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Effects of Propofol and Propofol-Remifentanil Combinations on Haemodynamics, Seizure Duration and Recovery during Electroconvulsive Therapy

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Abstract

Objective: This study aimed to evaluate the effects of adding different doses of remifentanil to propofol treatment compared with propofol alone with regard to parameters, including the seizure duration, haemodynamic changes and recovery time, in patients undergoing electroconvulsive therapy (ECT).

Methods: This study was designed as a self-controlled, prospective, double-blind investigation of 17 patients between the ages of 20 and 65 years who had planned treatment with ECT at a psychiatric clinic. Group P (propofol) was administered 10 mL of normal saline after 0.5 mg kg^{-1} intravenous (IV) bolus of propofol. Group R I (propofol plus remifentanil-1) was administered 1.5 μg kg^{-1} of remifentanil, and group R II (propofol plus remifentanil-2) was given 2 μg kg^{-1} of remifentanil after 0.5 mg kg^{-1} IV bolus of propofol. The haemodynamic variables after seizure and the seizure duration were recorded. Time to return to spontaneous respiration, eye opening and achieving Aldrete score >9 were recorded.

Results: The electroencephalography seizure duration was significantly longer in groups R I (34.7±13 s) and R II (34.9±12) than in group P (24±7.5). Motor seizure duration was longer in groups R I (29.70±12.8) and R II (28.1±10) than in group P (21±7.3). The amount of total propofol was 121±21 mg in group P, 69.4±2 mg in group R I and 67±17 mg in group R II. Times to eye opening, following simple commands, and achieving Aldrete score >9 were significantly shorter in groups R I and R II than in group P.

Conclusion: ECT is a safe and effective treatment for patients with psychiatric disorders. Propofol-remifentanil anaesthesia prolongs the seizure duration and shortens the recovery time, suggesting that this combination may particularly be well suited for use in this patient group.

Keywords: Electroconvulsive therapy, propofol, recovery, remifentanil, seizure duration

Introduction

Electroconvulsive therapy (ECT) is an effective treatment method in psychiatry used for more than half a century. ECT has long been known as a safe and effective treatment for severe and persistent depression, bipolar disorder and schizophrenia (1). It is based on generalised seizures induced by means of electrical stimulation. In patients who do not respond to medical treatment and psychotherapy, up to 55% are shown to respond to ECT. This rate is reported to be 80%–90% in patients with depression (2).

Use of anaesthetic drugs before ECT can reduce the side effects of tonic-clonic seizures and subjective unpleasantness. The anaesthetic approach can affect the safety of ECT (3-5), seizure threshold (6), cognitive side effects (7) and particularly the quality of seizures (8), even when the anaesthetic period is short. Intravenous anaesthetics

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can influence the induction and propagation of ECT seizures (9). Most of the previous studies have focused primarily on the differences between various anaesthetic agents in terms of their effects (7). Limited research has been conducted on the impact of other aspects of the anaesthetic technique, despite the fact that the practice continues to be markedly heterogeneous in ECT clinical settings (8). The potency of these anticonvulsant effects depends on several factors, including the anaesthetic used (6), the concentration of anaesthetic in the brain at the time of seizure induction (10), its dosage (5, 6, 10) and its pharmacokinetic profile (10). The majority of anaesthetic medications used for ECT have anticonvulsant effects, and the use of these at high doses has been reported to shorten the duration of seizures induced by ECT, which may negatively affect the success of ECT. Consequently, there is a delicate balance to be found between the optimal duration of ECT seizure activity and sufficient anaesthetic administration (11).

Propofol provides the short-duration loss of consciousness required for ECT and, owing to its relative lack of disruption to haemodynamic stability, it is widely used for ECT anaesthesia (12). However, propofol has been reported to reduce the seizure duration in a dose-dependent manner (13). Thus, despite the potentially attractive properties of propofol (such as haemodynamic stability and reduction of postictal agitation), concerns about its effect on seizure duration persist.

Remifentanil is a potent mu-opioid receptor agonist that can provide rapid onset and brief duration of general anaesthesia owing to its rapid metabolism and elimination. Opioid agonists have the added advantage of attenuating sympathetic response and not raising the seizure threshold. Adverse effects can include muscle rigidity, glottic closure, bradycardia, hypotension, nausea and respiratory depression (14).

Owing to their contribution to haemodynamic stability, rapid recovery time and lengthening of seizure duration, opioid analgesics with short efficacy, such as alfentanil and remifentanil, have been proposed for use in ECT (11, 15, 16). Administering short-duration opioid analgesics, such as remifentanil and alfentanil, at the start of anaesthesia has been linked to longer seizure duration and reduction of dose requirements for hypnotic agents (11, 17-19).

Main Points:

- An ideal anaesthesia for ECT must act quickly while maintaining haemodynamic stability and should be rapidly titrated to provide depth of anaesthesia.
- The procedure should have stable recovery time and minimal post-anaesthetic side effects.
- Propofol-remifentanil combinations that minimise side effects can provide high-quality ECT with adequate seizure times, shortened emergence times and no haemodynamic instability.

The effect of different anaesthetic medications on the successful reduction of depressive symptoms and adverse effects is unclear (20). Therefore, we evaluated the effects of propofol used in combination with different doses of remifentanil in comparison with propofol only in terms of seizure duration, haemodynamic changes and recovery duration.

Methods

After receiving permission from the Republic of Turkey Ministry of Health General Directorate of Pharmaceuticals and Pharmacy Clinical Medication Research Ethics Advisory Board (ethics committee approved: 2010/06) and informed written consent from all patients, the study included 17 patients treated at the Psychiatry Clinic of Dokuz Eylul University Hospital between the ages of 20 and 65 years with the American Society of Anesthesiologists (ASA) score of 1-2 who underwent a total of 102 ECT sessions. All ECT treatments were provided by a uniform team that included 2 anaesthesiologists, an attending psychiatrist and ECT staff.

The study design was self-controlled, double-blind, and prospective. We excluded the patients with cardiovascular system, endocrine or neuromuscular diseases and those who used alpha- or beta-blocker medications, were pregnant or had low cholinesterase levels. Participating patients' age, sex, body weight, psychiatric disease diagnosis and ASA score were recorded. For each patient, a vein was opened with a 20-G intravenous (IV) cannula and 250 mL of isotonic sodium chloride solution was administered. During the procedure, all the patients received standard monitoring, with heart rate (HR), systolic arterial pressure (SAP), mean arterial pressure (MAP) and peripheral oxygen saturation (SpO_2) measurements recorded.

General electroconvulsive therapy procedure

A maximum of 3 treatments were administered each week, typically on Monday, Wednesday and Friday. The psychiatrist adjusted the settings of the ECT device (Thymatron™ System IV Somatics, Inc, USA) after collecting baseline values and administered the protocol to all patients according to group. The prescribing psychiatrist determined initial electrode placement. The initial dose was determined using the age method for right unilateral placement and half-age for bilateral (bitemporal) placement. All the patients received right unilateral stimulus with an ultra-brief pulse width (0.25 ms). The first ECT session determined the seizure threshold, with subsequent sessions delivering a percent energy 6 times the seizure threshold. Short seizure durations (<25 s) or poor postictal suppression resulted in an incremental increase in percent energy.

Anaesthesia management for electroconvulsive therapy

Each patient was represented in each group twice. The patients were divided into 3 groups using the closed envelope lottery method. Group P (propofol) (Fresenius Kabi Avusturya GmbH, A-8055 Graz, Hafnerstrasse 36– Austria) patients were given 10 mL IV normal saline (NS), group R I patients were given 1.5 μg kg^{-1} remifentanil (GlaxoSmith-Kline Manufacturing S.p.A, Italia) plus10 mL NS and group R II patients were given 2 μg kg^{-1} remifentanil plus 10 mL NS over 30 seconds and then left for 1 minute. Later, all the groups were given 0.5 mg kg^{-1} IV bolus propofol over 20 seconds and then 10–20 mg IV bolus propofol titrated over 10-second intervals until the eyelash reflex was lost. MAP, HR and SpO_2 values in each session were recorded as basal values before anaesthesia, before ECT and in the 1st, 3rd, 5th, 7th and 10th minutes after ECT. After peripheral oxygen saturation values were recorded, 6 L min^{-1} oxygen (O_2) was administered through a mask.

For each session in all the 3 groups, the total propofol administered was recorded. After the patients lost consciousness, respiration was supported with a balloon valve mask and 0.5 mg kg^{-1} succinylcholine IV bolus was administered for sufficient muscle relaxation. While final checks of the ECT stimulus were performed, an airway was inserted before stimulation and the O_2 mask was replaced on the patient's face. The ECT stimulus was administered 90 seconds after a succinylcholine dose (0.5 mg kg^{-1}). The durations of identified seizures were noted.

Haemodynamic parameters were monitored and recorded every 2 minutes during the seizures. After administration, if the patients' MAP was increased 30% or more above the basal values over 3 minutes, intervention with previously prepared IV nitroglycerin (perlinganit 0.1 mg mL^{-1}) was planned. In general, MAP, HR and SpO_2 values were monitored every 2 minutes, and complications that may develop after the procedure, such as hypertension (30% or greater increase in MAP), hypotension (systolic arterial pressure below 90 mmHg), severe tachycardia (>100 beats min^{-1}), severe bradycardia (<50 beats min^{-1}), vomiting and desaturation, were recorded. Patient recovery was monitored using the modified Aldrete recovery criteria, and when Aldrete score was >9, the patients were sent to the ward (21).

Statistical analysis

We calculated mean arterial pressure. Minimum 102 ECT procedures were planned according to the G power program. The F test analysis of variance (ANOVA) repeated measures were used between factors test method by selecting the effect size of 0.3, alpha of 0.05 and power of 0.95 for 3 groups and 7 measurements.

Results are given as means±standard deviations and percentages (%). Data were tested for normal distribution by the Kolmogorow-Smirnov test. The study results were then tested using the ANOVA. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS Inc.; Chicago, IL, USA) statistical program for Windows statistical software, version 15.0. Mean values measured in each group were analysed with variance analysis. Measurements within the groups were analysed with the repeated measurement variance analysis. Results with $p<0.05$ were accepted as statistically significant.

Results

The study included 102 ECT sessions administered to 17 patients of age ranging from 17 to 65 years with ECT indications and treated at Dokuz Eylül University Psychiatry Clinic. The patients' demographic characteristics are shown in Table 1.

During ECT administration, addition of remifentanil (group R I: 1.5 μg kg^{-1} and group R II: 2 μg kg^{-1}) reduced the requirement for the hypnotic agent propofol by 42.7% in group R I and 44.6% in group R II compared with the general anaesthetic protocol using propofol alone (group P). In addition, the patients' recovery time was reduced, and electroencephalography (EEG) time and motor seizure durations lengthened. No differences in these properties were observed between the 2 tested doses of remifentanil. The EEG and motor seizure durations are shown in Table 2.

The groups did not significantly differ in MAP ($p>0.05$). To determine any change in the mean values before anaesthesia, before ECT or in the 1st, 3rd, 5th, 7th and 10th minutes after ECT values were assessed by using repeated measurements ANOVA. In all the 3 groups, a significant difference was observed between MAP values before and after ECT ($p<0.05$; this overall difference was because of the marked change in MAP values from before ECT to the 1st minute after ECT).

Table 1. Characteristics of patients

	Total n=17	%
Age (mean±SD) (years)	41.82±15.94	
Sex (male/female) (n)	7/10	58.8/41.2
Weight (mean±SD)	75.11±14.51	
ASA (I/II) (n)	11/6	64.7/35.3
Diagnosis		
Major depression	9	52.9
Bipolar disorder	4	23.5
Schizophrenia	4	23.5

n: number of patients; ASA: American Society for Anesthesiologists; SD: standard deviation

The average MAP values (mmHg) of all 3 groups are shown in Table 3.

There were no significant differences between the groups in terms of HR (p>0.05). When the 3 groups were evaluated by ANOVA, there was a significant difference between HR before ECT and HR after ECT (p<0.05; this difference was because of the values before ECT and in the 1st minute after ECT). The mean HR values in all 3 groups are shown in Table 3.

Table 2. Seizure parameters

	Group P n=34	Group R I n=34	Group R II n=34	p
EEG seizure durations (s)	24±7.5	34.7±12.7	34.9±11.5	<0.001
Motor seizure durations (s)	21±7.3	30±12.8	28.1±9.9	<0.05

n: Electroconvulsive therapy procedure; values are mean±standard deviation. EEG: electroencephalography

The groups also did not significantly differ in terms of SpO_2 (p>0.05). To identify any change in the mean values before anaesthesia, before ECT and in the 1st, 3rd, 5th, 7th and 10th minutes after ECT, values were assessed using repeated measurements ANOVA. A significant difference was found in SpO_2 before and after ECT (p<0.05; this overall difference was owing to the marked change in values from before ECT to the 1st minute after ECT).

No significant difference was observed among the groups with regard to the time to begin spontaneous respiration (p=0.497). However, the times to eye opening, responding to simple commands and reaching an Aldrete score of 9 were significantly shorter in groups R I and R II than in group P (p=0.000). There was no significant difference between group R I and R II (p=1.000) (Table 4).

No haemodynamic instability (hypertension/hypotension and tachycardia/bradycardia) or other complications were observed in any patient during or after the procedure.

Table 3. Heart rate values of patients

Variable	Group P n=34	Group R I n=34	Group R II n=34	p
Baseline values				
MAP (mmHg)	108.3±17.2	111±19.7	107.3±17.6	0.674
HR (beats min^{-1})	86±17.3	87.2±15.2	85.5±13.4	0.897
Before ECT				
MAP (mmHg)	91.3±10.1	92.7±16.8	92.4±16.9	0.920
HR (beats min^{-1})	92.4±14.4	90.1±14.7	89.2±13.6	0.649
ECT 1st minute				
MAP (mmHg)	120.7±20	122.3±22.6	119.8±15.3	0.870
HR (beats min^{-1})	96.9±18.3	100.5±17.7	99.3±20	0.731
ECT 3rd minute				
MAP (mmHg)	109.6±20.5	108.1±17	111.5±15.8	0.730
HR (beats min^{-1})	98.7±16	99.9±14.5	99.4±16.6	0.951
ECT 5th minute				
MAP (mmHg)	104.3±18	103±14.4	105.1±15.7	0.846
HR (beats min^{-1})	96.4±14	100.5±13.3	102.2±16	0.240
ECT 7th minute				
MAP (mmHg)	103±13.9	100.9±15.5	103.5±14.9	0.740
HR (beats min^{-1})	97.4±16.0	100.5±13.4	100.4±15.9	0.627
ECT 10th minute				
MAP (mmHg)	101.3±14.8	100.7±12.4	98.9±12.4	0.731
HR (beats min^{-1})	95.3±14.9	97.8±13.0	98.5±13.9	0.614
p* MAP	0.001	0.001	0.001	
P** HR	<0.05	<0.05	<0.05	

n: Electroconvulsive therapy procedure; HR: heart rate; MAP: mean arterial pressure; ECT: electroconvulsive therapy. p: Compared mean arterial pressure and heart rate between groups. p* MAP: Compared mean arterial pressure within groups. p**HR: Compared heart rate within groups

Table 4. Recovery parameters of patients

Variable	Group P n=34	Group R I n=34	Group R II n=34	p
Total amount of propofol (mg)	121.2±20.7	69.4±17*	67.1±16.6*	<0.05
Time to spontaneous breathing (min)	2.1±0.4	2.1±0.2	2.1±0.4	˃0.05
Time to eye opening (min)	3.9±1.0	3.2±0.8*	3.1±0.8*	<0.05
Time to response to basic commands (min)	6±1.1	5±1*	4.8±0.9*	<0.05
Time to Aldrete score of 9 (min)	10.1±1	8.8±1*	8.8±0.9*	<0.05

n: Electroconvulsive therapy procedure; values are mean±standard deviation.*p<0.05, compared with group P

Discussion

The use of short-acting opiates to potentiate the effect of an induction agent has repeatedly been shown to lengthen the seizure duration (15, 22-25). Unfortunately, seizure duration by itself does not predict therapeutic outcome (26, 27), and indeed a barely suprathreshold stimulus may result in a longer, but likely therapeutically ineffective, seizure. In this study, we found that the use of 1.5 mg kg^{-1} or 2.5 mg kg^{-1} remifentanil in conjunction with propofol reduced the necessity for propofol by 42%–44%. The reduction of emergence time and elongation of EEG and seizure times were also observed. We did not detect any differences in the effects of the different doses of remifentanil on these results.

The ideal anaesthetic agent during ECT should have rapid effects, be of short duration and not reduce the success of the treatment provided by epileptic seizures. However, a majority of hypnotic anaesthetic agents used during ECT, including propofol, have anticonvulsant effects and have been found to reduce seizure duration and activity (13, 28). However, as propofol provides the necessary short-duration consciousness loss required for ECT and does not disrupt the haemodynamic stability, it is still widely used for ECT anaesthesia (13). Rasmussen (29) has reported that using the lowest effective anaesthetic dosage minimises its effects on seizure elicitation and duration. ECT with the use of remifentanil, an opioid agent, combined with propofol allows the administration of lower doses of propofol (30). Remifentanil is associated with longer seizure durations when used as the sole anaesthetic or as an adjunct when the primary anaesthetic dose is lowered. Individual studies have reported a higher postictal suppression index, lower initial seizure thresholds and reduced rise in seizure thresholds with remifentanil (14).

In a study researching the effects of remifentanil during ECT, Recart et al. (22) have administered 3 different bolus remifentanil doses of 25, 50 and 100 µg or NS control after 1 mg kg^{-1} methohexital. These authors did not identify any significant difference between the groups in terms of motor and EEG seizure duration; however, in our study, the seizure duration was significantly longer in the groups that included remifentanil (groups R I and R II) than that in the group with no remifentanil (group P). This difference in seizure duration findings between our study and that of Recart et al. (22) may be linked to the lower propofol requirement in the groups with added remifentanil, with a dose reduction of 42.7% and 44.6% in groups R I and R II, respectively. Recart et al. (22) fixed the hypnotic agent dose (methohexital), whereas we titrated the hypnotic agent (propofol) to the required effect. In our groups with added remifentanil, the reduced dose of propofol may be responsible for the longer duration of seizures. Recart et al. (22) also observed no difference between the groups in terms of recovery duration, whereas in our study, the time for patients to open their eyes, respond to basic commands and reach an Aldrete score >9 was shorter in the groups with added remifentanil (groups R I and R II) than the propofol only group (group P). In this study, we found no difference between the groups in terms of the time to begin spontaneous respiration only.

The haemodynamic effects of ECT are related to a brief parasympathetic response during and immediately after the stimulus followed by a longer sympathetic surge. Typically, several seconds of bradycardia are followed by a 30%–40% rise in systolic blood pressure and a greater than 20% increase in the heart rate that may be sustained for several minutes beyond the termination of the seizure (14). Locala et al. (31) have studied the effects of a combination of methohexital with low-dose remifentanil on the haemodynamic response to ECT. In that study, 1 group was given 80–100 mg methohexital IV bolus and the other group was given 500 µg remifentanil IV bolus added to 40 mg IV methohexital; SAP and HR were clearly reduced in the remifentanil group. In this study, there was no difference in SAP and HR values detected between the groups. Compared with the study by Locala et al., (31) the remifentanil doses in our study were lower (1.5–2 µg kg^{-1}) and every patient was given 0.5 mg IV atropine before induction, which may underlie the difference in SAP and HR values between the studies. Andersen et al. (23) have studied the effect of adding remifentanil to methohexital for ECT in elderly patients (mean age, 74.3 years), with 1 group given 0.75 mg kg^{-1} methohexital and the other group given 0.5 mg kg^{-1} methohexital with 1 µg kg^{-1} added remifentanil. Although

no difference was found between the groups in terms of recovery time, time to begin spontaneous respiration and arterial pressure measurements, the motor seizure duration was significantly longer in the group in which additional remifentanil was given. This similarity between the study by Andersen et al. (23) and this study may be related to the reduction in the dose of hypnotic agent used with additional remifentanil. However, unlike that previous study, in our study, all the recovery parameters, apart from time to beginning spontaneous respiration, were significantly shorter in the groups given additional remifentanil. This difference between the 2 studies may be owing to our use of propofol as the hypnotic agent and our titration of the propofol dose according to requirements.

Akcaboy et al. (24) have compared the seizure duration and recovery parameters during ECT between an anaesthetic protocol using propofol alone and protocols with a reduced propofol dose and remifentanil or alfentanil added to the treatment. One group was administered only 0.75 mg kg^{-1} propofol, second group was administered 0.5 mg kg^{-1} propofol+10 µg kg^{-1} alfentanil, and third group was administered 0.5 mg kg^{-1} propofol+1 µg kg^{-1}remifentanil IV. To achieve loss of consciousness in the groups, additional propofol was titrated as required. In the groups with propofol administration combined with remifentanil or alfentanil, the motor seizure duration was significantly longer, whereas the times to beginning spontaneous respiration, eye opening and responding to simple commands were significantly shorter in the group given only propofol. In this study, similar results were found with regard to seizure duration. However, our study found no difference in the time to spontaneous respiration, whereas the times to eye opening and response to basic commands were significantly shorter in the groups administered remifentanil. The reason for the shorter duration of recovery parameters in the groups with remifentanil was that the propofol dose in the group given only propofol in our study was higher (group P; 1.64 mg kg^{-1}) than the propofol dose used in the study by Akcaboy et al. (24) (1.03 mg kg^{-1}).

We evaluated 102 ECT sessions administered to 17 patients. The EEG seizure durations of these patients over 102 sessions ranged from 15 to 77 seconds, with motor seizure durations of 14 to 75 seconds. All of these sessions were in group P administered only propofol. This result demonstrated that of the 102 sessions included in the study, reliable and effective seizure durations were obtained in 22 of 34 sessions with only propofol administration (64.7%) and all 68 sessions with propofol-remifentanil administration (100%). The administration of remifentanil for ECT reduced the dose of hypnotic agent and thus lengthened the seizure duration. The data obtained on seizure duration in our study support previous reports (15-19, 23, 24).

Addition of remifentanil (1 µg kg^{-1}) is suitable for the reduction of propofol dose during ECT, without any adverse haemodynamic effects, including effects on cerebral blood flow (32). The efficacy and rapid recovery time of propofol are the reasons for its common use for ECT anaesthesia. Although adding remifentanil to the treatment reduces the propofol dose, the sympathetic response linked to ECT, especially in the cardiovascular system, in the group given only propofol was suppressed to at least the same degree, and the seizure duration was held at the optimum interval. In the groups in our study with added remifentanil, the propofol dose requirements were nearly halved compared with the propofol dose in the control group. In the remifentanil groups, the observed lengthened seizure duration is largely in accordance with the literature and may be related to our use of a lower dose of propofol.

This study focused on 5 major considerations concerning the use of propofol for ECT: seizure time, haemodynamic affect, emergence time, cognitive adverse effects and therapeutic efficacy (29). The results of this study indicate that propofol is indeed strongly associated with shorter seizure durations than other anaesthetics but its antidepressant efficacy does not seem to be compromised. HR and blood pressure changes are less pronounced with propofol, and post-anaesthesia recovery may be quicker with propofol as well (29). Addition of remifentanil to anaesthesia for ECT may lead to prolonged seizure duration when it permits the use of reduced anaesthetic doses. The results of this study further indicate that the use of 1.5–2 µg kg^{-1} doses of remifentanil for sedoanalgesia for ECT is safe.

Limitations of this study include the absence of bispectral index monitoring for hypnotic agent titration and lack of investigation into EEG findings regarding seizure quality. In addition, we did not evaluate the post-anaesthetic cognitive tests.

Rapid recovery is important because the short-acting opioid agent remifentanil was associated with patients reaching an Aldrete score of ≥9 more quickly. An ideal opioid for ECT must act quickly while maintaining haemodynamic stability and should be rapidly titrated to provide depth of anaesthesia with a short, stable recovery time and minimal post-anaesthetic side effects (nausea and vomiting). All these features were apparent in the groups treated with remifentanil. This study focused only on outpatient ECT procedures and may be less applicable to inpatient ECT.

Conclusion

The short-time effect and rapid recovery time has led to the common use of propofol for ECT for many years. This study found that adding remifentanil to propofol lengthens the seizure duration and shortens the recovery time. Propo-

fol-remifentanil combinations that minimise side effects can provide high-quality ECT with adequate seizure times, shortened emergence times and no haemodynamic instability; these agents may be valuable for routine ECT anaesthesia. Future studies should assess optimal doses and rapid recovery.

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