Introduction

Patients in the intensive care unit setting require invasive monitoring and treatments that often lead to anxiety and pain ***(Rotondi et al., 2002).*** Use of sedation is essential for the comfort and safety of these patients ***(Jacobi et al., 2002).***

Because sedation is a dynamic process, it is often a balancing act to avoid suboptimal sedation and oversedation. Suboptimal sedation can place the patient at risk for physical stress such as unplanned extubations or catheter removal, and psychological stress such as anxiety, while oversedation increases the risks of ventilator-associated pneumonia, increased length of ICU stay, and psychological sequelae ***(Jackson et al., 2010).***

Many agents have been used for sedation in the ICU. The most frequently used agents include members of the following drug or drug classes: Opioid, benzodiazepines, propofol and dexmedetomidine. When choosing an agent for ICU sedation, multiple factors must be taken into consideration. Typical considerations include indication for sedation, onset of action, duration of action, route of elimination, drug interactions, and adverse effects. The potential impact of the sedative on cognition and neurological sequelae and the likelihood of the agent to achieve a state of 'cooperative sedation is important as well ***(Mirski and Lewin, 2007).***

A key transition in sedation management is the practice of protocolized sedation: that is, using structured approaches to utilize the available analgesics and sedatives to a patient-specific target endpoint ***(Brook et al., 1999).*** Many protocols include spontaneous awakening trials, which involve daily sedation interruptions in appropriate patients ***(Girard et al., 2008),***while other new strategies, like angiosedation focus on adequately treating a patient's pain before utilizing sedatives to avoid the significant adverse drug effects associated with benzodiazepines and other anxiolytics ***(Devabhakthuni et al., 2012).***

Cooperative sedation is optimizing patient comfort while maximizing systemic and neurological function ***(Goodwin et al., 2012),*** that is to say a state in which the patient can be aroused without discontinuing the drug infusion, and when awake, patients are able to communicate and follow commands. When arousal is no longer required, the patient is allowed to return to the prior state of sedation ***(Panzer et al., 2009).*** Cooperative sedation eliminates the symptoms while preserving patient wakefulness and interaction ***(Barr et al., 2013).***

Cooperative sedation is associated with lower incidence of delirium and shorter ventilator time ***(Riker et al., 2009).***

Aim of the Work

The aim of this work is to study cooperative sedation as a new trend of sedation in intensive care unit, comparing and contrasting it with other (commonly used) sedation protocols.

Pharmacological Aspects of Sedatives in ICU

1-Benzodiazepines

There are a large number of benzodiazepines in therapeutic use due to their pharmacologic properties, durations of action, and routes of administration. The most readily available intravenous agents used for sedation in the critical ill patient are diazepam, lorazepam and midazolam ***(Mitzi et al., 2004).***

A. Mechanism of Action

The majority (if not all) of the effect of benzodiazepines are through potentiation of the central nervous system actions of the inhibitory neurotransmitter, gamma-amino butyric acid (GABA). Benzodiazepines experimentally increase the frequency of opening of the GABA chloride channel in response to binding of GABA. Subsequent effects include anxiolysis, sedation, muscle relaxation, anterograde amnesia, respiratory depression (especially in children, patient with chronic pulmonary disease, hepatic insufficiency, or when combined with other sedatives),anticonvulsant activity and analgesia(only intravenous diazepam).Very high doses of several benzodiazepines will also lead to coronary vasodilatation and neuromuscular blockade through interaction with peripheral sites***(Charney et al., 2001).***

B. Pharmacokinetics

Because of their lipid solubility, intravenous benzodiazepines are rapidly distributed in the brain, followed by redistribution to muscle and fat. Diazepam is most rapidly redistributed due to its higher lipophilicity.Lorazepam and midazolam have slower redistribution out of the brain due to greater water solubility. All benzodiazepines are highly bound to plasma proteins, and all are extensively metabolized by hepatic microsomal enzyme ***(Charney et al., 2001).***

C. Routes of Administration

Diazepam, loazepam and midazolam are all available in oral, intramuscular (IM) and IV preparations ***(Mitzi et al.,2004).***

D. Titratability

Intravenous midazolam is the most easily titratable because of its shorter duration of action, and is most appropriate for use as continuous infusion. Because of their much longer half-lives, it is recommended that lorazepam and diazepam be used only as intermittent dosing in critical ill patient ***(Mitzi et al., 2004).***

E. Adverse Reactions

These include headache, nausea or vomiting, vertigo, confusion, excessive somnolence to obtundation, respiratory depression, hypotension, hypotonia/loss of reflexes, or muscular weakness ***(Charney et al., 2001).***

F. Hemodynamic Stability

Low (oral hypnotic) doses of benzodiazepines have little effect on blood pressure, but higher IV (sedative or anesthetic) doses may cause hypotension and increased heart rate ***(Charney et al., 2001).***

H. Reversibility

Benzodiazepines are reversible with the selective antagonist, flumazenil. Caution must be exerted with flumazenil; however, as this agent may precipitate rapid rises in intracranial pressure (ICP), systemic hypertension, and lowering of seizure threshold particularly in neurosurgical patients. Additionally, because of its short duration of action, patients may become resedated from longer-acting benzodiazepines after flumazenil has been metabolized ***(Marek et al., 2007).***

I. Drug–Drug Interactions

As with nearly all sedative agents, additive or synergistic effects may occur with benzodiazepines and any other medication which may alter level of consciousness, suppress respiratory drive, or decrease systemic blood pressure. As such, these agents should be used with caution in individuals who already have altered mental status, have questionable airway protective mechanisms (if not intubated and mechanically ventilated), or who are hypovolemic, septic, or otherwise hemodynamically unstable and on multiple other medications. Additionally, psychotic reactions have been reported with the combined use of benzodiazepines and valproic acid ***(Charney et al., 2001).***

J. Dosage Recommendations for Specific Agents

i. **Diazepam**use doses of 2 mg IV every 30-60min a needed. Half-life is 30-60 h.

ii. **Lorazepam**give 0.25-0.5 mg IV every 1-2 h as needed. Half-life is 10-20 h.

iii. **Midazolam** administer 0.5-1 mg IV every 5-30 min as needed (0.07 mg/kgIM).Maintenance infusions may be titrated from 0.25-1.0 mic/kg/min. Half-life is 1-2.5 h ***(Mitzi et al., 2004).***

2-Opioid Analgesics

A large number of natural opioids (e.g., morphine sulfate, codeine), semi-synthetic opioids (e.g. fentanyl, hydromorphone, oxycodone), and completely synthetic (e.g., meperidine) opioid-like compounds are available. These compounds act primarily as analgesics, but also serve as sedative-hypnoticsat low dosages. Their major disadvantage, particularly in neurologic patients, is their suppression of the hypercarbic respiratory drive. Advantages include easy titratability, provision of patient comfort, and reversibility ***(Mitzi et al., 2004)***.

A. Mechanism of Action

All opioids act by binding to opioid receptors in the central and peripheral nervous systems as agonists, partial agonists, or agonist-antagonists. These receptor interactions are the basis for the pharmacological effects of opioids

(analgesia, decreased level of consciousness, respiratory depression, miosis, gastrointestinal hypomotility, antitussive effects, euphoria or dysphoria, and vasodilatation), and vary by the specific opioid receptor subtypes bound by each drug. For the purposes of this work, discussion shall focus on fentanyl, remifentanil, and morphine, all mu-opioid receptor agonists ***(Gustin and Akil, 2001).***

B.Pharmacokinetics

Opioids are readily absorbed through mucosal surfaces, from the gastrointestinal tract, or through subcutaneous (SC), intramuscular (IM), intrathecal (IT), epidural, and IV routes of administration. Fentanyl is also easily absorbed via transdermal application. Morphine and other opioids arerapidly distributed to the brain, with the more lipophilic compounds (i.e., fentanyl, remifentanil) having the shortest time of onset. Peak effect following IV administration of morphine is approximately 15min; that for fentanyl is 5 min, and remifentanil is 1–2 min. After enteral administration, the bioavailability of morphine sulfate is only approximately 20–40% due to first-pass hepatic metabolism. IM and IV morphine sulfate is rapidly and readily available. Morphine is 20–36% protein bound in plasma, and has a volume of distribution of 1–6 L/kg, depending on route of administration ***(Gusteinand Akil, 2001).***

Morphine is eliminated in the liver by N-demethylation, N-dealkylation, O-dealkylation, conjugation, and hydrolysis. The majority of clearance is by glucuronidation to the active metabolites, morphine-3-glucuronide (approx. 50%) and morphine-6-glucuronide (5–15%), which are renally excreted; the latter is a more potent analgesic than the parent compound, and may accumulate in patients with renal insufficiency. The half-life of morphine varies greatly by route of administration, ranging from 1.5–4.5 h for IV, IM, and SC injection, to 15 h or more for sustained-release oral preparations. Time to onset following oral administration of fentanyl is 5–15 min, with a peak response at 20–30 min. For IM injection of fentanyl, onset is at 7–8 min and effects last 1–2 h. Transdermalfentanyl has a much slower onset of action, 12–24 h, although rate of absorption increases with higher skin temperature (i.e., febrile patients). Steady state is reached at 36–48 h, and duration of action is up to 72 h after removal of transdermal fentanyl. Following IV administration, the onset of action of fentanyl is immediate, although peak effects take several minutes to manifest. Duration of action after a single IV dose of fentanyl is 30–60 min, which increases after repeated or prolonged dosing due to accumulation in fat and skeletal muscle. Fentanyl is extensively plasma protein bound (80–86%), with a total volume of distribution of 3–6 L/kg in adults. Fentanyl is metabolized via N-dealkylation by the hepatic cytochromeP450 system, producing norfentanyl and other inactive metabolites, which are renally excreted.Half-

life is approx. 200 min following IV injection, and up to 17 h for transdermal administration. As up to 10% of fentanyl is excreted unchanged in the urine, its duration of action may be prolonged following high cumulative doses in patients with renal insufficiency. Fentanyl does not appearto be removed from the plasma compartment by hemodialysis Remifentanil is only given by IV injection or infusion, with a time to peak onset of action of 1–3min. Duration of action is only 3–10 min after a single dose, increased slightly after prolonged infusions. Remifentanil is 92% plasma protein bound, with a volume of distribution of 25–60 Land a distribution half-life of 1 min. Obese individuals require a reduction in remifentanil dosing, which should be based on ideal rather than actual body weight. Remifentanil is rapidly metabolized by plasma esterases to an inactive carboxylic acid, which is 90% renally excreted. Metabolism is independent of the cumulative remifentanil dose, and unaffected by hepatic or renal function ***(Marek et al., 2007).***

B. Routes of Administration

Morphine and fentanyl are available as oral preparations, and as sterile parenteral formulations for SC, IM, IV, IT, and epidural administration. For sedation and analgesia, the IV route is recommended from rapid onset and easy titratability. Because of its short duration of action, remifentanil is given only as an IV infusion ***(Mitzi et al., 2004).***

D.Titratability

Due to its rapid onset and short duration of action, which is independent of hepatic and renal clearance, remifentanil is easily titratable. Preliminary use of continuous remifentanil infusion for sedation of both intubated and unintubated patients has shown promising results, with blunting of hemodynamic instability and intracranial hypertension associated with agitation, coughing, and tracheal suctioning. Fentanyl may be given by either bolus dosing or continuous IV infusion. However, fentanyl is less easily titrated due to its longer duration of action and accumulation in lipid and muscle stores over time, requiring greater periods of drug interruption to permit frequent neurologic assessment ***(Tippset al., 2000).***

Morphine is the most difficult of these opioids to titrate, again due to its longer duration of action, dependence on hepatic and renal clearance, and prolonged clearance of active metabolites. For these reasons, infusions of morphine are not recommended for critically ill patients, although intermittent administration may facilitate patient comfort and hemodynamic stability ***(Mitzi et al., 2004).***

E. Adverse Reactions

These include pruritus, excessive somnolence, respiratory depression, chest wall and other muscular rigidity (primarily fentanyl and its congeners), dysphoria or hallucinations (primarily morphine), nausea and vomiting,

gastrointestinal dysmotility, hypotension, histamine release causing urticarial and flushing (primarily meperidine and morphine), anaphylaxis (rare), and immune suppression after repeated dosing ***(Gustin and Akil, 2001).***

F. Hemodynamic Stability

Although morphine may induce hypotension even at low therapeutic doses (partly due to promotion of histamine release), fentanyl and remifentanil tend to have little effect on blood pressure at sedative doses. Fentanyl also tends to reduce heart rate, which is favorable in the setting of cardiovascular disease ***(Mitzi et al 2004).***

G. Reversibility

One of the advantages of sedation with opioid narcotics is their rapid reversibility with the prototypic antagonist, naloxone. Although the recommended dosage for reversal of narcotic overdoseis generally 0.4 mg or above, in critically ill patients the starting dosage should be much lower (i.e., 0.04–0.08 mg by IV push) to avoid "overshoot" phenomena such as hypertension, tachycardia, and emergence agitation, which may precipitate or worsen intracerebral hemorrhage, intracranial hypertension, or myocardial ischemia. Dosage may be titrated to the desired level of arousal and reversal of respiratory depression, with effects seen within 1–2 min of each subsequent administration ***(Mitzi et al., 2004).***

H. Drug–Drug Interactions

Combined use of morphine and neuroleptics may produce greater than expected decreases in blood pressure. Additionally, the depressant effects of narcotics on respiration and level of consciousness may be potentiated by concurrent administration of phenothiazine neuroleptics, tricyclic antidepressants,and monoamine oxidase inhibitors***(Gustein and Akil, 2001).***

I. Dosage Recommendations for Specific Agents

Dosage recommendations are for narcotic-naïve patients. As a general guideline, fentanyl and remifentanil are approximately 100 times more potent than morphine.

i. Fentanyl

Although fentanyl may also be given by oral, transdermal, IM, IT, and epidural routes, IV administration is recommended for critically ill patients. For mild sedation and analgesia, recommended starting dosage is 12.5–50 μg IV every 30–60 min, or a continuous infusion of 0.01–0.03 μg/kg/min or 25–50μg/h (with or without initial IV bolus), titrating to effect every 15–30 min. Continuous infusions above 50–100 μg/h are not recommended in narcotic-naïve patients unless they are endotracheally intubated or otherwise have a protected airway, and mechanical ventilation is possible. For deeper sedation, as an adjunct to general anesthesia, or in narcotic-tolerant patients, continuous infusions greater than 100 μg/h may be used.

ii. Remifentanil

Intravenous bolus of 0.5–1.0 μg/kg is given followed by titration of continuous infusions of 0.05–0.2 μg/kg/min. No adjustment is needed for renal or hepatic insufficiency, although decreasing the dose by 50% is recommended for patients older than 65 yr of age.

iii.Morphine Sulfate

For analgesic dosing, titration doses of 5–20 mg IM every 4 h or 2–10 mg IV over 4–5 min every4 h is recommended. SC morphine is usually given up to 10 mg every 4 h. For oral dosing, give 5–30 mg of the immediate release (IR) formula every 4 h. To convert to extended release (ER) enteral morphine, divide the total daily dose of IM, IV, or IR morphine into 12–24 h dosing. These dosages are for narcotic naïve individuals, and may be increased substantially (with appropriate monitoring) in patients tolerant to opioids. Due to hepatic metabolism and renal clearance, dosages should be reduced in patients with hepatic or renal insufficiency or those at the extremes of age ***(Mitzi at al 2004).***

3-Neuroleptics

A large number of medications are available in this general category, and their use in critically ill patients is somewhat controversial due to their theoretical lowering of seizure threshold. However, in patients with significant pulmonary disease, dementia, or with agitation or delirium

significant enough to risk self-injury or aggression towards medical personnel, the lack of respiratory depression and antipsychotic features of the neuroleptics make them attractive sedatives for some patients. Discussion shall be limited to the three agents used most commonly in ICU, the butyrophenones, haloperidol and droperidol ***(Mitzi et al 2004).***

A.Mechanism of Action

Neuroleptics produce both therapeutic and adverse effects by blocking cerebral and peripheral (but not spinal) dopamine, adrenergic, serotonin, acetylcholine, and histamine receptors, with variable selectivity depending on the agent. These effects include sedation (tolerance develops with repeated dosing), anxiolysis, restlessness, suppression of emotional and aggressive outbursts, reduction of delusions, hallucinations, and disorganized thoughts (over repeated dosing), antiemetic properties, hypotension (varies by agent), and extrapyramidal side effects. Haloperidol and droperidol have limited anticholinergic properties compared with other neuroleptics, reducing the occurrence of blurred vision, urinary retention, and gastrointestinal hypomotility ***(Baldessarini and Tarazi 2001).***

B. Pharmacokinetics

Haloperidol is highly lipophilic; plasma-protein bound, and readily crosses the placenta to enter the fetal circulation.