

Introduction

Morbid obesity is associated with an increased prevalence of numerous physical ailments. The frequency and severity of co-morbid conditions is directly proportional to the weight of the patient. Based on the guide published by the National Institutes of Health, body mass index (BMI) (kg/m^2) is used to classify obesity. Most consider morbid obesity to refer to patients with a BMI $\geq 40 \text{ kg/m}^2$ or a BMI $\geq 35 \text{ kg/m}^2$ if co-morbid conditions exist (*Gross et al., 2006*).

The condition of morbid obesity presents a challenge to the anesthesiologist because of the altered cardiopulmonary physiology and the associated pathologies including hypertension, coronary artery disease, obstructive sleep apnea, and diabetes mellitus (*Ebert et al., 2006*).

During the past years, innovations in surgical techniques have improved. Surgery performed for the treatment of morbid obesity commonly referred to as bariatric surgery. As a result of the increase in the number of persons undergoing bariatric surgery, the anesthesiologist has been faced with the task of managing morbidly obese patients whose anesthetic managements are complicated not only by the virtue of their weight and the presence of significant co-existing diseases but

also by the complexity of the surgical procedure (*Vallejo et al., 2007*).

Obese patients may be sensitive to the respiratory depressant effect of opioid drugs and more likely to require postoperative ventilation to avoid hypoxic episodes and hypoventilation (*Javaheri et al., 2004*).

It has been recommended that opioid drugs to be avoided for analgesia in the morbidly obese patient because of the risk of respiratory depression. This requires alternative drugs to be used in place of opioids to provide analgesia during surgery. Several drugs, including clonidine, ketamine, magnesium, lidocaine, and ketorolac, have an analgesic effect. (*White, 2002*).

Dexmedetomidine is a specific α_2 -adrenergic receptor agonist with sedative properties. Reports indicate that dexmedetomidine decreased anesthetic requirements during surgery, provided postoperative analgesia, and decreased opioid use in the postanesthesia care unit (PACU). (*Arain et al., 2004*).

The choice of anesthetic technique for general anesthesia in morbidly obese patients remains controversial. The use of dexmedetomidine in patients receiving total intravenous anesthesia (TIVA) for laparoscopic Roux-en-Y gastric bypass (RYGBP) will offer intraoperative control of blood pressure

and heart rate, decrease the total amount of propofol required to maintain anesthesia (***Salihoglu et al.,2001***).

The decrease in postoperative opioids use in dexmedetomidine treated patients may be important for attenuating the risk of narcotic induced postoperative respiratory depression and hypoxemia in patients after laparoscopic RYGBP surgery (***Holmes and Maye, 2004***).

Aim of the Work

To study the effect of Dexmedetomidine infusion on anesthetic requirements, perioperative hemodynamics, and postoperative pain, sedation, Respiratory parameters, nausea, vomiting and analgesic consumption in morbidly obese patient undergoing laparoscopic gastric bypass surgery with propofol-based total intravenous anesthesia TIVA technique.

PHARMACOLOGY OF DEXMEDETOMIDINE

Since the first report of clonidine, an α_2 -adrenoceptor agonist, the indications for this class of drugs have continued to expand. In December 1999, Dexmedetomidine was approved by the Food and Drug Administration as the most recent agent in this group for use in humans as a short-term medication (<24 hours) for analgesia and sedation in the intensive care unit (ICU).

Molecular Pharmacology:

Structure of alpha-2 adrenoceptors

Bylund and Co-workers (1985) defined three alpha-2isoreceptors; alpha-2a, and alpha-2b and alpha-2c based on their affinity for alpha adrenoceptor ligands. The alpha-2 adrenoceptor is a transmembrane receptor; it is an example of G-protein-coupled receptor (*Matsui et al., 1989*)

Distribution of alpha-2 adrenoceptors:

Presynaptic alpha-2 adrenoceptors are present in sympathetic nerve ending and noradrenergic neurons in the central nervous system where they inhibit the release of noradrenaline. Postsynaptic alpha-2 adrenoceptors exist in a

number of tissues where they have a distinct physiological function: these include the liver, pancreas, platelets, kidney, adipose tissue and the eye. The medullary dorsal motor complex in the brain has a high density of alpha-2 adrenoceptors and activation of these may be responsible for the hypotensive and bradycardic effects of alpha-2 adrenoceptor agonists (**Langer, 2001**).

The locus coeruleus is a small neuronal nucleus located bilaterally in the upper brainstem and has a high density of alpha-2 receptors. A high density of alpha-2 adrenoceptors has also been demonstrated in the vagus nerve, intermediolateral cell column and the substantia gelatinosa. The dorsal horn of the spinal cord contains alpha-2a subtype adrenoceptors, while the primary sensory neurons contain both alpha-2a and alpha-2c subtypes of adrenoceptors (**Scheinin and Schwinn, 2004**).

Imidazoline receptor agonists:

First generation centrally acting antihypertensives such as clonidine and α -methyl dopa were originally thought to decrease sympathetic tone by stimulating alpha-2 adrenoceptors in the medulla. When substances with an imidazoline or catecholamine structure were injected directly into the medulla of anesthetized animals only imidazolines has hypotensive effects and there was no correlation between their affinity for

alpha-2 adrenoceptors and their hypotensive effects (*Ernsberger et al., 2005*).

The central hypotensive effects of clonidine can not be explained by their alpha-2 receptor action alone. It was suggested that this hypotensive action is due to the effect on imidazoline receptors found in the nucleus reticularis lateralis of the ventrolateral medulla (*Bousquet et al., 2005*).

Ernsberger et al. (2005) were the first to verify the existence of specific imidazoline-binding sites in the ventrolateral medulla which were insensitive to catecholamines. Two subtypes of imidazoline receptor (I) have been isolated, I1 and I2. I1 receptors are involved in blood pressure regulation. Unlike I1 receptors, I2 receptors have been implicated in neuron protection in animal model of ischemic infarction (*Khan et al., 2006*).

Mechanism of Action:

Dexmedetomidine, an imidazole compound, is the active pharmacologically dextroisomer of medetomidine that displays specific and selective alpha 2-adrenoceptor agonism. The mechanism of action is unique and differs from those of currently used sedatives agents, including clonidine. Activation of the imidazoline receptors in the brain and alpha-2 adrenoceptors in the spinal cord inhibits neuronal firing, causing hypotension, bradycardia, sedation, and analgesia. The

responses to activation of the alpha-2 adrenoceptors in other areas include decreased salivation, decreased secretion, and decreased bowel motility in the gastrointestinal tract; contraction of vascular and other smooth muscle; inhibition of renin release, increased glomerular filtration, and increased secretion of sodium and water in kidney; decreased intraocular pressure; and decreased insulin release from the pancreas **(Ralph et al., 2001)**. The mechanism of the analgesic actions of alpha-2 agonists has not been fully elucidated. A number of sites, both supraspinal and spinal, modulate the transmission of nociceptive signals in the CNS. Even peripheral alpha-2 adrenoceptors may mediate antinociception **(Nakamura and Ferreira, 2002)**.

The substantia gelatinosa of the dorsal horn of the spinal cord contains alpha-2 receptors which, when stimulated, inhibit the firing of nociceptive neurons stimulated by peripheral A-delta and C fibers and also inhibit the release of the nociceptive neurotransmitter substance P. The spinal mechanism explain why anesthesiologists have found success in using clonidine as an epidurally administered agent in addition to its primary use as an intravenous drug **(Tamsen and Gordh, 2001)**.

The improved specificity of dexmedetomidine for the alpha-2 receptor, especially for the 2A subtype of this receptor, causes it to be a much more effective sedative and analgesic agent than clonidine. Studies have shown that dexmedetomidine

is 8 times more specific for alpha-2adrenoceptors than clonidine (ratios of alpha 2 to alpha 1 activity, 1620:1 for dexmedetomidine, and 201:1 for clonidine) (*Hunter et al., 2003*).

Pharmacokinetics:

Following intravenous administration, dexmedetomidine exhibits the following pharmacokinetic parameters: a rapid distribution phase with a distribution half-life ($t_{1/2}$) of approximately 6 minutes; a terminal elimination half –life ($t_{1/2}$) of approximately 2 hours; and steady-state volume of distribution (V_{ss}) of approximately 118 liters. Clearance is estimated to be approximately 39 L/h. The mean body weight associated with this clearance estimate was 72 kg (*Venn et al., 2002*).

Distribution:

Dexmedetomidine protein binding was assessed in the plasma of normal healthy male and female volunteers. The average protein binding was 94% and was constant across the different concentrations tested.

Elimination:

Dexmedetomidine undergoes almost complete biotransformation with very little unchanged dexmede-tomidine excreted in urine and faeces. Biotransformation to produce

inactive metabolites involves both direct glucuronidation as well as cytochrome P450 mediated metabolism (**Dutta et al., 2000**).

The terminal elimination half-life ($t_{1/2}$) of dexmedetomidine is approximately 2 hours and clearance is estimated to be approximately 39 L/h. A mass balance study demonstrated that after nine days an average of 95% of the radioactivity, following IV administration of radiolabeled dexmedetomidine, was recovered in the urine and 4% in the feces. No unchanged dexmedetomidine was detected in the urine. Approximately 85% of the radioactivity recovered in the urine was excreted within 24 hours after the infusion (**Mantz, 2002**).

Renal Impairment:

Dexmedetomidine pharmacokinetics were not significantly different in subjects with severe renal impairment (creatinine clearance <30 L/min) compared to healthy subjects (**Khan et al., 2006**).

Hepatic Impairment:

In subjects with varying degrees of hepatic impairment (Child-Pugh Class A, B, or C), clearance values for dexmedetomidine were lower than in healthy subject. The mean clearance values for subjects with mild, moderate, and severe

hepatic impairment were 74%, 64% and 53% of those observed in the normal healthy subjects, respectively. Mean clearances for free drug were 59%, 51% and 32% of those observed in the normal healthy subjects, respectively, it may be necessary to consider dose reduction in patients with hepatic impairment (*Ralph et al., 2001*).

Pharmacodynamics

Central nervous system effects:

In a number of mammals including man, sedation ranging from sleep to surgical anesthesia has been described. This effect may be mediated by postsynaptic alpha-2a subtype adrenoceptors located in the locus coeruleus, causing a decrease in noradrenergic activity (*Lidbrink, 2002*).

The majority of patients receiving dexmedetomidine as a primary therapy experienced clinically effective sedation yet were still easily arousable, a unique feature not observed with other clinically available sedatives. Clinical trials indicate that patients treated with dexmedetomidine required either no additional sedative medication or only small doses of this drug (*Venn et al., 1999*). Dexmedetomidine provides dose-dependent sedative effects over the plasma concentration range of 0.3 to 1.25 ng/ml (*Morriso et al., 1999*). In healthy volunteers, dexmedetomidine 2.5 mcg/kg given intramuscularly

induced a 48-60 % reduction in Visual Analogue Scale (VAS) scores for anxiety (*Scheinin et al., 2004*).

Dexmedetomidine is an effective analgesic. Several studies have shown that dexmedetomidine provides analgesia, in addition dexmedetomidine reduces the requirement to use morphine for pain control (*Martin et al., 2003*).

Respiratory system effects:

Alpha-2 adrenoceptors have a minimal effect on ventilation. The locus coeruleus is an important site for the ventilation. The locus coeruleus is involved in arousal reactions; suppression of its activity by alpha-2 adrenoceptor agonists can result in a state similar to sleep with mild respiratory depression but this was not significantly different from that seen with placebo (*Belleville et al., 2003*).

In humans, respiratory rate and oxygen saturation remain within normal limits and there is no evidence of respiratory depression following treatment with dexmedetomidine, within the recommended dose range of 0.2 to 0.7 mcg/kg/hour, or significant effect on hypoxic and hypercapnic ventilatory drive (*Joseph et al., 2000*). The combination of alpha-2 adrenoceptor agonists with opioids does not lead to further ventilatory depression (*Jarvis et al., 2002*). At clinically effective doses, dexmedetomidine has been shown to cause

much less respiratory depression than other sedatives (**Belleville et al., 2003.**)

Cardiovascular system effects:

Intravenous alpha-2 adrenoceptor agonist administration leads to a decrease in heart rate, transient increase in arterial blood pressure and systemic vascular resistance, due to the activation of postjunctional vascular alpha-2 adrenoceptors. This initial response lasts for 5 to 10 minutes and is followed by a decrease in blood pressure of approximately 10% to 20% below baseline and a stabilization of the heart rate, also below baseline values; both of these effects are caused by the inhibition of the central sympathetic outflow. This is followed by a longer lasting decrease in heart rate and blood pressure due to a centrally mediated decrease in sympathetic tone and an increase in vagal activity (**Bloor et al., 2002.**)

The application of a single high dose of dexmedetomidine reduced norepinephrine and epinephrine release by 92 % in young healthy volunteers (**Scheinin et al., 2004.**)

In clinical use of dexmedetomidine, the haemodynamic response correlates with reductions in plasma levels of catecholamines. After cessation of treatment, return to baseline levels occurs within 4-6 hours and no rebound effects have been observed (**Hogue et al., 2002.**)

The incidence of postoperative bradycardia has been reported in healthy surgical patients who received dexmedetomidine, especially high doses. Usually, these temporary effects were successfully treated with atropine or ephedrine and volume infusions (*Jalonen et al., 2000*).

Alpha-2 adrenoceptor reduction in sympathetic tone and increase in parasympathetic tone results in a reduced heart rate, systemic metabolism, myocardial contractility and systemic vascular resistance. These all result in a decrease in the myocardial oxygen requirements. This is may be why clonidine has been successful in the treatment of angina pectoris (*Zochowski and Lada, 2003*).

The effect of alpha-2 adrenoceptor agonists on coronary vasculature in humans is not yet known. It is known that activation of alpha-2 adreno receptors result in endothelial release of nitric oxide in swine this has been postulated that the stimulation of alpha-2 adrenoceptors may lead to a postsynaptic coronary vasoconstriction, which may be countered by a nitric-oxide-mediated coronary vasodilatation (*Coughlan et al., 2003*)

Renal effects:

Stimulation of alpha-2 adrenoceptors has a number of effects that promote diuresis and natriuresis. They decrease the secretion of vasopressin and antagonize its action on renal

tubules. Also thought to inhibit the release of renin (**Chen et al., 2002**).

Neuroendocrine system effects:

The alpha-2 adrenoceptor agonists have a number of neuroendocrine effects, mainly related to their inhibition of sympathetic outflow and the decrease in plasma levels of circulating catecholamines. Stimulation of alpha-2 adrenoceptors located on the β cells of the islets of Langerhans can temporarily cause direct inhibition of insulin release. This effect has unproven clinical importance, because hyperglycemia has never been reported to be significant in patients receiving alpha-2 adrenoceptor agonists. Alpha-2 adrenoceptor antagonists have been shown to increase insulin release (**Ralph et al., 2001**).

Skeletal muscle effect:

Dexmedetomidine can reduce the incidence of postoperative shivering. That happens in 40% of postoperative cases with general anesthesia. The mechanism of this action is not established firmly yet (**Takahiko and Mervyn, 2000**).

Drug and receptor interactions:

Alpha-2 adrenoceptor agonists and opioids have some similar pharmacological effects. Therefore, if alpha-2