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Pharmacotherapy of Procedural Sedation in Morbidly Obese

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Abstract

Procedural sedation in morbidly obese patients can present special challenges, because of the cardiorespiratory changes associated with morbid obesity. This mini review presents various pharmacologic options available for sedation in these patients.

Keywords: Cardiorespiratory; Alfentanil; Dexmedetomidine; Remifentanil

Abbreviations: TBW: Total Body Weight; LBW: Lean Body Weight; GABA: G-Aminobutyric Acid.

Introduction

Obesity in the United States has been growing in number over the recent decades [1]. These patients present for a number of diagnostic and therapeutic procedures under sedation. The goals of every procedural sedation include providing anxiolysis, analgesia, and preventing movement during the most stimulating parts of the procedure. However, the choice of drugs varies on the provider's experience and comfort level. Morbid obesity by itself poses an increased risk of anesthetic complications. These patients are associated with a higher incidence of adverse respiratory events including upper airway obstruction, obstructive or central respiratory depression that may require some form of airway intervention.

Unique to obese patients is the altered physiologic and anatomic changes that affects the pharmacokinetic properties of the sedation drugs [2]. Drug distribution is altered including peak concentration and clearance due to physiologic increase in blood volume and cardiac output [2,3]. The volume of distribution of many drugs is affected, brought in part by the increased fat- and lean-body mass as well as changes in tissue perfusion in obese patients. The increased prevalence of sleep apnea with concomitant carbon dioxide retention, reduction in functional residual capacity, and cardiac dysfunction are some of the anatomic changes in obese patients that contributes to alteration in Pharmacodynamic agents of the drugs used for procedural sedation [3].

Pharmacokinetic and Pharmacodynamic Principles in Obesity

The increase in adiposity accounts for the pathophysiologic changes and multi-organ dysfunction associated with obesity. These changes thereby affect the pharmacokinetic and pharmacodynamic of the drugs used for procedural sedation. An increase in total body weight (TBW), lean body weight (LBW), and fat mass are found in obese patients. These can affect the pharmacokinetics of drugs. The increased fat mass also increases the volume of distribution of the lipophilic drugs [4,2]. Hence, a larger initial loading dose of drugs is necessary in obese patients. Drug distribution is also affected by the degree of plasma protein binding, cardiac output, and

tissue perfusion.

Obese patients are known to have an increase in cardiac output, but there has been no evidence that it alters protein binding to both albumin and alpha-acid glycoprotein [5,2]. There has been a direct strong correlation between the increased cardiac output and LBW. This creates confusion as to the best parameter to follow in dosing drugs, i.e., TBW that reflects the associated increase in volume of distribution or to LBW to account for the increase in cardiac output [6,7,2].

The increase in cardiac output in obese patients would also result in increased blood flow to the liver and kidneys. There are also regional differences in adipose tissue perfusion and the subcutaneous adipose tissues receive more blood flow than abdominal and visceral fat [8]. Even though there is an increase in drug clearance for obese patients, drug metabolism and clearance is mostly dependent on metabolic pathways [7,9].

Pharmacotherapy

Pharmacologic dosing strategies are dependent on the provider's choice of drug. Drug regimen can be a single drug or a combination of drugs to achieve the desired effect. As mentioned above, morbidly obese patients may require special dosing regimen and knowledge of the altered pharmacologic behavior of medication used is essential for optimal management.

Propofol

Propofol is one of the widely utilized drugs during procedural sedation. It is a highly lipophilic with rapid onset and short duration of action. Its rapid penetration of the blood-brain barrier and distribution to the central nervous system, followed by rapid redistribution to inactive tissue depots such as muscles and fat makes propofol's duration of action predictable [4]. Propofol's pharmacokinetics are highly dependent on cardiac output [2]. Since propofol is highly lipophilic, the volume of distribution is therefore higher in obese patients than in normal weight patients. The higher cardiac output in obese patients may contribute to the increase in clearance of propofol. There is a direct correlation of steady-state volume and clearance with increasing total body weight. It has been suggested that administration of propofol in obese patients be based on TBW [10]. However, it is judicious to titrate the recommended propofol does to effect in obese subjects.

Benzodiazepines

Benzodiazepines have been widely used as an anxiolytic, but the current trend is to move the tide away as a first line agent. Benzodiazepines are highly lipophilic drugs that act via G-aminobutyric acid (GABA)-ergic pathways. The excess fat tissue in obese patients increases the correlation between volume of distribution and elimination half-life [4]. Midazolam is one of the most extensively used drugs among the different benzodiazepines. After a single intravenous dose of midazolam, the intensity and duration of action of its sedative effects depend much more on the extent of drug distribution than on the rate of elimination and clearance. The initial distribution half-life of midazolam ranges between 14 and 22 minutes [4]. Regardless of a particular benzodiazepine used, the single intravenous dose should be based on TBW while for continuous infusion, the dose should be adjusted based on IBW. However, the availability of other effective agents with less respiratory compromise makes the utilization of benzodiazepines limited to premedication as a single bolus.

Opioids

Opioids are well known to contribute to upper airway obstruction and respiratory depression. These reasons make opioid use not suitable for situations requiring spontaneous voluntary effort and those with high likelihood of respiratory comprise such as in morbidly obese patients. Obese patients have increased incidence of obstructive sleep apnea, hypoxia, and central sleep apnea. The redundant upper pharyngeal tissue in these patients puts them at risk for upper airway obstruction [11,12].

Fentanyl is a potent synthetic opioid. It has a rapid onset and short duration of action. Administering intermittent boluses with caution is appropriate for painful procedures, but a continuous infusion is not recommended for procedural sedation. Its long context-sensitive half-life does not make it a preferred agent. Also, its lipophilicity results in increased volume of distribution due to excess adipose tissue in obese patients [13]. Thus, it is best to dose fentanyl based on LBW or IBW to prevent overdosing and respiratory depression.

Sufentanil is an extremely potent synthetic derivative of fentanyl. It has a more rapid onset and shorter duration of action compared to fentanyl. Similarly, its profound lipophilicity is the reason behind altered pharmacokinetics in obese patients. Aside from common side effects of opioids, sufentanil may also cause severe decrease in systolic blood pressure, bradycardia, and increased intracranial pressure. Due to its medium and long-lasting anesthetic effects, it is not ideal for procedural sedation [14].

Alfentanil is another synthetic derivative of fentanyl. It has the fastest onset of action followed by sufentanil and then fentanyl. The lipophilicity of alfentanil is less compared to fentanyl and sufentanil, indicating a smaller volume of

distribution [15]. Alfentanil also has a very short duration of action which makes it a favorable agent for short procedures or when quick adjustment of consciousness level is necessary [16]. Furthermore, alfentanil results in less hemodynamic instability compared to fentanyl and remifentanil. However, the likelihood of respiratory depression is higher. Hence, close monitoring of ventilation and vital signs is crucial.

Remifentanil is easy to use due to its rapid metabolism by tissue and plasma esterase resulting in organ-independent clearance [13]. The lack of context-sensitive accumulation of remifentanil makes it preferable where a continuous infusion is required. The short duration of action of remifentanil allows it to be dosed on lean body mass [17].

Ketamine

The use of ketamine has been widely used in pediatric population and procedural sedation done in the emergency room. In a systematic review done by Laskowski et.al, it has been suggested that ketamine may have a place in analog-sedation for adults due to its opioid-sparing effect [18]. It should be noted that higher dose of ketamine is sympathomimetic and is associated with hallucinations, however small doses used for sedation between 10-50 mg are not associated with these side effects.

A combination of ketamine and benzodiazepine or propofol may reduce the risk of hallucination. The risk of respiratory depression is low and has been reported to be a protective factor for sedation-related airway events by reducing the amount of other sedative agents needed to achieve the same effect [19]. In general, the newer, S-ketamine form has a better tolerability profile than the racemic form [20].

Ketamine is dosed based upon TBW. However, there's no formal study that has been conducted to evaluate which dosing should be utilized in obese patients for procedural sedation. However, it should be noted that increasing dosage can lead to higher rate of adverse effect such as over-sedation or respiratory depression, if combined with opioids. Under dosing, on the other hand, may lead to decreased efficacy or may need additional sedative agents.

Combination drugs such as ketofol (ketamine plus propofol) and ketodex (ketamine plus dexmedetomidine) have been gaining popularity but most of the literature is done in the pediatric population [21]. There is still paucity of data in adults and morbidly obese patients as to the appropriate dosing and concomitant adverse reaction.

Dexmedetomidine

Dexmedetomidine is a highly selective alpha-2-agonist that has been used for procedural sedation and as an adjunct to general anesthesia. It has been found to possess hypnotic, sedative, anxiolytic, sympatholytic properties without producing significant respiratory depression [3,22]. The opioid sparing effect of dexmedetomidine without causing respiratory depression has increased its popularity to be used in bariatric surgery [23]. The systemic disposition of dexmedetomidine is significantly altered in morbidly obese patients.

The clearance of dexmedetomidine predominantly depends on hepatic blood flow and Xu, et al. showed significantly lower clearance in obese patients compared to patients with normal body mass index [22]. An infusion rate of 0.2 ug/kg/hr has been recommended to avoid bradycardia and hypotension [2]. However, sedation levels were deeper and oxygen saturations were still lower in morbidly obese patients than in normal body weight patients [22]. Hence, careful attention should be paid when dexmedetomidine is used. To date, there is still paucity of data to guide therapy in morbidly obese patients.

Conclusion

Significant challenges exist in the management of morbidly obese patients presenting for procedural sedation. The choice of pharmacotherapy used in sedation can directly impact the success of the procedure itself. Obesity alters the pharmacokinetic parameters of drugs used for sedation, hence drug dosing must be based on the volume of distribution for the loading dose and on clearance for maintenance. However, it is imperative to preserve good practice and risk reduction during the conduct of the sedation in this subset of patients (Table 1).

Drugs	Bolus Dose	Maintenance Dose	Weight for Dosing (TBW,IBW, LBW)	Elimination half-life
Propofol	0.5-1 mg/kg	50-200 mcg/kg/min	TBW	4-7 hrs
Midazolam	0.01-0.1 mg/kg	0.02-0.1 mg/kg/hr	TBW (single dose) IBW (continuous)	1.7-2.6 hrs
Fentanyl	10-20 mcg/kg	2-50 mcg/kg	LBW	8-10 hrs
Sufentanil	0.2-0.4 mcg/kg	0.20-1 mcg/kg/hr	LBW	6-9 hrs

Alfentanil	8-100 mcg/kg	0.5-3 mcg/kg/min	IBW	70-99 mins
Remifentanil	0.05-0.3 mcg/kg/min	0.05-2 mcg/kg/min	LBW	3-10 mins
Ketamine	0.1-0.4 mg/kg	0.1-1 mg/kg/hr	TBW	2.5 hrs
Dexmedetomidine	1 mcg/kg over 10 mins	0.2-1.4 mcg/kg/hr	LBW	2.1-3.1 hrs

Table 1: Pharmacologic Drugs Used for Procedural Sedation [3,15,24-27].

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