Seizure Threshold in Electroconvulsive Therapy: Effect of Instrument Titration Schedule

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Abstract

Background: Determination of seizure threshold can help guide selection of stimulus dosage in electroconvulsive therapy (ECT); however, this threshold is subject to a variety of influences. _Objective_: To compare the effect of two stimulus-titration schedules on initial seizure threshold, in 88 patients. _Method_: One strategy was to use the factory-set stimulus characteristics on the Thymatron DGx instrument, which includes uniform stimulus dose increments of 5% of maximum charge. The other strategy was our approximation of stimulus dose increments of 5% of maximum charge on the MECTA SR1 instrument. Subjects were assigned randomly in groups with three age-related stratifications. _Results_: Measured seizure thresholds were higher with the stimuli used from the MECTA schedule than with Thymatron in 79% of patients. _Conclusions_: The stimulus titration schedule used in ECT administration is clinically significant since it may affect both adverse consequences and therapeutic insufficiency (German J. Psychiatry 2001;51-56).

Keywords: Seizure threshold, titration schedule, electroconvulsive therapy (ECT)

Introduction

Estimation of the seizure threshold can help guide the selection of the electrical stimulus dose at electroconvulsive therapy (ECT) [American Psychiatric Association (APA) Task Force on ECT, 1990]. In concept, this threshold is the smallest dose of electrical charge that can induce a seizure (Small et al., 1978). In practice this minimum dose depends not only on individual patient characteristics and treatment method, but also on several stimulus characteristics. Examples of the former include electrode placement (Weiner, 1980), anesthetic agents (APA, 1990) and concomitant medications (Kellner et al., 1997), age and sex (Sackeim et al., 1987), and the frequency of ECT sessions (Janakiramiah et al., 1992). Stimulus characteristics that influence seizure threshold include pulsewidth, charge rate (Swartz and Larson, 1989; Swartz, 1994), and waveshape such as square or sine (Weaver et al., 1977; Weiner, 1980); differences in these of stimulus titration schedule of two ECT instruments are the focus of this study.

The accurate communication of clinical issues and research results in ECT requires an understanding of how they apply with other common instrumentation. The only commercially available ECT instruments to incorporate the EEG monitoring features recommended by the APA Task Force on ECT (1990) are the MECTA and Thymatron instruments, and virtually all modern ECT publications note the use of one of these. The instrument models we used are usually cited in

recent studies, and so are representative. Although they both deliver constant current brief pulse stimuli, the ranges of stimulus parameters and the method of stimulus selection differ. A fundamental issue is the nature of the correspondence between the instruments about stimulus settings, particularly the charge dose. An associated concern is how much the stimulus parameter strategies that these instruments can employ vary in efficiency. The term "stimulus parameter strategy" refers to the selection of stimulus characteristics over the range of charge doses, e.g., pulsewidth, frequency, current, charge rate.

There has been no published study that compared effects of titration schedule on seizure threshold with different ECT instruments. We conducted a prospective, randomized controlled trial to compare initial seizure threshold estimated by stimulus dose-titration technique with the MECTA SR1 and Thymatron DGx instruments.

Methods

Subjects

The subjects were 88 patients hospitalized for acute exacerbation of psychosis who were selected to receive ECT on clinical grounds at the participating hospitals. Each met DSM-IV (APA, 1994) criteria for schizophrenia (n = 75) or schizoaffective disorder (n = 13). The study was IRB approved. After a detailed explanation, each subject gave written informed consent for ECT and for study participation. Subjects who had received ECT or depot neuroleptics within six months or were taking medications that inhibit seizure, e.g., anticonvulsants, benzodiazepines, beta-blockers, were excluded.

From the outset subjects were stratified by age into three groups: 30 or less, 31 to 40, and over 40 years. They were randomly assigned to receive ECT with either the MECTA SR1 or the Thymatron DGx instrument. All subjects were free of medications beginning 5 days prior to the first ECT, except for flupenthixol 12 mg/day and benzhexol 4-6 mg/day, which all received. All data were collected during the first two ECT sessions, which were given two to three days apart.

For both MECTA and Thymatron groups, average subject age was 38.2 years, with 9.6 years of education; 14 males and 30 females were in each group. Differences between groups were negligible for onset of illness (aver-

age 19.9 ± 3.4 years), illness duration (17.8 ± 9.5 years), episode duration (1.6 ± 1.5 years), numbers of admissions (8.6 ± 4.8 years), percent with prior ECT (85%), entry BPRS score (48.2 ± 8.9), entry GAF score (31.6 ± 6.3), and percent with schizoaffective disorder (15%). The oldest groups ranged in age from 41 to 67 years, with an average of 49.0 ± 7.2 years.

ECT Technique

After atropine 0.4 mg intravenously, anesthesia was given with a minimal dosage of thiopental (2-4 mg/kg) and 0.5-1 mg/kg of succinylcholine. Subjects were hyperventilated with oxygen from anesthetization until postictal spontaneous respiration.

Bitemporal bilateral electrode placement was used exclusively. Motor seizure activity was monitored by the cuffed ankle method (Kellner et al., 1997), and two channels of prefrontal electroencephalogram (EEG) were recorded from frontal and mastoid electrodes.

Determination of Seizure Threshold

Seizure threshold was measured according to a titration schedule (Table 1) at the first and second treatment sessions. This schedule incorporated the Thymatron factory default settings, as representative of it, which includes uniform stimulus dose increments of 5% of maximum charge. The percent of maximum stimulus charge is also the percent of maximum stimulus energy and is referred to as '%Energy.' The MECTA instrument included no default or standard settings specifications from the manufacturer. A series of stimulus settings of the MECTA SR1 to approximate the method of the Thymatron was constructed, with stimulus dose increments of 5% of its maximum charge. Matching these 5% increments was the first priority; in diminishing priority order the current, pulsewidth, and frequency were then matched. First priority was given to uniformity in stimulus dose increments because of the impression that it contributes impartiality to the measurement of seizure threshold, and because it simplifies the comparison of strategies for success. The stimulus settings chosen on the MECTA SR1 are not the only possible ones, of course. Because these stimulus settings are nonproprietary, and devices can change, the usage of the terms 'Thymatron' and 'MECTA' refers to the configurations of stimulus parameters that was studied rather than inevitably these instruments.

Operationally for study purposes an adequate seizure was defined as bilateral tonic-clonic motor activity that lasted for at least 30 seconds, together with EEG evidence of seizure. Accordingly, the thresholds measured are for vigorous rather than minimal seizures (Christensen et al., 1986). At the first treatment session, the first level of stimulus intensity (10% of maximum charge) was administered. If this failed to elicit an adequate seizure the stimulus charge was increased in increments of 10% Energy as listed in Table 1. A maximum of four stimulations per session was allowed, with an interval of at least 20 seconds (for missed seizure) or 40 seconds (short seizure) between stimulations. Additional thiopental was not administered. At the second treatment session for each subject, stimulus dose lower by 5% Energy than at the first session was given, as listed in Table 1. If an adequate seizure occurred, that dose was taken as the threshold; if not, the first session's stimulus dose was so taken.

Statistical Methods

Seizure threshold data expressed in millicoulombs (mC) were transformed logarithmically to increase the normality of the distribution. Separately, seizure threshold data was analyzed in %Energy units. Differences between groups on single continuous variables were evaluated by t test or analysis of variance (ANOVA). Relationships between continuous variables were characterized by Pearson's product-moment correlation coefficient. Prediction of seizure threshold was examined by stepwise multiple regression analysis. Values are given as mean $\pm$ SD. SPSS 10.0 (1996 SPSS Inc.) was used.

Results

Comparison of Seizure Threshold Estimates

Over the entire sample, seizure thresholds were higher with the stimuli used on the MECTA schedule than with Thymatron in 79% of patients (overall $p < 0.0001$); on average these thresholds were 61% higher (overall $p < 0.0001$). The threshold with the MECTA stimulus parameter strategy was significantly higher in each age group, as shown in Figure 1. There were no significant differences in motor seizure duration (49.7 $\pm$ 14.1s MECTA vs. 52.1 $\pm$ 15.1s Thymatron, $t = 0.77$, $p = 0.45$), EEG seizure duration (63.9 $\pm$ 34.2s vs. 62.4 $\pm$ 19.2s, $t = 0.25$, $p = 0.81$) or in doses of thiopental (141.5 $\pm$ 24.7 mg vs. 144.3 $\pm$ 30 mg, $t = 0.49$, $p = 0.63$) or succinylcholine (27.3 $\pm$ 14 mg vs. 24.5 $\pm$ 6.2 mg, $t = 1.23$, $p = 0.22$).

Figure 1. Seizure threshold determined by two titration schedules, by age group (values given in mean $\pm$ SD, in millicoulombs). M = MECTA SR 1; T = Thymatron DGx
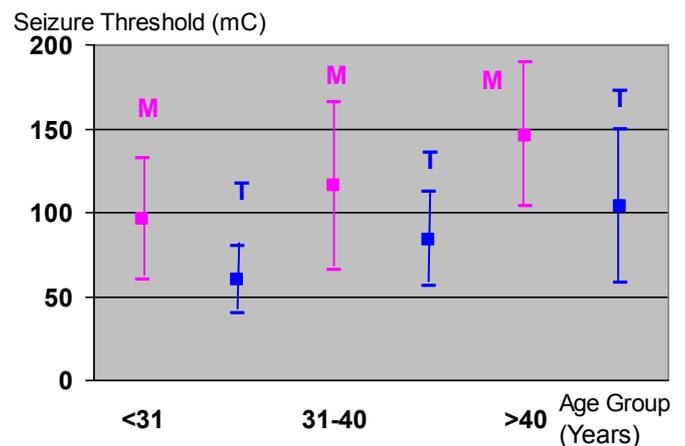

Table 1. Stimuli used for titration

| % | MECTA SR1 | | | | | | Thymatron DGx. PW=1 ms, I=0.9A | | | |
| | PW | Freq | Duration | I | Charge rate | Charge | Charge | Freq | Dura-tion | Charge rate |
	(ms)	(Hz)	(s)	(A)	(mC/s)	(mC)	(mC)	(Hz)	(s)	(mC/s)
5	1.0	40	0.5	0.8	64	32	25	30	0.47	54
10	1.0	40	1.25	0.6	48	60	50	30	0.93	54
15	1.0	40	1.5	0.7	56	84	76	30	1.4	54
20	1.0	40	2.0	0.75	60	120	101	30	1.87	54
25	1.0	90	1.0	0.8	144	144	126	30	2.33	54
30	1.0	60	2.0	0.75	90	180	151	50	1.68	90
35	1.0	60	2.0	0.8	96	192	176	50	1.96	90
40	1.2	60	2.0	0.8	115	230	202	50	2.24	90
45	1.2	70	2.0	0.75	126	252	227	50	2.52	90
50	1.0	90	2.0	0.8	144	288	252	50	2.8	90

Abbreviations: PW = pulsewidth; Freq = frequency; I = current

Seizure threshold varied from 25.2 to 252 mC, with an overall mean of 103.1 ± 45.5 mC. There was a nonsignificant trend for higher threshold in women than men (108.8 ± 46 mC, $n = 60$, vs. 90.9 ± 42.7 mC, $n = 28$; $t = 1.85$, $df = 86$, $p = 0.068$), consistent with their older age (40.7 ± 10.0 vs. 32.8 ± 8.9; $t = 3.59$, $df = 86$, $p = 0.001$). Seizure threshold correlated with age ($r = 0.51$, $p < 0.0001$), illness duration ($r = 0.54$, $p < 0.0001$) and stimulus parameter strategy (*Spearman's* $r = 0.46$, $p < 0.0001$; *Thymatron strategy* = 1, *MECTA strategy* = 2). Stepwise multiple regression revealed that illness duration ($t = 6.1$, $p < 0.0001$) followed by stimulus parameter strategy [$t = 4.5$, $p < 0.0001$; $F (2,85) = 31.69$, $p < 0.0001$] contributed to seizure threshold; these variables accounted for 42.7% of total variance.

Alternate Expression as Relative Dosage

Expression of the seizure threshold in '% Energy' units produced the same pattern of results as when expressed in terms of charge, with MECTA strategy groups showing higher thresholds than Thymatron groups [overall: $F (1,86) = 5.41$, $p = 0.022$]. Note that at each '% Energy' value the charge delivered by the MECTA instrument exceeds that of the Thymatron instrument, on average by one-sixth. Because this systematic dose difference biases against the observed results, expression in % Energy units understates them but makes their pattern easy to see, per Table 2.

Table 2. Tally of highest stimuli that failed to induce seizure, per subject, expressed as percent of maximum instrument charge (% Energy). The seizure threshold was 5% higher. MECTA charge exceeds Thymatron charge at each % Energy level, e.g., at 10% Energy 60 mC vs 50.4 mC.

% Energy Stimulus Dose	MECTA SR-1	Thymatron DGx
Under 5%	0	1
5%	8	10
10%	7	15
15%	15	15
20%	4	0
25%	8	2
35%	2	0
45%	0	1

Number of ECT Stimulations

All subjects except one showed an adequate seizure at the first session. At the first session the numbers of subjects who seized at 10%, 20%, 30%, and 40% Energy were

19 (22%), 52 (60%), 14 (16%), and 2 (2%), respectively. The most resistant subject had an adequate seizure at the second session, at 50% Energy. On average there were 2.0 ± 0.7 stimulations. MECTA strategy subjects required more stimulations than Thymatron subjects (2.2 ± 0.8 vs. 1.8 ± 0.6; $t = 2.28$, $df = 86$, $p = 0.025$). Seizure threshold was determined at the second session in 28 subjects (32%), at which the stimulus dose was 5% lower than at the first session.

Comparison of Dose-titration with Age and Half-age Methods

The present data indicates the rate of success in seizure induction by setting the stimulus dose according to the full-age (% Energy = age; Swartz and Abrams, 1989) and half-age (% Energy = half the age; Petrides and Fink, 1996) methods with the stimuli we used. By our observations, the half-age method produces a valid stimulus dose (i.e., above seizure threshold) reasonably often with the Thymatron default stimulus characteristics. Only three patients would have failed to seize at the first stimulation with the half-age method on the Thymatron.

The mean seizure threshold by stimulus titration for subjects who received the MECTA stimulus parameter strategy (121.5 ± 46.6 mC) was not lower than the dosage from the half-age method for Thymatron subjects (105.4 ± 27.9 mC). This adds to the reasonability of using the half-age method for bilateral ECT with the Thymatron instrument.

Discussion

Because the observations of seizure threshold in three separate groups constitute three independent trials, and each trial produced statistical significance, the overall statistical significance is the product of the three separate results, which is $p < 0.0001$, $F (1,86) = 18.38$. The intention in making three stratifications by age was to determine if the results varied substantially by age; they do not, despite a 50-75% effect of age on seizure threshold.

Underlying the results are a variety of differences in stimulus characteristics, and presumably the greater efficiency associated with stimuli of lower charge rate (Swartz, 1994), lower pulsewidth (Swartz and Manly, 1997), lower pulse frequency (Devanand et al., 1998), and longer train duration (Swartz and Larson, 1989; Devanand et al., 1998). The present study did not examine individual stimulus parameters, but rather compared sets of stimuli that represent uniform increment stimulus titration with different instruments.

The highest stimulus that failed to induce seizure for each subject was tallied in Table 2. Differences in these highest-failure stimuli represent differences between instruments. As illustrated by this table, seizure thresholds above 20% Energy

occurred in 7% of Thymatron patients versus 32% of patients who received the stimulus parameter strategy used on the MECTA instrument ($p = 0.0029$, Fisher's exact).

The results might have been somewhat different if the stimulus parameter strategies had been different. For example, if 0.5 ms pulsewidth on the Thymatron DGx instrument had been selected instead of 1 ms, without altering the charge, current, or frequency. This should have lowered seizure thresholds with the Thymatron instrument, because the 0.5 ms pulsewidth is more efficient (Swartz & Manly 1997). With the MECTA SR1 no pulsewidth narrower than 1 ms is available. Conversely, if wider pulsewidths had been selected seizure thresholds should have been higher. The data show that all seizure induction failures occurred at 1 ms pulsewidth with both stimulus parameter strategies; therefore, the strong effect of pulsewidth on efficiency did not influence our results, and differences are attributable to other stimulus parameters. If a frequency lower than 90 Hz at 25% Energy on the MECTA SR1 had been selected, some of the 8 patients who did not seize at that setting might have seized. Nevertheless, similar statistical significance would be maintained if such an improvement occurred; for example, 32% of patients who received the MECTA stimulus parameter strategy would continue to show seizure thresholds above 20% Energy, the same statistic noted in the previous paragraph ($p = 0.0029$, Fisher's exact). Such a potential change, about 20% in up to 18% of MECTA subjects or up to 3.6% overall, is much smaller than the 61% overall difference between the two strategies. Similarly, if a current higher than 0.6A at 10% Energy on the MECTA SR1 had been selected, some of the 7 patients who seized at 15% Energy might have seized at 10% Energy; again, this would not have changed the statistic noted and its maximum impact of up to 5.2% compares with the 61% overall difference.

The higher seizure threshold shown in female patients probably follows from their older average age (40.7 ± 10.0 vs. 32.8 ± 8.9; $t = 3.59$, $df = 86$, $p = 0.001$). Similarly, the relationship between seizure threshold and illness duration presumably follows the correlation between illness duration and age ($r = 0.93$, $p < 0.0001$).

The differences observed between the sets of ECT stimuli that was compared have potential clinical implications because high seizure threshold can have adverse consequences, including therapeutic insufficiency. For example, with a MECTA SR1 instrument 'the maximum available stimulus output was therapeutically insufficient for 5% of the patients studied even when available means to augment response were instituted' (Krystal et al., 2000). This maximum stimulus invariably has '576 mC defined at settings of a pulsewidth of 2.0 ms, frequency of 90 Hz, duration of 2.0 s, and current of 0.8A,' which indicates a 288 mC/s charge rate. Lower pulsewidths, frequencies, and charge rates are associated with greater stimulus efficiency (Swartz, 1994; Swartz and Manly, 1997; Devanand et al. 1998). The implementation of the threshold-multiple method of stimulus dosing in unilateral ECT can be prevented when the seizure threshold is high. For example, a multiple of 4.5 is not possible with a seizure threshold above 128 mC (22% of maximum charge). Inefficient stimuli might also have more cognitive side effects (Swartz, 1994). Another clinical consideration occurs when there is a change in the stimulus parameter strategy used with a patient, as might happen when switching instruments. The present results suggest that an increase in stimulus dose may be needed when changing to a less efficient stimulus parameter strategy.

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