CLINICAL AND PHARMACOLOGICAL EFFECTS OF ESMOLOL HYDROCHLORIDE IN HYPOTENSIVE ANESTHESIA

Thesis

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INTRODUCTION

The concept of intentianally decreasing arterial blood pressure to hypotensive levels during surgery was introduced into clinical practice by Gardner in (1946). Deliberate hypotension gained popularity after Griffiths and Gillies (1948) advocated the "hypotensive spinal technique" Enderby, (1959) introduce ganglionic blockade using pentamethonium to decrease arterial blood pressure. Subsequent techniques including decreasing cardiac output with volatile anesthetics such as halothane, administering vasadilators such as sodium nitroprusside, B-adrenergic receptor blocking drugs which were initially used with trimethaphan and the combination of α-and β-adrenergic receptor blocking drugs, nitroglycerin, purine derivatives and isoflurane have also been used ***(Aken and Miller, 1994).***

The most important factor determining the extent of intraoperative haemorrhage is the mean arterial blood pressure (MAP), this is directely related to both cardiac output and total peripheral resistance, cardiac output is dependent not only on the volume of blood returning through the veins but also upon myocardial contractility ***(Simpson, 1989).***

The main purpose of deliberately inducing hypotension is to decrease blood loss, thereby improving operating conditions or decreasing the need for blood transfusions. The potential for transmitting disease by blood transfusion has made deliberate hypotension an even more important consideration today than ever before. Most studies define deliberate hypotension either as a reduction in systolic blood pressure to 80 to 90 mm

Hg or a decrease in MAP to 50 to 65 mmHg in normotensive patients *(Aken and Milleri, 1994).*

Introduction of beta- adrenoreceptor blocking drugs in clinical medicine has provided one of the major pharmacotherapeutic advances in this century. Beta-blocking drugs initially were conceived for the treatment of patients with angina pectoris and arrhythmias; it soon become clear, however, that they had much to offer in a diversity of clinical disorders, including systemic hypertension, mitral value prolopse, hypertrophic cardiomyopathy, migraine, glucoma and thyrotoxicosis *(Frishman, 1988).*

Increasingly, propranolol and other β-blocking drugs have been administered intravenously in acute setting. Because of the relatively long half-lives of the currently available β-blocking drugs (between 2 and 12 hours), their use may involve potential risk to the patient if serious adverse reactions such as atrioventricular block, excessive bradycardia, bronchospasm or worsening of left ventricular function develop. These adverse reactions may dissipate slowly or require treatment. However, a beta-adrenoceptor-blocking agent with a short duration of action would allow rapid titration to a therapeutic level and rapid reversal of effects upon discontinuation. Esmolol is the first beta-blocker developed for intravenous use with a very brief duration of action. It is one of synthetized compounds that contain an ester group on the aromatic ring; the basic structure of beta-adrenergic antagonists, this feature permits rapid metabolism of esmolol at the site of esterification *(Anderson et al., 1986).*

TECHNIQUES USED TO ACHIEVE DELIBERATE HYPOTENSION

Controlled Haemorrhage :

Gardner (1964) describe the production of deliberate hypotension with a controlled haemorrhage through the technique of arteriotomy in which blood was taken through an arterial cannula until the blood pressure was reduced to 80mmHg. In this way, up to 3000 ml of blood could be withdrawn to be reinfused after surgery to restore blood pressure.

Arteriotomy was used exclusively during neurosurgical operations with excellent operating conditions through reduction of arterial pressure and intense vasoconstriction with a small increase in heart rate if blood was withdrawn slowly ***(Jackson, 1954).***

However, this became historical because it is too dangerous since cardiac output and organ perfusion must be severely impaired before a significant decrease in mean arterial pressure occurs ***(Miller, 1986).***

Spinal and Epidural Block :

Griffiths and Gillies (1948) described the technique of high spinal anesthesia to achieve a dry field for surgery. A high spinal block aiming to total sympathetic block (from T_1 to L_2) together with analgesia and muscle relxation, designed to produce a maximum decrease in arterial pressure while sparing the respiratory and medullary centers.

The technique implied that after induction of general anesthesia and the patient in the lateral position, a lumber puncture at L_2/L_3 interspace

low concentration (0.5%) is extremely effective as an adjuvant to the hypotension produced by other intravenous hypotensive drugs *(Prys Roberts et al., 1974).*

Chiache et al. (1982) have drown the attention to the fact that although halothane had been widely used, yet severe cardiac depression and inadequate tissue perfusion is well-known to occur. In a number of patients particularly young patients with high sympathetic tone and anxious patients with relative tachycardia, it can be difficult to produce adequate hypotension using halothane alone, unless undesirably high concentration is administered. Increased concentration of halothane augment the risk of cardiac arrhythmias as a result of endogenous release of catecholamines. Furthermore, there is a risk of instability in arterial pressure probably as a result of catecholamine release or activation of renin - angiotensin mechanism or both. Considering these drowbacks related to halothane induced hypotension, pretreatment with β-blockers seems to decrease the effects of increases in symptathetic tone.

Jakobson et al. (1986) studied the effect of metoprolol, cardioselective β-blocker, on controlled hypotension during halothane anesthesia. Metoprolol was given 10-12 hours before operations. They reported that halothane concentration needed to induce and maintain hypotension was much reduced. The time to awakening was shorter and rebound hypertension was well controlled. The rate-pressure product was decreased, anticipating that metoprolol reduces the myocardial oxygen demand during and after the operative procedure.

The main advantages of using halothane include lack of tachyphylaxis, lack of rebound hypertension and increased or maintained cereberal blood flow (CBF). The major disadvantage of halothane induced hypotension is that it has a relatively slow onset of action with prolonged recovery time and now it is considered to be inferior to other methods ***(Miller, 1990).***

Isoflurane :

Unlike halothane, isoflurane has no effect on myocardial contractility. The peripheral vasodilatory effect is readily reversible by alterations in inspired concentration of the drug. For this reason, it is becoming increasingly used as a hypotensive agent, particularly when only moderate reduction in arterial pressure is required. It has the additional benefit that increasing doses not only produces vasodilatation and hypotension but also produce central nervous system depression, thus presumably reducing any reflex vasoconstriction and tachycardia, which might occur as a result of baroreceptor inhibition ***(Murphy et al., 1974).***

Early attempts were done by ***Lamb and Gelb (1983)*** testing the efficacy of isoflurane as the sole hypotensive agent during neurosurgical procedures. They have demonstrated that isoflurane at inhaled concentrations of 2-4% promptly lowered blood pressure. The dose-response curve was steep, allowing precise control of blood pressure.

Interestingly, there was no correlation between duration of hypotension and recovery time which can be attributed to the low blood gas solubility coefficient ***(Knill et al., 1983).***

Isoflurane decreased blood pressure by decreasing systemic vascular resistance (SVR), wheres cardiac output was maintained constantly at clinically relevant concentrations of the anesthetic ***(Van et al., 1986).***

Bernard et al., (1988) have studied the sympathetic activity during isoflurane hypotension for total hip replacement. They reported increases in the level of epinephrine, norepinephrine as well as plasma renin activity and they claimed that cardiac output is probably maintained during hypotension due to increased sympathetic activity. Isoflurane provides the best preservation of cardiac output.

The administration of low concentrations of isoflurane (≤ 1 minimal alveolar concentration (MAC)) produces controllable decrease in MAP and a concentration-related depression of cerebral metabolism while preserving the physiological relationships between flow and pressure, and flow and metabolism. With higher concentrations of isolfurane, the direct vasodilatory effects predominate: cerebral blood flow (CBF) increases and autoregulation is impaired ***(Madsen et al., 1987).***

However, even low concentration of isoflurane may increase intracranial pressure (ICP) in patients who have reduced intracranial compliance. In the presence of cerebral vasodilation, cerebral oedema is more likely to occur if systemic blood pressure is allowed to increase. Therefore, the possibility of secondary neurological injury exists ***(Grosslight et al., 1985).***

Volatile anesthetics should not be used as the sole agent to induce hypotension in patients who have intracranial disease, as the high concentrations that may be required can worsen brain oedema. Such a technique may also increase ICP before opening of the dura and may affect autoregulation. The combination of increased ICP and decreased MAP can reduce cerebral perfusion pressure to less than 40mmHg, a circumstance that can induce brain ischemia. Recent studies in animals and patients showed that combining isoflurane with either α-adrenergic receptor blocking drug or a combined α- and β-adrenergic receptor blocking drug attenuated the negative effects of using isoflurane as the sole hypotensive agent *(Toivonen et al., 1992).*

Enflurane :

Enflurane is infrequently used to produce controlled hypotension. It may induce electro-encephalo-graphic seizure like activity in certain patient especially during hypocapnia *(Colley, 1984).* Enflurane-induced hypotension is due to marked depression of myocardial contractility and decreased cardiac output. The onset of action of hypotension compared with isoflurane is relatively longer. Sympathetic activity during enflurane anesthesia is depressed, suggesting that cardiovascular depression resulted, at least partly, from blunted responsiveness to increase in sympathetic tone *(Bernard et al., 1989).*

INTRAVENOUS DRUGS :

Sodium nitroprusside :

Sodium nitroprusside is a vasodilating drug most commonly used to induce hypotension during surgery. It's onset of action is rapid, of short