COMPARISON OF PROPOFOL AND ETOMIDATE REGARDING IMPACT ON SEIZURE THRESHOLD DURING ELECTROCONVULSIVE THERAPY IN PATIENTS WITH SCHIZOPHRENIA

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A PROPOFOL ÉS AZ ETOMIDATE GÖRCSKÜSZÖBRE KIFEJTETT HATÁSÁNAK ÖSSZEHASONLÍTÁSA SZKIZOFRÉN BETEGEK ELEKTROKONVULZÍV KEZELÉSE SORÁN

Háttér. Az elektrokonvulzív kezelés (ECT) anesztéziájában használt szerek közül a propofol jelentősebb mértékben csökkenti a görcsroham hosszát, mint az etomidate. Szkizofrén betegeken végzett korábbi vizsgálatunkban ugyanakkor a görcsroham megrövidülése miatt propofol használata mellett sem volt szükség gyakoribb restimulációra. Ennek alapján azt feltételeztük, hogy a propofol és az etomidate görcstevékenységre kifejtett hatása 20 másodpercnél rövidebb görcsroham esetén azonos. Jelen vizsgálatunkban az etomidate-ot és a propofolt hasonlítjuk össze, szkizofrén betegek elektrokonvulzív kezelése során a görcsküszöbre és a görcsroham hosszára kifejtett hatásuk alapján.

Módszer. A randomizált, keresztezett elrendezésű vizsgálatban 30 szkizofrén beteg vett részt. Az egymást követő ülések során 1 mg/kg propofol és 0,2 mg/kg etomidate felváltva került alkalmazásra. A görcsküszöböt mindkét altatószernél a görcstevékenység kialakulásához szükséges stimulus dózisának titrálásával határoztuk meg. A görcsrohamok hosszát az EEG-vel és az EMG-vel regisztrált értékek alapján hasonlítottuk össze.

Eredmények. Etomidate-tal történt altatás esetén az EEG-vel (49,6±23,1 s, 39,7±19 s p=0,026), és az EMG-vel (41,4±22 s, 32,8±17,6 s p=0,016) regisztrált görcsroham is hosszabbnak bizonyult, mint propofol alkalmazásakor. Ugyanakkor sem a görcsroham kiváltásához szükséges minimális stimulus intenzitás tekintetében (41,58mC±13,6 mC, 41,58±11,1 mC, p=1,0), sem a szükséges restimulációk számában nem találtunk a két szer között különbséget.

Megbeszélés. Vizsgálatunkban az etomidate-hoz képest a propofol szignifikáns görcsrohamhossz csökkentő hatását mutattuk ki szkizofrén betegek ECT kezelése során. Ugyanakkor sem a két szer görcsküszöbre kifejtett hatásában, sem a szükséges restimulációk számában nem találtunk szignifikáns különbséget. Eredményeink alapján a propofol ismert görcsgátló hatása ellenére az ECT kezelés során a görcsküszöböt az etomidate-hoz képest nem emeli meg, használata tehát nem okoz a betegek számára fokozott áramterhelést.

KULCSSZAVAK: propofol, etomidate, elektrokonvulzív kezelés, szkizofrénia, görcsküszöb

SUMMARY

Background. While propofol is known to shorten seizures during electroconvulsive therapy, in our previous study on patients with schizophrenia, there was no need for more frequent restimulations when using propofol compared with etomidate. We hypothesized that etomidate and propofol have similar effects on seizure activity in cases where seizure duration is shorter than 20 seconds. In this study, etomidate and propofol are compared regarding their impact on seizure threshold and seizure duration.

Method. 30 schizophrenic patients participated in this prospective randomized cross-over study. For anesthetic induction were 1 mg/kg of propofol or 0.2 mg/kg of etomidate used alternately. For both anesthetics, seizure threshold was determined by titrating the dose of the stimulus necessary for eliciting a seizure. Seizure dura-

tions were also compared.
Results. After etomidate induction, seizure durations registered either by EEG or by EMG were longer than propofol treated cases (EEG: 49.6± 23.1 s, versus 39.7±19 s, p=0.026; EMG: 41.4± 22 s, versus 32.8±17.6 s, p=0.016). However, no significant differences were found for minimum seizure eliciting stimulation energy or the number of restimulations between the two anesthetics (41.58 mC±13.6 mC, versus 41.58 mC±11.1 mC, p=1.00).
Conclusion. During the ECT of patients with schizophrenia, propofol was shown to possess significant seizure-shortening properties, but it does not elevate seizure threshold or drop seizure duration under the minimal threshold more frequently than etomidate does. Based on these findings, we conclude that the use of propofol does not result in a greater electric load on the patients than etomidate.
KEYWORDS: propofol, etomidate, electroconvulsive therapy, schizophrenia, seizure threshold

INTRODUCTION

Reports published on the impact of propofol on seizure activity have been controversial. Several case reports describe seizures during anesthesia with propofol (1-4) and epileptiform patterns induced by propofol appearing on EEG (5). However, another publication reported that propofol did not significantly affect the EEG of those patients who have partial epileptic seizures (6). In the literature there is also a report showing that, under the effect of propofol, spikes on the EEG of epileptic patients become scarcer (7). Tests on animals proved propofol to have seizure-threshold-elevating properties dependent on dose (8-10). The controversy can partially be resolved by the results of a study in which it was found that low doses of propofol tend to have epileptic, while high doses tend to have antiepileptic effects (5). Propofol, when compared to methohexital, shortens seizure duration during ECT has been reported by numerous studies, but significant differences have not been found in clinical efficacy (11-14), or various electrophysiological and vital parameters (15). During the ECT increasing doses of propofol resulted in shortened seizure duration compared to etomidate (16). In another study, the switch from propofol to etomidate resulted in a significant prolongation of the seizure duration (17). In a randomized cross-over study during the ECT of patients with schizophrenia, seizure durations registered both by EEG and EMG were significantly shorter with propofol than with etomidate. Meanwhile, in the number of restimulations necessitated by seizures shorter than 20 s there was no difference between the two drugs (18). The explanation for this result could be that propofol drops the duration of the seizure under the minimal 20 s and may affects only seizure duration and not threshold.

Aims

To compare, during the ECT of patients with schizophrenia, the effect of propofol on seizure duration and seizure threshold with that of etomidate. Hypothesis: Although propofol reduces seizure duration during ECT treatment, does not elevate seizure threshold comparing with etomidate.

PATIENTS AND METHODS

Patients

Between October 2003 and February 2005, at the Department of Psychiatry and Psychotherapy of Semmelweis University, 68 patients were treated with ECT. The indication for treatment was in 16 cases depression and in 52 cases schizophrenia. Patients were diagnosed on the basis of the opinion of the treating physician, and that of an investigator (JT), who made her own diagnoses, after reviewing the clinical reports retrospectively, independently. (Interrater reliability was 95%). The three cases where the individual diagnoses differed were reevaluated by another investigator (GG) and the diagnoses were made after identical opinions had been reached.

Involved in this prospective, randomized, cross-over study were patients over 18 for whom the indication of ECT was a form of schizophrenia. Each subject or guardian gave informed consent for ECT and study participation.

Seven patients did not consent, in three cases, the treatment, on the basis of the decision of the treating physician, was discontinued after the first session and in three cases no epileptic activity were reached during one of the first two sessions.

In one case, the organic origin of the psychosis was revealed subsequently, and in two cases the use of the anesthetics was not done in accordance with the study protocol. The seven schizoaffective patients were also excluded. Eventually, 30 patients were involved in the examination. The study was approved by the Institutional Review Board of Semmelweis University.

ECT Procedure

ECT was performed twice a week (Tuesday and Friday) early in the morning. The patients had 6 hour fastening period before the therapy. After entering, a blood pressure cuff was applied to the left upper limb and the blood pressure was measured. EEG electrodes were then placed frontally and above the right mastoid. A pulsoxymetric sensor was fixed on the right. After registering the baseline blood pressures and heart frequency, 0.5 mg atropine was administered intravenously, and the patient was preoxygenated using 6 l/min O_2 via a facemask. Two minutes after atropine administration, 10 mg lidocain at a concentration of 1% was given, in order to prevent the venous irritation caused by either propofol or etomidate. As an induction agent for anaesthesia, each patient received 1 mg/kg propofol or 0,2 mg etomidate in a randomised order, using a cross over study design. The appropriate induction agent was injected over 5 sec. After loss of responsiveness to verbal command, the blood pressure cuff was inflated 50 mmHg above the systolic blood pressure to isolate the circulation to the upper limb and ensure accurate registration of the motor seizure. Succinylcholine 50 mg was then given in order to avoid convulsion induced musculoskeletal injuries. Ventilation was assisted using face mask, AMBU balloon and 4 l/min oxygen, until the electrical stimuli was performed. Just before the delivery of stimulus the ventilation was stopped. An electrical stimulus was delivered 1 min after succinylcholine administration via bifrontotemporal electrodes, using a Thymatron DGx (Somatics, Lake Bluff, IL, USA) instrument, providing bidirectional 1 ms square impulse by constant (0,9 A) current . Dose titration was started with the smallest dose available (25.2 mC), and was increased in each subsequent stimulation by 25.2 mC. In each session, up to four stimulations were performed using gradually increased doses, with a 60-second pause between the stimulations, without the administration of additional anesthetic. The dose of stimulation was increased until the development of seizure activity was shown by clinical signs and on EEG-registration unambiguously. During the seizure both EEG and the EMG of the isolated upper limb were monitored and recorded. Only those cases were enrolled in which the stimulation was successful during the first two sessions. When stimulation with one of the anesthetics resulted in seizure activity, in the next session the other one was used for sleep induction and the titration procedure was restarted at a dose of 25.2 mC.

Concomitant Medication

Concomitant antipsychotic medication was received by all except one of the patients. The drugs used were the following: haloperidol, zuclopenthixol, clozapine, risperidone, olanzapine, quetiapine and amisulpiride. Concomitant sedative therapy – involving clonazepam and diazepam – was received by 18 patients. Concomitant antidepressant therapy using sertraline was applied in one case. Mood stabilizers were applied in 4 cases, with lithium used in 3 cases, and carbamazepine in one case.

During the two days preceding the ECT and during the treatment, there were no changes made in the concomitant medication, either in doses or in the drugs applied.

Measurements and Calculations

Seizure threshold was defined as the lowest dose of stimulation which could elicit seizure activity proven both clinically and by EEG.

The lengths of EEG- and EMG-registered seizure activities were determined and documented by the computer of the Thymatron DGx device. These data were validated and corrected when necessary by the investigators.

Statistical Analyses

Sample size was determined on the basis of our pilot study using the PASS statistical software (Hintze J. 2001; NCSS and PASS. Number Cruncher Statistical Systems. Kaysville, Utah, USA). In order to prove a difference in stimulus dose of 25.2 mC, with a standard deviation of 50,4 mC, to reach a power of 0.8 at a significance level of 0.05, using a one-sample, two-sided nonparametric t-test were 29 patients required.

Data were analyzed using an SPSS 10.0 package (Statistical Package for Social Sciences, Chicago, IL, USA). Descriptive data were presented

through their means, confidence intervals and standard deviations. The normality of the distribution was examined by calculating skewness and kurtosis. If their distribution was normal, the paired data were compared with t-tests and in case of non-normal distribution with Mann-Whitney U-tests. As the values in some cells were less than five, binomial data were evaluated with a McNemar test.

RESULTS

In the study, there were 14 male and 16 female patients enrolled. Their mean age was 36.9 years (CI:32.0-41.9; SD:13.3). The underlying indications for ECT were the following: schizophrenia paranoid type (295.0): 3 patients, schizophrenia disorganized type (295.1): 8 patients, schizophrenia catatonic type (295.2): 19 patients.

In the sessions, that were analyzed in pairs, the first anesthesia was accomplished using etomidate in 17 cases and propofol in 13 cases (p=0.58).

Electroencephalographic (EEG) and motor (EMG) mean seizure durations and seizure threshold values are shown in Table 1.

On the basis of the 20-second minimal seizure duration recommended by Swartz (19), EEG seizure duration, during the first stimulation to exceed seizure threshold, was shorter than necessary in case of propofol in 3 instances and in case of etomidate in 2 instances (p=1.00). If minimal seizure duration is defined as 25 sec, EEG seizure duration was shorter in 3 cases with propofol and in 4 cases with etomidate (p=1.00).

DISCUSSION

In our study, propofol and etomidate were compared regarding their impact on seizure threshold and seizure duration in the ECT of patients with schizophrenia. In our pilot study we tried to determine the lowest dose, which produces a satisfactorily deep sleep for ECT treatment. We were not able to achieve reliable anesthesia with 0.75 mg/kg propofol or 0.15 mg/kg etomidate, but we managed to trigger a satisfactory hypnosis using 1.0 mg/kg propofol and 0.2 mg/kg etomidate, which supports the assumption of Avramov (16) that these are potentially equihypnotic doses. Ineffectiveness of low doses can be explained by the difference between the two samples (Avramov had depressed patients in his group, we had schizophrenics in ours), or by the interaction in our study between concomitant psychopharmacological medication and anesthetics.

In this study in accordance with our previous results (18), propofol, compared to etomidate, reduced both the electric (p=0.026) and the motoric (p=0,016) seizure duration to a significant degree. In spite of this difference, during the analysis of the data of stimulations exceeding the initial seizure threshold, neither the occurrence rate of seizures shorter than 20 sec, nor that of seizures shorter than 25 sec showed a significant difference between the two drugs. Also, no difference could be demonstrated for seizure threshold for either anesthetic.

Based on all these findings, we conclude that the antiepileptic properties of propofol are manifested only in a reduction in seizure duration, without an elevation of seizure threshold. The fact that we were unable to prove any antiepileptic impact on seizure threshold can be explained with the dose dependency of the antiepileptic properties of propofol (5): in this study, we utilized low doses of propofol (1 mg/kg). In another study, epileptic seizure during anesthesia with propofol was explained with the changing of the cerebral concentration of the drug (4). This hypothesis can also partially explain our findings. In order to exactly describe the effects of propofol on seizure activity and the mechanism of this action are further investigations required.

Table 1

Seizure thresholds, EEG and EMG measured seizure durations after propofol and etomidate induction (Data are presented with mean, confidence interval and standard deviation)

	Seizure threshold (mC)	EEG (sec)	EMG (sec)
Propofol	41.58 (CI: 37.5-45.6; SD:13.6)	39.7 (CI:32.6-46.8; SD:19.0)	32.8 (CI:26.2-39.4; SD:17.6)
Etomidate	41.58 (CI: 36.46-46.7; SD:11.1)	49.6 (CI:41.0-58.2; SD:23.1)	41.4 (CI:33.2-49.6; SD:22.0)
Statistics	Z=0; p=1.00	T=-2.23; p=0.026	T=-2.40; p=0.016

The value of our study is reduced by the pharmacotherapy concomitant with the seizure treatment. This was necessary because the patients subjected to ECT were almost exclusively showing severe symptoms, were resistant even to combined psychopharmacotherapy; their medical treatment was for ethical reasons indispensable. Therefore, the various concomitant medications might interact with propofol in a different way than with etomidate could not be ruled out. The antiepileptic properties of the low doses of lidocaine (20), administered to prevent the local irritation of the vein walls by the anesthetics, might also have affected our results. Furthermore, lidocaine might interact with the two anesthetics differently.

A fixed dose of induction agents may have different effects on people of different ages (21). In our study, the age range of the participants was 19-63 years. As no recommendation for the age-dependent dosing of the anesthetics was found, fix doses were administered.

Although a dosage regime which had been published before was used, there is no hard evidence that in schizophrenic patients 1 mg/kg of propofol and 0.2 mg/kg of etomidate can be considered equianesthetic doses. As it had earlier been published (22), there is no reliable tool for measuring the depth of anesthesia, especially when two different hypnotics are compared.

CONCLUSION

Although propofol, reduced both the electric (p=0.026) and the motoric (p=0,016) seizure duration to a significant degree in our study during the ECT of patients with schizophrenia did not elevate seizure threshold, and did not resulted more abortive seizures compared to etomidate. Based on these findings, we conclude that the use of propofol does not result in a greater electric load on the patients than etomidate, and can be a safe alternative drug for the anesthesia of ECT.

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