Low-dose esmolol bolus reduces seizure duration during electroconvulsive therapy: a double-blind, placebo-controlled study

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We have measured the effect of a bolus dose of esmolol 80 mg i.v. on heart rate, and systolic (SAP), diastolic (DAP) and mean (MAP) arterial pressures during electroconvulsive therapy (ECT). We also assessed seizure duration using both the cuff method and two-lead EEG. We studied 20 patients in a double-blind, placebo-controlled, within-patient blocked randomized study. No patient was receiving psychotherapeutic drugs or had cardiovascular disease. Esmolol significantly reduced heart rate, SAP and MAP before the stimulus, and also significantly reduced the increases in these variables during the convulsion, compared with placebo. However, seizure duration was also significantly reduced, possibly making ECT less effective. The reduction in seizure duration was 5.83 s when monitored clinically and 9.9 s when measured by the EEG. Because of the reduction in seizure duration, routine administration of esmolol is not advisable because it may interfere with the efficacy of ECT, but administration of esmolol during ECT could be useful to reduce tachycardia and hypertension in high-risk patients.

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During electroconvulsive therapy (ECT), tachycardia and an increase in arterial pressure may be dangerous, even in patients with no apparent cardiovascular disease.[1–3] A treatment that could reduce this haemodynamic response, without impairing the efficacy of the treatment, would be useful for routine use.

Theoretically, the beta-blocking agent esmolol is suitable for attenuating the cardiovascular response as it can be administered i.v. and has an extremely short half-life of 9 min. In this study, we have investigated the effect of a low-dose esmolol bolus on heart rate, arterial pressure and seizure duration during ECT in patients without cardiovascular disease.

ECT is a widely used and effective treatment for severe depression, especially when alternative methods of treatment have failed. It is generally considered to be a low-risk procedure. However, ECT is accompanied by a cardiovascular response that can be dangerous in patients with cardiovascular disease. This response consists of an initial parasympathetic and a subsequent sympathetic reaction. During and immediately after administration of the electrical stimulus, a vagal reaction occurs, which may cause a transient sinus bradycardia or, rarely, asystole. In some treatment centres, atropine or glycopyrrolate are given before induction of anaesthesia to attenuate this vagal effect.[1] The vagal reaction is followed by a transient tachycardia and an increase in arterial pressure during the clonic phase of the convulsion.[1 4] This cardiovascular response may be harmful in patients with cardiovascular disease. Pretreatment screening and adequate management of cardiovascular risk factors remain the most important methods of preventing cardiovascular complications caused by ECT. In addition, attenuation of the hyperdynamic reaction during ECT can be important in patients with cardiac conduction defects, hypertension, recent myocardial infarction, haemorrhagic stroke, and aortic or cerebral aneurysms.[4]

Patients and methods

The study was performed in the University Hospital Rotterdam-Dijkzigt and approved by the Hospital's Ethics Com-

mittee. Written informed consent was obtained from all patients.

We studied 22 patients with a major depressive episode, as defined by the DSM-IV criteria.[5] Patients were undergoing ECT because they had failed to respond to treatment with a tricyclic antidepressant, followed by adding lithium and a non-reversible monoamine oxidase inhibitor. Exclusion criteria were diastolic arterial pressure greater than 100 mm Hg, use of other beta-adrenergic or calcium-channel blocking drugs, second or third degree atrioventricular block, arrhythmia, hypotension, sinus bradycardia, chronic obstructive pulmonary disease, congestive heart failure, and renal or hepatic failure.

Psychotherapeutic drugs were discontinued in all patients at least 7 days before ECT. This is common practice in the Netherlands. In this study, this gave an additional advantage of eliminating possible interference of psychotherapeutic drugs with the cardiovascular measures during treatment. We aimed to study 20 patients. In all patients the lungs were preoxygenated. I.v. administration of glycopyrrolate 0.004 mg kg^{-1} and alfentanil 0.010–0.015 mg kg^{-1} was followed by etomidate 0.2–0.3 mg kg^{-1} and succinylcholine 0.5–1.0 mg kg^{-1}. Either esmolol or placebo was administered i.v. after glycopyrrolate, just before induction of anaesthesia.

Seizure duration was recorded both clinically, using the cuff method, and by a two-channel electroencephalograph (EEG). The cuff method consists of inflating a blood pressure cuff to 300 mm Hg just above the right knee, before administration of succinylcholine; as there is no neuromuscular block in the right lower leg, duration of the convulsion can be timed clinically.

Patients were monitored routinely with a five-lead ECG and a pulse oximeter. Systolic and diastolic arterial pressures (SAP, DAP), mean arterial pressure (MAP) and heart rate (HR) were monitored continuously using the Datex Capnomac from arrival in the ECT suite until the patient started breathing spontaneously after the convulsion.

Clinical evaluation of depressive symptoms was performed each week using the 17-item Hamilton rating scale for depression (HRSD).[6] Response was defined as a reduction of at least 50% on the HRSD.

Patients were treated twice a week. The first two ECT sessions were not part of the study; they were used to determine the most appropriate doses of etomidate and succinylcholine and these doses were not altered during the remainder of the study. In the subsequent six sessions, patients received a bolus injection of either esmolol 80 mg (10 mg ml^{-1}; 8 ml) or placebo (0.9% NaCl 8 ml) before induction of anaesthesia. This was done in a double-blind manner using a within-patient randomized block design, consisting of three two-treatment blocks. In every block, one treatment session was the experiment and the other the control condition. Thus every patient received esmolol and placebo on three occasions each during these consecutive sessions. Blinded syringes were prepared by the pharmacy after allocation from a random number table.

Esmolol has a wide therapeutic index and short half-life and can be given as a fixed dose rather than by patient weight.[7] ECT was started with unilateral brief pulse, constant current stimulation using the Thymatron DGx. The initial dose of the stimulus was based on the age of the patient.[4] If there was no clinical improvement after four sessions, as measured by the HRSD, bifrontotemporal ECT was substituted. In one patient, ECT was started bilaterally because of the severity of the depression and previous good response to this mode of treatment.

If the depressive symptoms ceased before the end of the six double-blind sessions, only data already obtained were used for analysis. If a partial therapeutic response was obtained after the six study sessions, ECT was continued for as long as was indicated clinically. These sessions were not included in the study.

Differences in haemodynamic variables between the esmolol and placebo sessions were calculated, in addition to a possible carry-over effect, using repeated measures analysis of variance (rmANOVA). All calculations were performed using the Biomedical Computer Programs P-series (BMDP, module 5 V) software package. We analysed the six measurement sessions with respect to time, three of which were placebo and three esmolol treatment. In each session, the outcome variable was measured twice: immediately before and immediately after the stimulus; a baseline measurement of the outcome variable was obtained 1 h before treatment. In the rmANOVA, the explanatory factors were time (six levels) and random (two levels), with the baseline measurement in each session taken as covariate. Statistical significance was defined as $P<0.05$

Results

The number of patients enrolled initially was 22; two patients were excluded, one because of bradycardia and asystole in the first two sessions (without study medication) and the second, a 76-yr-old man, because he failed to convulse during the first two sessions and required theophylline to facilitate seizures.[8]

Of the 20 patients studied, mean age was 52.7 (range 31–86) yr and mean weight was 63.7 (48.4–87.1) kg. Five patients recovered before the end of the study. Eleven patients were changed to bilateral ECT during the study.

At the end of the study, 10 of the participating patients fulfilled the criteria for a good response, showing at least a 50% reduction on the HRDS. This outcome is comparable with other ECT outcome studies in medication-resistant depressed patients.[9 10] There were no significant differences in baseline measures of HR, SAP, DAP or MAP between experimental and control sessions.

Cardiovascular variables, measured before and after the stimulus, were compared with baseline measurements recorded 1 h before treatment (Tables 1–3). Immediately before the stimulus, HR, SAP and MAP values were significantly less after esmolol than after placebo (Table 2).

The increase in HR, SAP and MAP after the stimulus were all significantly less after esmolol (Table 3). The increase in DAP did not differ significantly between the esmolol and placebo groups. No significant carry-over effect was found for any of the measured variables, as was expected because of the short half-life of esmolol.

Doses of etomidate, succinylcholine, alfentanil and glycopyrrolate did not differ significantly over the total course of ECT treatment, as calculated using rmANOVA. This test revealed mean constant doses of etomidate 16.0 mg (chi-square (7)=3.46; P=0.840), succinylcholine 68.1 mg (chi-square (7)=3.46; P=0.840), alfentanil 0.91 mg (chi-square (7)=6.75; P=0.455) and glycopyrrolate 0.33 mg (chi-square (7)=10.58; P=0.158).

There was no significant difference in the age-based dose of the stimulus between the esmolol and placebo sessions (P=0.678). Esmolol significantly reduced seizure duration, as measured using the cuff method and also using the EEG (Table 4). Clinically, seizure duration was 5.83 s (SEM 1.71 s) (P=0.0007) shorter after esmolol. Seizure duration, as measured by the EEG, was reduced significantly by 9.9 s (SEM 3.20 s) (P=0.002) after esmolol compared with placebo. To obtain an impression of mean seizure duration, we calculated the mean in all patients of a within-patient average of the greatest three measurements (Table 4). These calculated averages gave a good impression of the mean; correct estimates of mean differences can be obtained only from MANOVA.

There were no adverse events that could be attributed to esmolol.

Discussion

We have assessed the effects of a single i.v. dose of esmolol 80 mg before anaesthesia on cardiovascular response and seizure duration during ECT. Using a double-blind, placebo-controlled, randomized block design and standard anaesthetic and ECT procedures, we attempted to overcome the methodological flaws of earlier studies in the field. In our study, anaesthesia was not changed after the first two sessions; concomitant medication remained unchanged for every patient during the study. In other studies, the ECT procedure (dose and stimulus characteristics) were not specified.[11–13] We used an age-based method to determine the initial stimulus and adjusted the dose according to seizure duration. Kovac and colleagues used a single dose for all patients, but did not report the dose.[14] In general, fixed high-dose ECT is recommended only for unilateral ECT. For bilateral ECT, the dose should be 1.5 times threshold. The Thymatron DGx is designed to deliver a stimulus dose that is approximately 2.5 times the seizure threshold with unilateral electrode placement when using the age-based dose method.[15]

Our patients were comparable in age and weight to those in other studies.[11–14] The response of a 50% remission rate would be expected in medication-resistant patients with a major depression.[10]

Esmolol significantly reduced pre-stimulus values of HR, SAP and MAP and the increase in HR, SAP and MAP during the convulsion. Attenuation of the cardiovascular response is brought about by two effects: reduction of baseline values of haemodynamic variables and reduction in their increase during the convulsion. However, the

Table 1 Baseline variables recorded 1 h before treatment for experimental and control sessions (mean (SD)). No significant differences

Variable	Control	Experiment
Heart rate (beat min^{-1})	78.8 (11.1)	79.2 (11.5)
Systolic arterial pressure (mm Hg)	113.5 (12.3)	113.0 (12.2)
Diastolic arterial pressure (mm Hg)	72.4 (11.2)	74.5 (11.2)
Mean arterial pressure (mm Hg)	86.0 (11.1)	87.3 (11.0)

Table 4 Mean seizure duration: the mean of all patients of a within-patient average of the three maximum measurements (in s)

	Cuff method	Electroencephalograph
Control	45.6	69.1
Experiment	38.7	55.1

Table 2 Effect of esmolol compared with placebo on variables measured immediately before the stimulus (rmANOVA); control and experimental values are the mean of all patients of each patient's averages of three measurements

Variable	Control	Experiment	Effect	SEM	P
Heart rate (beat min^{-1})	86.8	80.4	–6.6	1.40	<0.001
Systolic arterial pressure (mm Hg)	127.6	123.8	–3.8	1.38	0.005
Diastolic arterial pressure (mm Hg)	78.5	76.4	–1.4	0.97	0.158
Mean arterial pressure (mm Hg)	94.8	92.2	–2.3	1.02	0.025

Table 3 Effect of esmolol compared with placebo on variables measured immediately after the stimulus (rmANOVA); control and experimental values are the mean of all patients of each patient's averages of three measurements

Variable	Control	Experiment	Effect	SEM	P
Heart rate (beat min^{-1})	98.4	86.3	–9.0	1.35	<0.001
Systolic arterial pressure (mm Hg)	157.6	142.9	–9.4	1.36	<0.001
Diastolic arterial pressure (mm Hg)	93.8	88.8	–1.7	1.27	0.148
Mean arterial pressure (mm Hg)	115.1	106.8	–3.1	1.03	0.002

reduction in the increase in the cardiovascular variables during the convulsion was less than reported in other studies. These studies all used higher esmolol doses, so it is likely that the effect on the haemodynamic variables was dose-dependent. This supports the findings of the study of Kovac and colleagues, who compared the effects of two esmolol bolus doses.[14] Attenuation of the haemodynamic response during ECT can be used to protect patients at risk of cardiovascular complications.

Unfortunately, in addition to attenuating the haemodynamic response, esmolol also significantly reduced seizure duration, confirming findings from earlier studies with esmolol.[13] It is not clear if this effect was dose-related. The study by Kovac and colleagues is the only one that compared two bolus doses of esmolol; both 100 and 200 mg bolus doses significantly reduced seizure duration, but the extent was not significantly different between doses.[14]

Seizure duration is one of the variables used to assess the adequacy of convulsions, and reduction in seizure duration may interfere with therapeutic efficacy. Seizure duration, as measured using the cuff method, should be at least 25 s.[4] However, the relation between therapeutic efficacy and seizure characteristics has recently proved to be more complicated than originally thought. In unilateral ECT, electrical doses far higher than seizure threshold were thought to determine efficacy.[15] With bilateral electrode placement, seizure duration is related to efficacy. High electrical dose related to seizure threshold with bilateral placement caused more severe cognitive side effects.[15] Generally, it has become clear that neurophysiological characteristics other than seizure duration are important for seizure quality, such as amplitude, symmetry, coherence and postictal suppression. It is not known as yet how esmolol influences these characteristics and further research is warranted.

In summary, an i.v. bolus dose of esmolol 80 mg, administered immediately before anaesthesia, reduced significantly pre-stimulus HR, SAP and MAP and the increase in HR, SAP and MAP during the convulsion. However, esmolol also significantly reduced seizure duration. While esmolol can be useful in attenuating the haemodynamic response in patients at risk of cardiovascular complications, its effect in reducing seizure duration may interfere with the efficacy of ECT. For this reason its use as a routine prophylactic measure is not advised.

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