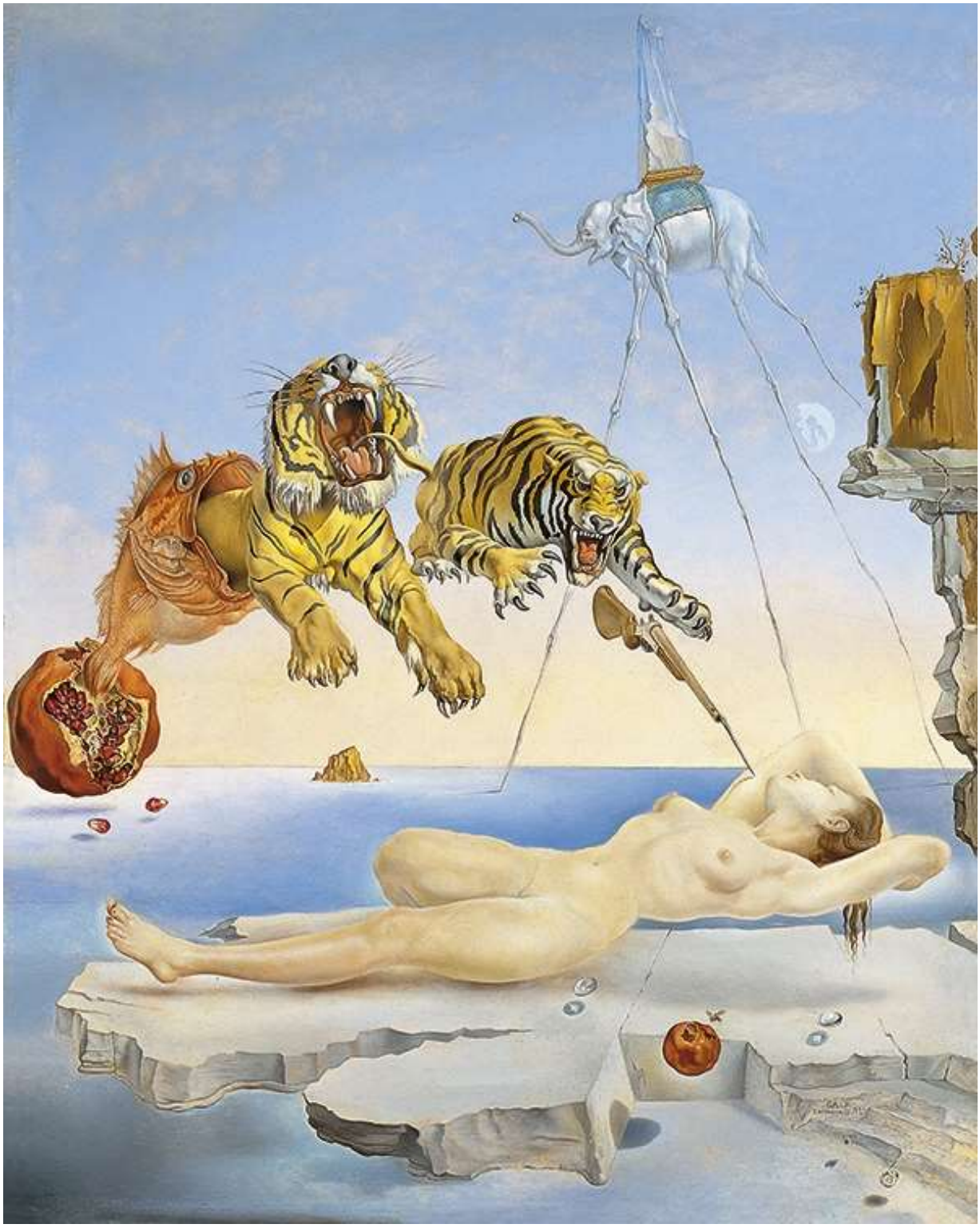
THE NORTHERN HOSPITAL

KETAMINE (PARENTERAL)



"Dream Caused by the Flight of a Bumblebee around a Pomegranate a Second Before Awakening", oil on canvas Salvador Dali, 1944. Thyssen-Bornemisza Museum, Madrid.

On a hot summer's day in 1944, Salvador Dali's mistress, Elena Diakonova, better known to posterity as "Gala" decided to sunbake on the warm rocks in a secluded beach near their home. Despite the heat, the cooling spray off the waves allowed her to drift off to sleep. After a short while however she was suddenly startled by an intensely vivid, bizarre and alarming dream. She had been vaguely aware in her sleep of a soft distant buzzing sound when the vision came to her, waking her abruptly to the blinding light of the Sun and a painful stinging sensation in her skin.

After some moments of terrified confusion she was able to re-orientate her herself to the real world and realised what had happened. She had been stung by a bee that had no doubt been buzzing around a pomegranate she had left half eaten beside her on the rocks.

That same evening she recounted her dream to Salvador, who was immediately captivated by it. Electrified by Gala's story, and no doubt to her mild amusement, he immediately rushed off to his canvas and oils to recreate what he later described in 1962 as, the first ever artistic depiction of one of Sigmund Freud's theories about dreams, being that they could be triggered by an external stimulus of which the person was not consciously aware.

The work he created carried the long title that indicated his intention to give it a rigorously psychoanalytical flavour, "Dream Caused by the Flight of a Bumblebee around a Pomegranate a Second Before Awakening". This work has subsequently become one of his most famous and recognizable paintings. In his younger years Dali was intensely fascinated by Freud's work and in particular on his work concerning the subconscious and how it manifested itself in dreams. One of Freud's most famous works was "The Interpretation of Dreams" which was published in 1899. Dali's copy of this work is extant and that he studied it intently is evidenced by the numerous underlinings that appear throughout his copy.

In Dali's work, Gala is seen sunbaking, (nude as she preferred) but as in a dream she floats above the warm rocks against the backdrop of a brilliant blue sea. The faint cool sea spray is seen as water droplets surrounding her. The half eaten pomegranate lies beside her on the rocks and the bee which will soon sting her is seen being attracted toward it. In the background is one of the Dalian hallmarks of surrealism, the giant elephant on physics defying long spidery legs striding through the sea. It represents the unreality of the dream world, where anything is possible; the laws of physics do not apply. A second enormous pomegranate hangs over the water, spilling a few seeds into it, representing the root cause of the whole incident. From it suddenly emerges a giant fish, as if at first Gala fears something from the sea is the cause of her sudden alarm, but then a mere fish does not seem to account for the sudden shock of events, and so emerging from the fishes' mouth, comes the more appropriate vision of two terrifying tigers about to attack her. Finally her vision culminates in the image of a rocketing rifle with bayonet poised to pierce her arm, her final subconscious attempt to understand the sting of the bee.

Dali's work brilliantly captures the moment of delirium, "one second" before fully awakening, when the conscious and subconscious are merged as one and reality cannot be distinguished from dream.

Fascinatingly, and despite Dali's claim that he was the first artist in history to explore the subconscious workings of the mind as they relate to dreams, another artist seven centuries previously had in fact been just as intensely interested in these phenomena. This person was not a painter however, he was a writer.

As sleep is broken when a sudden light
strikes on closed eyes and, broken,
flickers before it dies,

so my imaginings grew faint within me
as soon as a light, far brighter
than the light we know, struck my face.

I was turning to discover where I was
When a voice said: "Here is your ascent,"
and drew me away from any other thought.

Dante Alighieri, "Purgatorio", XVII, 40-57(1306-1317).

When we administer ketamine to any patient, we need to remember that it induces a powerful dissociative or "dream-like" state. On sudden awakening this agent sometimes has a propensity to enhance the confusional state that momentarily exists between the unconscious and the conscious. This is known as the "re-emergence phenomenon" and it can on occasions be as vivid and terrifying as any vision from Dali or Dante. Young children, whose last conscious thought may have been the fear of a needle, and who suddenly awake to the brilliant glare of a hospital lamp, may be momentarily terrified from their subconscious imaginings. To his end it is essential to quickly reassure and orientate them as to their true surroundings. Constant reassurance even whilst they are apparently dreaming will also contribute to a less traumatic re-emergence back into the real world. Enlisting the help of a parent may be invaluable in this regard, as will be reducing all unnecessary external stimuli, such as the bright glare of hospital lights.

KETAMINE (PARENTERAL)

Introduction

Ketamine is an N-methyl-D-aspartate (NMDA) antagonist that induces **dissociative anaesthesia** due to dissociation between the thalamocortical and limbic systems.

It is a potent short acting **sedative, amnesic, analgesic** and **anaesthetic** agent.

It has relatively little effect on the respiratory centre or cardiovascular system at the usual therapeutic doses used, making it an ideal short acting anaesthetic agent for use in the Emergency Department for short painful procedures or procedures that require absolute stillness in the patient.

Unlike most other anaesthetic induction agents, a patent airway is maintained partly by virtue of relatively unimpaired pharyngeal and laryngeal reflexes.

It is most useful for use in children, but can be used in adults as well.

Ketamine should be used by or under the direction of medical practitioners experienced in airway management respiratory support.

As with any anaesthetic agents full resuscitative equipment and drugs should be at hand.

Ketamine is on the World Health Organization's List of Essential Medicines, as one of the most important medications needed in a basic health system.

Ketamine has also become a drug of abuse, where it has the "street name", of "**special K**".

See also separate document on:

- **Ketamine -Sublingual Wafer (in Drugs folder).**

History

Ketamine was first synthesized in **1961** by **Dr. Calvin Lee Stevens**, (1923 - 2014) a professor of organic chemistry who worked at Wayne State University and Parke - Davis Laboratories.

After promising preclinical research in animals, ketamine was introduced to testing in human prisoners in 1964. These investigations demonstrated ketamine's short duration of action and reduced behavioural toxicity made it a favourable choice over phencyclidine (PCP) as a dissociative anaesthetic

It was approved for human use in 1965.

It was given FDA approval as an anaesthetic agent in 1970.

It was then used for wounded soldiers during the Vietnam War.

During the 1980s it began to be used as a drug of abuse, favoured because of its dissociative effects. In 1995 it was listed by the DEA as an emerging drug of abuse.

In 1999 ketamine was listed as a controlled substance in the United States.

Chemistry

Ketamine, is a phencyclidine derivative.

Preparation

Ketamine as:

Ampoules:

- 200 mg / 2 ml vial.

Mechanism of Action

Ketamine is an **N-methyl-D-aspartate (NMDA) antagonist** that induces dissociative anaesthesia due to dissociation between the thalamocortical and limbic systems, effectively dissociating the central nervous system from all outside stimuli (touch, sight, sound, taste, smell).

It also interacts with opioid receptors.

Pharmacokinetics

Absorption:

- Ketamine is given IM or IV

  Ketamine is rapidly absorbed following IM administration.

  The IM route is useful when IV access is problematic, however sedation is less readily titrated by this route and time of onset and recovery times will be more prolonged.

Distribution:

- Ketamine (as a hydrochloride) is rapidly and extensively distributed throughout the body into highly perfused tissues including the brain.
- Ketamine is highly lipid soluble and not highly protein bound
- The mean volume of distribution ranges from approximately 1 - 3 L/kg
- It is unknown if whether ketamine is excreted into human breast milk

- Placental transfer in humans can occur.

Metabolism and excretion:

- Ketamine undergoes extensive hepatic metabolism by the cytochrome P450 system, mainly by CYP3A4 and 2B6.

- Some metabolites are active, including norketamine which is about 1/3 to 1/5 as potent as ketamine

- Redistribution half - life is 5 - 15 min and the elimination half - life is about 1 - 2 hours.

Pharmacodynamics

Actions include:

1. CNS:

   Dissociation:

   - The patient passes into a "trance like" state with the eyes open but the patient is not responding.

     Dissociation has been defines as: "A trancelike cataleptic state characterized by profound analgesia and amnesia, with retention of protective airway reflexes, spontaneous respirations, and cardiopulmonary stability," [6]

   See also Appendix 1 below for the unique dose related spectrum of clinical effects of ketamine.

2. Analgesia:

   - Excellent analgesia is seen with ketamine, even at sub-anaesthetic doses. [1]

   - Tissue damage causing persistent nociception, and neuropathic pain states, can activate N-methyl-D-aspartate (NMDA)-receptors in the spinal dorsal horn, producing the phenomenon of "wind-up", with spinal hyperexcitability, allodynia and hyperalgesia (central sensitisation).

     NMDA-receptor antagonists (such as ketamine and methadone) can be used as an **adjunct to opioids** to attenuate this central sensitisation, with consequent improved analgesia. This technique is particularly useful in patients who are opioid-tolerant.

4. Amnesia is usually profound

5. Airway is maintained:

    - Pharyngeal and laryngeal reflexes are maintained.

6. Respiratory:

    - This is usually well maintained, though there may be depression with IV higher dosing.

    - Ketamine has some bronchodilator activity.

7. Cardiovascular state:

    - Blood pressure and heart rate tend to **increase** slightly.

8. Ocular:

    - Nystagmus is typical

    - The patient's eye may remain open - (an unsettling aspect for relatives - requiring strong reassurance on occasions).

9. Normal or slightly increased muscle tone is maintained.

10. Random purposeless movements:

    - Muscle twitching or myoclonic jerking are frequently seen.

Indications

1. Procedural sedation and analgesia for short painful procedures:

    - Especially those requiring immobilisation, examples of these include: lacerations - especially of the face, and fracture reduction.

    - Dissociative sedation is very useful for children, where traditionally is was mostly used, but can also be used for adults.

    - Dissociative sedation is extremely useful for procedures in the mentally disabled, who are often uncooperative.

2. Induction (and maintenance) of anaesthesia:

    - Especially useful for rapid sequence inductions in patients with severe asthma. Neuromuscular blocker is coadministered to eliminate the possibility of laryngospasm.

3. Procedural sedation for investigations such as CT/MRI imaging:

- For procedures that require motionless sedation, such as computed tomography or magnetic resonance imaging, ketamine is less effective because of occasional random movements typical of dissociative sedation, which may result in poor-quality radiographic study results.

- It does however have the significant advantage of preservation of airway and respiration, so may be suitable for short CT imaging protocols.

4. **Adjunctive** therapy to opioids in patients with intractable pain.

5. It may have a role in patients with **excited delirium**

Contraindications/ Precautions

Absolute:

Avoid in children < 12 months: [5, 6]

- There is an increased risk of airway complications in children less than 12 months and particularly less than **3 months.**

Relative

The following are **precautions** (rather than absolute contraindications):

1. Non-fasted patients (as with any anaesthetic agent).

2. Conditions that may be worsened by an **increase in blood pressure** and/or heart rate:

    - Poorly controlled hypertension, stroke, intracerebral haemorrhage, angina, recent MI, stenotic valvular heart disease, tachyarrhythmias, chronic heart failure, thyrotoxicosis.

3. Procedures that will stimulate the posterior pharynx.

    - Major procedures stimulating the posterior pharynx (eg, endoscopy) increase the risk of laryngospasm, whereas typical minor ED oropharyngeal procedures do not.

4. Caution when used in association with other CNS depressant drugs, including **ethanol.**

Despite traditional cautions against the use of ketamine in psychotic patients, it has been used in these scenarios without adverse effect. [9]

Hallucinations, irrational behaviour and other effects, should they occur, can usually be controlled with reassurance, or standard agents such as benzodiazepines, olanzapine, droperidol.

Head trauma and seizure disorders are no longer considered contraindications to ketamine use. [6]

Pregnancy:

Ketamine is classified as a category B3 drug with respect to pregnancy.

B3 drugs are those drugs which have been taken by only a limited number of pregnant women and women of childbearing age, without an increase in the frequency of malformation or other direct or indirect harmful effects on the human foetus having been observed. Studies in animals have shown evidence of an increased occurrence of foetal damage, the significance of which is considered uncertain in humans.

Reports of congenital malformations following ketamine use during pregnancy have not been located.

However, maternal use of ketamine, especially at high doses or prolonged use near term may increase the risk of maternal and neonatal complications such as increased maternal blood pressure, increased uterine tone, respiratory depression and increased skeletal musculature tone in newborns.

Ketamine is considered safe to during pregnancy when used at the lowest effective dose for the shortest duration possible.

Breastfeeding:

There is limited information describing the use of ketamine during breastfeeding.

Ketamine undergoes rapid degradation in the plasma, which may limit the amount of ketamine excreted into breast milk.

Ketamine is considered safe to use during breastfeeding when used at the lowest effective dose for the shortest duration possible.

However, observe the breastfed infant for potential adverse effects, such as drowsiness, poor feeding and sleeping pattern changes.

Adverse Effects

These may include:

1. Transient **apnoea or respiratory depression**

    - This is the most common potentially serious adverse effect.
    - Although mild stimulation of respiration is most commonly seen, respiratory depression, even apnoea, can occur, usually in the setting of excessively rapid and high dose IV administration.

2. Hypersalivation:

   - Gentle suctioning is useful to remove excess secretions, but this should only be at the **anterior** buccal cavity. Deeper airway suction may aggravate airway reflexes.

   - *Prophylactic* anticholinergics are **no longer** recommended.

   - Atropine **(0.02 mg/kg to a maximum of 0.6 mg IV/IM)** or glycopyrrolate may be considered if hypersalivation occurs that is not readily controlled by gentle suction.

3. Transient laryngospasm

4. Vomiting, (uncommon, risk slightly greater by IM route)

   - Prophylactic ondansetron can slightly reduce vomiting

5. Myoclonic jerking movements

6. Allergic reactions, (very uncommon):

   - A benign evanescent patchy erythematous rash about the upper torso may be seen, (presumably due to an "anaphylactoid" type histamine release).

   - True anaphylaxis is very rare, but has been well described in isolated case reports. [11]

7. **Emergence phenomena:**

   - Emergence reactions are relatively frequent occurring in approximately 10 % of patients.

   - These may take the form of hallucinations, both visual and auditory.

     Severity may range from pleasant dream-like states or depersonalisation, to very vivid hallucinations to frank delirium.

   - Most patients cannot recall the reactions but a few can recall them as an unsettling experience.

   - Emergence phenomena, occur more commonly beyond mid-adolescence (after about 15 years). They are also more common in the elderly (> 65 years).

   - The duration of these reactions is usually no more than a few hours.

   - **Simple and constant reassurance** is usually sufficient treatment, but occasionally benzodiazepine sedation may be required.

Prophylactic benzodiazepines are no longer recommended.

Maintaining minimal sensory stimulation will help reduce the effects of emergence phenomenon.

Maintain the patient in a quiet area with **dim lighting**, when possible.

Dosing

Ketamine effects are dose related and can be divided into 4 levels: [8]

On an IV basis these are:

1. **An analgesic dose** (0.15 - **0.3** mg/kg IV):

    - At this dose range, ketamine has a minimal effect on perception or emotion but is a powerful analgesic.

2. **A "Recreational dose"** (0.2 - **0.5 mg/kg IV):**

    - This provides very good analgesia but can induce distortions of perception.

      Patients can converse and follow commands but may frequently hallucinate. Constant reassurance may be necessary.

3. **A partially dissociating dose (0.4-0.8 mg/kg IV):**

    - Patients have some awareness and can make some purposeful actions, but they are not fully connected to the outside world.

      Some may tolerate it but others may find it unsettling or even terrifying.

      Emergence reactions occur when patients are partially dissociated.

4. **A fully dissociated dose (> 0.8 - 2 mg/kg IV):**

    - The patient is isolated from all external stimuli. This is the desired state to facilitate a procedure or endotracheal intubation.

      This can be used for RSI, procedural sedation, and states of excited delirium.

      Higher doses really just *prolong the duration of action*; making ketamine a very safe drug to use for things like RSI or procedural sedation.

Induction of anaesthesia:

- **1.0 - 2.0 mg / kg IV (generally around 100 - 200mg IV for an adult).**

  Patients should be cautioned that driving in an automobile, operating machinery or engaging in other hazardous activities should not be undertaken for 24 hours or more (depending on dose and other drugs employed) after anaesthesia.

For procedural sedation IM versus IV:

Route of Administration	**IM**	**IV**
Advantages	No IV necessary	Ease of repeat dosing, slightly faster recovery
Clinical onset	5 minutes	30-60 seconds
Effective sedation	15-30 minutes	10-20 minutes
Dose	**4 -5 mg/kg IM** (*Published product information including, the AMH, quote a dose range up to 10 mg/kg IM - even 13 mg/Kg IM - as the "maximum" dose, though this is not commonly used in practice*) *	**1 -1.5 mg/kg slowly IV (1-2 mins)**
Repeat Dosing	**1-2 mg/kg IM** **After 10 minutes if sedation is inadequate.**	**0.5 mg/kg slowly (1-2 mins), or less IV**
Time to discharge (average)	**100 -140 minutes**	**90-120 minutes**

** Anecdotally doses of 20 mg/Kg IM have been **inadvertently** used without ill effect - of course doses this high are **not** recommended, though the point does illustrate the relative safety of ketamine compared to other sedative/ anaesthetic agents, (personal communication Minh Le Cong, July 2017).*

Adjunct to opioid analgesia:

Although opioids can provide rapid and effective pain relief, dosages needed to produce adequate analgesia can also result in adverse effects such as over- sedation and respiratory depression.

In addition, morphine dosed at the frequently recommended 0.1 mg/kg can be ineffective in controlling severe acute pain.

Low-dose ketamine can be used as an analgesic adjunct to morphine for the treatment of severe acute pain.

- A dose of **0.15 mg/kg - 0.3 mg/kg IV** is given. [7]

Analgesia adjunct for intractable pain:

Ketamine can also be given as a **low dose continual infusion.**

It can be delivered by Patient Controlled Analgesia - (P.C.A) devices.

- The infusion dosage rate is: **0.1 - 0.3 mg / kg / hr.**

Excited delirium:

Ketamine sedation has been shown to be effective and safe in agitated patients with a psychiatric illness in the aeromedical setting and has *not* led to worsening agitation in the subsequent 72 hour period. [9, 10]

Ketamine sedation may also be a useful way to transport violent/ severely agitated psychiatric patients by road ambulance, or to quickly and safely get control in the ED setting.

IM:

- **Ketamine 4 - 5 mg/kg IM has been proposed for intimal control of the patient.**

IV:

- **If IV access is available:**

  1-1.5 mg/kg initial bolus with a follow-up maintenance infusion of 1 mg/kg/hr as an initial rate, then titrated to response

Currently ketamine sedation is generally considered a "second line" option, after standard IM antipsychotic agents have been used.

Appendix 1

The unique clinical spectrum of ketamine anaesthesia: [6]

Rather than displaying the dose-response continuum observed with all other procedural sedation and analgesia agents, ketamine dissociation appears at a ***dosing threshold*** *of approximately 1.0 to 1.5 mg/kg intravenously (IV) or 3 to 4 mg/kg intramuscularly (IM).*

In smaller doses, ketamine exhibits analgesia and disorientation. Once the dissociative threshold is reached, administration of additional ketamine does not enhance or deepen sedation, as would be the case with opioids, sedative-hypnotics, or inhalational agents. For these other agents, the more drug administered, the more the patient progresses along the sedation continuum, with increasing probability of ventilatory depression.

In contrast, the quantity of ketamine administered has no clinically important effect on airway integrity and respirations ***within the range of clinically administered doses and using standard administration methods.*** *Accordingly, dissociative sedation can be readily achieved by administration of a single IV or IM loading dose, and the only need for titration, in contrast to other sedatives, is to maintain the dissociative state over time.*

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