Comparison of two esmolol bolus doses on the haemodynamic response and seizure duration during electroconvulsive therapy

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Twelve ASA physical status I–III patients were enrolled in a double-blind, prospective, randomized, three-way, within-patient crossover study designed to determine the effect of two standard esmolol bolus doses (100 and 200 mg) on the haemodynamic response and seizure duration during electroconvulsive therapy (ECT). Esmolol or placebo was administered one minute prior to induction of anaesthesia and exactly two minutes before ECT. Both the 100 and 200 mg bolus doses significantly blunted the maximum increase in heart rate (HR) and mean arterial pressure (MAP) following ECT in comparison with placebo. Compared with placebo, esmolol 100 mg decreased maximum HR by $23 \pm 3\%$, maximum MAP by $17 \pm 7\%$ and maximum rate-pressure product (RPP) by $40 \pm 9\%$. Esmolol 200 mg decreased maximum HR by $25 \pm 3\%$, maximum MAP by $19 \pm 3\%$ and maximum RPP by $42 \pm 5\%$. No significant difference was found between the two esmolol doses at corresponding measurement points before and after ECT. Treatment

with esmolol 200 mg resulted in a significantly shorter mean seizure duration than with placebo. As the 200 mg dose caused a shorter seizure duration and the haemodynamic effects of 100 mg and 200 mg doses were similar, it was concluded that the 100 mg esmolol bolus dose was the better dose for ECT.

Douze patients de classe ASA I–III ont participé à trois séances variées de notre étude randomisée à double insu sur l'effet de deux doses d'esmolol en bolus (100 et 200 mg) sur les variables hémodynamiques et la durée des convulsions associées aux électrochocs (EC). On leur injectait l'esmolol ou un placebo une minute avant l'induction de l'anesthésie puis deux minutes avant l'EC. Comparativement au placebo, les deux doses d'esmolol émoussaient significativement les augmentations maximales de la fréquence cardiaque, de la tension artérielle et du produit pouls-pression, les réduisant respectivement de $23 \pm 3\%$, $17 \pm 7\%$ et $40 \pm 9\%$ pour la dose de 100 mg et de $25 \pm 3\%$, $19 \pm 3\%$ et $42 \pm 5\%$ pour celle de 200 mg. Avant et après l'EC, les valeurs hémodynamiques associées aux deux doses d'esmolol étaient comparables. Toutefois, avec la dose de 200 mg, les convulsions duraient significativement moins longtemps qu'avec le placebo. Dans un contexte d'EC, une dose de 100 mg d'esmolol est donc préférable.

Key words

ANAESTHESIA: electroconvulsive therapy, brain, seizure duration;

COMPLICATIONS: hypertension, tachycardia;

SYMPATHETIC NERVOUS SYSTEM: beta-adrenergic antagonists, esmolol.

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Presented in part at the 1989 Annual Meeting of the American Society of Anesthesiologists in New Orleans, Louisiana.

Supported by a grant from Dupont Pharmaceuticals.

Electroconvulsive therapy (ECT) may produce intense stimulation of the central nervous system resulting in hypertension and tachycardia.^{1,2} The haemodynamic effects of ECT could place the patient with coronary or cerebrovascular disease at risk of myocardial ischaemia/infarction or stroke.^{3–5} Esmolol hydrochloride (Brevibloc) is a new ultra-short acting beta₁ selective adrenergic blocking agent. Esmolol bolus⁶ and infusion⁷ have been found to be effective in attenuating the cardiovascular response to ECT. However, comparison of the effects of different standardized bolus doses and their effect on the

TABLE I Exclusion criteria

Pregnant women
Less than 21 yr
AV conduction block greater than 1°
Systolic BP < 100 mmHg or diastolic BP < 50 mmHg
Heart rate < 50 bpm
Bronchospasm or bronchial asthma
Drug allergy or idiosyncrasy to beta-adrenergic drugs
Experimental drugs within two weeks
Patients on beta blockers or calcium channel blockers

(i) compare the effect of two standardized esmolol bolus doses (100 and 200 mg) on heart rate (HR) and blood pressure (BP), and (ii) investigate the effect of these doses on seizure duration during ECT.

Methods

This study was approved by the Human Subjects Committee of our institution and written informed consent was obtained from each patient. The study patients were ASA physical status I, II, or III and selected from those receiving general anaesthesia for ECT. Exclusion criteria are listed in Table I.

All patients received premedication with glycopyrrolate 0.3 mg im 30–60 min before ECT. The HR was monitored by ECG, BP by manual cuff, oxygen saturation by pulse oximeter, carbon dioxide by end-tidal CO₂ monitor, and seizure duration by EEG. Recording times for HR and BP did not occur during the actual seizure period. All patients received esmolol 100 mg, 200 mg, and placebo (normal saline) in a prospective, randomized, double-blind, three-way, within-patient, crossover design. Thus, each patient served as his or her own control.

Esmolol (or placebo) was administered at time zero by hand-held bolus over 15 sec, one minute before induction of anaesthesia and exactly two minutes before ECT. Anaesthesia was induced with methohexitone 1.0 mg · kg⁻¹ and succinylcholine 0.75 mg · kg⁻¹. The HR and BP were recorded pre-bolus and every minute for ten minutes post-bolus, then at 12, 15, 20, 25 and 40 min following bolus injection. Three to five days later the patients crossed over to the alternative treatment and repeated the procedures outlined above.

A monitored electroconvulsive therapy apparatus (MECTA) machine was used to administer the electrical shock current charge. All ECT shocks were unilateral. All patients received the same electrical shock current for each ECT and received only one shock per treatment (70 Hz, with 1.5 msec pulse width and 2.0 sec duration).

Statistical analysis

Data were evaluated as per cent change from pre-bolus baseline values. All statistical analyses were performed

TABLE II Number of patients receiving concomitant medications

Medications	Number of patients
Levothyroxine	3
Thioridazine	3
Ibuprofen	3
Nortriptyline	3
Desipramine	2
Trihexylphenidyl	2
Triamterene	2
Haloperidol	1
Protriptyline	1
Alprazolam	1
Fluoxetine	1
Trazodone	1
Dipyridamole	1
Amitriptyline	1
Imipramine	1

using the statistical analysis system.⁸ Analysis of variance (in a crossover model) was used to analyze HR, BP, rate-pressure product (RPP) and seizure duration at the successive measurement times. T tests, using the pooled mean square error from the variation among patients within the three treatment groups, were used to determine the relation among the treatments. A *P* < 0.05 level was set for statistical significance.

Results

Of the 12 patients studied, the mean ($\pm$ SD) age was 52 $\pm$ 19 yr (range 23–78) and mean weight was 70 $\pm$ 13 kg (range 54–95). As this was a within-patient comparison, 12 patients were in each study group. Concomitant patient medications are listed in Table II. Medications and/or dosages did not change during the treatment periods. Both the esmolol 100 mg and 200 mg bolus doses were found to blunt significantly the increase in HR (Figure 1), mean arterial pressure (MAP) (Figure 2), and RPP (Figure 3) following ECT in comparison to placebo. HR, MAP, and RPP declined after both esmolol bolus administrations and increased after ECT. Treatment with both esmolol bolus doses resulted in significantly lower maximum per cent changes in HR, MAP, and RPP. There was a significant difference in HR between the 100 mg esmolol dose and placebo for up to four minutes post-ECT and up to 18 min post-ECT for the 200 mg dose (Figure 1). HR baseline control values (mean $\pm$ SEM) for placebo, 100 mg, and 200 mg esmolol doses were 85 $\pm$ 5, 87 $\pm$ 7, and 89 $\pm$ 5 bpm respectively. There was a significant difference in MAP between the 100 mg esmolol dose and placebo for up to two minutes post-ECT and up to four minutes post-ECT for the 200 mg dose (Figure 2). MAP baseline control values for placebo, 100 mg, and 200 mg esmolol doses were 98 $\pm$ 3, 96 $\pm$ 4, and 105 $\pm$ 4 mmHg

FIGURE 1 Heart rate per cent change (mean $\pm$ SEM).

respectively. There was a significant difference in RPP between the 100 mg esmolol dose and placebo for up to four minutes post-ECT and up to 13 minutes post-ECT for the 200 mg dose (Figure 3). RPP baseline control values for placebo, 100 mg, and 200 mg esmolol doses were $11,000 \pm 600$, $10,900 \pm 700$, and $12,700 \pm 800$ respectively. Esmolol bolus had a more significant effect on HR than on MAP. There were no significant differences between the two doses with respect to HR, MAP, RPP or seizure duration. However, seizure duration was significantly shorter with 200 mg of esmolol compared with placebo (Table III). No arrhythmias or adverse experiences occurred.

Discussion

Electroconvulsive therapy is an important modality in the treatment of depression, especially in patients resistant to pharmacological therapy. Electroconvulsive therapy accounts for approximately 4% of psychiatric admissions in the United States^{1,9} with about 100,000 treatments administered annually.^{5,10}

A hyperdynamic cardiovascular response occurs as a result of autonomic nervous system stimulation. Parasympathetic discharge occurs immediately with sympa-

thetic discharge following within seconds. Hypertension, tachycardia, and an increase in cardiac output often occur.^{1,2} Although rare, cardiovascular complications are the main cause of death during ECT with a mortality rate of 0.03% of patients treated, and 0.0045% of individual ECT treatments.^{2,5,11} This is higher than the often quoted overall anaesthetic mortality of 1:10,000.¹² Morbidity and mortality during ECT is usually secondary to myocardial ischaemia/infarction or stroke.²⁻⁵ Patients who are elderly, have chronic hypertension, or pre-existing cardiac disease are especially at risk for an adverse event occurring in the peri-ECT period.^{3,4}

Similar to techniques used for tracheal intubation, many pharmacological methods have been used in at-

TABLE III Seizure duration ($n = 12$)

	Seconds $\pm$ SEM
Placebo	52.75 $\pm$ 4.61
Esmolol 100 mg	44.58 $\pm$ 4.61
Esmolol 200 mg	40.00 $\pm$ 3.09*

* $P < 0.05$ significant difference between placebo and indicated esmolol bolus dose.

FIGURE 2 Mean arterial pressure per cent change (mean $\pm$ SEM).

tempting to blunt the haemodynamic effects of ECT. These include oral clonidine,¹³ intranasal nifedipine,¹⁴ nitroglycerin ointment,¹⁵ iv sodium nitroprusside,¹³ methohexitone,¹⁶ thiopentone, and propofol,¹⁶ trimethaphan,¹⁷ propranolol,^{18,19} hydralazine,¹⁹ labetalol,²⁰ and diazoxide.²¹ Both continuous infusion and bolus techniques have been used. Although numerous techniques are available, many have side-effects with durations of action longer than the short ECT stimulus itself.

The ideal agent and/or technique for attenuating the hyperdynamic response of ECT would be convenient, easy to prepare and administer, rapid-acting, brief, non-toxic, and have minimal or no side-effects. Ideally, duration of action should correspond to the period of time the drug and/or technique is needed.

Esmolol hydrochloride is an ultrashort-acting, beta-one selective blocker with a distribution half-life of two minutes and an elimination half-life of nine minutes.²² Esmolol appears quite suitable for use during a short-lived stress such as tracheal intubation or ECT. Administration of esmolol by bolus and infusion has been found to be effective in blunting the haemodynamic effects of laryngoscopy and intubation²³ as well as intra-operative²⁴ and postoperative²⁵ stresses.

Previous dosing regimens of esmolol have been confusing and complex. Esmolol originally required dilution of a 2.5 g, 10 ml ampule (250 mg $\cdot$ ml⁻¹ in 250 ml of D5W to obtain a 10 mg $\cdot$ ml⁻¹ solution). The manufacturer developed a 100 mg vial (10 mg $\cdot$ ml⁻¹) for convenience and ease of administration. Our selection of 100 and 200 mg bolus doses was selected on this basis (one and two unit vials respectively). A 100 mg and 200 mg dose in a 70 kg patient corresponds to 1.43 mg $\cdot$ kg⁻¹ and 2.86 mg $\cdot$ kg⁻¹ respectively. Esmolol can effectively be administered as a set dose rather than adjusting for patient weight.²² However, if one desires, a mg $\cdot$ kg⁻¹ dose can also be administered.

Proper bolus timing and dosage in relation to the stimulus is important. The esmolol bolus should be given within two minutes of the expected stimulus²⁶ since a bolus dose given three to four minutes before the stimulus may be too early.²⁷ We administered esmolol one minute before anaesthesia induction and exactly two minutes before ECT shock. In our experience, esmolol can also be administered immediately after methohexitone and succinylcholine within two minutes before ECT shock and be equally effective.

Comparisons between this bolus study and our previous

FIGURE 3 Rate-pressure product per cent change (mean $\pm$ SEM).

infusion study⁷ can be made. In the esmolol infusion study, HR remained below baseline for the entire study. Also, mean MAP increased to 20% above baseline compared with 43% in the "no esmolol" group. In this bolus study (Figures 1 and 2), HR remained below baseline for one and four minutes post-ECT for the 100 mg and 200 mg esmolol bolus doses respectively. The mean MAP increased to a maximum of 30% and 23% above baseline for the 100 mg and 200 mg doses respectively compared with a maximum 54% increase above baseline for placebo. The increase in MAP was similar for both the bolus and infusion methods.

As seen in Figures 1 and 2, esmolol's effect is primarily on HR (negative chronotropic effect) and secondarily on BP. This effect was also seen in the esmolol infusion study. The decrease in cardiac output and thus BP is likely secondary not only to decreases in HR but also from decreases in stroke volume secondary to a negative inotropic effect.⁷ The RPP paralleled the course of HR and MAP (Figure 3). While esmolol bolus is more convenient and easier to administer than the infusion method, a more brief control of HR also occurs. Repeat bolus doses may be required post-ECT if further control of

HR and BP is desired. Esmolol infusion produces better HR and BP control for a longer time than bolus administration.

The therapeutic effect of ECT depends on a cerebral seizure. There appears to be a dose-response concept to the therapeutic efficacy of ECT with an optimal therapeutic outcome occurring if the seizure lasts approximately 30 sec or longer.²⁸ Seizure duration during ECT is influenced by the age and sex of the patient, electrode placement, type of electrical stimulus producing the seizure, blood gas tensions (PO_2 and CO_2), number of treatments already completed, and choice and dose of induction agent.²⁹ A within-patient crossover design was chosen to eliminate these variables. An end-tidal CO_2 monitor was used to keep CO_2 approximately 28–30 mmHg and a pulse oximeter was used to keep oxygen saturation 98–100%.

Esmolol bolus appears to have a dose-related effect on seizure duration (Table III). However, it should also be stressed that for both the 100 and 200 mg bolus doses, seizure durations were longer (40 and 45 sec, respectively) than the recommended 30 sec minimum.

In summary, both esmolol 100 mg and 200 mg bolus

doses were found effective in blunting the haemodynamic response during and following ECT in ASA physical status I, II, and III patients. As the 200 mg dose caused a shorter seizure duration and the haemodynamic effects of the 100 and 200 mg doses were similar, the 100 mg esmolol bolus dose was considered to be the better dose for ECT.

References

- 1 Gaines GY, Rees I. Electroconvulsive therapy and anesthetic considerations. *Anesth Analg* 1986; 65: 1345–56.
- 2 Selvin BL. Electroconvulsive therapy – 1987. *Anesthesiology* 1987; 67: 367–85.
- 3 Gerring J, Shields H. The identification and management of patients with a high risk for cardiac arrhythmias during modified ECT. *J Clin Psychiatry* 1982; 43: 140–3.
- 4 Alexopoulos GS, Shamoian CJ, Lucas J, Weiser N, Berger H. Medical problems of geriatric psychiatric patients and younger controls during electroconvulsive therapy. *J Am Geriatr Soc* 1984; 32: 651–4.
- 5 Knos GB, Sung YF, Cooper RC, Stoudemire A. Electroconvulsive therapy induced hemodynamic changes unmask unsuspected coronary artery disease. *Journal of Clinical Anesthesia* 1990; 2: 37–41.
- 6 Klein M, Martin O, Soloff P, Dealy RS, Ghignone M. Comparison of the effect of nitroglycerin and esmolol on the cardiovascular response to ECT. *Anesthesiology* 1988; 69: A41.
- 7 Kovac AL, Goto H, Arakawa K, Pardo MP. Esmolol bolus and infusion attenuates increases in blood pressure and heart rate during electroconvulsive therapy. *Can J Anaesth* 1990; 37: 58–62.
- 8 SAS Institute Inc. SAS users' guide: statistics, 1982 edition. Cary, NC: SAS Institute Inc, 1982: 113.
- 9 Asnis G, Fink M, Saferstein S. ECT in metropolitan New York hospitals. *Am J Psychiatry* 1978; 135: 479–82.
- 10 Holden C. A guarded endorsement for electroshock therapy. *Science* 1985; 228: 1510–1.
- 11 The Royal College of Psychiatrists' memorandum on the use of electroconvulsive therapy. *Br J Psychiatry* 1977; 131: 261–72.
- 12 Tinker J, Roberts S. Anesthesia risk. In: Miller R (Ed.). *Anesthesia* Vol. 1. 2nd ed. New York: Churchill Livingstone. 1986: 368.
- 13 Liu WS, Petty WC, Jeppsen A, Wade EJ, Pace NL. Attenuation of hemodynamic and hormonal responses to ECT with propranolol, xylocaine, sodium nitroprusside or clonidine. *Anesth Analg* 1984; 63: 244.
- 14 Kalayam B, Alexopoulos GS. Nifedipine in the treatment of blood pressure rise after ECT. *Convulsive Therapy* 1989; 5: 110–3.
- 15 Lee JT, Erbguth PH, Stevens WC, Sack RL. Modification of electroconvulsive therapy induced hypertension with nitroglycerin ointment. *Anesthesiology* 1985; 62: 793–6.
- 16 Rampton AJ, Griffin RM, Stuart CS, Durcan JJ, Huddy NC, Abbott MA. Comparison of methohexital and propofol for electroconvulsive therapy: effects on hemodynamic response and seizure duration. *Anesthesiology* 1989; 70: 412–7.
- 17 Regenstein QR, Lind LJ. Management of electroconvulsive treatment in an elderly woman with severe hypertension and cardiac arrhythmias. *Compr Psychiatry* 1980; 21: 288–91.
- 18 Jones RM, Knight PR. Cardiovascular and hormonal responses to electroconvulsive therapy: modification of an exaggerated response in a hypertensive patient by B-receptor blockade. *Anaesthesia* 1981; 36: 795–9.
- 19 Husum B, Vester-Anderson T, Buchmann G, Bolwig TG. Electroconvulsive therapy and intracranial aneurysm. Prevention of blood pressure elevation in a normotensive patient by hydralazine and propranolol. *Anaesthesia* 1983; 38: 1205–7.
- 20 Knos GB, Sung YF, Stoudemire A, Gladson M, Cooper R, Markwalter H. Use of labetalol to control cardiovascular responses to electroconvulsive therapy. *Anesth Analg* 1990; 70: S210.
- 21 Kraus RP, Remick RA. Diazoxide in the management of severe hypertension after electroconvulsive therapy. *Am J Psychiatry* 1982; 139: 504–5.
- 22 Sintetos AL, Hulse J, Pritchett ELC. Pharmacokinetics and pharmacodynamics of esmolol administered as an intravenous bolus. *Clin Pharmacol Ther* 1987; 41: 112–7.
- 23 Sheppard S, Eagle CJ, Strunin L. A bolus dose of esmolol attenuates tachycardia and hypertension after tracheal intubation. *Can J Anaesth* 1990; 37: 202–5.
- 24 Oxorn D, Knox JWD, Hill J. Bolus doses of esmolol for the prevention of perioperative hypertension and tachycardia. *Can J Anaesth* 1990; 37: 206–9.
- 25 Gibson BE, Oliver SB, Maass L, Cucchiara RF. Esmolol for the control of hypertension following neurologic surgery. *Anesth Analg* 1988; 67: S71.
- 26 Jacque JJ, Gold MI, Grosnoff D, Whirley J, Herrington C. Does single bolus esmolol 2 minutes before intubation prevent tachycardia? *Anesth Analg* 1989; 68: S133.
- 27 Jacque JJ, Grosnoff DB, Whirley J, Gold MI, Herrington CA. Esmolol bolus before anesthetic induction for tachycardia-hypertension. *Anesth Analg* 1989; 68: S134.
- 28 O'Connell RA. A review of the use of electroconvulsive therapy. *Hosp Comm Psychiatry* 1982; 33: 469–73.
- 29 Sackeim H, Decima P, Prohovnik I, Malitz S. Seizure threshold in electroconvulsive therapy. *Arch Gen Psychiatry* 1987; 44: 355–60.