

KETAMINE

Phencyclidine derivative, like PCP but fewer hallucinogenic effects and delirium
One of 200 derivatives
Introduced in 1962 in animals and humans in 1965
Unique because of lack of depression of CVS and resp systems, though this is not quite true

PHYSIOCHEMICAL

SMALL MOLECULE WT. 238, PKA 7.5
Supplied in saline solution with benzethonium chloride and can contain chlorobutanol which is neurotoxic. Therefore not suitable for intrathecal use

2 optical isomers with different properties (enantiomers)

S(+) 3-4 times more potent and more analgesic
Increased contractility and improved relaxation phase
High doses decreased inotropy

R(-) more emergence reactions

PHARMACOKINETICS

High 1st pass losses if oral/rectal/nasal routes
High availability IV or IM

Ketamine → norketamine → hydroxynorketamine → urine
(20-30% activity)

cyto P450 system
diazepam inhibits ketamine metabolism
clearance is inhibited by halothane (decreased blood flow) and other mediators of hepatic blood flow

elimination 1/2 life 3 hrs--- low protein binding
t1/2 11-16 minutes
anaesthetic doses 2-2.5 mg/kg

PHARMACODYNAMICS

IM dosing results in higher norketamine
Rectally—excellent absorption

10mg/kg no anesthesia but excellent analgesia
high norketamine component
epidurally
rapid absorption into plasma though higher levels in CSF
1/2 life is similar
Ketamine tends towards brainstem
Norketamine tends to cerebellum and cortex

PHARMACOLOGY

CNS

Dose related analgesia and unconsciousness
Enhances thalamic and limbic systems and suppresses the thalamo-neocortical pathways
At subanaesthetic doses it impairs some elements of cognition (vigilance and memory), alters mood states and produces a dose related impairment of sensory processing

“dissociative” state appear cataleptic
eyes open/protective reflexes intact as is cough, corneals and swallowing

onset 30 seconds/ maximal effect 1 minute
pupils dilate / nystagmus / lacrimation / salivation
increased skeletal muscle tone-purposeless movements

duration 10-15 minutes
full orientation 15-30 minutes
emergence phenomena

recent theory relating NMDA receptor antagonists to schizophrenia due to the similarity of responses in healthy patients expose to subanaesthetic doses the effects resembling Schizophrenia are mediated by non NMDA receptors but rather 5HT(2A) and non NMDA glutamate receptors examples—paranoia, thought disorder, negative symptoms, cognitive deficits

DATE RAPE DRUG

short time course due to redistribution
analgesia occurs at much lower serum levels than unconsciousness

maintains motor and somatosensory spinal cord transmission

? drug of choice for spinal cord monitoring

NO synthetase inhibitors mediate effects

- augments the hypnotic effects

May have a protective effect on brain because of NMDA antagonism—given after stable anesthesia. Has been demonstrated in models of brain ischemia

L-arginine a precursor of NO blocks the pressor effect of ketamine

Depresses the cortex and thalamus but stimulates the limbic structures

This leads to a state of FUNCTIONAL DISORGANISATION

SITES OF ACTION

Central and spinal sites

NMDA receptor—n-methyl-d-aspartate---excitatory amine

- implicated in ischemic injury
- secondary hyperalgesia(windup) In the spinal cord its analgesic effect is due to inhibition of wide dynamic range neuronal activity.
- may represent a subgroup of the sigma receptor
- displaces naloxone at opiate receptors with dose dependency acting more at sigma and kappa than mu receptors
- S greater than R form
- Cross tolerance with opiates
- Not reversed by naloxone
- Naloxone does not reverse ketamine induced reductions in secondary hyperalgesia/ unclear if additive or supraditive with narcotics in treating pain

Misc. receptors

- Sigma opiate receptors—dysphoria
- Muscarinic cholinergic receptors in CNS
 - Helps explain potentiation of NMB

No specific receptors

Increased CMRO₂ and more increase in CBF resulting in increased ICP (THE PARTY LINE). It is excitatory in the CNS as shown by increased theta activity and petit mal –Like activity in the hippocampus
And increased sympathetic tone, stimulates the release of norepinephrine

BUT ---many studies were performed in spontaneously breathing patients therefore CO₂ was not controlled

-when controlled there was little change

- no direct effect on cerebral vessels
- ant. fontanelle pressure decreased in ventilated premies

EMERGENCE

Commonest reaction – vivid dreams

- extracorporeal experiences
- thought to occur secondary to ketamine depression of auditory and visual relay nuclei leading to misperception or misinterpretation of these stimuli
- incidence of 10-30% in adults

Factors

- age----greater in adults
- sex female > males
- dose and rapidity of dosing
- personality types
- persons scoring high in psychoticism
- people who dream vividly at home
- significantly block by benzodiazepines and propofol. Not attenuated by music

RESPIRATORY SYSTEM

Shifts CO₂ response curve to the right like the opiates

After bolus there's a transient decrease in rate for 1-3 minutes

- FRC is maintained as is ETCO₂, MV and TV
- The pattern is sometimes irregular with increased intercostal use and less diaphragmatic breathing
- Attenuates the hypoventilation from fentanyl and alfentanil

Upper airway tone

Well maintained as found in EMG studies

When compared to thiopental under Rocuronium there are much better intubating conditions

Bronchomotor tone

Dose dependent attenuation of vagal nerve stimulation induced bronchoconstriction

Smooth muscle relaxant ---as good as halothane

Combination of SNS, direct via ACH receptors and nonspecific. Not mediated by beta receptors

Antagonized by all agonists ---beta blockers, indomethacin, ACH, KCL in vitro

Thought to be due to dose dependent inhibition on extracellular calcium transport

LOCAL ANAESTHETIC PROPERTY

In vivo

Beta blockade will reverse the bronchodilator effects

Despite maintenance of reflexes, silent aspiration can occur—use usual caution

HPV not blocked and the effect of isoflurane is blocked

CVS

Increased myocardial work and O₂ consumption

NOT a significant dose relationship

May exert its effects by altering myocardial ionic currents. This would explain different effects in different species and tissues.

- in congenital heart disease
 - no significant change in shunt direction or fraction
 - if increased PVR—causes slightly greater increase in PVR than SVR
 - PVR is not increased in adults if airway is maintained
 - IN VITRO negative inotrope and chronotrope like a local anaesthetic
 - Decrease catecholamine reuptake peripherally
 - If preexisting anaesthetic IE > halothane may cause hemodynamic depression
 - Mechanism in trauma patients—if no further SNS release possible
 - May increase sensitivity to epinephrine leading to dysrhythmias
 - If use midazolam --- will blunt hemodynamic changes
 - In open heart surgery a mixture of mid/ket/vec resulted in a stable course and earlier extubation
 - In sepsis and CHF Increased in C.O. and BP due to inhibition of proinflammatory cytokines whose release results in alpha receptor hypofunction due to a decrease in adenylylase

Children and Neonates

If mechanically ventilated / therefore no airway obstruction—stable in those with increase PVR or normal PVR

Premies 2mg/kg

Less hypotension than 20ugm/kg fentanyl,
0.5% halothane or .75% isoflurane

Other Effects

1. NMB -- alone it increases NM tone but with NMB it potentiates block
2. IOP – maintained if used with atracurium but increased if with succ
3. Safe in MH

CLINICAL USES

1. Poor Risk Patients

- --resp/CVS—a drug of choice in status asthmaticus
- not recommended in ischemic heart disease unless specific measures to counter CVS effects
- trauma—still need fluid resuscitation
- cardiac tamponade and pericarditis
- congenital heart disease esp. when R to L shunt

2. Sedation

- Many routes/ oral/nasal/rectal/ IM/IV, therefore lots of options
- IV 0.5-1.5 mg/kg
- IM 3-5 mg/kg
- Rectal 8-10 mg/kg
- Nasal 4 mg/kg
- Caudal 0.5 mg/kg
- Epidural – similar dose
- Caudal ketamine and bupivacaine(0.25%) study ketamine was better than bupivacaine alone with easier separation from parents and no urinary retention or motor weakness, better than caudal narcotics except duration of postop analgesia is less/4-6 hours
- ACTA SCAND 1994 38:259-261
Mix mid and ketamine nasally 0.25ml of a mix of 0.56mg kg mid and ketamine 5 mg/kg
83% success rate

- Other reports when compared to narcotics there was less sedation, nystagmus, vomiting with no emergence phenomenon
- Ketamine 4mg/kg used in children 10-42 months
- Long history of safety in ER's and in the therapeutic radiation suites
- CJA1994/41:3/pp221-6 midazolam and ketamine found to offer similar benefits---doses used mid 0.5mg/kg and ket 5mg/kg

3. Maintenance

0.5- 1 mg/kg IV prn
 15-45 ugm/kg/min IV with N2O
 30-90 ugm/kg/min without N2O

4. Wartime

Combination of ketamine/mid/vec TIVA
 Mixed 200 mgK +5mgM + 12mgVEC in 50 mls of N/S
 and used a rate of equal to 1/2 pt wt. In kg
 Simple/effective did cause increase in HR and BP
 but generally young healthy hearts

5. Obstetrics

Parturients at risk of hypotension -- dose 1mg/kg
 At 2mg/kg get neonatal depression and rigidity
 Give midazolam after cord clamped

Small doses can be used for analgesia
 0.25mg/kg q 15=20 minutes

NO human data on teratogenicity. Recent articles in Science have implicated most induction agents, i.v. and inhalational as well as any drugs interacting with GABA and NMDA receptors in massive neuronal dropout when developing fetuses and young children are exposed during periods of synaptogenesis. In rats this was shown in exposures of greater than 4 hours. This is the mechanism in fetal alcohol syndrome.

Studies with N2o and ketamine have demonstrated a synergistic effect on neurotoxicity. This neurotoxicity is blocked by Benzodiazepines. These rats were exposed for 3 hours.

Seems there is a lot we don't know