CEEA 2013

# Pharmacology of intravenous anaesthetic drug in hypovolemic shock

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# History

## World War II

- increased mortality of wounded military personnel during surgery under **thiopental** anesthesia

Halford FJ. *Anesthesiology* 1943; 4:67-69
Price HL. *Anesthesiology* 1960; 21:40–45

# History

- The mortality associated with 240.483 anaesthetics administered over 10 years at Groote Schuur Hospital, Cape Town
- Mortality - 0.22/ 1000 anaesthetics

Harrison GG. *Br J Anaesth* 1978; 50: 1041-1046

# Right dose?

## Underdosing

sedation

inadequate pain relief

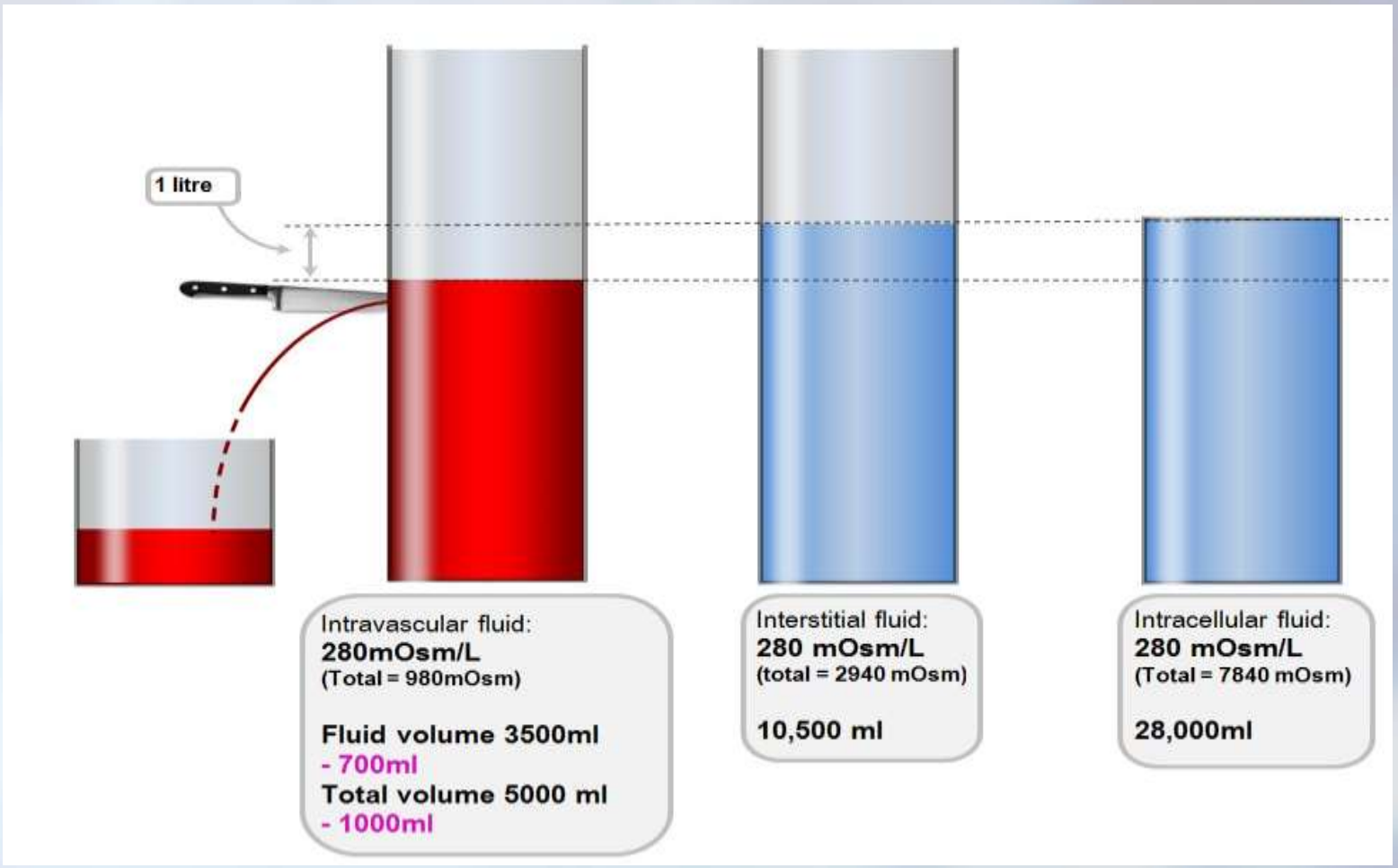
## Overdosing

Cardiorespiratory depression

(-)inotropism and vasodilatation (hTA)

in patients who are already hemodynamically compromised

# Compartment changes




Benowitz N, Forsyth RP, Melman KL and Rowland M. *Clin Pharmacol Ther* 1977; 16: 99–109

# Pharmacokinetic changes

- activation of the sympathetic nervous system
- Autoregulation of heart and brain circulation
- a disproportionate fraction of the available cardiac output is delivered to the heart and brain

- influence one or more of the four classic phases of drug disposition: absorption, distribution, metabolism and elimination.

# Absorption

- Only intravascular route
- the oral, transdermal, subcutaneous, and intramuscular routes are not reliable

# Distribution

- ↓drug distribution
- ↓blood volume

- ↑blood concentration and drug content in brain and heart (early phase)

# Distribution

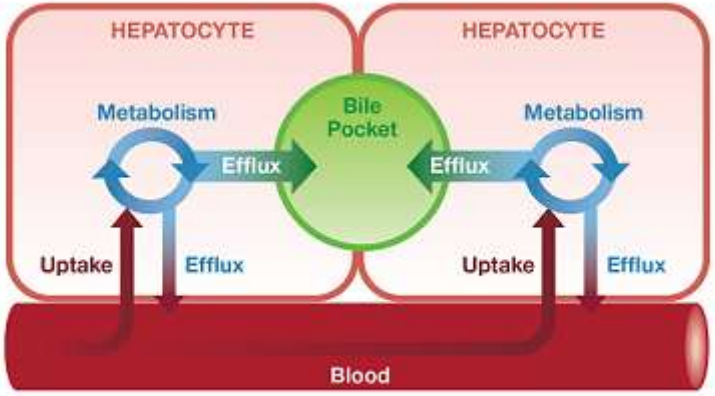
- Changes in the plasma protein binding influence drug distribution
- ↑ $\alpha$1–acid glycoprotein (alfentanil), ↓albumin level

# Distribution

- anaerobic metabolism and metabolic acidosis which may alter the distribution of ionisable drugs
- E.g. acidosis ↑ brain concentration of morphine

# Metabolism

- Hepatic dysfunction
- Hepatic clearance
  - hepatic blood flow
  - free fraction of drug
  - intrinsic ability of the hepatic enzymes to metabolize the drug or intrinsic clearance



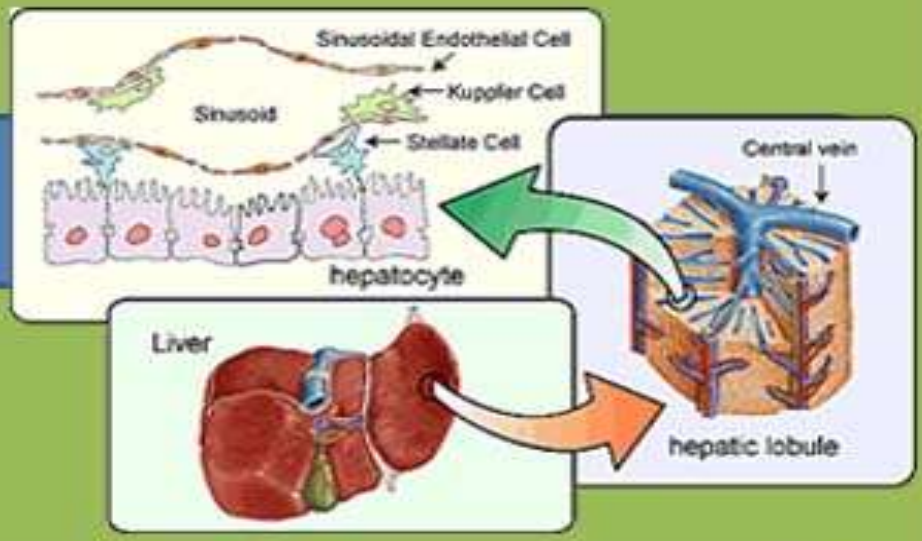
http://csb.yonsei.ac.kr

## Organ

- e-Liver
- e-Heart
- e-Organs

## Cell

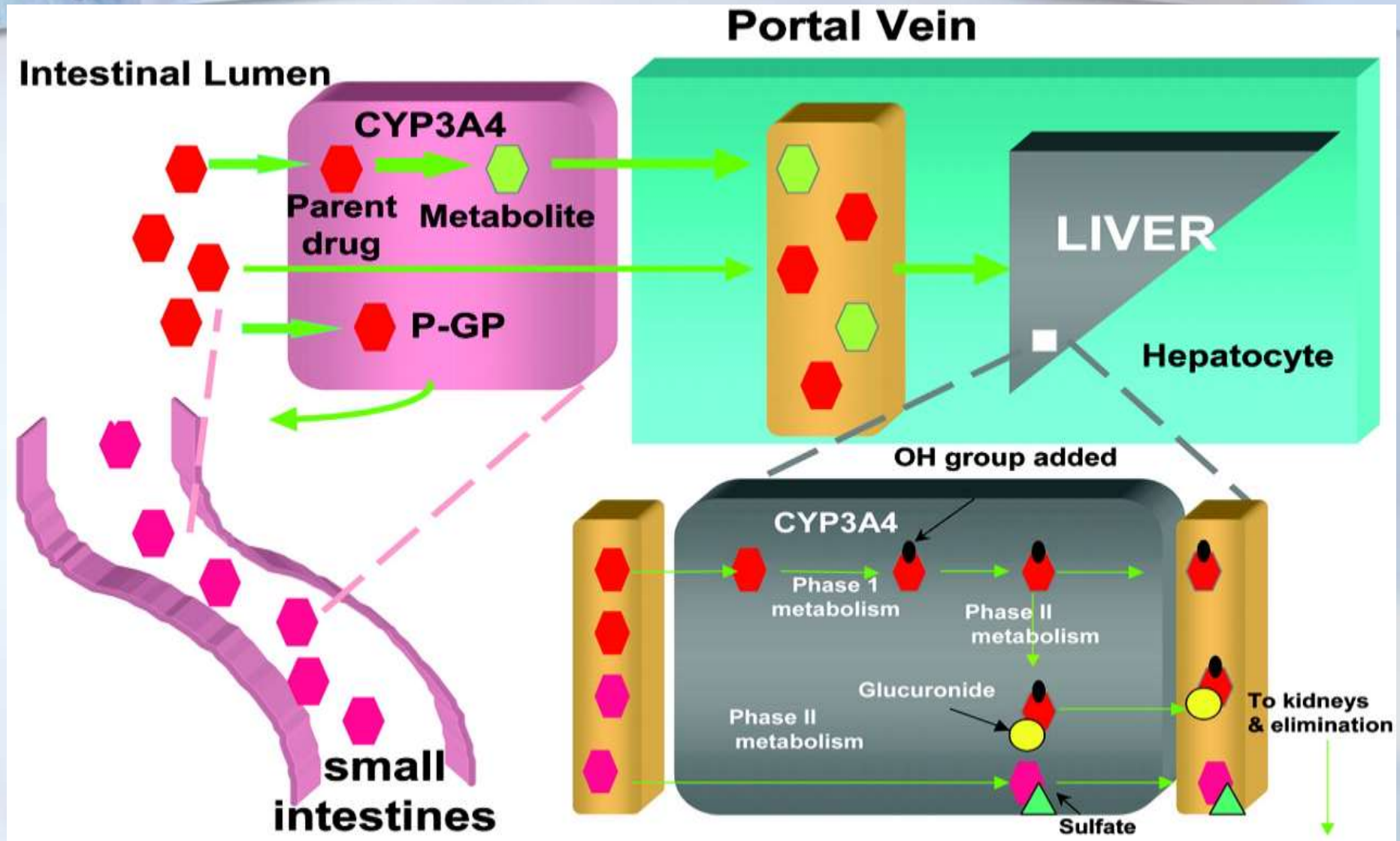
- e-Hepatocyte




## Functions

- CYP Substrate
- CYP Inhibitor
- CYP Regio selectivity
- Transporter
- Phase II Metabolism
- PXR / CAR
- Reaction Rate (Km, Vmax)
- Inhibition Rate (IC50, Ki)
- Induction Rate (Kind)

# Cytochrome P-450 enzyme system

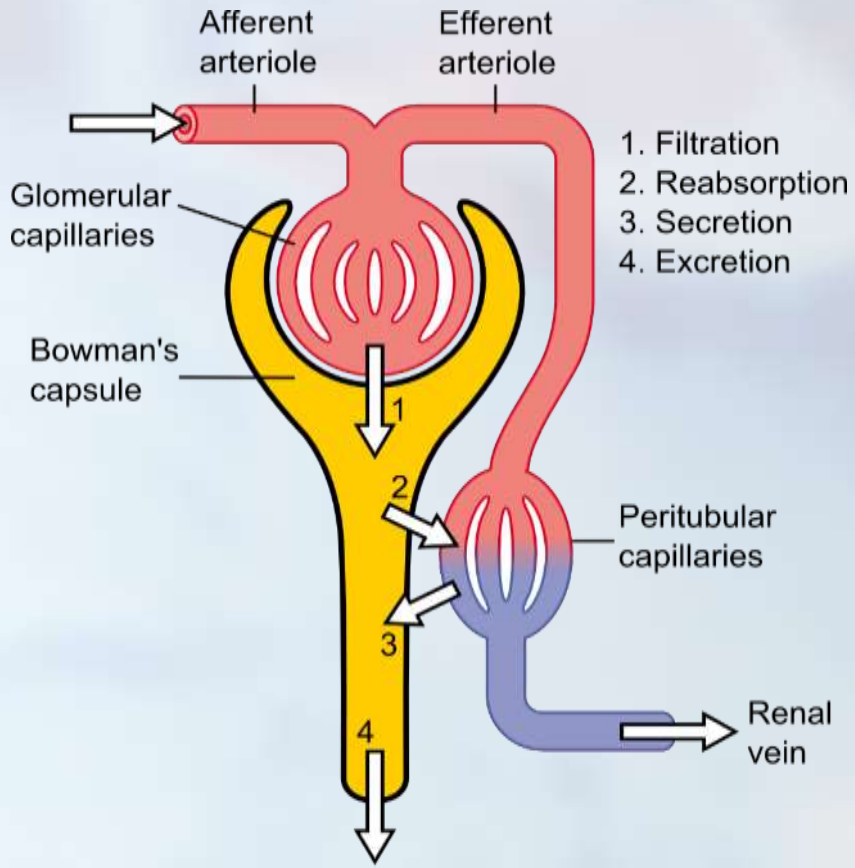


# Hepatic extraction ratios (ER) for intravenous anesthetic drugs

| Low hepatic ER (ER < 0.3) | Intermediate hepatic ER (ER 0.3-0.7) | High hepatic ER (ER > 0.7) |
|---|---|---|
| Chlordiazepoxide | Alfentanil | Fentanyl |
| Diazepam | Chlorpromazine | Flumazenil |
| Lorazepam | Diphenhydramine | Ketamine |
| Methadone | Droperidol | Morphine |
| Pentobarbital | Etomidate | Nalmefene |
| | Haloperidol | Naloxone |
| | Hydromorphone | Propofol |
| | Pethidine (meperidine) | Sufentanil |
| | Midazolam | |

De Paepe P, Belpaire FM, Van Hoey G et al. *J Pharmacol Exp Ther* 1999; 290:1048–53

# Renal excretion




Excretion = Filtration – Reabsorption + Secretion

# Pharmacological properties of intravenous induction agents

| Intravenous induction agent | Effector site equilibration and t1/2Keo | Haemodynamic effects in vivo | Comments |
|---|---|---|---|
| **Ketamine** | ≅ 2 min | ↑CO, ↑HR, ↑ABP Sympathomimetic | ↑CPP and ICP |
| **Thiopental** | 1.5 min | ↑HR, →CO, ↓ABP →laryngeal reflexes, ↓inotropism vasodilatation | unlikely to tolerate induction dose > 3 mg.kg−1 |
| **Propofol** | ≤20 min | →HR, ↓CO, ↓ABP Vagotonic, ↓laryngeal reflexes | elderly, ASA 3 or more or hypovolaemic patients |

Pandit JJ. Anaesthesia and Intensive Care Medicine 2008; 9: 154–9

# Pharmacological properties of intravenous induction agents

| Intravenous induction agent | Effector site equilibration and t1/2Keo | Haemodynamic effects in vivo | Comments |
|---|---|---|---|
| **Etomidate** | ~2.5 min | →CO, →ABP<br>Minimal dose adjustment in shock | Prolonged inhibition of steroid synthesis in the critically ill |
| **Opioide** | 6 min (fentanyl) | ↓CO, ↓HR, ↓ABP<br>↓laryngeal reflexes<br>Vagotonic | Potent vagally mediated bradycardia |
| **Benzodiazepenes** | ~9 min (e.g. lorazepam) | →CO, →HR | Induction time of anaesthesia incompatible with RSI |

Pandit JJ. Anaesthesia and Intensive Care Medicine 2008; 9: 154–9

# Ketamine

- Racemic ketamine is highly lipid soluble with a pKa of 7.5, almost 50% dissociated at pH 7.45
- only 12% bound to plasma proteins
- t1/2Keo of ~2 min
- intact autonomic nervous system - sympathomimetic ↑heart rate, arterial pressure, and cardiac output
- ↓inotropism in heart failure

Pagel PS, Kampine JP, Schmeling WT, Warltier DC. *Anesthesiology* 1992; 76: 564–72
Gelissen HP, Epema AH, Henning RH, et al. *Anesthesiology* 1996; 84: 397–403
Tweed WA, Minuck M, Mymin D. *Anaesthesia* 1972; 37: 613–9

# Ketamine and TBI

- ↑intracranial pressure
- impair cerebral blood flow
- cerebral autoregulation is impaired and CBF is essentially pressure (CPP) related
- reduces cerebral oxygen consumption
- the overall balance of CBF and CMRO2 may be favourable


Mayberg TS, Lam AM, Matta BF et al.*Anesthesia and Analgesia* 1995; 81: 84–9
Engelhard K, Werner C, Mollenberg O, Kochs E. *Canadian Journal of Anesthesia* 2001; 48: 1034–95
Albanese J, Arnaud S, Rey M, et al. *Anesthesiology* 1997; 87: 1328–34
Himmelseher S, Durieux ME. *Anesthesia and Analgesia* 2005; 101: 524–34

# Thiopental

- a short t1/2Keo ~1.5 min
- preserve autonomic responsiveness (e.g. reflex tachycardia and pressor response to laryngoscopy)
- arteriolar vasodilatation, negative inotropy and obtunded baroreceptor responses

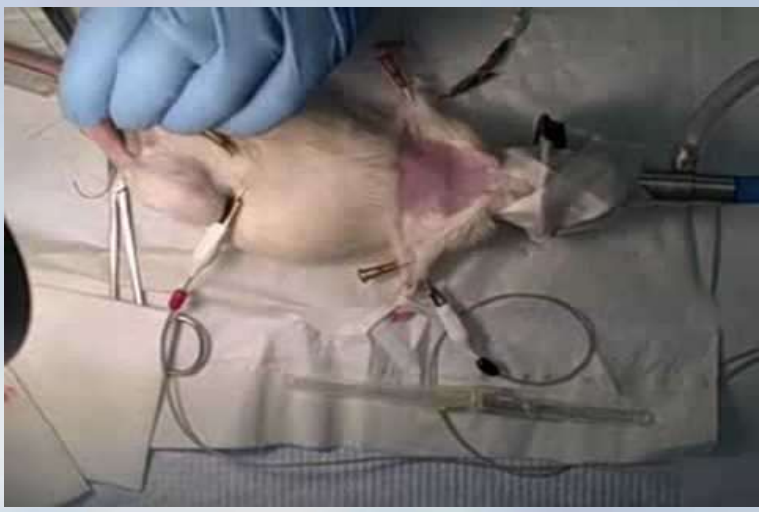
# Thiopental

- less convincing a choice in patients with severe haemodynamic compromise
- shocked patients rarely tolerate higher doses of thiopental
- thiopental, fentanyl, midazolam – severe hypotension in ¼ of cases

Sivilotti ML, Ducharme J. *Annals of Emergency Medicine* 1998; 31: 313–24
Reynolds SF, Heffner J. *Chest* 2005; 127: 1397–412

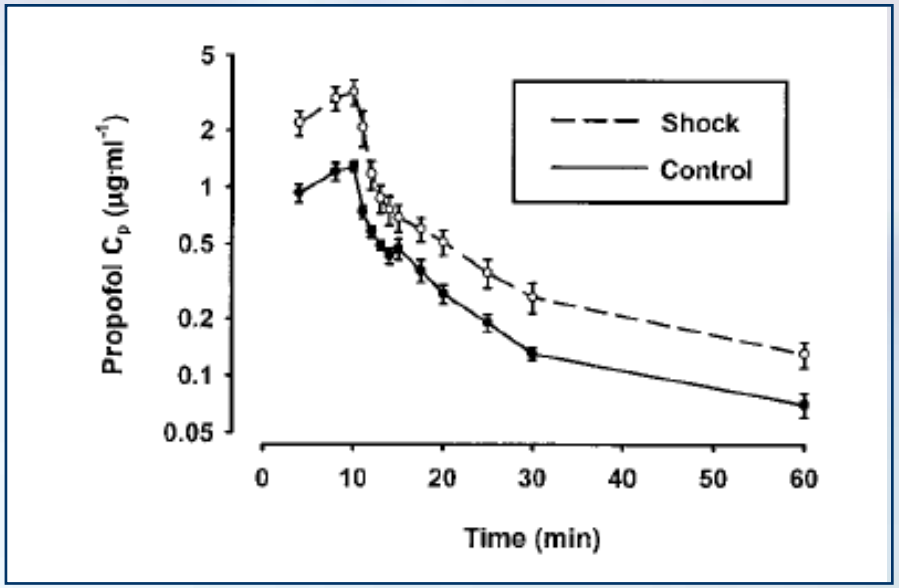
# Propofol

- DePaepe, 2000: 17 ml/kgc blood loss - ↓ by 2.5x clearance and volume of central compartment in continuous administration

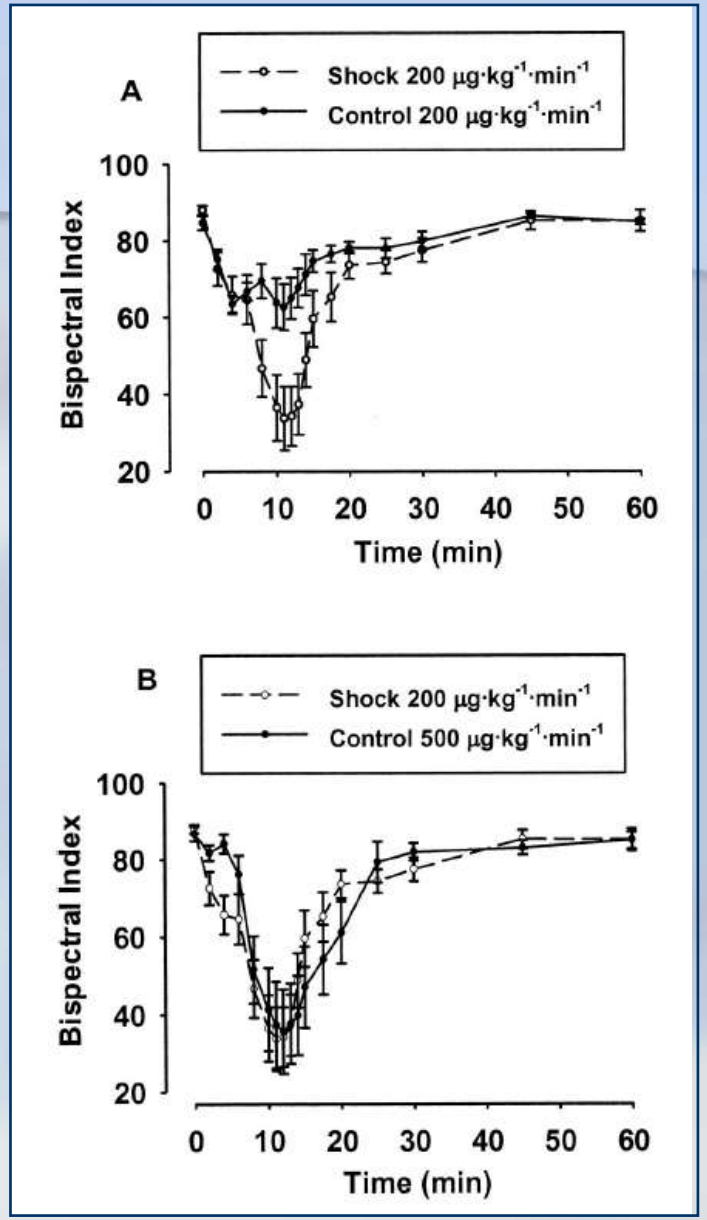


De Paepe P, Belpaire FM, Rosseel MT, et al. *Anesthesiology* 2000; 93:1482–90

# Propofol




Hemorrhagic shock altered the pharmacokinetics and pharmacodynamics of propofol. Changes in intercompartmental clearances and an increase in the potency of propofol suggest that less propofol would be required to achieve a desired drug effect during hemorrhagic shock.



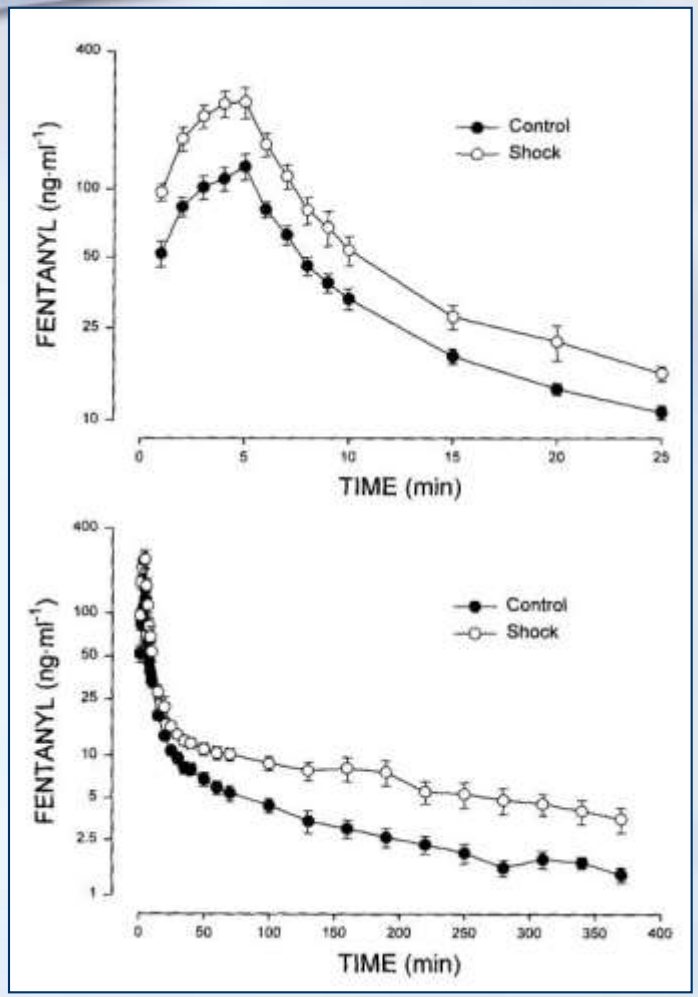

Johnson et al. Anesthesiology 2003;99:409-20

# Propofol

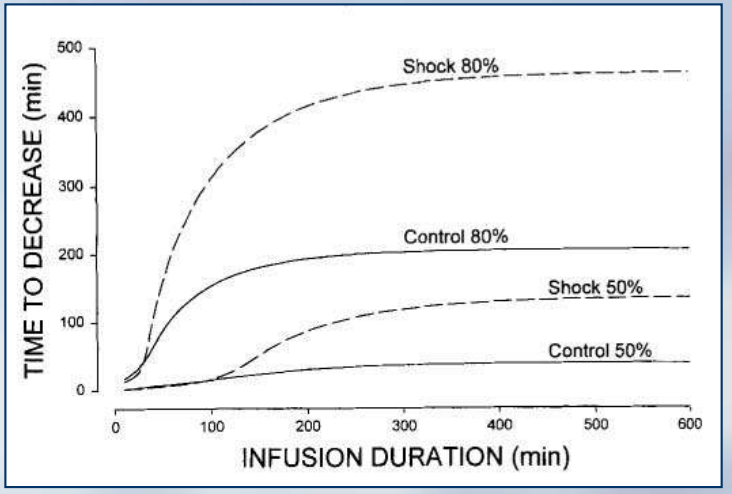
- Avoid propofol if SBP ≤ 70 mmHg or hypovolemic pts

Shafer SL. *Anesthesiology* 2004; 101: 567–8
Reich DL, Hossain S, Krol M, et al. *Anesthesia and Analgesia* 2005; 101: 622–8

# Fentanyl

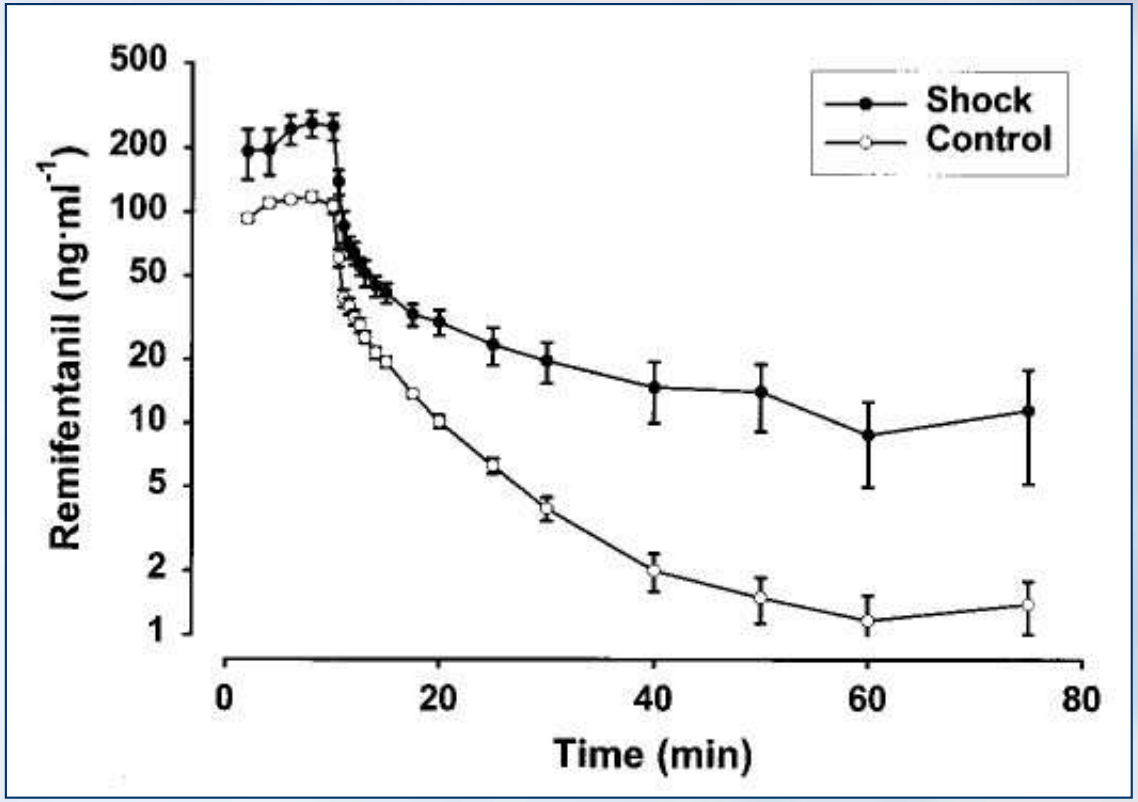



The essential finding of the study is that fentanyl pharmacokinetics are substantially altered by hemorrhagic shock. The reduced opioid requirement commonly observed during hemorrhagic shock is at least partially attributable to pharmacokinetic mechanisms.




Talmade DE et al. Anesthesiology 1999;91:156-166

# Remifentanil




Hemorrhagic shock altered the pharmacokinetics of remifentanil, suggesting that less remifentanil would be required to maintain a target plasma concentration. However, because of its rapid metabolism, the impact of hemorrhagic shock on the concentration decline of remifentanil after termination of the infusion was minimal. Hemorrhagic shock did not alter the pharmacodynamics of remifentanil.

Johnson K et al. Anesthesiology 2001;94:322-32

# Influence of blood loss on opioids behavior

| Drug | PK changes with BL | PD changes with BL | Reference |
|---|---|---|---|
| ***Opioids*** | | | |
| Morphine | ++ | - | DePaepe et al., 1998 |
| Fentanyl | +++ | - | Egan et al., 1999 |
| Remifentanil | +++ | 0 | Johnson et al., 2001 |

Modified after Johnson K and Talmage DG, Trauma Anesthesia, 2008: 139

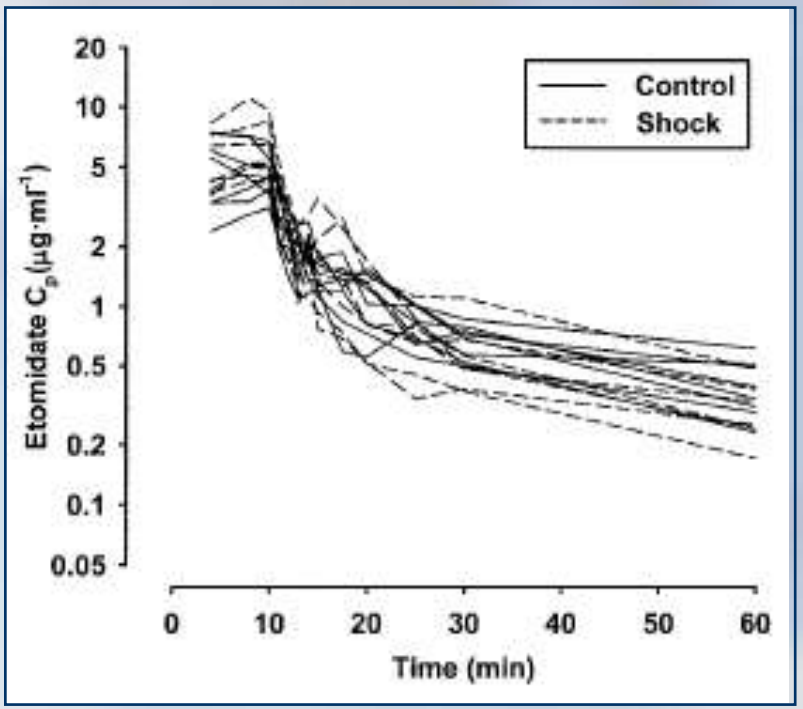
# Etomidate

- a very popular choice for haemodynamically compromised patients
- preserve the pressor response to laryngoscopy

Jabre P, Combes X, Lapostolle F, et al. *Lancet* 2009, 374: 293- 300
Walz JM, Zayaruzny M, Heard SO. *Chest* 2007, 131: 608- 620

# Etomidate

We evaluated the influence of moderate hemorrhage (30 mL/kg) on the pharmacokinetics and pharmacodynamics of etomidate. We found that **hemorrhagic shock produced small changes in the pharmacokinetics and no changes in the pharmacodynamics of this sedative hypnotic**. These results illustrate the potential advantages of using etomidate over other sedative hypnotics in settings of intravascular
volume depletion.




Johnson K et al. Anesth Analg 2003;96:1360-8

# Etomidate

- etomidate has been withdrawn from use in a number of countries due to concerns that its use impairs endogenous steroid synthesis in the critically ill
- CORTICUS Study
- Surviving sepsis campaign 2012

Sprung CL, Annane D, Keh D, et al. CORTICUS Study Group. *N Engl J Med* 2008; 358: 111– 124
Dellinger RP, Gerlach H, Douglas I et al. Critical Care Medicine 2013; 41(2): 580- 640,
www.ccmjournal.org

# Influence of blood loss on intravenous drug behavior

| Drug | PK changes with BL | PD changes with BL | Reference |
|---|---|---|---|
| ***Sedative Hypnotics*** | | | |
| **Propofol** | **+++** | **+++** | **De Paepe et al, 2000**<br>**Johnson et al., 2003** |
| **Thiopental** | **+++** | **-** | **Holford and Sheiner, 1981** |
| **Etomidate** | **+** | **0** | **DePaepe et al., 1999**<br>**Johnson et al., 2003** |
| Ketamine | + | - | Black et al., 2006<br>Weiskopf et al., 1984 |
| Midazolam | ++ | - | Adams et al, 1985 |

Modified after Johnson K and Talmage DG, Trauma Anesthesia, 2008: 139

# Induction doses and characteristics

| Drug | Dose [mg/kg] | Onset [s] | Duration [min] | Excitation | Pain |
|---|---|---|---|---|---|
| **Thiopental** | 3 - 5 (less in suspec. hypovolemia) | 30 | 5 - 8 | + | + |
| **Etomidate** | 0.2 - 0.4 | 15 - 45 | 3 - 12 | +++ | +++ |
| **Propofol** | 1.5 - 3.0 | 15 - 45 | 5 - 10 | + | ++ |
| **Midazolam** | 0.2 - 0.4 | 30 - 60 | 15 - 30 | 0 | 0 |
| **Ketamine** | 1 - 3 | 45 | 10 - 20 | + | 0 |


Thank you!