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Clinical Pharmacokinetics and Therapeutic Efficacy of Esmolol

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Abstract

Esmolol is a unique cardioselective β_1-receptor blocking agent with a rapid onset and short duration of action. Since our previous review in 1995, the pharmacokinetics and efficacy of esmolol have been investigated in a number of acute care settings. Three studies investigated the pharmacokinetics and safety of esmolol in the paediatric population. The disposition of esmolol in children was found to be linear with plasma concentrations increasing in proportion to dose over the ranges studied. The pharmacokinetic estimates for esmolol showed a shorter elimination half-life ($t_{1/2}$) [2.7–4.8 minutes] and a higher clearance (281 mL/kg/min) in newborns and infants than that found in children (>2 years old) and adults. Dosing requirements to achieve targeted blood pressure in post-coarctectomy patients were substantially higher (mean 700 μg/kg/min) than that used in adults. Esmolol was effective in controlling hypertension following cardiac surgery and terminating supraventricular arrhythmias in children.

The efficacy of esmolol has been established in a variety of patients, including those with unstable angina, myocardial ischaemia, supraventricular arrhythmias, peri- and postoperative tachycardia and hypertension, and electroconvulsive therapy. With careful titration and monitoring, esmolol can be used effectively in patients with congestive heart failure and chronic obstructive lung disease because of its unique short $t_{1/2}$ and β_1-selectivity. Different dosage schedules have been developed depending on clinical setting and diagnosis. Generally, a loading dose of ≤500 μg/kg/min over 1 minute is administered followed by a continuous infusion of 25–300 μg/kg/min. Hypotension, being the primary adverse effect, can be minimized by careful dosage titration and patient monitoring.

In the perioperative setting involving tracheal intubation and extubation, a number of recent studies have suggested that titration of esmolol to a haemodynamic endpoint can be safe and effective, resulting in a decreased incidence of myocardial ischaemia. The most effective regimen in attenuating the response to heart rate and blood pressure after laryngeal tracheal intubation was a loading dose of 500 μg/kg/min for 4 minutes followed by a continuous infusion of 200–300 μg/kg/min. In cardiac and non-cardiac surgical

patients esmolol has been shown to decrease episodes of myocardial ischaemia and arrhythmias. In the perioperative period for non-cardiac surgery routine use of β-blockers (β-adrenoceptor antagonists) is no longer recommended. However, in patients at high risk for myocardial ischaemia or undergoing high-risk surgery where a β-blocker is indicated, esmolol is the ideal perioperative agent to minimize the risk of hypotension and bradycardia based on its pharmacodynamic and pharmacokinetic characteristics. For postoperative patients in atrial fibrillation, esmolol achieves rapid ventricular rate control. However, for the prevention of postoperative atrial fibrillation esmolol provides no advantage over oral β-blockers. In other situations where emergent β-blockade is required, such as electroconvulsive therapy, esmolol has been shown to effectively control haemodynamic response. After more than 2 decades of use esmolol continues to provide an important therapeutic option in the acute care setting.

1. Introduction

This review summarizes the available literature published since 1995 on the pharmacokinetics, pharmacodynamics and therapeutic applications of esmolol. In our previous review[1] we reported that esmolol was an ultra-short-acting β_1-selective adrenergic blocker (mean elimination half-life [$t_{½}$] = 9 minutes) with rapid onset and offset of effects that provided an element of safety not previously available with longer acting β-blockers (β-adrenoceptor antagonists). When esmolol is administered as a bolus followed by continuous infusion, onset of activity occurs within 2 minutes, with 90% of β-blockade at 5 minutes. Full recovery from β-blockade takes 18–30 minutes after stopping the infusion. Generally, a loading dose of 500 μg/kg/min over 1 minute is administered prior to an esmolol maintenance infusion dose of 50–300 μg/kg/min. Red blood cell esterases metabolize esmolol to an acid metabolite (ASL-8123) and methanol, eliminating the need for dosing adjustments in renal or hepatic dysfunction. Pharmacokinetic interactions of esmolol with other cardiovascular drugs, including digoxin, morphine and warfarin, have been investigated and found not to be clinically significant. The most common adverse effect with esmolol is hypotension. The incidence of hypotension (0–50%) increases with bolus doses of 100 mg (25%) to 200 mg (33%) or continuous infusions exceeding 150 μg/kg/min. Hypotension rarely requires intervention other than decreasing the dose or discontinuing the infusion. Esmolol is ideally suited for emergency rooms, critical care units and surgical settings where rapid control of heart rate (HR) and/or blood pressure (BP) is desirable for brief periods of time.

The literature for this review was identified using PubMed and Ovid MEDLINE searches for articles on esmolol published in humans between 1995 and October 2011 in English language. Additional studies were identified from the cited references of retrieved articles.

2. Pharmacokinetics

As previously described, the pharmacokinetics of esmolol have been reported in healthy volunteers, surgical patients, patients with hepatic and renal failure, and paediatric patients.[1] Since 1995, three studies have been published that provide a better understanding of the pharmacokinetics, efficacy and safety of esmolol in the paediatric population.

In an open-labelled pharmacokinetics and efficacy trial,[2] esmolol was administered to children with postoperative hypertension (>95th percentile for age) after repair of various congenital heart defects. Esmolol was titrated to achieve a BP ≤90th percentile for age or a dose of 1000 μg/kg/min was reached. The final dose was maintained for 30 minutes, to ensure steady-state conditions, and then discontinued. Esmolol arterial blood samples, analysed by high-performance liquid chromatography, were obtained prior to, during and after the infusion for noncompartmental pharmacokinetic analysis. Twenty patients aged 1 month to 12 years (median 25.6 months) were enrolled into the study. Ten patients underwent repair of aortic coarctation. Seven patients had preoperative hypertension (six patients with coarctation). Postoperatively, 17 patients had severe hypertension (>99th percentile for age) and three had significant hypertension (>95th percentile for age). Eighteen patients were receiving sodium nitroprusside (mean dose 3.5 μg/kg/min). Sodium nitroprusside was discontinued and replaced with esmolol in 17 patients and discontinued in the 18th patient when an esmolol dose of 700 μg/kg/min was achieved. The mean esmolol dose required to normalize BP was 700 μg/kg/min. This dose was substantially higher than that used to control hypertension after cardiac operations in adults.[3] The patients with coarctation of the aorta repair required significantly higher esmolol doses than those patients having repair of other congenital heart defects (mean 830 vs 570 μg/kg/min, respectively). The model independent pharmacokinetic parameter

estimates for the 20 patients were (mean ± standard deviation): apparent volume of distribution at steady-state = 0.53 ± 0.33 L/kg; apparent total body clearance = 126 ± 37 mL/kg/min; and terminal elimination half-life ($t_{½\beta}$) = 2.7 ± 1.3 minutes. On administration of the final esmolol dose there was a significant percentage decrease in HR and systolic and diastolic BP from postoperative values. A significant association was found between esmolol dose and esmolol blood concentration at steady-state, as well as percentage reduction in systolic BP. Total body clearance was significantly higher in patients that had coarctation repair than patients having repair of other congenital heart defects. The higher doses required in patients with coarctation repair may be related to increased adrenergic load (e.g. norepinephrine [noradrenaline] concentrations), increased total body clearance, or both. This preliminary investigation in the paediatric cardiac intensive care unit (ICU) showed that esmolol was easily titratable and effective for the management of postoperative hypertension following cardiac surgery in children.[2]

In a larger, multicentre, double-blind, randomized, dose-ranging study,[4] esmolol was investigated to control postoperative hypertension in 116 children (newborn to 6 years of age) who underwent surgical repair of coarctation of the aorta. Subjects were randomly assigned to three esmolol dosing schemes: (i) 36 children received low-dose esmolol (125 μg/kg bolus followed by 125 μg/kg/min infusion); (ii) 43 received medium-dose esmolol (250 μg/kg bolus followed by 250 μg/kg/min infusion); and (iii) 37 received high-dose esmolol (500 μg/kg bolus followed by 500 μg/kg/min infusion) for 15 minutes to assess efficacy and for pharmacokinetic sampling. Esmolol arterial blood samples were obtained before dosing and at 5, 10 and 15 minutes after the loading dose. Noncompartmental pharmacokinetic analyses were performed using data from the population as a result of sparse sampling. Esmolol blood concentrations appeared to increase in relation to the dose. The 15-minute arterial plasma concentration was significantly higher in children than in newborns. The $t_{½}$ reported for the population was 4.8 minutes. Steady-state esmolol blood concentrations were achieved 20 minutes after the bolus was administered. Esmolol clearance for newborns and infants was higher than children (281 mL/kg/min [95% CI 267, 296] vs 126 mL/kg/min [95% CI 83, 169]). A correlation between age and clearance could not be performed because of the high degree of interpatient variability. All dose groups showed a statistically significant decrease in systolic BP from baseline ($p < 0.001$). A statistically significant difference ($p = 0.007$) was found in mean HR from baseline to 5 minutes post-esmolol administration for the per-protocol efficacy analyses but not for the intent-to-treat analyses ($p = 0.06$). No statistical difference was found between dose groups in systolic BP, diastolic BP or mean arterial pressure at 5 minutes after esmolol administration compared with baseline. However, the limited esmolol blood sampling strategy for pharmacokinetic and dynamic modelling along with the primary measures of efficacy taken at 5 minutes likely led to a premature (i.e. steady-state plasma drug concentration during constant-rate infusion = 20 minutes) estimate of esmolol's ability to decrease BP and whether a dose-response relationship was present. This study, as well as the previous study, demonstrated that esmolol can safely and effectively be administered to patients younger than 6 years old after repair of coarctation of the aorta and other congenital heart defects.[2,4]

A third study[5] evaluated the pharmacokinetics of esmolol in children with a history of supraventricular tachycardia (SVT) who were scheduled for diagnostic electrophysiology study or catheter ablation. In the electrophysiology laboratory, following baseline assessment, programmed stimulation was used to induce SVT. Immediately after SVT was initiated esmolol was administered as a loading dose of 1 mg/kg followed by a continuous infusion of 300 μg/kg/min for 15 minutes. Arterial blood samples were collected prior to esmolol, at 5, 10 and 15 minutes after the loading dose and at 3, 6, 9, 12, 15 and 20 minutes after the infusion was completed. In addition, a single venous sample was collected distant from the infusion site at the same time the 10-minute arterial sample was collected. Twenty-seven patients were enrolled and stratified by age. Fourteen patients were in the 2–11 years of age group and 13 patients in the 12–16 years of age group. Esmolol terminated SVT in 17 (63%) subjects. In the patients successfully converting from SVT to normal sinus rhythm (NSR), the mean time to conversion was 2 minutes from the start of the infusion (range: 0–5 minutes). There was no significant difference from baseline in mean systolic or diastolic BP at any timepoint. Pharmacokinetic data were available for 25 of the 27 subjects. A significant difference was found between the concurrent esmolol arterial and venous sample drawn at 10 minutes into the infusion. Median arterial esmolol concentrations were approximately 5 times higher than the simultaneous venous sample (2276 vs 424 ng/mL). All pharmacokinetic analyses were performed on arterial esmolol concentrations. Model-independent and -dependent approaches were used to analyse the data. Model-independent parameter estimates reported were a mean $t_{½}$ of 7.8 minutes and total body clearance of 130 mL/kg/min, which are similar to adult pharmacokinetic parameter estimates.[6] As documented in previous studies,[6,7] specifying the sampling site for esmolol blood concentrations is critical.[5]

Jacobs et al.[7] reported that arterial samples were 6.9 times greater than simultaneous venous samples in patients undergoing hypothermic cardiopulmonary bypass (CPB). The explanations for this finding were hypothetical but felt to be related to temperature-dependent esterase activity and insufficient time for equilibrium to be achieved between arterial and venous blood supply.

3. Perioperative Use

Esmolol has US FDA-approved indications for short-term ventricular rate control in patients with SVT and in patients with noncompensatory sinus tachycardia where rapid HR requires intervention. Esmolol is also approved for the management of intraoperative and postoperative tachycardia and/or hypertension that occur during anaesthesia induction, tracheal intubation, during surgery, upon emergence from anaesthesia and in the postoperative period.[8] With careful titration and monitoring, esmolol can be used effectively in patients with congestive heart failure and chronic obstructive lung disease because of its unique short $t_{½}$ and β_1-selectivity.

Laryngoscopy, tracheal intubation (LTI) and extubation induce marked increases in HR and BP, which increase myocardial oxygen demand. Usually these haemodynamic changes are transient and without consequences. However, in susceptible patients with pre-existing cardiac disease, an increase in these parameters can lead to myocardial ischaemia, arrhythmias and infarction.[9,10] A number of studies have suggested that titration of esmolol to a haemodynamic endpoint can be safe and effective, resulting in a decreased incidence of myocardial ischaemia.[11] In a meta-analysis of 38 randomized controlled trials containing 2009 patients, esmolol was found effective, in a dose-dependent manner, in attenuating the adrenergic response to LTI.[12] Eleven different dosing regimens of esmolol demonstrated effectiveness in attenuating the response of HR and BP after LTI. The most effective regimen was a loading dose of 500 μg/kg/min for 4 minutes followed by continuous infusion of 200–300 μg/kg/min.[12] A study in ASA (American Society of Anesthesiologists) class I or II patients undergoing noncardiac elective surgery considered the efficacy of esmolol, fentanyl or lidocaine in attenuating increases in BP and HR during LTI. Esmolol (2 mg/kg) was effective in controlling both the BP and HR responses, unlike low-dose fentanyl (3 μg/kg), which controlled increases in BP but had no effect on HR, and lidocaine (2 mg/kg), which had little effect on either cardiovascular response.[13]

Patients with pre-existing hypertension, even if controlled, have an exaggerated increase in BP during LTI. In these hypertensive patients, at risk for myocardial ischaemia or stroke, many practitioners consider some form of additional treatment to oppose the associated increase in BP or HR. Nicardipine, an intravenous dihydropyridine calcium channel antagonist, was used in conjunction with esmolol, testing the premise that concomitant use, in a reduced dosage, would be more effective than either alone to counter the increased BP and HR after LTI.[14] In this study, neither esmolol (1 mg/kg) alone or combined (0.5 mg/kg) with nicardipine (15 μg/kg) was effective in blunting the peak increase in HR after LTI. However, the combination of esmolol (0.5 mg/kg) and nicardipine (15 μg/kg) was effective in controlling the peak BP after LTI. The authors speculate that the esmolol dose may have been too low.[14] In a similar study,[15] esmolol (1.5 mg/kg) was compared with nicardipine (30 μg/kg) in controlling HR and BP responses to anaesthesia emergence and tracheal extubation. Esmolol was more effective than nicardipine at attenuating HR response but less effective at controlling the BP response to extubation.

The ideal dose of esmolol for LTI remains unclear. This is likely due to a variety of factors including suboptimal dosing, pharmacodynamic variability, underlying co-morbidities, and level of adrenergic tone at time of study (e.g. pain, anxiety, difficult intubation, etc.). There is some evidence that perioperative esmolol may attenuate the bispectral index response and reduce intraoperative anaesthetic requirements and postoperative opioid pain relief (reviewed by Garnock-Jones[16]).

3.1 Cardiac Surgery

Esmolol utilization during cardiac surgery has increased in the last 20 years to protect the myocardium against ischaemia and reperfusion injury, control perioperative haemodynamic variability and prevent postoperative atrial fibrillation (AF). Hyperkalaemia-based cardioplegia solutions have been the gold standard since the mid-1970s to temporarily provide a flaccid, bloodless heart for complicated surgeries and protect against ischaemia-reperfusion injury. However, myocardial contracture and cell death still occur during this depolarized arrest, possibly resulting in reversible and/or irreversible ischaemic myocardial damage.[17-21]

Esmolol has been used as an alternative to hyperkalaemic cardioplegia in experimental[22] and clinical studies[21,23-26] because of its ability to produce a polarized arrest and provide myocardial protective effects against ischaemia-reperfusion injury, while also being rapidly hydrolyzed by erythrocyte esterases.[17-19,25] Continuous perfusion of the coronary arteries with oxygenated, normothermic, esmolol-enriched blood has been compared with conventional, cold blood cardioplegia in

routine patients undergoing coronary artery bypass grafting (CABG). Esmolol-induced hypocontractile bradycardia provided slightly better left ventricular functional recovery and less structural damage in the immediate postoperative period,[21,23] with equivocal or significantly better longer-term patient outcomes (catecholamine and mechanical support requirement, ICU stay, ventilation time and hospital mortality).[21,26] Esmolol cardioplegia has shown similar outcomes in high-risk adult and paediatric patients undergoing cardiac surgery[24,25,27-29] and in patients undergoing variations of beating-heart surgery.[27,30-32] Intermittent boluses of esmolol without cross-clamping the aorta have also been effective for procedures requiring fairly short diastolic cardioplegia.[19] Although esmolol-induced polarized arrest is unlikely to replace traditional hyperkalaemic cardioplegia, it remains a viable alternative for myocardial protection.

Coronary artery disease increases patient susceptibility to perioperative myocardial ischaemia, yet current American College of Cardiology/American Heart Association (AHA) guidelines for CABG surgery[33] state that ''there is no 'ideal' or universally applicable myocardial protection technique'' to reduce perioperative myocardial dysfunction. There is a paucity of clinical data regarding the efficacy of esmolol to improve myocardial salvage in patients undergoing CPB with acute myocardial ischaemia-reperfusion injury. Additionally, the available studies are limited by small sample sizes. Animal studies in this urgent setting of evolving ischaemia have shown that esmolol improves myocardial function and reduces infarct size.[22,34]

Postoperative silent myocardial ischaemia has been shown to be temporally related to tracheal extubation in up to 27% of patients post-CABG surgery.[35] In a randomized controlled trial,[36] continuous esmolol infusion was investigated to determine its influence on the incidence of myocardial ischaemia during tracheal extubation after coronary surgery. Significant myocardial ischaemia was defined as reversible ST-segment depression ≥2 mm or elevation ≥3 mm relative to the baseline taken at 60 msec after the J point and lasting for at least 1 minute in lead V_2, V_5 or aVF. In the ICU, a sliding scale esmolol infusion was titrated to maintain HR in the range of 55–75 beats per minute (bpm) prior to and post-extubation. Patients in the esmolol group had a lower incidence of myocardial ischaemia than the control group (3/31 vs 12/37). The mean esmolol infusion rate was 155 μg/kg/min. Three patients in the esmolol group had hypotension requiring discontinuation of esmolol.[36]

Esmolol was prospectively studied in 30 patients undergoing elective CABG.[37] Patients with a HR >90 bpm and systolic BP >130 mmHg without inotropic support were randomly assigned to esmolol or control (normal saline). Esmolol was administered as a 500 μg/kg bolus followed by an infusion titrated up to 100 μg/kg/min. Esmolol significantly decreased systolic BP, HR and cardiac index at 5 minutes and throughout the study period with maximal HR and BP reduction occurring at 45 minutes.[37]

A recent meta-analysis of 20 randomized trials (778 patients) was conducted to evaluate the clinical effects of esmolol in cardiac surgery.[38] The following outcomes were seen for patients receiving esmolol compared with various control groups: (i) significantly fewer episodes of myocardial ischaemia (12.2% vs 25.7%, odds ratio [OR] = 0.42 [95% CI 0.23, 0.79]; p = 0.007); (ii) a trend toward significantly fewer arrhythmias after CPB (23.1% vs 35.9%, OR = 0.42 [95% CI 0.18, 1.01]; p = 0.05); (iii) significantly more episodes of bradycardia (14.7% vs 2.3%, OR = 5.49 [95% CI 2.21, 13.62]; p = 0.0002); and (iv) an increased incidence of hypotension (24.8% vs 11.8%, OR = 2.73 [95% CI 0.83, 9.04]; p = 0.10). However, there was no difference in the reduction of perioperative inotropic drugs between the two groups (18.9% vs 32.8%, OR = 0.43 [95% CI 0.16, 1.1]; p = 0.08) or in mortality (1.29% vs 1.36%, OR = 0.97 [95% CI 0.14, 6.87]; p = 0.97). The major limitations of the meta-analysis include the diverse methods of esmolol administration, subsequent variations in the comparison control group and the limited reporting of clinically relevant outcomes by the included studies.[38]

Acute postoperative hypertension occurs frequently and may lead to significant neurological, cardiovascular or surgical site complications if left untreated. Postoperative hypertension often begins 10–20 minutes after surgery and may continue for up to 4 hours or longer. Patients chronically taking β-blockers will be particularly sensitive to the postoperative adrenergic state as they have an up-regulated number of β-receptors. An increased HR (110–130 bpm) is commonly tolerated in the early postoperative period as myocardial contractility usually deteriorates in the first 4–6 hours after surgery and then improves to at least the preoperative baseline within 24 hours.[39] However, in order to reduce postoperative myocardial dysfunction, particularly in cases of severe tachycardia and/or hypertension, cautious esmolol dosing appears appropriate and allows for rapid titration to effect.

3.2 Non-Cardiac Surgery

β-Blockers have also been shown to reduce perioperative acute myocardial ischaemia, myocardial infarction and cardiovascular death in noncardiac surgeries. In patients undergoing major abdominal vascular surgery, esmolol was prospectively studied in 40 randomized patients for intraoperative HR control

to determine its effects on myocardial ischaemia.[40] Esmolol was started at 50 μg/kg/min at induction of anaesthesia and titrated by 25 μg/kg/min increments every 5 minutes to achieve a goal HR of <80 bpm (group 80) or <110 bpm (group 110) for 48 hours thereafter. Median infusion rates were 100 (range 0–400) and 12.5 (range 0–200) μg/kg/min for groups 80 and 110, respectively. Esmolol achieved adequate intraoperative HR control and produced similar ischaemia patterns between groups. However, 98% of the perioperative ischaemia occurred during the postoperative period, which was when esmolol was less effective at controlling HR.[40]

Raby et al.[41] randomized high-risk patients with preoperative myocardial ischaemia, as detected by Holter monitoring, and undergoing elective vascular surgery to receive esmolol or placebo. The minimal HR at which ST-segment depression occurred was identified as the ischaemic threshold. The goal for β-blockade was to reduce the postoperative HR to 20% below the ischaemic threshold but above 60 bpm. Esmolol dosing was started as a continuous infusion (i.e. without a bolus dose) at 100 μg/kg/min beginning immediately after surgery and titrated hourly to the targeted HR or maximum dose of 300 μg/kg/min for 48 hours postoperatively. No ischaemic episodes occurred in patients on esmolol whose HR remained below the ischaemic threshold.[41]

Similar observations were made by Urban et al.,[42] who investigated the effect of esmolol in 107 patients undergoing elective total knee arthroplasty with epidural anaesthesia and postoperative epidural analgesia. Patients were randomized to receive either β-blockers or control postoperatively. None of the patients received β-blockers pre- or intraoperatively. Esmolol was initiated at 250 mg/h (mean 49.6 μg/kg/min; mean weight 84 ± 25 kg for β-blocker group) within 1 hour after surgery and titrated to maintain HR <80 bpm. Esmolol was shown to significantly reduce perioperative ischaemia on Holter monitoring.[42]

A recent meta-analysis of 67 randomized controlled trials in 3766 patients undergoing noncardiac surgery found that esmolol was associated with a dose-related increase in unplanned hypotension.[11] Hypotension was more common in patients given bolus doses (e.g. >500 μg/kg) of esmolol than in patients given esmolol infusions. In seven of the studies esmolol decreased the frequency of myocardial ischaemia. This meta-analysis documented that titration of esmolol to targeted reductions in both HR and BP can be achieved with a decreased incidence of myocardial ischaemia.[11]

In light of conflicting data from two large clinical trials,[43,44] the most recent American College of Cardiology Foundation/AHA guidelines on perioperative care for noncardiac surgeries recommend continuing β-blockers in patients already taking them and considering them for patients at high risk who are undergoing intermediate- or high-risk surgery. However, routine perioperative β-blockade is no longer advocated as patient-specific risks and benefits should be considered.[45] In high-risk patients undergoing elective, noncardiac surgery, β-blockers should be started days to weeks before surgery and titrated to adequate HR control to optimize the likelihood of perioperative benefit. Due to the dynamic clinical condition, variable sympathetic tone and pharmacodynamic response of the perioperative patient, the short $t_{1/2}$ and duration of action of esmolol appear ideal for the perioperative titration to achieve adequate HR control and maximize the benefits of β-blockade while minimizing the deleterious effects of hypotension and bradycardia. Once the postoperative patient stabilizes, esmolol may be transitioned to a suitable oral agent.

3.3 Use in Acute Myocardial Ischaemia

Myocardial ischaemia occurs when a clinical condition causes myocardial oxygen demand to exceed oxygen supply. HR, contractility and systolic myocardial wall tension are the primary determinants of myocardial oxygen demand. β-Blockers have beneficial effects in both acute and chronic ischaemic heart disease as they decrease myocardial oxygen demand by effectively lowering HR and BP and decreasing myocardial contractility, while also decreasing left ventricular wall tension.[46,47]

The early use of β-blockers during hospitalization for acute myocardial infarction has been shown to decrease post-infarction angina, arrhythmias, and the risk of reinfarction or progression of infarction. Esmolol, with its short duration of activity, has allowed safe and rapid titration with minimal risk of severe adverse effects. Esmolol has been shown to produce favourable haemodynamic effects, including a controlled HR and decreased rate-pressure product, in patients with myocardial ischaemia (acute and remote) and diminished left ventricular function. Esmolol has also effectively abated chest pain associated with unstable angina, while also being well tolerated.[48]

During acute myocardial infarction, esmolol has been reported to control tachycardia and reduce myocardial oxygen demand,[18-21] as well as increase diastolic filling during acute ischaemic cardiogenic shock.[49] However, the mortality benefit of early β-blocker use during acute myocardial infarction remains controversial[50] and their administration in the first 24 hours of hospitalization has been shown to increase the risk of cardiogenic shock, particularly in patients with heart failure or haemodynamic instability on presentation.[51]

3.4 Use in Supraventricular Arrhythmias

Esmolol can be titrated to effect, controlling ventricular rate in most tachycardias of supraventricular origin, and is capable of converting about half of re-entrant SVT. With aggressive dosing regimens, hypotension occurs in approximately 50% of patients but can be quickly reversed by halting the infusion.

Postoperative AF occurs in 30% of patients undergoing CABG and is associated with significant morbidity, particularly a 2- to 3-fold increased risk of stroke. Due to clinically compelling data showing approximate 60% reduction in the risk of postoperative AF, the most recent guidelines for CABG surgery[33] recommend preoperative or early postoperative β-blockers as the standard therapy to reduce the incidence and/or clinical sequelae of AF after CABG. Despite the slow titration and variable absorption of oral β-blockers and the early peak incidence of postoperative AF (second to third postoperative day), esmolol has not been shown to be more efficacious than oral β-blocker therapy in preventing postoperative AF.[52]

β-Blockers are one of the most effective agents for controlling the ventricular response to AF and are recommended by current guidelines for acute treatment of AF without an accessory pathway while exercising caution in patients with hypotension or heart failure.[53] Esmolol and other intravenous β-blockers should be considered first-line therapy in situations where increased adrenergic tone is a major precipitant of AF, such as after surgery. Esmolol has been shown to more rapidly achieve ventricular rate control in both cardiac and noncardiac post-surgical patients.

Sixty-three noncardiac surgical ICU patients with recent onset of AF were randomized to receive intravenous diltiazem or esmolol to determine which therapy achieved faster cardioversion to NSR.[54] Prior to randomization, patients received an adenosine challenge to rule out re-entrant AV nodal rhythms and ventricular tachycardias. Loading and continuous infusion rates were adjusted to achieve similar degrees of ventricular rate control. Diltiazem patients received a loading dose of 20 mg followed by a maintenance infusion of 10 mg/h. If HR exceeded 110 bpm, diltiazem was titrated every 15–30 minutes to a maximum infusion 20 mg/h. Esmolol patients received 12.5 mg bolus followed by 25–50 mg boluses every 3–5 minutes until HR <110 bpm or a total loading dose of 250 mg was administered. The maintenance infusion rate was between 50 and 150 μg/kg/min. Twelve-lead electrocardiograms were obtained before drug administration, after 2 hours and again after 12 hours of continuous infusion maintenance drug. Although similar rate control was achieved with both agents, 59% of patients receiving esmolol converted to NSR within 2 hours compared with 33% of diltiazem patients ($p = 0.049$). At 12 hours, the percentage of patients converting to NSR was similar (85% vs 62%), as was the length of hospital stay. The authors concluded that esmolol provided faster conversion to NSR than diltiazem in ICU patients with SVT following major surgery.[54]

Similar results were found by Mooss et al.,[55] who compared intravenous esmolol and diltiazem in 30 post-cardiac surgery patients (CABG or valve replacement) experiencing AF or atrial flutter with a ventricular rate ≥100 bpm for at least 5 minutes and who were haemodynamically stable. Esmolol patients received a 500 μg/kg bolus followed by an infusion of 25–50 μg/kg/min. The esmolol infusion was titrated every 10 minutes by 25–50 μg/kg/min to achieve a ventricular rate of <90 bpm. Diltiazem patients received a 0.25 mg/kg bolus over 2 minutes, followed by an additional 0.35 mg/kg over 2 minutes if the response was inadequate. A maintenance infusion of diltiazem was initiated at 5 mg/h and titrated hourly to a maximum rate of 15 mg/h or until the goal ventricular rate (<90 bpm) was achieved. A greater percentage of patients in the esmolol group converted to NSR within the first 6 hours (66.6% vs 13.3%; $p < 0.05$), whereas the 24-hour conversion rates (80% vs 66.6%) and length of hospital stay were similar between groups.[55]

3.5 Electroconvulsive Therapy

Electroconvulsive therapy (ECT) is primarily used in the treatment of major affective disorders and certain cases of schizophrenia, catatonia and acute mania.[56] This therapy works by electrically producing grand mal seizures. Typically, electrical stimulation results in an initial parasympathetic response, immediately followed by intense sympathetic outflow. ECT results in an acute cardiovascular response with increases in HR, BP and plasma catecholamines.[57] For patients at risk of cardiovascular or cerebrovascular complications, esmolol is frequently used to prevent increases in HR and BP experienced with ECT. Esmolol effectively controls haemodynamic responses to ECT; however, discrete patient-oriented outcome data are lacking.

In a prospective, randomized study, 37 patients undergoing ECT were evaluated for changes in cerebral blood flow using esmolol, labetalol or no β-blocker.[58] All patients received anaesthesia with etomidate and succinylcholine along with pulse oximetry and left middle cerebral artery blood flow measurement. Patients with no hypertension received no β-blocker. Patients with pre-existing hypertension (mean arterial pressure >85 mmHg) were randomly pretreated with either esmolol or

labetalol. The median dose for esmolol and labetalol was 25 mg and 20 mg, respectively. In the esmolol and labetalol groups HR did not significantly increase. However, labetalol attenuated the increase in cerebral blood flow better than esmolol.[58]

In another study, esmolol was used to determine its effect on ST-segment depression after ECT.[59] Nineteen patients, randomized to placebo or esmolol, underwent 71 ECT treatments using Holter monitoring for at least 2 hours post each ECT session. Each patient served as their own control. Esmolol was administered as a loading dose (500 μg/kg over 1 minute) followed by a continuous infusion of 200 μg/kg/min. Esmolol or placebo was started 5 minutes before anaesthesia induction and discontinued 5 minutes after induction of seizure. The results of this study found HR and BP were significantly lower during the esmolol infusion than placebo. However, esmolol did not prevent ST-segment depression during the post-ECT period.[59]

4. Conclusions

Esmolol is a unique, cardioselective, ultra-short-acting β-blocking agent. After more than 2 decades of use, it continues to play a primary role in clinical situations where β-adrenergic control is required for short periods. The efficacy and safety of esmolol in adults has been established in patients with unstable angina, myocardial ischaemia, supraventricular arrhythmias and peri- and postoperative tachycardia and hypertension. In the perioperative setting involving LTI and extubation, the effects esmolol appears to be dose dependent, which likely explains the dissimilar findings for HR and BP control among various studies. Esmolol has also been shown to be effective in other emergent situations where β-blockade is required, such as ECT. The paediatric pharmacokinetic estimates for esmolol showed a shorter $t_{½}$ (2.7–4.8 minutes) and a higher clearance (281 mL/kg/min) in newborns and infants than that found in children (>2 years old) and adults. Dosing requirements to achieve targeted BP (<90% for age) in post-coarctectomy patients were substantially higher (mean 700 μg/kg/min) than that used in adults. The explanation for these observations requires further research. Esmolol was well tolerated and effective as a single agent in controlling hypertension following cardiac surgery and terminating supraventricular arrhythmias in children.

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