Sedative/Hypnotics

Joseph Cotten

CA-1 Lecture Series

November 7, 2017

“Hypnotic” vs “Anesthetic”

- General anesthesia is a drug-induced, reversible condition that includes specific behavioral and physiological traits:
  1) unconsciousness, 2) amnesia, 3) analgesia, and 4) akinesia -- with concomitant stability of the autonomic, cardiovascular, respiratory, and thermoregulatory systems.

Drugs we'll cover

- Propofol
- Etomidate
- Ketamine
- Thiopental (2011 no U.S.); Methohexital

Special considerations

- Propofol: Egg allergy, Injection pain, Sepsis, Infusion syndrome
- Thiopental/Methohexital: Acute intermittent porphyria; Arterial injection
- Etomidate: Adrenal suppression
- Ketamine: Postop dreaming, delirium

Intravenous Hypnotics

	Propofol	Thiopental	Etomidate	Ketamine
Preparation	Lip. Emulsion	Alkaline Soln.	Prop. Glycol	Neutral Soln.
Mechanism	GABA	GABA	GABA	NMDA
Analgesia	+	0 (-?)	0	+++
Administration	IV	IV	IV	IM/IV

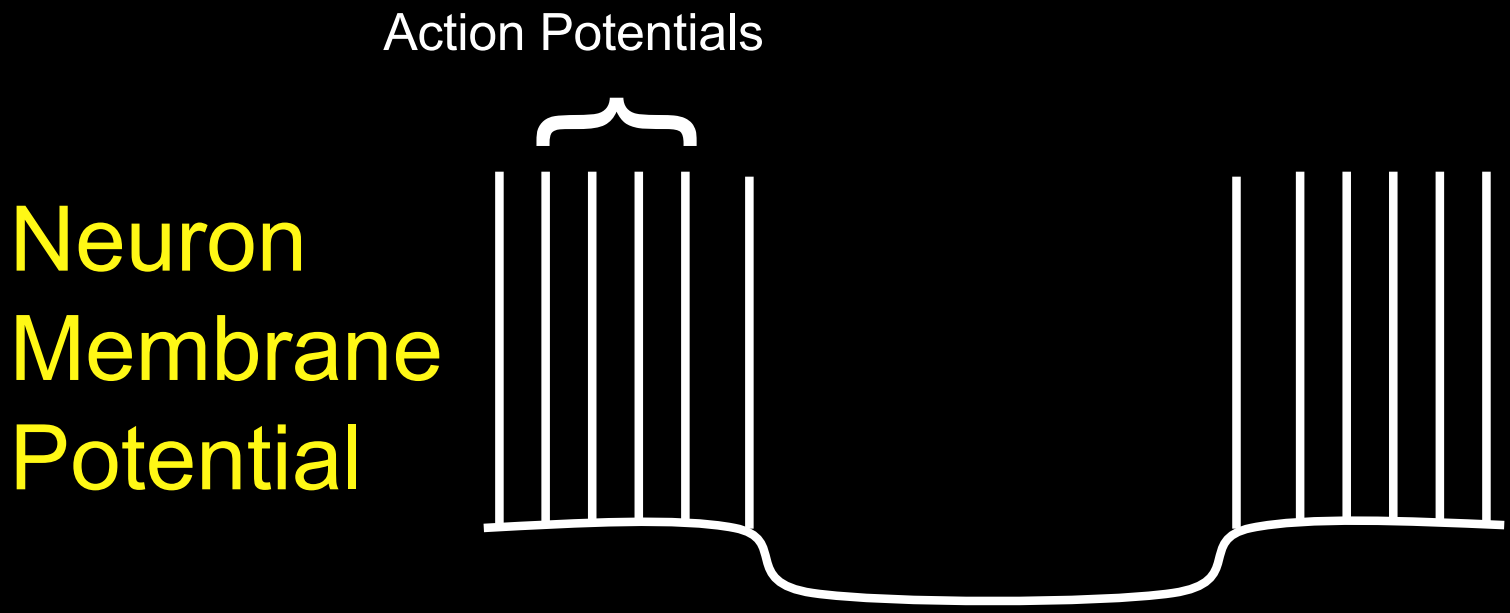
Intravenous Hypnotics

	Propofol	Thiopental	Etomidate	Ketamine
Induction dose (mg/kg)	1.5-2.5	3-5	0.2-0.3	1-2

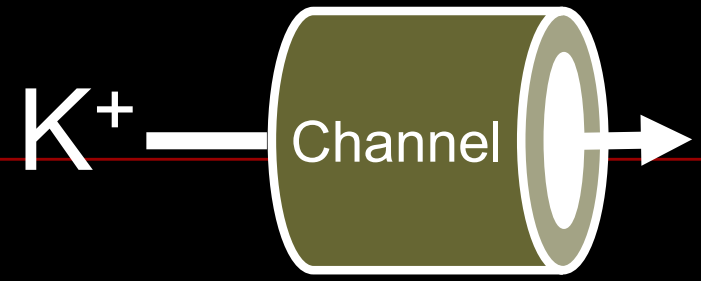
-- Methohexital 1-1.5 mg/kg induction

Anesthetics Hyperpolarize Neurons to Shut Them "OFF" (i.e., make membranes more NEGATIVE

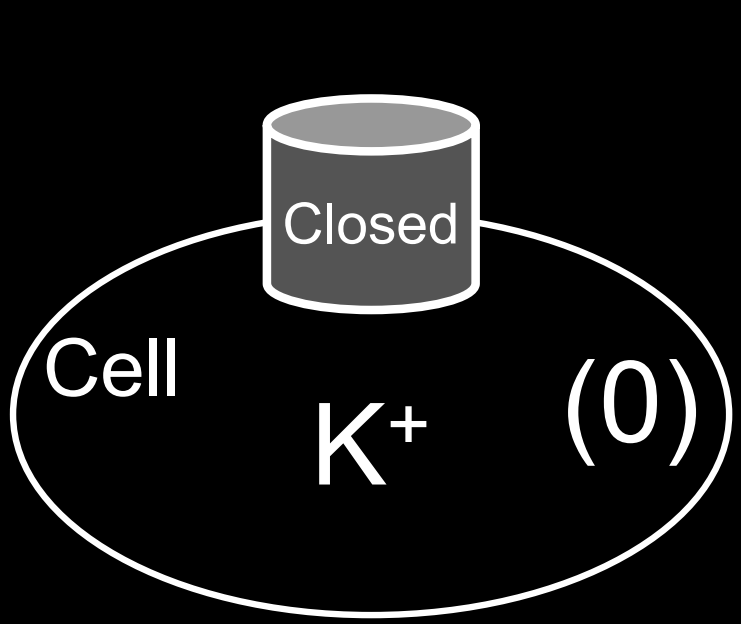
Anesthetic

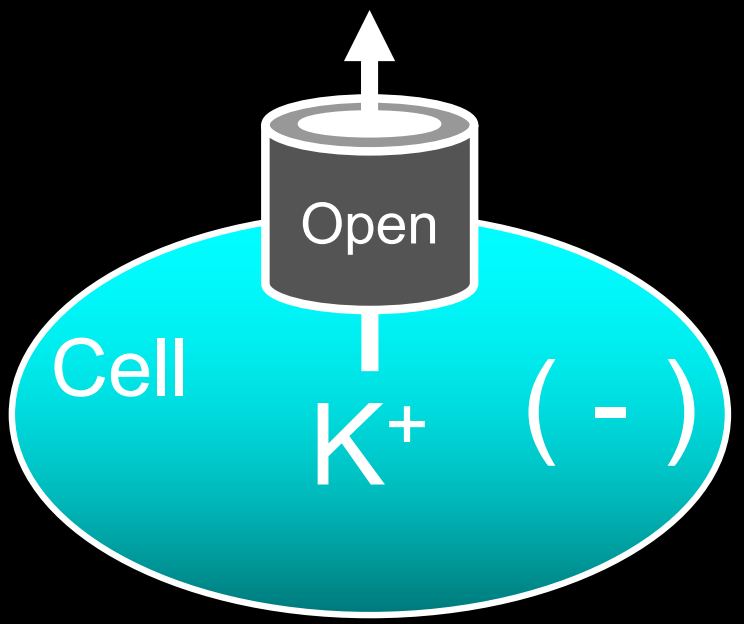


Potassium Channels: membrane protein pores that conduct ONLY potassium.



Function: keep membrane potential NEGATIVE.

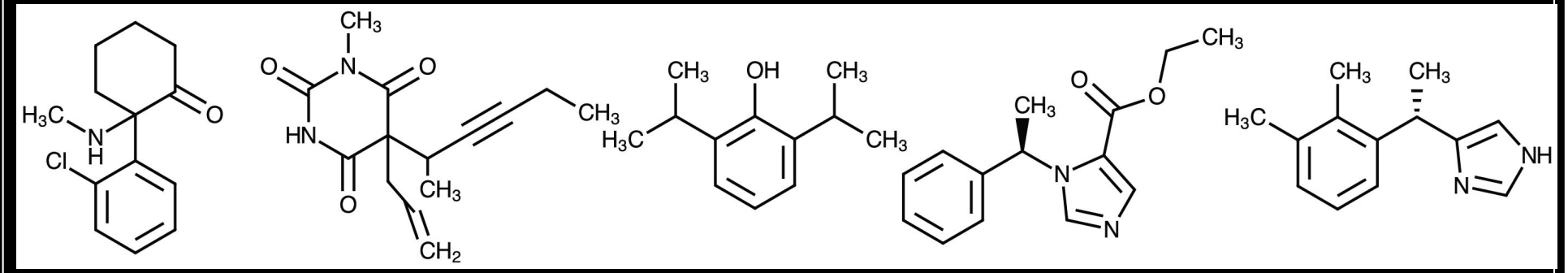




NEUTRAL

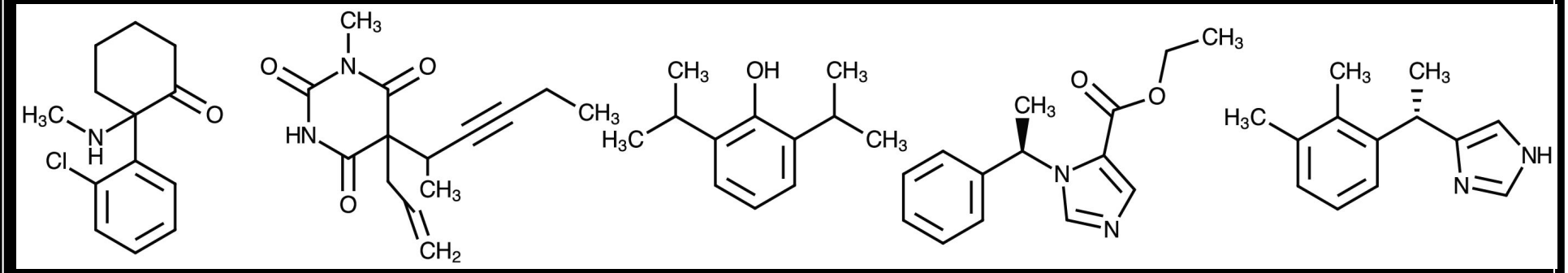
NEGATIVE = HYPERPOLARIZED

Identify structures:



1 2 3 4 5

Identify structures:



Ketamine Methohexital Propofol Etomidate Dexmeditomidine

Comparison of induction characteristics of four intravenous anaesthetic agents

J. S. C. McCOLLUM AND J. W. DUNDEE

Anaesthesia, 1986, Volume 41, pages 995–1000

Table 1. Mean (SD) ages and weights ($n = 50$)

Agent, mg/kg	Age (year)	Weight (kg)
Thiopentone, 4.0	37 (12.3)	62 (12.8)
Thiopentone, 5.0	33 (11.8)	62 (11.2)
Etomidate, 0.3	34 (10.0)	59 (11.0)
Methohexitone, 1.5	33 (11.5)	62 (10.1)
Propofol, 2.0	33 (12.0)	63 (8.8)
Propofol, 2.5	37 (12.2)	63 (12.3)

Table 2. Successful inductions ($n = 50$)

Agent	mg/kg	Induced	Rapid lightening
Thiopentone	4.0	45	6
Thiopentone	5.0	50	5
Etomidate	0.3	50	0
Methohexitone	1.5	48	2
Propofol	2.0	45	5
Propofol	2.5	50	0

Pain on inject:

Table 6. Percent incidence of pain at injection site

Agent	mg/kg	Antecubital fossa	Dorsum of hand
Thiopentone	4.0–5.0	4	5
Etomidate	0.3	14*	29‡
Methohexitone	1.5	18†	41‡
Propofol	2.0–2.5	8	31‡

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ compared to thiopentone.

Apnea:

Table 5. Number of patients exhibiting apnoea >30 seconds

Agent	mg/kg	31–60 seconds	>61 seconds
Thiopentone	4.0	10	1
Thiopentone	5.0	18	1
Etomidate	0.3	0	0
Methohexitone	1.5	9	1
Propofol	2.0	7	5
Propofol	2.5	16	6

Hypotension:

Table 3. Cardiovascular changes in patients in whom an adequate depth of anaesthesia was induced

			Systolic blood pressure decrease			Heart rate increase
Agent	mg/kg	*n*	21–40 mmHg	>41 mmHg	Mean %	mean %
Thiopentone	4.0	39	3	0	6	6
Thiopentone	5.0	45	7	3	10	9
Etomidate	0.3	50	4	0	5	3
Methohexitone	1.5	46	1	0	1†	24‡
Propofol	2.0	40	17	2	15	5
Propofol	2.5	50	17	5	17*	5

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ compared to thiopentone 5 mg/kg.

Excitatory: myoclonus, movement, tremor; cough, hiccup, laryngospasm

Table 4. Percent incidence of excitatory and respiratory side effects in patients in whom an adequate depth of anaesthesia was induced

Agent	mg/kg	*n*	Excitatory	Respiratory
Thiopentone	4.0	39	8	8
Thiopentone	5.0	45	9	9
Etomidate	0.3	50	70‡	10
Methohexitone	1.5	46	37†	20
Propofol	2.0	40	33†	5
Propofol	2.5	50	24*	6

*$p < 0.05$; †$p < 0.01$; ‡$p < 0.001$ compared to thiopentone 5 mg/kg.

studies.[8,9] Although propofol exhibits excitatory sequelae these were more mild and transient than those produced by the other two drugs and they are not a problem in clinical practice.

Propofol:

- +GABA-A chloride channel
- Decreased CMRO2, CBF, and ICP
- Antiemetic, short terminal half-life
- Hypotension, apnea, loss airway tone
- Pain on injection
- Intralipid vehicle: soybean oil, egg lecithin, glycerol, preservatives = > infection, allergy, triglycerides, and infusion syndrome

Propofol (cont):

- EDTA (Diprivan) or sodium metabisulfite (generic) are included as antimicrobial agents; drug used within 6 hours of opening vial.

-Prolonged high dose infusions (> 48 hours) hypertriglyceridemia (pancreatitis) and/or “propofol infusion syndrome” metabolic acidosis, rhabdomyolysis (cardiac/skeletal), renal failure, heptomegaly, fever, and CV instability/failure (children & critically ill on pressors/steroids; supportive Rx); 4-5 mg/kg/hour for > 48 hours avoided; “all or none sudden onset and death”, rare highly lethal

Propofol (cont):

- Soybean (e.g., tofu) or egg allergy. Most studies consider safe in such patients (e.g., lecithin is from yolk and most allergies are to egg white/protein)

Br J Anaesth. 2016 Jan;116(1):77-82. doi: 10.1093/bja/aev360.

No evidence for contraindications to the use of propofol in adults allergic to egg, soy or peanut†.

Asserhøj LL[1], Mosbech H[2], Krøigaard M[2], Garvey LH[2].

CONCLUSION: No connection between allergy to propofol and allergy to egg, soy or peanut was found. The present practice of choosing alternatives to propofol in patients with this kind of food allergy is not evidence based and should be reconsidered.

NEJM 1995

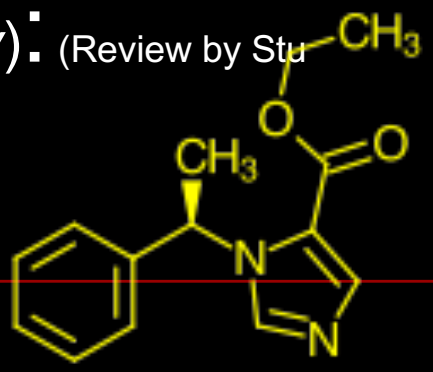
POSTOPERATIVE INFECTIONS TRACED TO CONTAMINATION OF AN INTRAVENOUS ANESTHETIC, PROPOFOL

SIIRI N. BENNETT, M.D., MICHAEL M. MCNEIL, M.B., B.S., M.P.H., LEE A. BLAND, M.A., M.P.H., MATTHEW J. ARDUINO, M.S., DR.P.H., M. ELSA VILLARINO, M.D., M.P.H., DENNIS M. PERROTTA, PH.D., DALE R. BURWEN, M.D., SHARON F. WELBEL, M.D., DAVID A. PEGUES, M.D., LEONARDO STROUD, M.D., M.P.H., PAUL S. ZEITZ, D.O., M.P.H., AND WILLIAM R. JARVIS, M.D.

Abstract *Background. Between June 1990 and February 1993, the Centers for Disease Control and Prevention conducted investigations at seven hospitals because of unusual outbreaks of bloodstream infections, surgical-site infections, and acute febrile episodes after surgical procedures.*

patients. Interviews with and observation of anesthesiology personnel documented a wide variety of lapses in aseptic techniques.

Etomidate (Forman SA (2011) *Anesthesiology*): (Review by Stu Forman (2011) *Anesthesiology*)



- Imidazole-based intravenous hypnotic discovered thru serendipity in antifungal screen by Janssen Pharmaceutica in 1965 (developed fentanyl and droperidol).

-Hypnotic effects clearly through GABA-A chloride channels.

THE GOOD:

- Limited effects on blood pressure and breathing => highest therapeutic index of all anesthetic-hypnotics. Often used in trauma or critically ill patients and those with "bad" hearts.

Therapeutic Index (LD50/ED50)

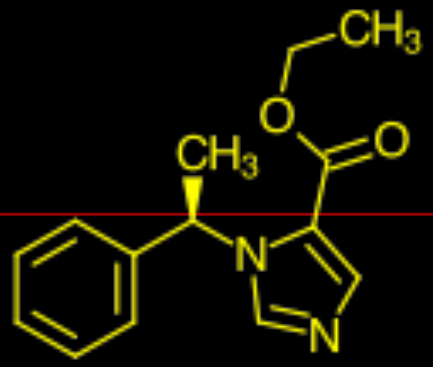
R(+)-Etomidate ~27

Ketamine ~6

Thiopental ~4

Propofol ~3

Etomidate:



THE BAD:

- Myoclonus, “the etomidate shakes”
- PONV (> propofol, formulation dependent)
- Pain on injection

THE UGLY:

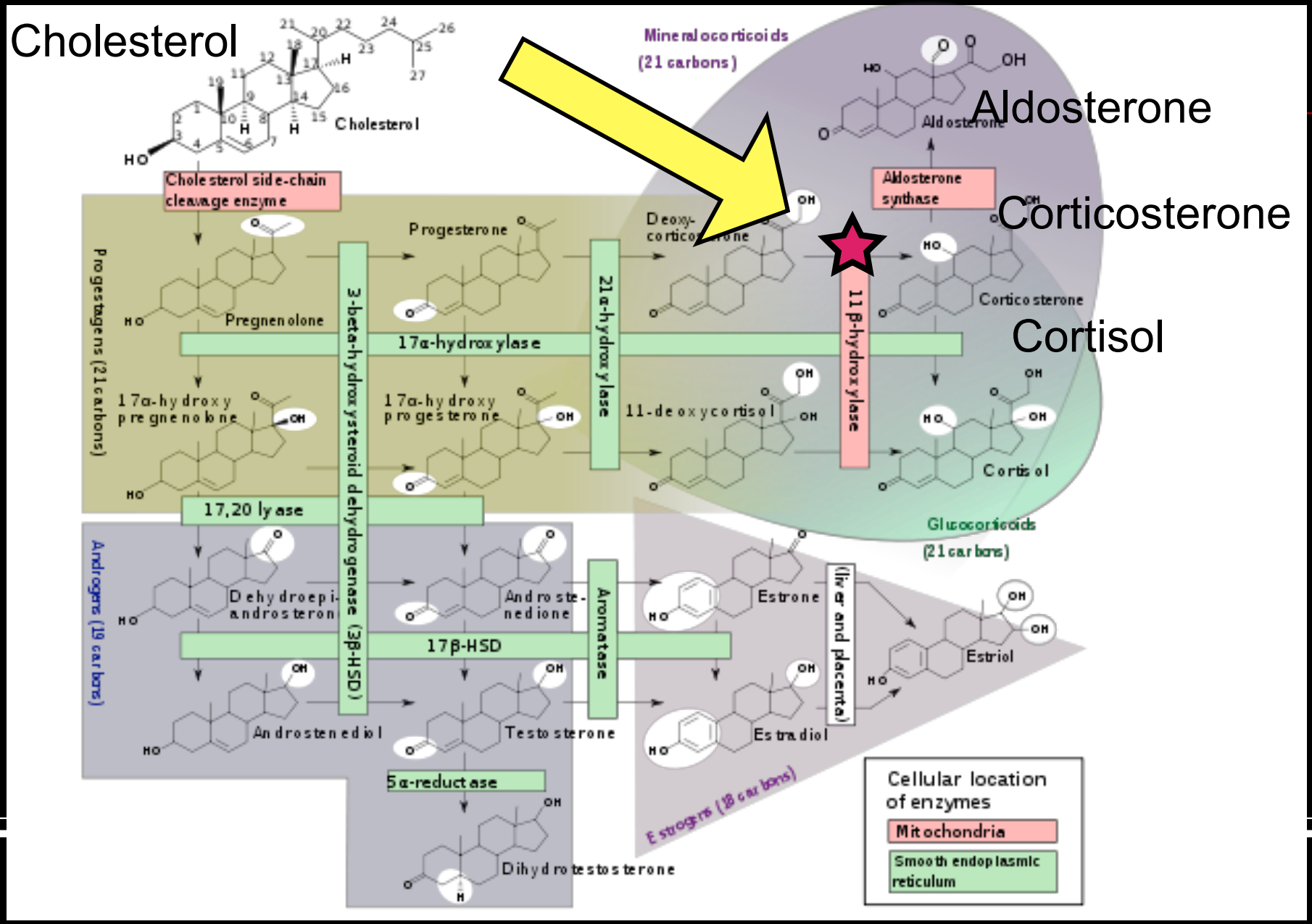
-Adrenal suppression; “chemical adrenalectomy”; etomidate is the most potent inhibitor of adrenal function known.

-- Hypnosis (1 μM)
-- (-) cortisol/aldosterone (< 50 nM)
-- Duration: 6-8 hours (in healthy) and 1-3 days (in critically ill).
-- Prolonged infusions clearly increase mortality.
-- Bolus dose in critically ill *controversial*.
-- ** Adrenalectomized rats die at 1/1000 the LPS dose required to kill control rats **

Ledingham & Watt, Letter to Editor in Lancet (1983)
"Influence of Sedation on Mortality in Multiple Trauma Patients"

"Dear Sir, . . ."
-- 428 patients mortality of 22-29% (1960-80) but increased to 44% (1981-82)
-- Injury severity was unchanged, referral the same, age was younger (55 to 35yo)
-- Further narrowed increased mortality to patients surviving > 5 days and mechanically ventilated (ie, not acute deaths)
-- Only difference was mode of sedation of ventilated patients: morphine/benzo (1960-80) (25% mortality) vs morphine/etomidate (1981-82)(69% mortality).
-- Those with highest injury severity score: 35% mortality => 100% mortality!

Etomidate Inhibits Adrenal Enzyme CYP11B1



Methohexital (Brevital; 500 mg powder):

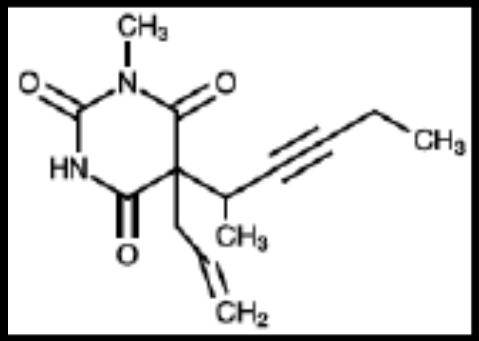
-Dosing/PK similar to propofol.

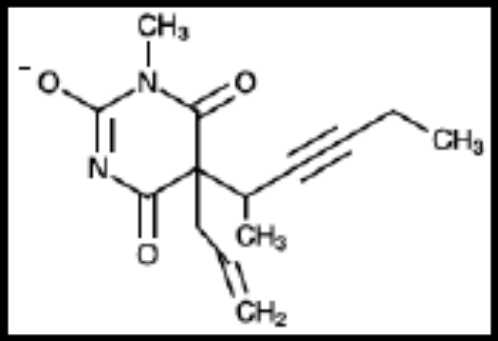
-Myoclonus, injection pain, N/V, lowers seizure threshold (ECT Rx)

-Barbiturate and should not be used in patients with porphyria (disorder of heme production).

-Very alkaline pH 10-11 to maintain solubility; precipitant can form with acidic solutions (succinylcholine, atropine, non-depolarizing muscle relaxants) and intra-arterial injection can be bad.

Methohexital:





Methohexital Drug Insert:

"DANGER OF INTRA-ARTERIAL INJECTION—Unintended intra-arterial injection of barbiturate solutions may be followed by the production of platelet aggregates and thrombosis, starting in arterioles distal to the site of injection. The resulting necrosis may lead to gangrene, which may require amputation."

Ketamine:

-NMDA glutamate receptor antagonist with analgesic properties

-Preserves resp drive, airway/muscle tone

-“Dissociative” anesthetic, eyes open, appear conscious, nystagmus

-Opioid sparing; may prevent/reverse tolerance

-Activates sympathetics => increased BP/HR but also provides bronchodilation

-Very rapid onset; IM bioavailability

Ketamine:

-Related to phenycyclidine; hallucations and postoperative delirium (benzo Pre-Rx)

-Though may prevent excito-toxicity, activates EEG and may increase CMRO2/CBF, so avoided in neuroanesthesia

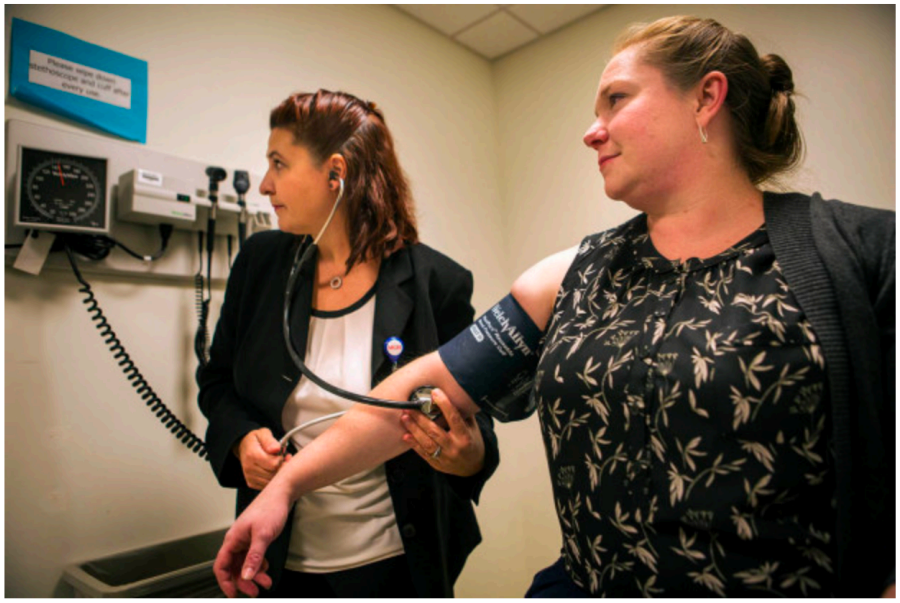
- +Oral/pharyngeal secretions => problematic in fiberoptic intubation

-May have rapid antidepressant properties

‘I Don’t Feel Trapped On Earth’: Ketamine Lifts Many From Depths Of Major Depression

WBUR Radio on Ketamine as an antidepressant.

February 25, 2016 | By Lisa Mullins and Lynn Jolicoeur | Share



“During the first administration [of intranasal ketamine] we take vitals every 10 minutes," says Dr. Christina Cusin, a psychiatrist and lead researcher at the Massachusetts General Hospital outpatient clinic. (Jesse Costa/WBUR)

Within about three minutes, the ketamine kicks in. It makes Kramer feel kind of loopy. The drug has psychoactive effects that leave patients high or out-of-sorts for about an hour.

The Reversal of Fentanyl-Induced Tolerance by Administration of "Small-Dose" Ketamine

Helge Eilers, MD, Lisa A. Philip, MD, Philip E. Bickler, MD, PhD, Warren R. McKay, MD, and Mark A. Schumacher, PhD, MD

Department of Anesthesia and Perioperative Care, University of California, San Francisco, San Francisco, California

Anesth Analg 2001;93:213–4

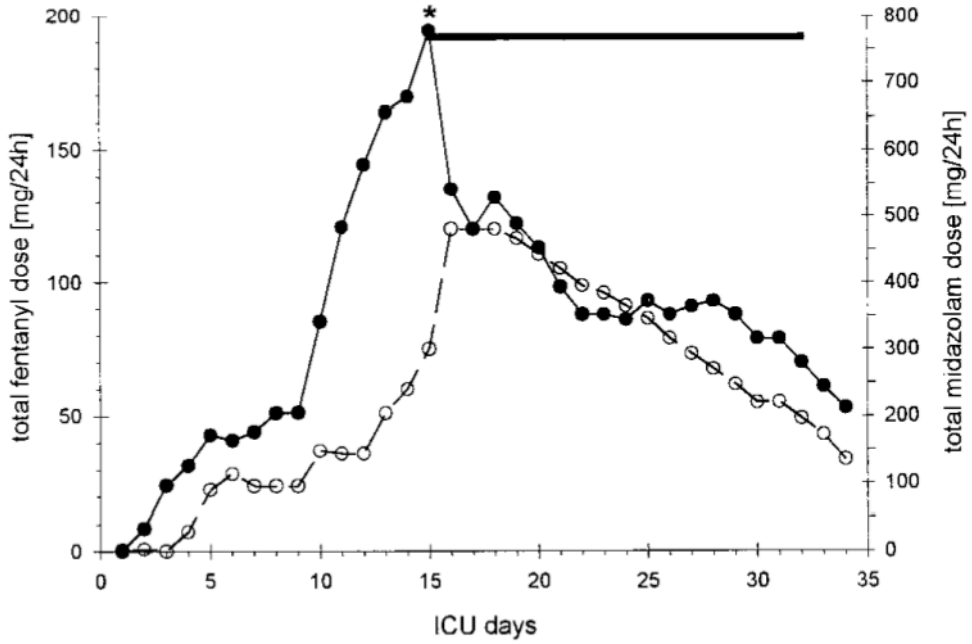


Figure 1. Daily doses of midazolam (open circles), fentanyl (closed circles), and ketamine (black bar, indicating continuous infusion at 0.1 $mg \cdot kg^{-1} \cdot hr^{-1}$) during the patient's intensive care unit (ICU) stay. The x-axis shows the number of ICU days. The fentanyl dose on ICU day 15 just before the start of the ketamine infusion (*) is inclusive of 2065 mg of hydromorphone that was converted to an equipotent dose of fentanyl. We used a conversion factor of 20.

Intravenous Hypnotics

	Propofol	Thiopental	Etomidate	Ketamine
Recovery	Redistribution	Redistribution	Redistribution	Redistribution
Metabolism	Liver/ lung	Liver	Liver/Blood	Liver
Active Metab	No	Yes	No	Yes
Excretion	Renal	Renal	Renal	Renal
Context sensitive half-life (after 6hr)	30 min	>150 min	15 min	45 min

Intravenous Hypnotics

	Propofol	Thiopental	Etomidate	Ketamine
Respiration	↓↓↓	↓↓	0/↓	0
PVR	↓↓↓	↓↓	0	↑↑
Contractility	↓	↓	0	↑↑
Heart Rate	↓↓	↓	0	↑↑↑
CBF/CMRO2	↓↓	↓↓	↓↓	↑↑

Intravenous Hypnotics

	Propofol	Thiopental	Etomidate	Ketamine
Anti-convulsant	++	++	0	0
Neuroprotectant	++	++	0/+	0
Myoclonus	+	0	+++	+++
Anti-pruritic	+	0	0	0
Emetogenic	-	+	+++	+

Case 6

- 26 yo male, developmentally delayed, agitated and combative s/f routine dental evaluation/treament under general anesthesia
- o.w. healthy

  Which induction agent would you choose?

Case 1

- 3 a.m. call from the ED: coming right up with a 19 yo s/p GSW to the abdomen. He is agitated, tachycardic to 120s, BP 80/40. FAST was positive

  Which induction agent would you choose?

Case 2

- 34 yo G4P3 s/p Cesarean delivery under spinal, needs hysterectomy for placenta accreta. EBL now >2.5L.
- PMH significant for severe asthma. Exacerbations during this pregnancy resulted in 2 ER visits.
- Patient becoming very agitated. BP 85/50 HR 120
  Which induction agent would you choose?

Case 3

- Dr. Sacco has emergency case in OR 14.
- 82 yo man w/ hx kidney stones needs ureteral stent. Has R flank pain, temp 102, renal pelvis distended on U/S.
- Hx of CAD; A.S. w/ valve area 0.7 cm^2, EF 27%, BP 135/80, HR 95.

  Which induction agent would you choose?

Case 4

- 52 yo woman with stage IV small cell lung Ca has had recurrent malignant effusions that have been drained. She now presents with 5 day hx of SOB and orthopnea. Dr Gaissert wants to do a subxiphoid pericardial window. BP 90/50 HR 115. Which induction agent would you choose?

Case 5

- 63 yo woman p/w headache, blurry vision, and nausea was found to have a large frontal meningioma. She is to undergo a craniotomy.
- Hx of CAD (recent stress test neg.), HTN, and DM. EF 29%. BP 170/90 HR 56.
  Which induction agent would you choose?