

Ketamine – It's Not Just for Anesthesia Anymore!

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OBJECTIVES

- ▶ Discuss pharmacology of Ketamine.
 - ▶ List indications for the use of Ketamine infusions in pain management services.
 - ▶ Describe adverse effects of Ketamine infusions.
 - ▶ Identify dosing parameters and nursing implications
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Ketamine

- ▶ FULL GENERIC NAME: Ketamine hydrochloride
- ▶ BRAND NAME: Ketalar
- ▶ PHARMACOLOGICAL CLASSIFICATION: anesthetic agent for human and veterinary procedures
 - Schedule III drug under Controlled Substance Act (1997) because it *can lead to physical and psychological dependence*.
- ▶ LEGAL CLASSIFICATION: **DANGEROUS DRUG**
 - ▶ *This means it is illegal to sell without a DEA license and illegal to buy or possess without a license or prescription.*

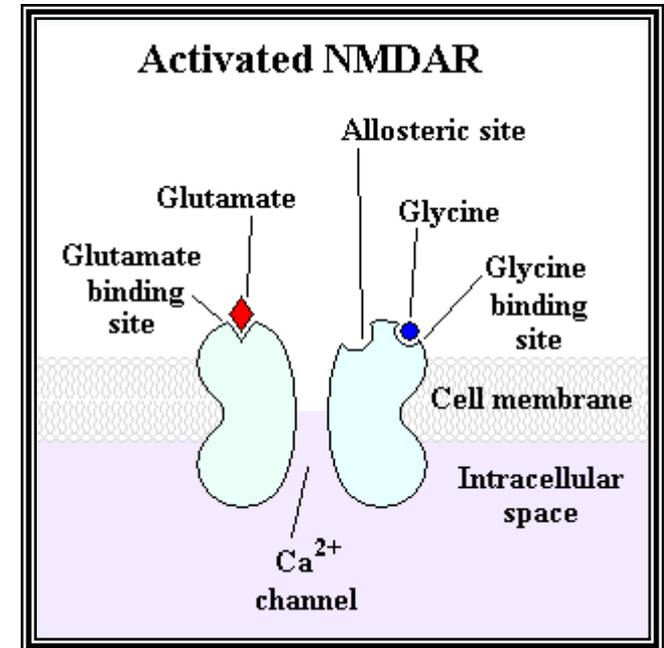
HISTORY

- ▶ Ketamine was first synthesized in 1962 in an attempt to find a safer anesthetic alternative to PCP (phencyclidine)
 - PCP: as an anesthetic was more likely to cause hallucinations, mania and neurotoxic effects (seizures).
- ▶ The drug was first used on American soldiers during the WWII and the Vietnam War.

Pharmacology

▶ Mechanism of action

- The NMDA (N-methyl-D-aspartate) receptor, belongs to a family of cellular receptors that mediate excitatory nerve transmission in the brain.
- An open NMDA channel allows calcium ions to flow into the neuron which plays a critical role in “synaptic plasticity” which is the cellular mechanism for *learning* and *memory*.



Pharmacology

- ▶ Ketamine is a **NMDA Antagonist**...
- ▶ Mechanism of action
 - Ketamine **blocks** the flow of ions NMDA receptors on neurons
 - Blocks the ability to process information...
 - → this results in a state of “dissociative anesthesia”
 - → sensory loss, analgesia, amnesia without actual loc

Pharmacodynamics

- **Dosing**

- Induction

- IV: 1.0 – 2.5 mg/kg
- IM/ rectal: 5 – 10 mg/kg

- Sedation/Analgesia

- IV: 0.5 – 1.0 mg/kg
- IM/ rectal: 2.5 – 5.0 mg/kg
- PO: 5 – 6 mg/kg

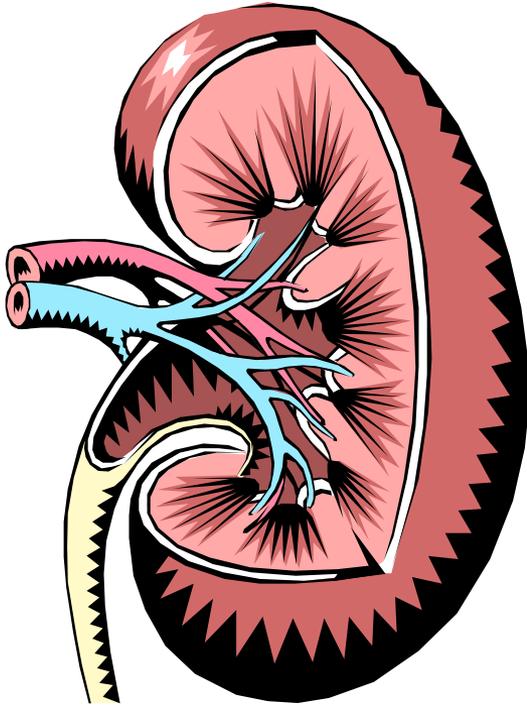


Pharmacokinetics

- ▶ Onset of action
 - IV: < 30 seconds
 - IM: 3 - 4 min
- ▶ Peak effect
 - IV: one minute
 - IM: 5 – 20 minutes
 - PO: 30 minutes



Pharmacokinetics



▶ Duration

- IV 5 – 15 minutes
- IM 12 – 25 minutes
- Epidural 4 hours

▶ Excretion

- metabolized in the liver
- excreted via renals

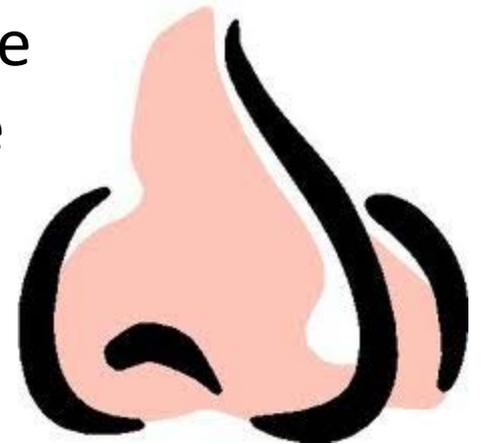
ROUTES

- ▶ Intravenous
- ▶ Intramuscular
- ▶ Subcutaneous
- ▶ Oral
- ▶ Rectal
- ▶ Nasal
- ▶ Transdermal
- ▶ Epidural
- ▶ Intrathecal
- ▶ Intra-articular



ROUTES

- ▶ Oral ketamine mixed with cola syrup has been used as a premed in KIDS in a dose of 6 - 8 mg/kg.
 - PO administration is extremely **bitter** to taste alone.
- ▶ Intranasal ketamine is undergoing trials as a safe non-opioid analgesic alternative for the treatment of moderate to severe postoperative pain. Intranasal route has been used as premed for KIDS.



ROUTES

- ▶ Epidural dose of 20-30 mg/day has been reported to be effective in complex regional pain syndrome (CRPS)
 - Epidural ketamine is useful as an adjuvant to morphine for postoperative pain relief.
- ▶ Studies of a transdermal ketamine patch reported significant analgesic effects for postop pain after gyn surgery.



ROUTES

- ▶ Although ketamine is often used in topical preparations (gels/ointments) for chronic pain, there are no controlled studies to substantiate its beneficial effects.
 - ▶ Studies underway proposing that intra-articular prophylactic ketamine and local anesthetics might reduce arthritic pain.
- 

CONTRAINDICATIONS

- ▶ Hypersensitivity to Ketamine
 - ▶ Severe hypertension
 - Angina
 - CHF
 - ▶ Thyrotoxicosis
 - ▶ Elevated ICP
 - ▶ Aneurysms
 - ▶ Psychotic disorders
- 

PRECAUTIONS

- ▶ mild to moderate hypertension, tachycardia, or acute myocardial infarction (AMI)
 - ▶ beta-blockers (monitor closely due to the block of ketamine's sympathetic cardiac stimulation)
 - ▶ neurotic traits or psychiatric illness
 - ▶ alcohol intoxication or history of alcohol abuse
 - ▶ ? Seizures
- 

PRECAUTIONS

- ▶ glaucoma or elevated intraocular pressure
 - ▶ hyperthyroidism or receiving thyroid replacement
 - ▶ pulmonary or upper respiratory infection
 - ▶ intracranial mass lesions, presence of head injury, globe injuries or hydrocephalus
 - ▶ receiving other medications that may cause sedation (for example, antihistamines, benzodiazepines, opioids or anticonvulsants) which may increase the risk for sedation and respiratory depression
- 

Side Effects (<10%)

▶ Cardiovascular system:

- Myocardial stimulant
- Increases systemic arterial pressure
- Increases heart rate
- Increases cardiac output

○

*Reported adverse effects are based on anesthetic doses of ketamine.



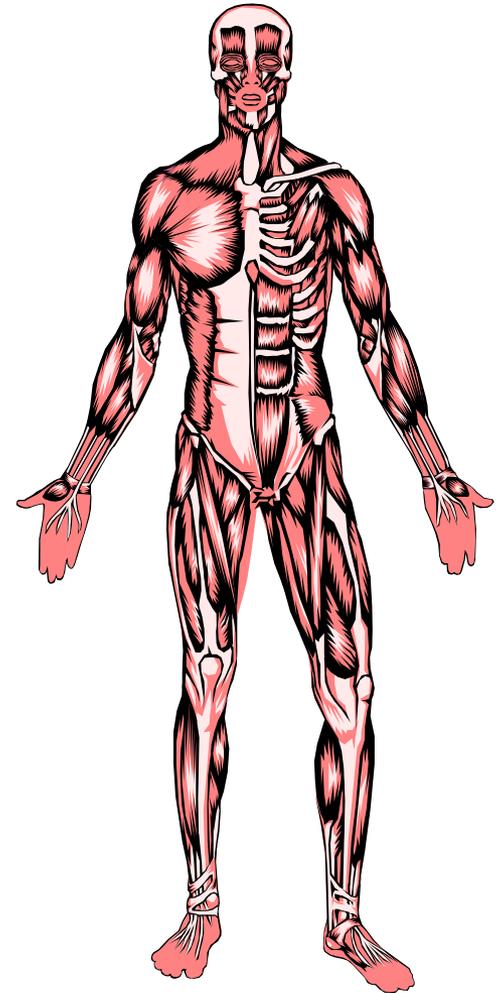
Side Effects



- ▶ Pulmonary system:
 - Bronchial smooth muscle relaxant
 - *Can be as effective as inhalational agents in preventing bronchospasm!*
 - Increases pulmonary arterial pressure
 - Increases salivary & tracheobronchial secretions

Side Effects

- ▶ Neurological system:
 - Seizure threshold is not altered
 - Increase in cerebral metabolism, blood flow, & ICP
- ▶ Other:
 - Increases uterine tone without adverse effects on uterine blood flow
 - Does not release histamine



Side Effects (1-10%)

- ▶ *Cardiovascular*: bradycardia, hypotension
 - ▶ *Dermatologic*: pain at injection site, skin rash
 - ▶ *Gastrointestinal*: nausea, vomiting, anorexia
 - ▶ *Ocular*: nystagmus, diplopia
 - ▶ *Respiratory*: respiratory depression (usually have normal pharyngeal-laryngeal reflexes)
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Side Effects

- ▶ At high doses, ketamine has also been found to bind to opioid mu receptors and sigma receptors which causes the loss of consciousness



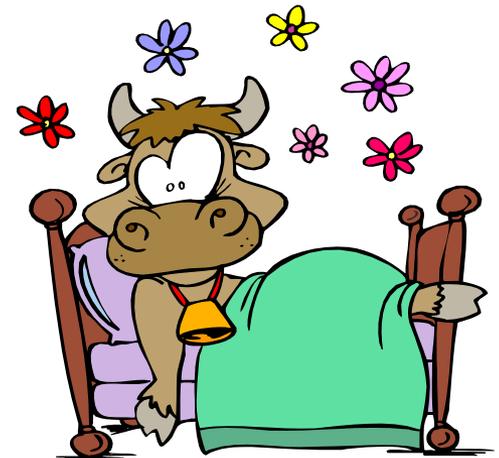
NEUROPHARMACOLOGY



- ▶ Ketamine, is primarily a non-competitive NMDA receptor antagonist.
 - Evidence for this is reinforced by the fact that NARCAN, an opioid antagonist, does not reverse the analgesia.
- ▶ **Atipamezole** (brand name Antisedan) 1 to 2.5 mg per kilogram may be used as reversal

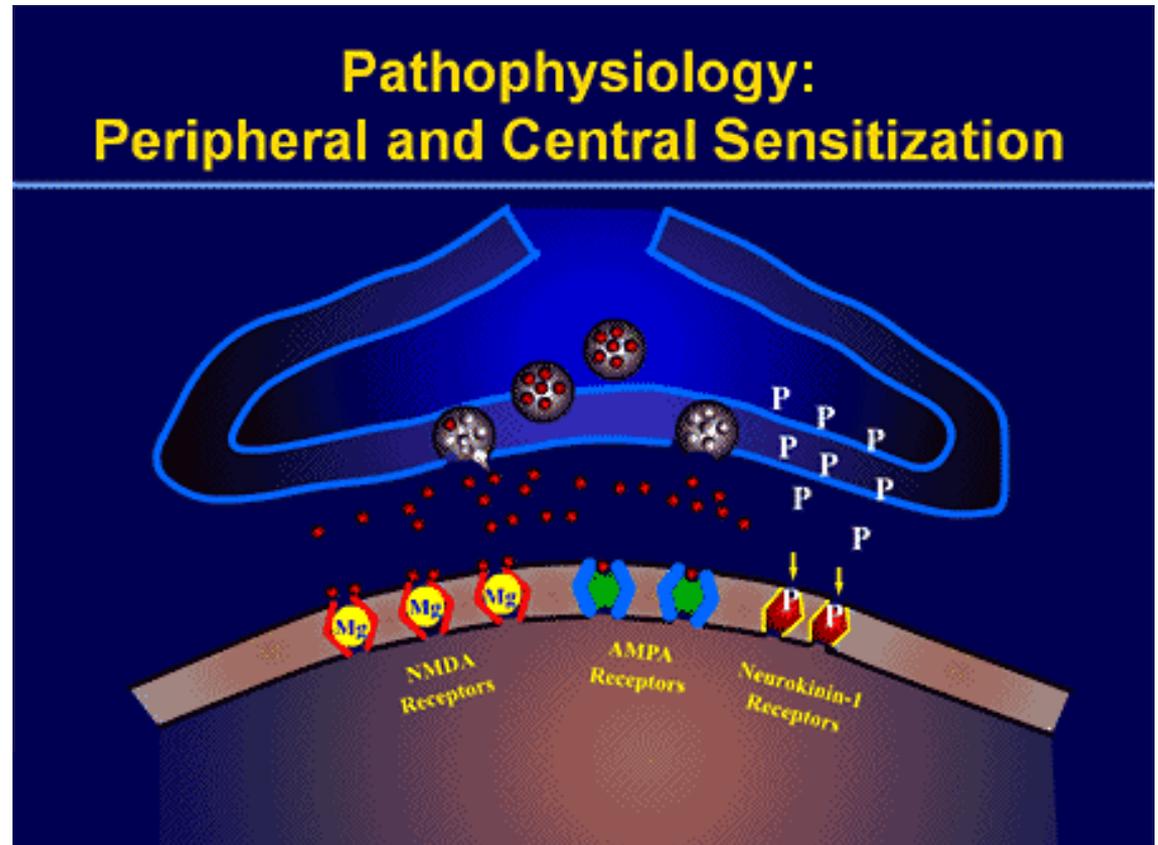
“DISSOCIATIVE ANESTHETIC”

- ▶ Produces an atypical behavioral state.
 - State of sedation
 - Immobility
 - Amnesia
 - Marked analgesia
 - Feeling of dissociation from the environment
 - No true unconsciousness



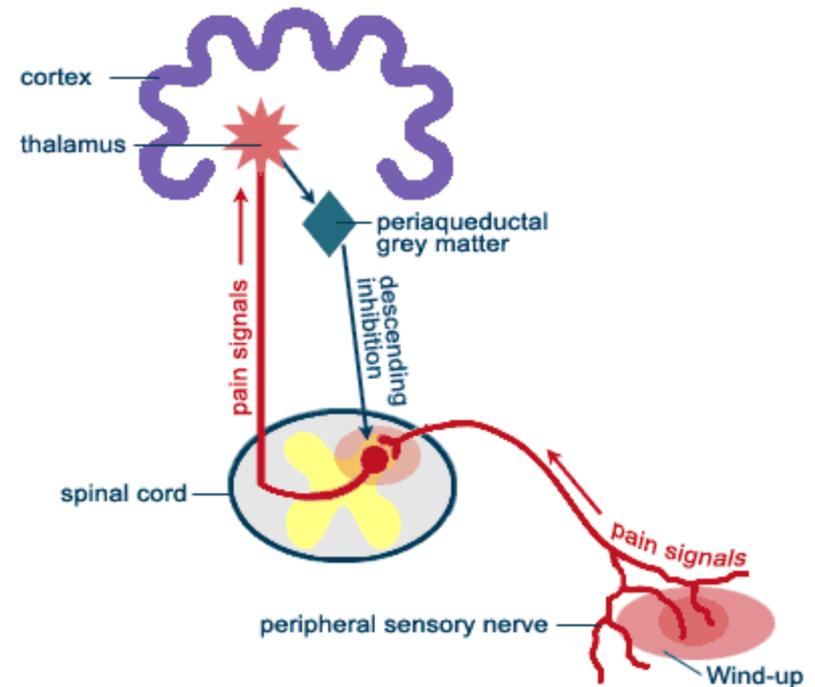
Effect on PAIN

- ▶ Strong pain stimuli activate NMDA receptors and produce hyperexcitability of dorsal root neurons. This induces central sensitization, wind-up phenomenon, and pain memory.

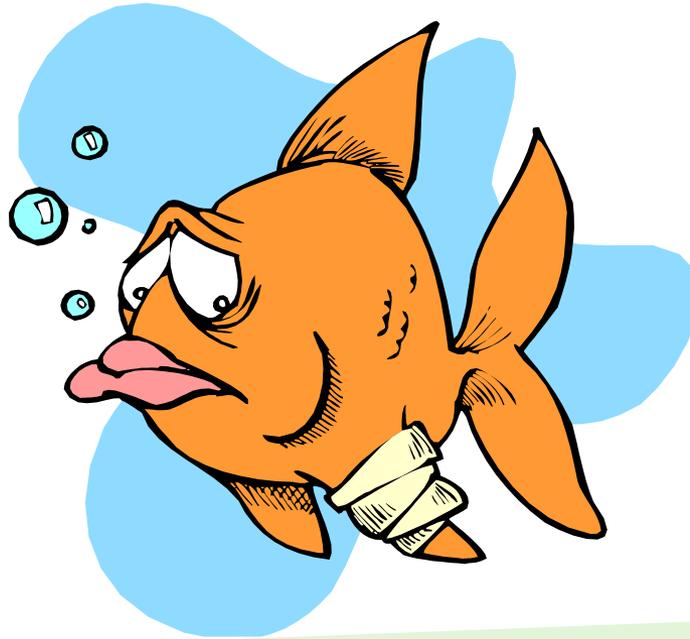


Effect on PAIN

- ▶ Ketamine can block the initiation of central sensitization (pain threshold changes, responses to pain magnified) caused by stimulation of the pain pathways



The Many Uses of Ketamine



Preemptive analgesia

- ▶ Pain is thought to be inadequately treated in ½ of all pts
- ▶ In addition to the immediate unpleasantness, *painful experience can get imprinted on the nervous system, amplifying the response to subsequent noxious stimuli (hyperalgesia) and typically causing painless sensations to be experienced as pain (allodynia).*
- ▶ Prior painful experiences are a known predictor of increased pain and analgesia requirement in subsequent surgeries.
- ▶ IV opiates or ketamine given before incision can decrease wound hyperalgesia for several days after surgery.

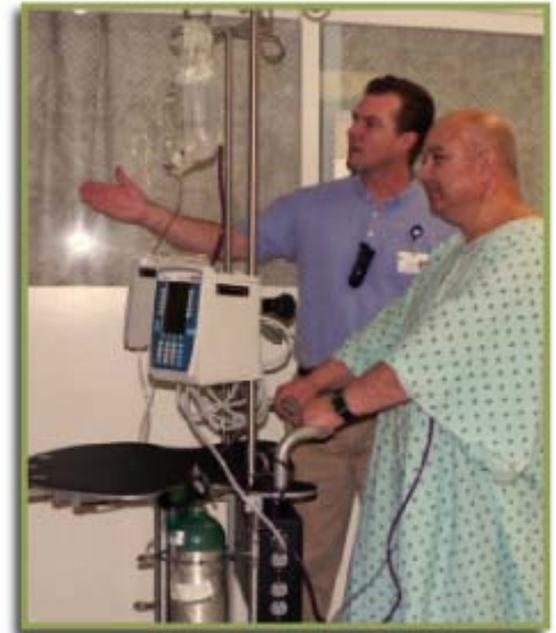
Preemptive analgesia - studies

- ▶ “preemptive” effect from epidurally administered morphine & ketamine prior to surgical incision in 60 pts undergoing upper abdominal surgery under GA
- ▶ Ketamine just before skin incision followed by a continuous infusion intra-operatively resulted in lower VRS-scores for both acute & chronic postop pain after thoracotomy.

0		No Hurt
1		Hurts Little Bit
2		Hurts Little More
3		Hurts Even More
4		Hurts Whole Lot
5		Hurts Worst

Postoperative pain relief

- ▶ Intraop small dose ketamine successfully used as an adjunct to opioids for postop analgesia.
- ▶ *Reduces postop morphine needs*
- ▶ *Improves mobilization 24 hours*



Bell RF, Dahl JB, Moore RA, Kalso E. Perioperative ketamine for acute postoperative pain. *The Cochrane Database of Systematic Reviews*. 2006; 3; 1-61.

- ▶ N = 37 trials (2240 participants)

- ▶ Methods:
 - Search from 1966-2004
 - Randomized, controlled trials being treated with perioperative ketamine or placebo

- ▶ Results & Conclusion:
 - Subanesthetic doses of ketamine **reduce rescue analgesia requirements, pain intensity, PCA morphine consumption, PONV.**
 - Adverse effects were mild or absent.

Joly V, Richebe P, Guignard B, Fletcher D, Maurette P, Sessler DI, Chauvin M. Remifentanil-induced postoperative hyperanalgesia and its prevention with small-dose ketamine. *Anesthesiology*. 2005; 103: 147-55

▶ Methods:

- N = 75
- Major upper abdominal surgery
- Treatment groups
 - Varying doses remifentanil with or without Ketamine

▶ Results:

- Hyperanalgesia with just remifentanil was greater

▶ Conclusion:

- Large doses of intraop remifentanil triggers postop hyperanalgesia
- **Hyperanalgesia is prevented by small-dose ketamine**
 - NMDA pain-facilitator process

Adam F, Chauvin M, DaManoir B, Langlois M, Sessler DI, Fletcher D. Small-dose ketamine infusion improves postoperative analgesia and rehabilitation after total knee arthroplasty. *Analgesia & Anesthesia*. 2005;100: 475-80.

- ▶ N = 40
- ▶ Elective total knee arthroplasty with GA & continuous femoral nerve block
- ▶ Methods:
 - Treatment groups
 - 1) Ketamine infusion
 - 2) Placebo
- ▶ Results & Conclusions:
 - **Group 1 required less morphine, reached 90 ° flexion more rapidly.**
 - No difference in side effects

Cancer related pain

- ▶ Ketamine has been used as an adjuvant analgesic for the treatment of cancer related pain when other agents fail or are intolerable.
- ▶ Pain scores ↓ from ave. 8 to 1
- ▶ Potentiation of analgesia noted when ketamine is added to the mixture.
- ▶ Ketamine has an *opioid tolerance sparing* effect.
- ▶ Ketamine is a useful adjuvant analgesic for the treatment of cancer related pain when other agents fail or are intolerable.

Neuropathic pain

- ▶ Ketamine infusions over a period of few months were effective in providing pain relief in a patient with neuropathic pain.
- ▶ Low dose PO ketamine effective in alleviating symptoms of “Restless leg syndrome”
- ▶ World Health Organization (WHO): “Agents, which block the activity of NMDA receptors, are helpful to treat poorly responsive pain syndromes, especially, neuropathic pain. The *addition of ketamine to opioid treatment has been shown to be beneficial in chronic pain.....*”

Complex Regional Pain Syndrome (formerly known as “RSD”)

- ▶ Chronic pain condition
 - ▶ Result of dysfunction in the central or peripheral nervous systems frequently triggered by tissue injury
 - ▶ Changes in the color and temperature of the skin over the affected limb or body part
 - ▶ Intense burning pain
 - ▶ Skin sensitivity
 - ▶ Sweating
 - ▶ Swelling
 - ▶ Old term: RDS - "reflex sympathetic dystrophy syndrome" and "causalgia,"
- 

Neuropathic pain

- ▶ Ketamine over a period of 4 yrs in a pt with severe postherpetic neuralgia achieved good pain relief.
- ▶ Not all patients with nociceptive and/or neuropathic pain respond to ketamine.
 - likelihood of response is increased in the younger patient with a shorter history of pain less than 5 years.



Obstetrics



- ▶ Ketamine used in short procedures where muscle relaxation is not required (e.g. repair of perineal or cervical tears, manual removal of placenta etc.)
- ▶ ↑ uterine tone/no adverse effects on uterine blood flow.
- ▶ Well tolerated by both mother & infant.
- ▶ ↑ incidence of dreaming (43%) during anesthesia
- ▶ Postop delirium rare (3%).
- ▶ Significant rise in BP noted.
- ▶ Ketamine infusions have been used in labor analgesia but may result in an uncooperative parturient.

Brief procedures

- ▶ Used for **short painful procedures**: burns and dressings, I&D of abscesses, operations involving several sites at once in which local anesthetic dose would be exceeded.
- ▶ Due to the **higher rates of laryngospasm** associated with pharyngeal stimulation the drug is not ideally suited for intra-oral or airway procedures
- ▶ It is also used for transporting patients with overwhelming pain, particularly those with malignant disease who are being transferred or mobilized for radiotherapy.
- ▶ It would also appear to have an important use for patients with severe pain who have difficulty in tolerating a course of radiotherapy.

Emergency and disaster medicine

- ▶ It is ideal for transport of critical patients needing minimal anesthetic backup since airway reflexes are maintained under ketamine anesthesia.
- ▶ Types of procedures: amputations, emergency cardioversion, chest tube placements in hypotensive patients



Co-induction agent and TIVA

- ▶ Low dose ketamine is a safe alternative to midazolam for co-induction with propofol
- ▶ It offers better hemodynamic stability



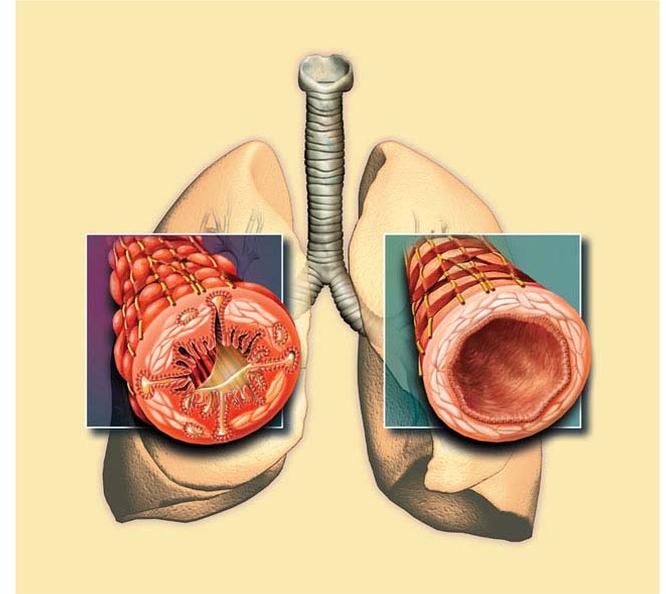
ICU sedation

- ▶ Low dose ketamine can also be used for sedation and analgesia during MAC or in ICU sedation
- ▶ Ketamine was the preferred adjuvant analgesic in cases of sedation lasting longer than 24 hours.



Bronchodilator

- ▶ Increased circulating catecholamine levels lead to bronchodilation.
- ▶ It also has direct relaxant effect on airway smooth muscles making ketamine a preferred agent for asthmatics.
- ▶ It is particularly useful in patients of status asthmaticus when other agents have failed.



Post-operative shivering

- ▶ Low dose ketamine (0.5 mg/kg) administered 20 minutes before end of surgery under GA resulted in lower incidence of post-operative shivering.





Ketamine and the Pediatric Patient

KIDS



▶ MULTIPLE STUDIES

- painful procedures in children with cancer (bone marrow aspiration, biopsy or lumbar puncture)
- procedures undertaken after ketamine sedation were associated with fewer side effects (hypoxia, hypotension and respiratory depression) than with meperidine, and recovery time after the procedure was faster.
- **ORAL KETAMINE EASILY ADMINISTERED AND WELL ACCEPTED BY YOUNG CHILDREN AND PROVIDES PREDICTABLE, SATISFACTORY PREMEDICATION WITHOUT SIGNIFICANT SIDE EFFECTS.**

Dalens BJ, Pinard AM, Letourneau DR, Albert NT, Truchon RJY. Prevention of emergence agitation after sevoflurane anesthesia for pediatric cerebral magnetic resonance imaging by small doses of ketamine or nalbuphine administered just before discontinuing anesthesia.

Anesthesia & Analgesia. 2006; 102: 1056-61.

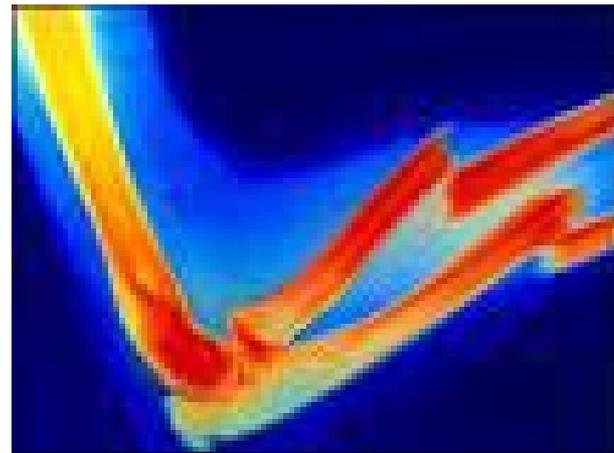
- ▶ N = 90
- ▶ 6 mo to 8 yrs → cerebral MRI under GA

- ▶ Methods:
 - Treatment groups at end of procedure received:
 - 1) Ketamine 0.25 mg/kg
 - 2) Nalbuphine 0.1 mg/kg
 - 3) Placebo

- ▶ Results & Conclusions:
 - Group 3 was most agitated at all times
 - Group 1 & 2 more obtunded at 5/10 mins BUT all groups met discharge criteria at 30 mins
 - **Group 1 were more awake/quiet**

Migita RT, Klein EJ, Garrison MM. Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. *Archives of Pediatric & Adolescent Medicine*. 2006; 160: 46-51.

- ▶ N = 8 studies (1086 participants)
- ▶ Assess safety & efficacy of various forms of analgesia and sedation
- ▶ Results:
 - *Ketamine-midazolam was more effective & had fewer side effects* than fentanyl-midazolam or propofol-fentanyl.



Ketamine Infusion: “Our” Policy

▶ KETAMINE INFUSION SET-UP

- The ketamine infusion is prepared in accordance with pharmacy policies including the application of the orange IV label “Controlled Meds” on the infusion bag.
- A Hospira Gemstar Pain Management Pump is used for all ketamine infusions. Use only epidural tubing (no additional access ports).
- The two nurses verify the drug calculations and pump settings prior to the initiation of the infusion.
- Infusions and lines are changed every 96 hours.

Ketamine Infusion Policy

▶ KETAMINE INFUSION SET-UP

The infusion pump is clearly labeled as an additional safety feature. In addition, the ketamine infusion line is labeled clearly.

- Ketamine infusions are initiated in a critical care patient area (CCU or PACU) for monitoring and titration of initial infusions unless otherwise determined by the prescribing anesthesiologist**
- A loading dose may be ordered at the commencement of the infusion.
- A bolus dose may be ordered for rapid relief of pain.

LOW DOSE KETAMINE

- ▶ During the infusion of low dose ketamine (less than 0.5 mg/kg/hr) hemodynamic abnormalities and respiratory depression are uncommon but usually evident during the first hour of observation.
 - ▶ Low dose ketamine can be started on the floor at the discretion of the prescribing anesthesiologist.
- 

HIGH DOSE KETAMINE

- ▶ Higher dose ketamine infusions should be started and titrated only in areas where frequent observation is assured (CCU, PACU).
 - ▶ Titration of high dose infusions should not be adjusted on the med-surg floors.
 - ▶ Patients who have been successfully titrated to a maintenance infusion dose of ketamine are candidates for floor care providing that frequent VS obtained as well as assessments for dysphoria and airway patency can be performed.
- 

Monitoring

- ▶ Check VS and Pain scores and Sedation levels and look for adverse effects 15 minutes after IV dose and 30 minutes after oral dose and with any dose increase, then q2h
- ▶ Stop drug if SBP is less than 85, HR less than 60, RR is less 10, or intolerable psychotomimetic effects occur
 - Nystagmus, blurry vision, excessive lacrimation/salivation, tachycardia, hallucinations, and vivid dreams

Other key points

- ▶ Be alert to opioid sparing effects!
 - Decrease opioid dose by 25-50% if increased sedation is detected in opioid-naïve patients
 - Decrease opioid dosage by 50% at initiation of treatment for chronic pain and then decrease by 25% every 6-12 hrs
 - Watch closely for withdrawal S&S – diaphoresis, cramps, diarrhea)

Summary

- ▶ Ketamine may have lost favor as a primary anesthetic agent owing to undesirable effects; however low doses may be a useful adjunct in patients suffering from incapacitating chronic and postop pain refractory to conventional pharmacological therapy.
 - ▶ Newer roles of ketamine are emerging.
 - ▶ The incidence of side effects seems to be minimal at these subanaesthetic doses.
- 



VITAMIN K

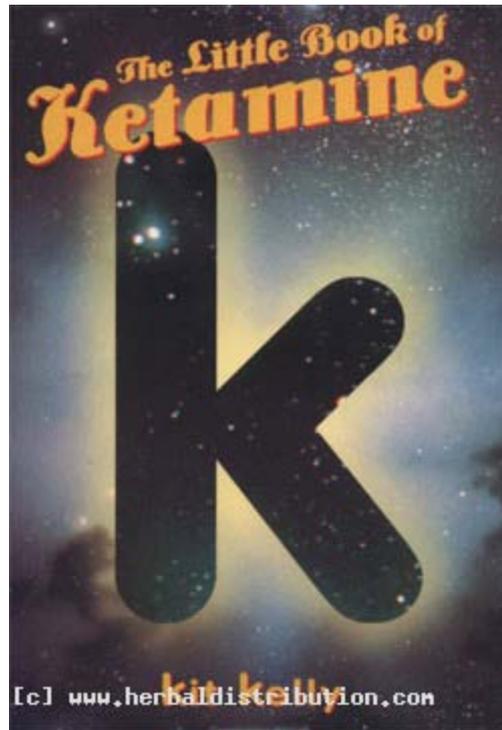
Lagniappe (LAN-yap): Abuse of Ketamine

- In the early 1990's Ketamine became a popular drug of abuse among the **RAVE** and techno scene due to its hallucinogenic properties.
- It is acquired for illegal use mainly by theft from veterinary clinics.



Street Talk

- ▶ Cat killer
- ▶ Cat valium
 - ▶ Green
- ▶ PCP Honey
 - ▶ Jet
 - ▶ Ket



- ▶ Kit kat
- ▶ Purple
- ▶ Special "K"
- ▶ Special la coke
 - ▶ Super acid
 - ▶ Super C
 - ▶ Vitamin K

Abuse of Ketamine

- ▶ Forms : powder for snorting, liquid for injection
 - ▶ Adulterants/Additives : often mixed with MDMA (ecstasy), “Ice” (methamphetamine), benzodiazepines etc
 - ▶ Hallucinogenic dose : 30mg po
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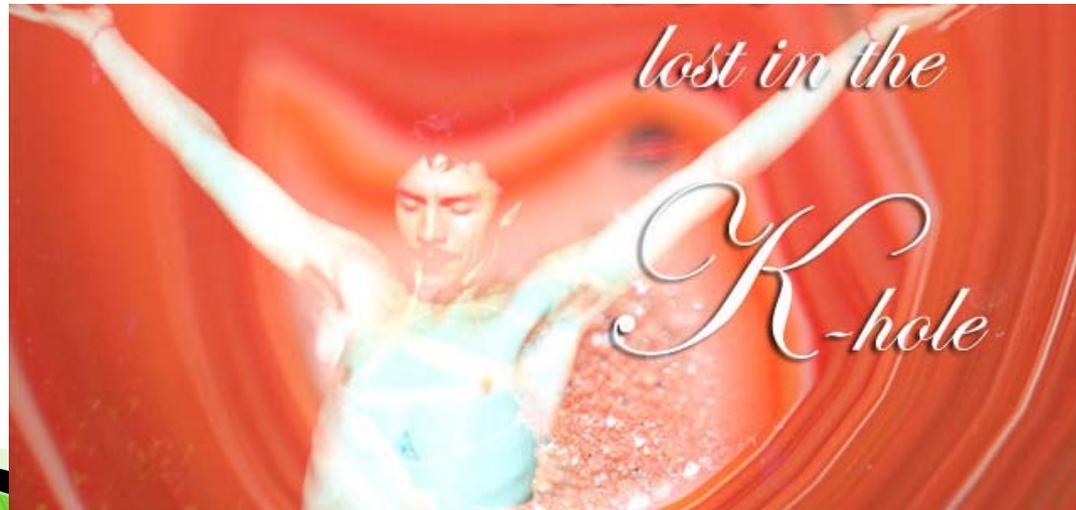
Dream states.....

- ▶ When taken in low doses (25 -100 mg), Ketamine produces a dream like state, altering perceptions and causing dissociation between the user and his or her surroundings (the user is aware of his/her surroundings, but is unable to respond).
- The effects of Ketamine last from 1 to 6 hours, and it is usually 24–48 hours before the user feels completely “normal” again.



K what?

- At high doses, the user will encounter “out of body” experiences referred to as “K-Holes.”
- Very high doses, approximately 1 gram, can be fatal.
- Chronic use ↑ the risk of heart attack and stroke.



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