Anesthesia and Electroconvulsive Therapy: A Retrospective Study Comparing Etomidate and Propofol

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Background: The choice of anesthetic can influence the efficacy of electroconvulsive therapy (ECT). In the UK, propofol is a popular induction agent for ECT, but is associated with higher stimulus charge, shorter seizures, and known to affect seizure threshold. Etomidate is an alternative induction agent but there are concerns over its adverse events and safety.

Objectives: We examined the differences between propofol and etomidate in the real life situation of an ECT clinic by assessing their effect on (i) length of course of ECT (ie, number of treatments required to remission), (ii) adverse effects of each induction agent, (iii) the number of 'missed seizures,' and (iv) stimulus dose (charge in mC), which relates to seizure threshold.

Method: Using a retrospective naturalistic study design, 94 patients were identified over a 36-month period in our ECT clinic, of which, 65 met the inclusion criteria. Of these, 36 had received etomidate and 29 had received propofol as induction agents throughout their course of ECT.

Results: Patients who received propofol had a significantly longer course of ECT, higher seizure thresholds, and increased amounts of electrical charge (mC) over their course. There were no significant differences in adverse events with either of the induction agents.

Conclusions: When used for acute courses of ECT, propofol and etomidate are equally well tolerated as induction agents. Patients who received propofol had longer acute courses of ECT and, consequently, longer and costlier inpatient stays. Etomidate could be a better alternative induction agent in ECT.

Key Words: electroconvulsive therapy, etomidate, propofol, anesthesia

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Over recent years, several new guidelines for electroconvulsive therapy (ECT) have been produced in the United Kingdom.[1–3] Although several anesthetic agents are suggested, it is still unclear which is preferred.

The choice of anesthetic may have an effect on the course of ECT.[4] Historically, methohexitone was used in the UK but is no longer easily available. From an anesthetic point of view, propofol has become increasingly popular because it attenuates the hemodynamic response to ECT, offers rapid recovery with little nausea, and is considered to be the agent of choice for day-stay surgery.[5] Etomidate has retained its popularity in emergency anesthesia because of its cardiovascular stability as opposed to propofol, which can cause profound hypotension in the frail, elderly, and emergency patient.

Regarding the effect of anesthesia on the course of ECT, propofol is known to reduce seizure length[6,7] and has been suggested to be indicated in patients with excessively long seizures; to induce shorter seizures during ECT.[8] Benbow et al[9] argued for the use of etomidate in patients with high-seizure thresholds. Propofol, when compared to thiopental, reduces cognitive impairments in the early recovery period after ECT.[10] Aldridge et al[11] reported shorter seizures, higher stimulus charges, and increased post-ECT confusion when methohexitone was replaced with propofol.

Several studies have directly compared the effects of propofol to etomidate during ECT,[12–14] but the effect of anesthetic agents on seizure threshold and length of course has received little attention. We know that the degree to which stimulus dose exceeds seizure threshold is more important than seizure duration in terms of efficacy of ECT. In bilateral ECT, stimulus dose should be 50% above the patient's seizure threshold to be effective. In fact, some patients will continue to get better with very short fits.[15]

Adverse effects of etomidate include myoclonus, dystonic reactions, and nausea and vomiting (in up to one-third of patients). A more serious concern is that etomidate is a potent inhibitor of the adrenal steroid synthesis pathway, which has led to a moratorium being placed on its use as prolonged infusions for sedation in the Intensive Care Unit due to a substantial increase in mortality (28%–77% $P < 0.0005$). Although a single dose of etomidate has been shown to abolish the cortisol response to surgery, this has not been associated with adverse outcomes, although there is limited data to confirm this.[16]

The question remains as to whether we know enough about how different anesthetics affect the course and outcome of ECT. In this study, propofol and etomidate were compared by assessing their effect on (i) length of course of ECT (ie, number of treatments required to remission), (ii) adverse effects of each induction agent, (iii) the number of 'missed seizures,' and (iv) stimulus dose (charge in mC), which relates to seizure threshold.

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MATERIALS AND METHODS

In the Worthing ECT clinic, propofol and etomidate are currently used in approximate equal numbers — the choice of agent is left to each consultant anesthetist's personal choice. However, once started, the induction agent is continued throughout the ECT course. This situation provides ideal conditions for comparison of the 2 agents.

ECT and Anesthesia Procedure

The ECT within Worthing is performed on a biweekly basis. Currently, a Thymatron IV System is used (manufacturer Somatics, IL). Before February 2004, an Ectron 6 series machine was in place (manufacturer Ectron, Letchworth Garden City, U.K.). Both machines deliver a wide range of charge measured in millicoulombs (mC) and are dose equivalent. The stimulus dose titration method is used, whereby, the dose of electrical charge is titrated to each individuals seizure threshold and adjusted throughout the course, to be approximately 50% above the threshold at all times for bilateral treatment and at least 200% above threshold for unilateral ECT.[15] Seizure duration is monitored by electroencephalogram and is timed visibly by the treating psychiatrist. Record keeping of ECT is done via standardized treatment prescription and record sheets used across our Trust by all professionals involved in the ECT process, including the anesthetist. The total number of treatments given to each patient is determined on clinical grounds; the referring psychiatrist assesses the patient each week and ECT is terminated when they reach remission. All ECT is performed under the supervision of a consultant psychiatrist (CGU), and a pool of 6 consultant anesthetists who routinely administer the anesthetic.

Etomidate and propofol are the only 2 induction agents used within our Trust during ECT. The induction agent is administered intravenously using the minimum dose required for loss of consciousness, with either propofol (1–2 mg/kg) or etomidate (0.15–0.3 mg/kg). Suxamethonium (0.5 mg/kg) is used for muscle relaxation for appropriate seizure modification. Although there is no formal randomization procedure involved, the choice of induction agent is left up to the individual anesthetist involved and is based on personal preference rather than on clinical grounds.

Study Design and Sample

A naturalistic retrospective study design was adopted to conduct our investigations. All case notes of patients registered with the West Sussex Health and Social Care NHS Trust over the age of 18 who had received ECT at the Worthing ECT Suite over the period from July 2002 to December 2005 were reviewed.

Individuals were excluded from further study if: (1) their file could not be found or the ECT data in it was missing; (2) did not complete their intended course of ECT for any reason not related to the choice of induction agent (eg, if patient withdrew consent); (3) did not have a diagnosis of a severe depressive episode with or without psychotic features according to the ICD-10 Classification of Mental and Behavioural Disorders; (4) were not prescribed with antidepressant medication before or during their ECT course (ie, patients needed to meet UK guidelines)[1]; (5) did not receive the same induction agent throughout their course of ECT; (6) if had been given unilateral ECT; and (7) were receiving maintenance ECT. (The latter 2 cases are known to involve different seizure thresholds to bilateral acute ECT).

Data Collection

We designed a data collection form, which all 3 researchers (AP,CGU,YJ) used in recording the relevant information from each patient's file; all data were anonymized.

The information recorded included: *patient information* — age, sex, diagnosis and medication; *anesthetic details* for each ECT session — induction agent, dose, cardiovascular/respiratory measurements, and any adverse events recorded as a consequence of the anesthesia (defined as an event occurring on more than 1 occasion during the course of ECT); and *ECT details* recorded included — total number of stimulations during each ECT session, dose delivered measured in millicoulombs (mC), length of seizure observed measured in seconds, number of 'missed fits' (defined as seizures of less than 10 seconds duration), initial electrical charge to achieve seizure and the final electrical charge to achieve seizure (charge is kept 50% above the patient's seizure threshold throughout the course and can increase by up to 200% during the course of ECT).[17]

Outcome Measures

After the collection of all available data, 2 groups of patients who had received a course of ECT with either etomidate or propofol as induction agents were formed. The

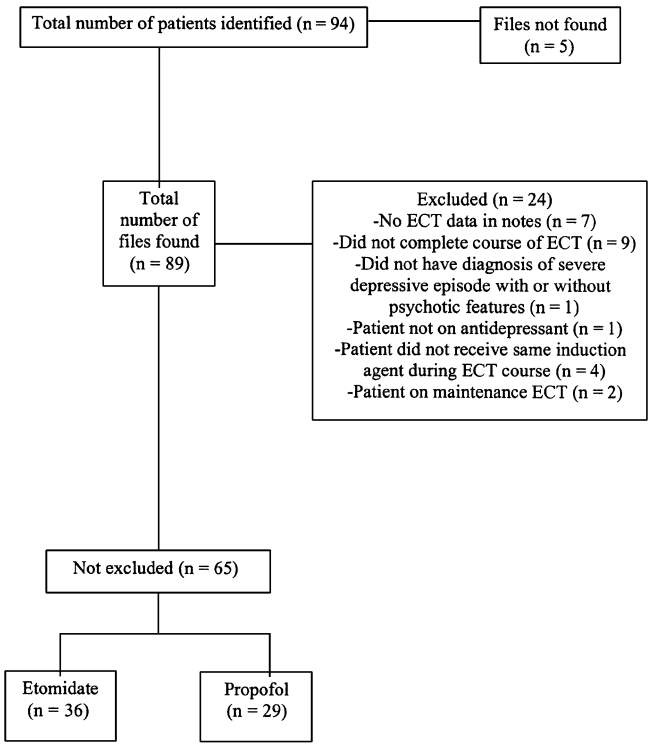

FIGURE 1. Patient flow diagram.

TABLE 1. Patient Characteristics at Baseline

Variable	Etomidate Group (n = 36)	Propofol Group (n = 29)
Mean age, years	61.0	61.7
Sex ratio (M:F)	11:25	7:22
Female	69.4%	75.9%
Medication at ECT		
Antidepressant	36 (100%)	29 (100%)
Antipsychotic	27 (75%)	17 (58.6%)
Lithium	5 (13.9%)	4 (13.8%)
Other mood stabilizer	6 (16.7%)	2 (6.9%)
Benzodiazepines	23 (63.9%)	19 (65.5%)

effect of the 2 induction agents on ECT was determined by the following 4 outcome measures:

1. The length of course of ECT as defined by the number of stimuli required to remission. Remission was determined by the referring psychiatrist based on global clinical assessment.
2. The safety profile of the 2 induction agents as determined by the frequency of adverse events recorded during the course of ECT treatment.
3. The total number of 'missed fits' (defined as no seizure or 1 lasting less than 10 seconds).
4. Initial stimulus dose, final stimulus dose, and the total charge needed for each patient during their course of ECT.

Statistical Analysis

Analyses were performed using the Statistical Package for the Social Sciences (SPSS for WINDOWS, version 12.1.01). The distributions of the outcome variables were approximately normal at baseline. The group mean differences between continuous variables were analyzed by *T*-tests and dichotomous variables by χ^2 tests between the 2 groups, where appropriate. All statistics are 2-tailed, with differences between the groups reported with *P* values, and confidence intervals at a 0.5 or 0.01 level of significance. Power calculations indicated that 31 patients were needed in each group. The study had 80% power to detect a difference of 2 sessions in the average length of a course of ECT between the 2 groups. Two sessions were chosen as a clinically significant difference as this represents an extra 1 week inpatient stay. The sample size was calculated using a *T*-test with a significance level of 5%, 2-tailed.

RESULTS

Data collection spanned a 36-month period from July 2002 to December 2005. A total of 94 patients were identified, of which, 65 met the inclusion criteria. Of these, 36 had received etomidate and 29 had received propofol as induction agents during their course of ECT (Fig. 1). Baseline demographic and clinical characteristics showed no significant differences between the 2 groups (Table 1). There were no significant differences in the etomidate and propofol groups in terms of medication received during the course of ECT. Although several patients received medication known to affect seizure threshold (eg, benzodiazepines, mood stabilizers), there were no significant differences in dosage ranges between the 2 groups. No patients in this study received Clozaril.

Effect of the Induction Agents on the Course of ECT

Table 2 shows the differences in the outcome measures. Data was collected during the course of ECT between the 2 groups.

Length of Course Until Recovery

There is a significant mean difference [$t(63) = 3.06$, $P = 0.004$] in the time of recovery between the 2 groups (etomidate 9.8, SD 3.5 vs propofol 12.3, SD 3.0), equivalent clinically to almost an additional 3 ECT stimulations in the propofol group to reach remission.

Effect of Induction Agent on Seizure Threshold

There was no significant difference in the initial threshold (electrical charge required to achieve the first seizure) between the 2 groups (etomidate 113.8, SD 63.2 vs propofol 138.9, SD 71.3). There were highly significant differences in the final seizure threshold (electrical charge required to achieve the final seizure), [$t(63) = 4.9$, $P < 0.0001$; etomidate 193.4, SD 114.4 vs propofol 384.0, SD 195.7].

The Total Stimulus Dose

There was a highly significant difference [$t(63) = 4.9$, $P < 0.0001$] in the total amount of electricity delivered in mC during the course of ECT treatment between the 2 groups, (etomidate 1506.2, SD 912.3 vs propofol 3077.0, SD 1608.5).

TABLE 2. Comparison of the Effects of Etomidate and Propofol as Induction Agents on the Course and Outcome of ECT Treatment

Variable	Etomidate Mean (SD)	Propofol Mean (SD)	*P*	95% CI of the Mean Difference
Mean length of ECT course	9.8 (3.5)	12.3 (3.0)	0.004	0.84–4.16
Mean starting threshold (mC)	113.8 (63.2)	138.9 (71.3)	*n/s*	8.31–58.4
Mean final threshold (mC)	193.4 (114.4)	384.0 (195.7)	0.0001	112.8–268.3
Mean difference between starting and final threshold (mC)	82.6 (99.17)	245.1 (160.5)	0.0001	97.5–227.3
Mean total amount of electricity delivered during ECT course (mC)	1506.2 (912.3)	3077.0 (1608.5)	0.0001	937.6–2203.9
Mean number of 'missed fits'	1.6 (1.3)	2.4 (2.6)	*n/s*	0.21–1.84

TABLE 3. Adverse Events Recorded as a Consequence of Induction Agent During ECT

Event	Etomidate Group (n = 36)	Propofol (n = 29)
None	20 (55.6%)	14 (48.3%)
1 or more adverse event	16 (44.4%)	15 (51.7%)
Frequency of adverse events		
Tachycardia	6	7
Bradycardia	1	0
Hypertension	3	6
Hypotension	0	4
Tachypnoea	9	5
Bradypnoea	0	0
Nausea/Vomiting	0	2
Arrhythmias	3	0

It is unclear whether this has any clinical relevance, but it is possible that higher total stimulus dose could lead to a higher incidence of cognitive side effects.

Missed Fits

There was no significant difference in 'missed fits' between the 2 groups (etomidate 1.6, SD 1.3 vs propofol 2.4, SD 2.6).

Adverse Events of Induction Agent

Table 3 shows the frequency of adverse events recorded as a consequence of the induction agent during ECT; with 20 (55.6%) of 36 patients in the etomidate group and 14 (48.3%) of 29 in the propofol group having no adverse events during ECT. These were not significant differences using χ^2 analysis between the 2 groups. A total of 22 adverse events were recorded in the etomidate group vs 24 in the propofol group. There were no reported symptoms suggesting that adrenal suppression was clinically significant.

DISCUSSION

The aim of this study was to compare 2 induction agents that are currently being used in the U.K. for ECT, in terms of their safety profile and their effect on the course of ECT. This was a naturalistic retrospective study within a district general hospital setting. All of the patients included in the study have severe depressive illness, all of them have tried one or more combinations of psychotropics.[1] The courses of ECT in this study were acute treatment courses and did not include continuation or maintenance ECT.

Implications of the Findings

Propofol and etomidate seem to be equally well tolerated as induction agents during ECT. However, the use of propofol compared to etomidate as an induction agent, when using strict stimulus dose titration technique, results in a significant increase in a patient's seizure threshold; with an average final threshold of 384 mC required to induce a seizure in the propofol group compared to only 193 mC in the etomidate group. This results in significantly higher amounts of electrical charge being delivered over a patient's course of ECT, resulting in a doubling of the total electricity delivered to the patient in the propofol group (average 3077 mC per patient) compared to the etomidate group (average 1506 mC per patient).

There was no significant difference in the number of 'missed fits' between the 2 groups, however, patients who received a course of ECT with propofol compared to etomidate took significantly longer until recovery, requiring on average almost 3 additional ECT sessions to reach remission. This equates to approximately 10 more days as an inpatient (if ECT is on a biweekly basis, as is the case in most U.K. ECT centers). This has significant economic implications to the already financially overstretched mental health trusts. Using the recent NICE appraisal estimates,[1] the cost of 3 ECT sessions and 10 days inpatient stay is $5359 (£2947; 4261 euros) per patient.

There may be practical difficulties with ECT machines reaching their limits to deliver higher doses in patients receiving propofol, especially if older and/or British made machines are used.[18]

Strengths and Weaknesses of the Study

The study has a number of important strengths and limitations that warrant further comment.

As this was a naturalistic study, it included patients most likely to be referred for ECT in a typical district general hospital setting. The patients were not a highly selected population as would have been the case in a randomized controlled trail, thus, improving the external validity of the results. Despite the lack of randomization, the 2 groups were well matched in terms of demographic variables and clinical factors that are known to affect seizure threshold, such as medication, anesthetic technique, and electrode placement. We looked at those patients who received only 1 type of induction agent throughout their course of ECT, which allowed us to use the stimulus dose technique. Previous studies have tended to switch induction agents within the same course, therefore, making it impossible to use a consistent stimulus dose titration technique. Numbers in this study were larger than those in previous work, with a total of 710 applications of ECT in 65 individual patients.

Limitations of this study include the fact that it is retrospective, nonrandomized, and unblinded. Our main outcome measure regarding the time of recovery was dependent on clinicians' global assessment, as opposed to standardized rating scales (this is, however, closer to practice in real life). We included all patients given the diagnostic label of severe depression, with or without psychotic features. This was again based on individual clinicians' judgement and did not take into account any objective measurement of severity of illness, comorbidity, and past psychiatric history of depression, which all could affect the length of an ECT course.

Implications for Future Research

This study has generated useful preliminary data to suggest significant differences in the course and outcome of ECT between 2 commonly used induction agents. The longer course of ECT with propofol has economic implications, but we are

unable to comment whether there are clinical implications in terms of cognitive side effects. A well-designed prospective randomized controlled trial would largely overcome the limitations of this study and, thus, provides a higher quality of evidence relating to the choice of anesthetic in ECT. This would also need to incorporate a well-validated universally accepted cognitive tool to measure post-ECT side effects. Unfortunately in the UK, such a cognitive tool has not yet been developed.

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