indirectly quantified narcotic agent influence with bispectral index monitoring.

Results: In contrast to the impact of psychiatric comedication, this measure of "depth of narcosis" prior stimulation turned out to influence most seizure adequacy parameters in a highly significant manner.

Conclusions: Thus, we concluded that the anticonvulsive properties of narcotic agents have much higher influence than concomitant psychotropic medication. Our data support the view that a significant influence of concurrent psychotropic drugs on seizure adequacy markers is missing, especially when directly compared with other confounders like stimulation energy, age, and depth of narcosis. The latter suggests to further prove the idea that lighter anesthesia is indeed an important tool to get patients faster into remission.

J Clin Psychiatry 2010;71(6):775–777

Submitted: *December 20, 2008; accepted February 19, 2009.*
Online ahead of print: *December 29, 2009 (doi:10.4088/JCP.08m04971gre).*
Corresponding author: *Alexander Sartorius, MD, PhD, Department of Psychiatry and Psychotherapy, Central Institute of Mental Health (CIMH), Medical Faculty Mannheim, University of Heidelberg, Square J 5, D-68159 Mannheim, Germany (alexander.sartorius@zi-mannheim.de).*

The antidepressive effect of electroconvulsive therapy (ECT) is not caused by the electrical current itself but by generalized seizure activity.[1,2] The induction of well-generalized seizures with high "adequacy" can be potentially influenced by several variables, a major one being concurrent medication. Drugs commonly used for ECT anesthesia like thiopental, propofol, etomidate, or methohexital exhibit potent anticonvulsive properties. Accordingly, we have previously shown that patients can directly benefit from lighter anesthesia during ECT sessions.[3,4] However, concurrent psychopharmacologic drugs may additionally influence seizure adequacy.[5,6] We hypothesized a negative influence of anesthetics and benzodiazepines but a positive effect of antidepressives and antipsychotics concurrently applied during ECT on seizure adequacy.

METHOD

During a period of 20 months, we included all depressed inpatients treated with ECT (n = 41). All patients met the criteria of a major depressive episode according to the *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition (*DSM-IV*),[7] and only patients with a prior ECT treatment less than 6 months ago were excluded. Since this was an open label and noncontrolled study, the clinical decision to use ECT was strictly independent from study participation. All patients provided written informed consent, and the study was approved by the local ethics committee. Electroconvulsive treatment was started right unilaterally at minimal 2.5 times over seizure threshold or bilaterally at minimal 1.5 times over seizure threshold, respectively. Switching was allowed due to clinical necessity. Seizure threshold was titrated during the first treatment, and energy was subsequently increased if patients did not respond clinically or showed insufficient seizures during the ECT course (ie, motor response time < 20 seconds and electroencephalogram (EEG) seizure activity < 30 seconds).

Bispectral EEG index (BIS) was recorded with a BIS XP quatro TM device (Aspect Medical Systems, Norwood, Massachusetts). Bispectral EEG index is sometimes recorded during general anesthesia to gain information about the "depth of anesthesia" and reduce the risk of awareness. This index was similarly recorded (directly before ECT stimulation), as in our 2 previous ECT studies.[3,4]

Concurrent usage of a specific drug was defined as taking the drug during 24 hours before an individual ECT session. Weighing factors were drawn from a World Health Organization table[8] and from Möller et al.[9]

Table 1. Influence of Concurrent Drugs on Seizure Adequacy[a]

		Independent Variable															
		Energy[b]		BIS[c]		Age		$HDRS_i$[d]		Dose of Thiopental as Anesthetic Drug		Equivalent Dose of Benzodiazepine		Equivalent Dose of Antipsychotic		Equivalent Dose of Antidepressant	
Dependent Variable	r^2[e]	CC	*P*	CC	*P*	CC	*P*	CC	*P*	CC	*P*	CC	*P*	CC	*P*	CC	*P*
EEG seizure duration	0.19	−0.17	**.001**[f]	0.22	**.001**[f]	−0.18	.13	0.29	.33	−0.78	.58	−0.20	.12	0.00	.72	−0.02	.08
Motor response time	0.43	−0.17	**.001**[f]	0.21	**.001**[f]	−0.25	**.002**[f]	0.41	**.03**	−0.41	.66	−0.08	.34	0.00	.61	−0.00	.94
Midictal amplitude	0.26	−0.29	**.05**	0.26	.32	−2.02	**.001**[f]	0.73	.46	1.68	.75	0.15	.76	−0.02	.41	−0.01	.89
Seizure energy index	0.26	1.25	.92	41	**.04**	−216	**.001**[f]	121	.29	697	.16	20	.64	−0.63	.83	−2.8	.45
Postictal suppression	0.14	−0.12	**.03**	0.23	**.01**	−0.21	.11	−0.11	.72	0.11	.95	0.28	.09	0.01	.55	−0.01	.57
Concordance[g]	0.33	−0.002	**.001**[f]	0.002	**.001**[f]	−0.003	**.004**[f]	0.004	.07	0.00	.97	−0.00	.36	0.00	.68	0.0002	**.03**
Ictal coherence	0.14	−0.08	**.05**	0.18	**.02**	−0.36	**.004**[f]	−0.09	.77	2.64	.09	0.02	.90	0.01	.26	−0.02	.14
Maximal heart rate	0.20	−0.02	.67	0.22	**.008**	−0.68	**.001**[f]	0.28	.45	−2.5	.15	−0.20	.21	−0.01	.20	−0.01	.48

[a]The multivariate repeated measurement regression analysis was separately computed for every dependent variable, including all independent variables. All dependent variables were quantified by the Thymatron electroconvulsive therapy device. Significant results are shown in **bold**.
[b]Energy = electroconvulsive therapy stimulation energy.
[c]BIS = depth of induced narcosis (quantified as bispectral index or BIS).
[d]$HDRS_i$ = initial severeness of depressive episode (quantified as Hamilton Depression Rating Scale-21 items).
[e]r^2 = explained variance.
[f]Results that are statistically significant after correction for multiple testing. Bonferroni correction was set at $\alpha = .05/8 = 0.00625$.
[g]Concordance is the ratio of motor response time and EEG seizure duration and a marker of the central inhibition power.
Abbreviations: CC = correlation coefficient, EEG = electroencephalogram.

A multivariate repeated measurement regression analysis was performed (ie, multilevel mixed-effects linear regression using STATA 9 "xtregar" [Statacorp LP, College Station, Texas]) to test our main hypothesis. This procedure has been described previously.[3,4] We included seizure adequacy markers (Table 1) as dependent variables. We covariately implicated the amount of applicated energy, since it is well known that it directly impacts on seizure adequacy. Age, initial severeness of the depressive episode (quantified via Hamilton Depression Rating Scale[10]), and depth of the induced narcosis were also included as covariates.

RESULTS

Patients who received psychotropic drugs received them with relevant doses (ie, 11.3 mg/d diazepam, 166 mg/d amitriptyline, and 274 mg/d chlorpromazine). Mean ± SD recorded BIS was 61 ± 17. Mean ± SD age was 55 ± 16 years (range, 18–83 years).

Seizure duration correlated positively with BIS and negatively with stimulation energy after Bonferroni correction (see Table 1). In other words, a lighter narcosis prolonged seizure durations (both EEG and motor response time), and more stimulation energy shortened them. Additionally, older patients exhibited shorter motor response time and better seizure concordance. For example, mean EEG seizure duration and motor response time were 42 seconds and 21 seconds for patients older than 60 years (n = 187), 48 seconds and 30 seconds for patients younger than 60 years (n = 223), and 51 seconds and 35 seconds for patients younger than 45 years (n = 151), respectively. Age and BIS did not correlate ($P = .66$), but age and thiopental per body weight were directly and negatively correlated ($P < .001$). Thus, patients at older ages received less thiopental (eg, mean thiopental doses for patients at ages < 70 years, 3.9 mg/kg; at ages > 70 years, 3.1 mg/kg), resulting in similar BIS ranges.

Seizure concordance improved with lighter narcosis and worsened with higher stimulation energy (see Table 1).

DISCUSSION

The main result of this investigation of 411 ECT sessions is the lack of a significant influence of all investigated concurrent drugs. Particularly, the influence of concurrent medication on seizure adequacy is small with regard to other confounding variables like stimulation energy, age, and depth of the narcosis. Stimulation energy (and age) negatively influenced almost all seizure adequacy markers, and reduced depth of narcosis (quantified by BIS) improved almost all seizure adequacy markers. This corroborates our previous finding of the positive influence of lighter anesthesia on treatment success.[4]

From our point of view, the impact of benzodiazepines at routinely given doses on seizure adequacy is low, but we still would recommend to avoid benzodiazepine administration directly prior to ECT. On the other hand, our data suggest that randomized, BIS-controlled ECT studies are promising to prove the idea that lighter anesthesia is indeed an important tool to get patients faster into remission.

Drug names: diazepam (Diastat, Valium, and others), etomidate (Amidate and others), methohexital (Brevital), propofol (Lusedra, Diprivan, and others).

Author affiliations: Department of Psychiatry and Psychotherapy, Central Institute of Mental Health, Mannheim (Drs Bundy, Hewer, Gass, and Sartorius); the Department of Geriatric Psychiatry and Psychotherapy, Vinzenz von Paul Hospital, Rottweil (Dr Hewer); and the Institut für Anästhesiologie und Operative Intensivmedizin, Fakultät für Klinische Medizin Mannheim–Universitätsklinikum Mannheim (Dr Andres), Germany.

Author contributions: Drs Bundy and Hewer made equal contributions to this paper.
Potential conflicts of interest: None reported.
Funding/support: None reported.

© Copyright 2010 Physicians Postgraduate Press, Inc.

Acknowledgment: The authors would like to acknowledge the work of Karin Bopp (study administrator) of the Department of Psychiatry and Psychotherapy at the Central Institute of Mental Health in Mannheim, Germany for maintenance of the electroconvulsive therapy database. Parts of this work were incorporated into a doctoral thesis presented to the University of Heidelberg by Dr Bundy.

REFERENCES

1. Sebag-Montefiore SE. Flurothyl (Indoklon) in depression [letter]. *Br J Psychiatry.* 1974;124(0):616–617.
2. Folkerts H. The ictal electroencephalogram as a marker for the efficacy of electroconvulsive therapy. *Eur Arch Psychiatry Clin Neurosci.* 1996;246(3):155–164.
3. Sartorius A, Krier A, Andres FJ, et al. Bispectral index monitoring for more effective electroconvulsive therapy? *Br J Anaesth.* 2006;96(6):806–807.
4. Sartorius A, Muñoz-Canales EM, Krumm B, et al. ECT anesthesia: the lighter the better? *Pharmacopsychiatry.* 2006;39(6):201–204.
5. Guevara-Cuellar CA, Pineda-Cañar CA. Electroconvulsive therapy for depression [letter]. *N Engl J Med.* 2008;358(6):645.
6. Lisanby SH. Electroconvulsive therapy for depression. *N Engl J Med.* 2007;357(19):1939–1945.
7. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*, Fourth Edition. Washington, DC: American Psychiatric Association; 1994.
8. World Health Organization. http://www.whocc.no/atcddd/. Accessibility verified November 13, 2009.
9. Möller HJ, Müller WE, Bandelow B. *Neuroleptik–Pharmakologische Grundlagen, Klinisches Wissen, Therapeutisches Vorgehen*. Stuttgart, Germany: Wissenschaftliche Verlagsgesellschaft; 2001.
10. Hamilton M. A rating scale for depression. *J Neurol Neurosurg Psychiatry.* 1960;23(1):56–62.