Esmolol (Brevibloc®): A review for anesthesia practice

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Esmolol (Brevibloc®) is an ultrashort-acting beta-adrenergic antagonist that was developed in 1982. It has been used in the critical care setting for the treatment of supraventricular arrhythmias. Because of its short tissue elimination half-life (9 minutes), the objectionable side effect(s) which may make the practitioner reluctant to use the long-acting beta-blockers propranolol and metoprolol, dissipate rapidly after discontinuing esmolol. Esmolol is currently finding acceptance in the perioperative setting. The adrenergic response to intubation and painful surgical stimuli can be attenuated by the administration of esmolol prior to the induction of anesthesia. Several studies describing the interactions of esmolol with common anesthetic agents, side effects and routes of administration are reviewed. Esmolol is a useful addition to the anesthetist’s repertoire as a safe, effective agent for mediating harmful responses to the stresses of anesthesia and surgery.

Introduction

Esmolol (Brevibloc®) is a cardioselective, ultrashort-acting beta antagonist originally described by Zaroslinski and associates and first synthesized in 1982.1-3 Esmolol is unique among beta-blockers, because of its extremely rapid onset and short duration.4 Unlike most beta-blockers, which are metabolized by the liver, esmolol is hydrolyzed by cytosol esterase in the red blood cells.4-5 It is broken down into methanol and an acid metabolite which has only 1/1,500th of the activity of esmolol itself and is excreted by the kidneys.6 Esmolol has a rapid distribution half-life of about 2 minutes and a short elimination half-life of about 9 minutes.7-8 In accordance with its high rate of metabolism in the blood, less than 2% of the drug is excreted unchanged in the urine.9

The pharmacokinetics, pharmacodynamics and implications for use in other disciplines have been extensively reviewed.4-5,9-12 The purpose of the current discussion is to demonstrate a proposed role for esmolol in anesthesia practice.

Role of beta-blockers in anesthesia

In surgical patients, laryngoscopy and intubation trigger a transient hyperadrenergic response that results in tachycardia and hypertension.13-16 This response could have serious consequences for patients with preexisting hypertension or coronary artery disease.17 A number of interventions have been proposed to blunt the adrenergic response to intubation and surgical stimuli including the administration of high doses of inhalational agents and narcotics, intravenous or topical lidocaine, nitroprusside and nitroglycerin.17,18 None of these agents is without its limitations: Neither fentanyl nor sufentanil completely suppresses cardiovascular response to intubation.19,20 However, high doses of these narcotics may cause delayed recovery as a result of respiratory depression. Neither sodium nitroprusside nor nitroglycerin inhibits the increase in heart rate that occurs during intubation.17 Lido-
caine is frequently administered prior to intuba-
tion, although the use of topical lidocaine has been
found to be inadequate.  

Beta-blockers have been used successfully to
attenuate the adrenergic response to perioperative
stimuli. However, the relatively long duration of
action of propranolol and metoprolol, the only beta-
blockers previously available in the United States
for intravenous use, can produce potentially ad-
verse side effects such as bradycardia, atrioventricu-
lar block, heart failure or bronchospasm. In con-
trast to the lingering effects of propranolol and metoprolol, both the therapeutic and adverse ef-
fects of esmolol disappear rapidly when the drug is
discontinued.

Beta-blockers act to lower heart rate (HR),
blood pressure (BP), cardiac index (CI) and stroke
work index (SWI). This action results in decreased
oxygen consumption ($\text{MVO}_2$) by the myocardium,
which is especially important for cardiac patients
undergoing surgery.

Currently available beta-blockers have long
plasma half-lives and, hence, long durations of
action. This raises concern about using such agents
in patients who are at an increased risk for surgery
and anesthesia, i.e., patients with left ventricular
(LV) dysfunction, slightly prolonged pulse rate (PR)
intervals, emphysema or bronchospastic disease,
etc.

Esmolol has a very short half-life; therefore,
patients can receive this drug with relative safety.
Even though there may be side effects (as will be
mentioned later), if adverse effects to esmolol occur,
the infusion can be stopped and the effects rapidly
dissipated. It has been demonstrated that a dose of
300 $\mu$g/kg/min of esmolol does not precipitate bron-
chospasms in asthmatic patients. Thus, in acute
settings, esmolol is preferred over propranolol in
patients with asthma who require a beta-blocker.

**Potential uses of esmolol**

**Critical care setting.** Esmolol has typical beta-
blocker electrophysiologic effects, producing a de-
crease in sinus node rate and atrioventricular conduction. By slowing the heart, esmolol de-
creases the $\text{MVO}_2$, an energy sparing effect that may prevent arrhythmias precipitated by myocardial ischemia in patients with ischemic heart disease.

Esmolol administered by continuous infusion has
been found to be as effective as propranolol in the
treatment of supraventricular tachyarrhyth-
mi"a. Esmolol blocks catecholamine-induced in-
creases in HR, is a negative inotropic agent and
decreases blood pressure. Reducing HR and BP
results in a decreased rate-pressure product, which
suggests a lessening of myocardial oxygen de-
mand. As yet, esmolol has not been approved for
clinical use in patients with acute myocardial isch-
emia, but more research needs to be done in this
area.

Other proposed uses for esmolol in the critical
care setting include:

1. Treatment of unstable angina.
2. Prehospital management of acute myocar-
dial infarction.
3. Treatment of arrhythmia in patients with
hyperthyroidism.
4. Concurrent therapy with a thrombolytic.
5. Management of congestive cardiomyo-
pathies.

**Perioperative setting.** As mentioned earlier,
stressful surgical stimuli elicit adrenergic responses
that precipitate transient but intense increases in
HR and BP. Patients normally tolerate the extremes of BP and HR without deleterious effects; however, in the patient who is already cardiovascually compromised, sudden increases in HR and BP increase myocardial oxygen demand. Therefore, these patients are at greater risk for myo-
cardial ischemia and infarction, and some method
must be undertaken to protect them from the stress
of surgery. The use of esmolol infusions to blunt adrenergic responses to induction, intubation and
other stresses of surgery has been studied in several
clinical settings.

Additional applications for esmolol in the
perioperative setting include treatment of postop-
erative hypertension, controlled or deliberate hy-
potension, day surgery in coronary artery disease
patients and management of HR and BP in dissect-
ing aortic aneurysms, in pheochromocytoma pa-
tients and in patients with preeclampsia of preg-
nancy.
Thiopental and succinylcholine are two of the most commonly used drugs during the induction of anesthesia. Two research teams performed studies to evaluate the effectiveness of esmolol in attenuating tachycardia caused by the use of these drugs. In one study, patients were all ASA I-III and were premedicated with 1.5 mg/kg hydroxyzine (Vistaril®), 1.5 mg/kg meperidine (Demerol®) and 3.0 μg/kg glycopyrrolate (Robinul®) intramuscularly (IM) 90 minutes prior to general anesthesia. Twelve patients received an infusion loading dose of 500 μg/kg/min esmolol for 4 minutes prior to induction with thiopental and succinylcholine, as well as 300 μg/kg/min for maintenance for 6 additional minutes during endotracheal intubation. The control group received an infusion of D5W. The patients were induced at minute 4 of the initial infusion. The results showed that HR was significantly greater in the control group than in the esmolol-treated group. There was no significant difference in BP between the two groups.

Liu and associates also used the thiopental and succinylcholine induction technique in a double-blind prospective study with 30 ASA I patients receiving 12-minute infusions of esmolol. Results showed a significant depressant effect on HR and systolic pressure.

Ketamine is an induction agent that typically produces increases in HR and BP. When esmolol was infused (300 μg/kg/min) prior to induction with ketamine, an increase in HR was prevented.

All of the inhalational agents have been studied in conjunction with esmolol, and the results have shown a significant reduction of the adrenergic response to induction and endotracheal intubation.

The safety and efficacy of esmolol during high-dose fentanyl anesthesia were studied in patients undergoing coronary artery bypass surgery. In two studies, esmolol infusions were administered prior to induction and intubation. Once again, there were no significant increases in HR or BP in the patients receiving esmolol. Both groups concluded that esmolol was effective in attenuating deleterious responses to induction in patients receiving fentanyl-pancuronium anesthesia for coronary artery bypass grafting.

Esmolol is an ester that is hydrolyzed in the red blood cells. Succinylcholine is an ester that is inactivated by pseudocholinesterase in the vascular compartment. The concomitant use of esmolol and succinylcholine creates the potential for drug interaction. Two studies deal with the possible interactions between the drugs. Both conclude that esmolol infusions cause a small but statistically significant delay in recovery from succinylcholine. One author found this delay to be less than 3 minutes, an interval that is not likely to have an impact on most surgical procedures.

Bernstein and associates (1989) actually studied the effects of bolus intravenous administration of esmolol in doses of 100-200 mg preceding rapid sequence induction and intubation. They found that HR and changes in mean arterial pressure (MAP) were blunted by bolus esmolol, while peripheral sympathetic responses were not diminished. Similarly, Jacque and associates further studied the effects of bolus administration of esmolol prior to intubation. Their study showed that 2 minutes or less must elapse between administration and intubation. They also felt that a dose of 100-200 mg or more must be given for effect.

Interactions with other drugs

Medications that are commonly used in acute care situations have been evaluated for their interaction with esmolol. It has been shown that digitoxin levels are slightly increased when it is administered concomitant with esmolol, but the pharmacology of esmolol is not affected. In the same study, no significant interaction could be demonstrated between esmolol and warfarin.

Adverse effects

Adverse effects, when they occur, are reversed rapidly by discontinuing esmolol infusion. The most profound and commonly reported side effect is hypotension, which is related to dose and speed of delivery. Other side effects include nausea, vomiting, headache, fatigue and somnolence. An open-labeled, baseline-controlled multicenter study found that those patients most at risk for adverse effects, i.e., diabetics, asthmatics and those with congestive heart failure, etc., during beta blockade tolerated esmolol therapy with minimal side effects. Thus, the risk of severe bradycardia, bronchospasm, etc. is minimal and can be abated by stopping the drug.

Conclusion

Esmolol is an ultrashort-acting, cardioselective beta-adrenergic blocker that has been demonstrated to be a useful adjunct in the administration of general anesthesia.

Most clinical studies have dealt with esmolol administered as an infusion. Ellenbogen and associates investigated the effects of a bolus dose of esmolol on HR, BP and PR intervals in healthy, exercising male subjects. They found that esmolol boluses of up to 300 mg may be administered safely to such subjects. Although they did not administer boluses of esmolol to patients undergoing induction of general anesthesia, the researchers felt that...
the exercise protocol in their study simulated the higher sympathetic tone to be found in these clinical settings. Obviously, esmolol is a welcome addition to the anesthetist's armamentarium. However, further research must be done to determine adequate dosages and mode of administration, i.e., bolus versus infusion.

REFERENCES


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