

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

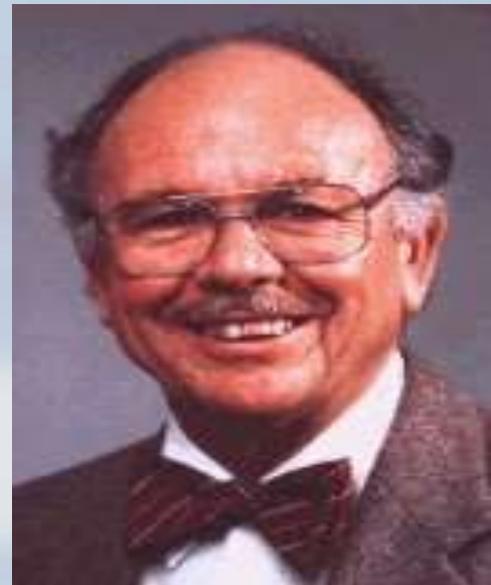
Halford FJ. *Anesthesiology* 1943; 4:67-69
Price HL. *Anesthesiology* 1960; 21:40–45





History

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





Right dose?

Underdosing



sedation

inadequate pain relief

Cardiorespiratory depression

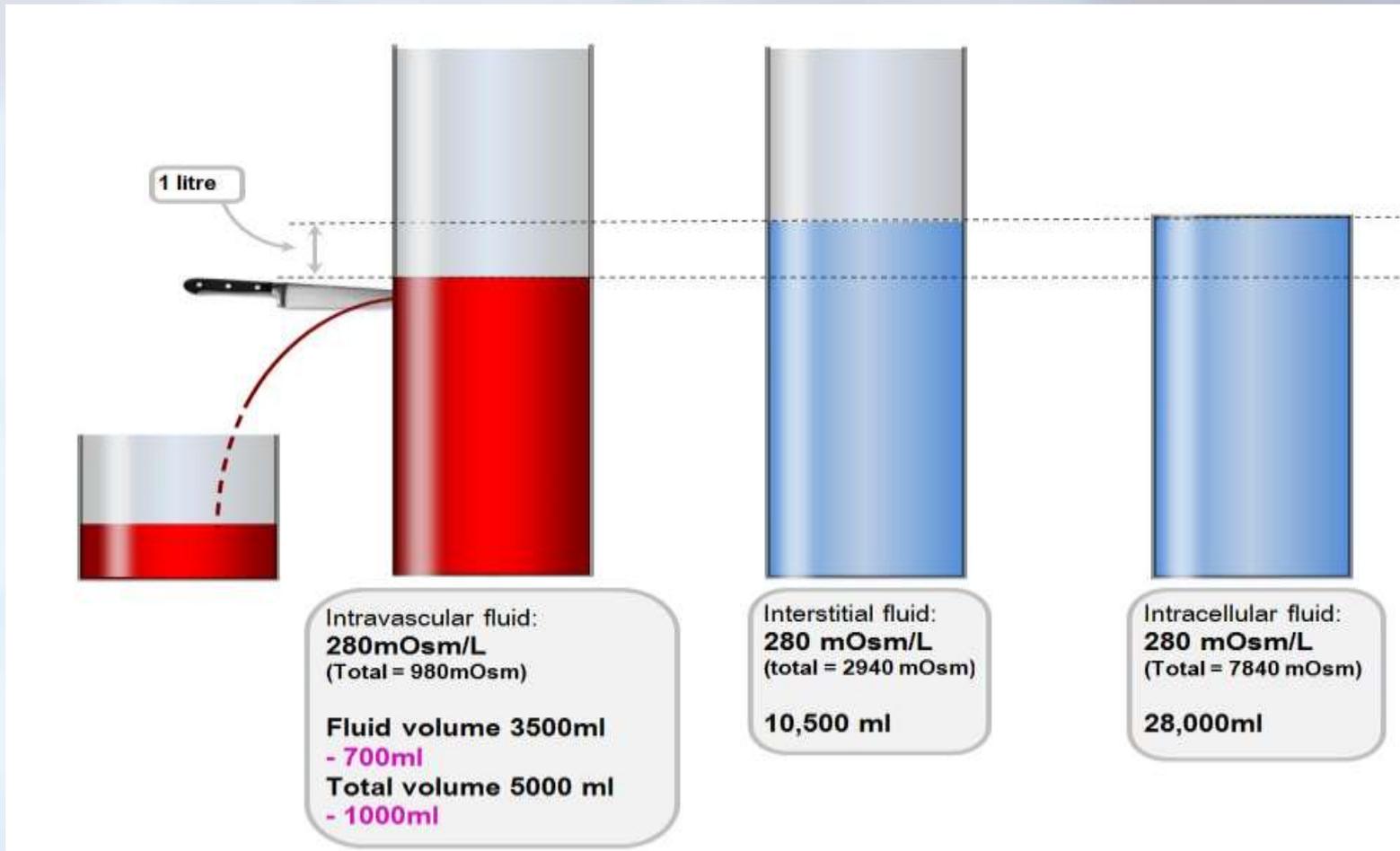
Overdosing



(-)inotropism and
vasodilatation (hTA)

in patients who are already hemodynamically compromised

Compartment changes





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
- ↑ α 1-acid glycoprotein (alfentanil),
↓ albumin level



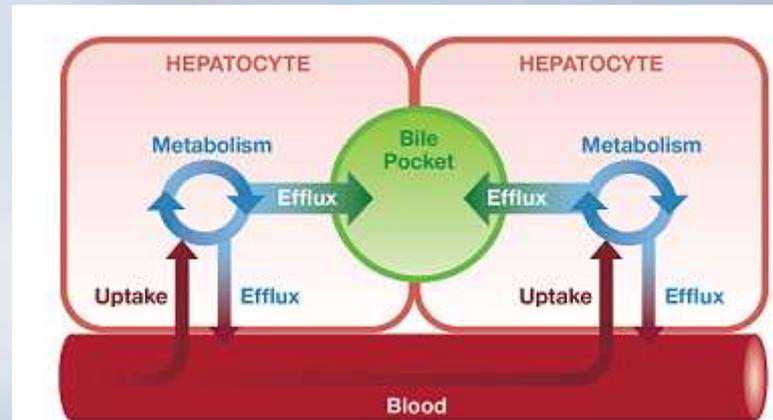
Distribution

- anaerobic metabolism and metabolic acidosis which may alter the distribution of ionisable drugs
- E.g. acidosis \uparrow 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



Organ

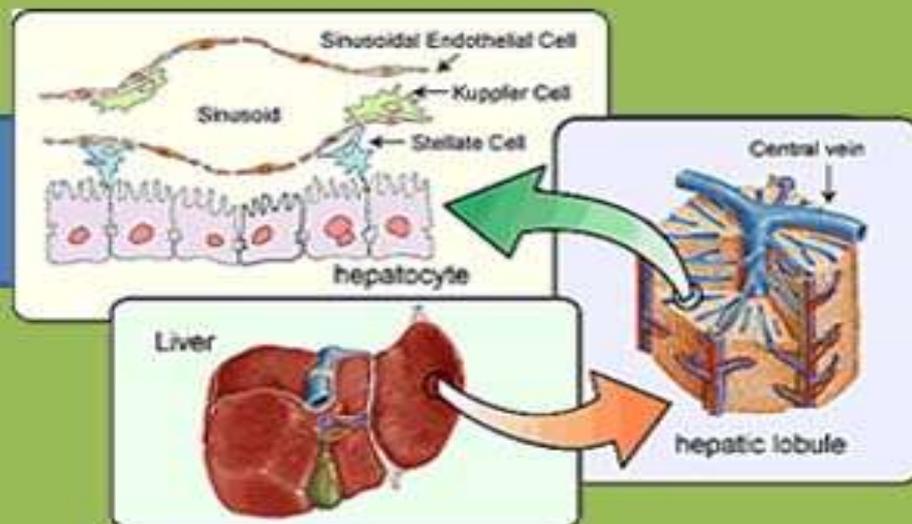
e-Liver

e-Heart

e-Organs

Cell

e-Hepatocyte



Functions

CYP Substrate

CYP Inhibitor

CYP Regio
selectivity

Transporter

Phase II
Metabolism

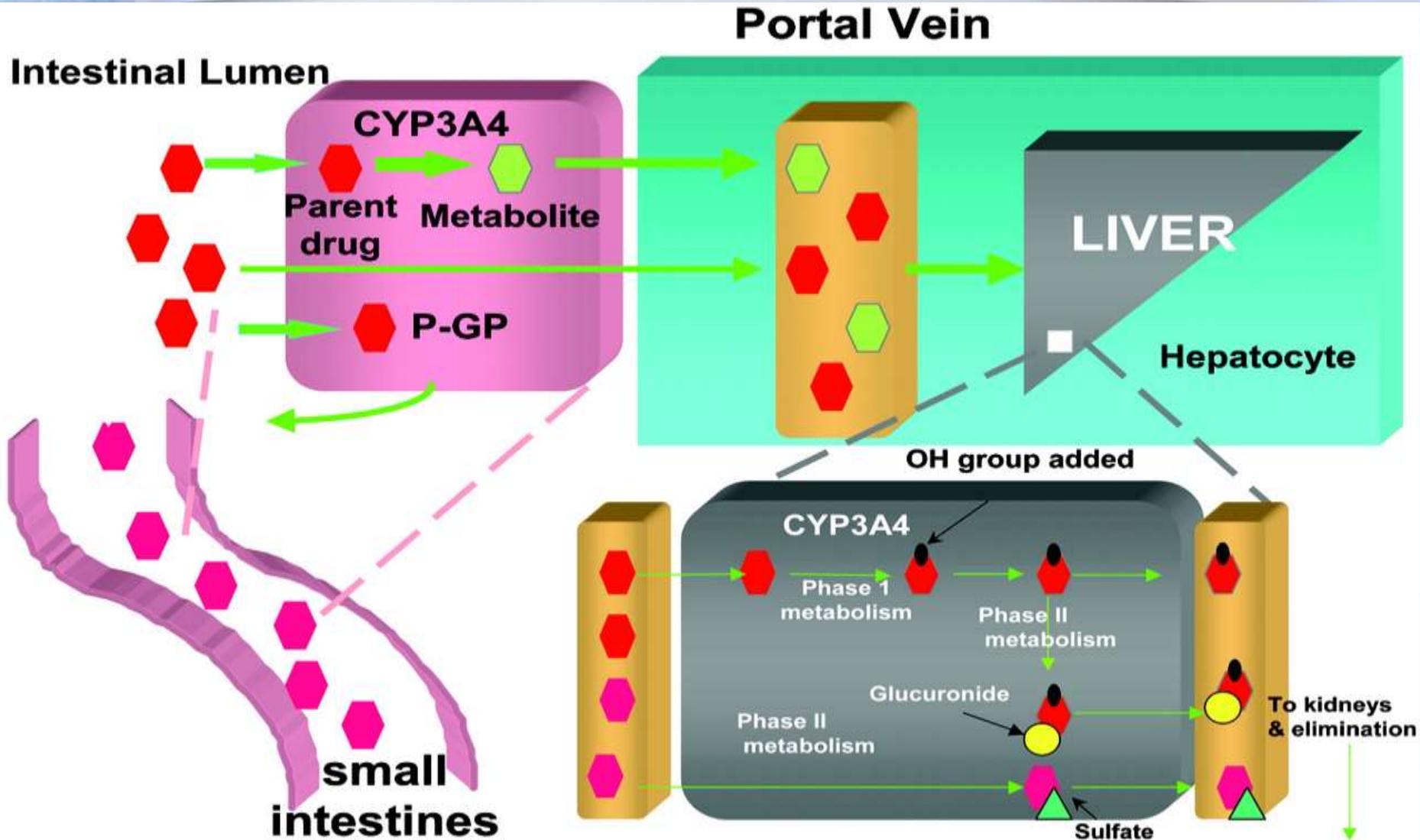
PXR / CAR

Reaction Rate
(K_m , V_{max})

Inhibition Rate
(IC_{50} , K_i)

Induction Rate
(K_{ind})

Cytochrome P-450 enzyme system

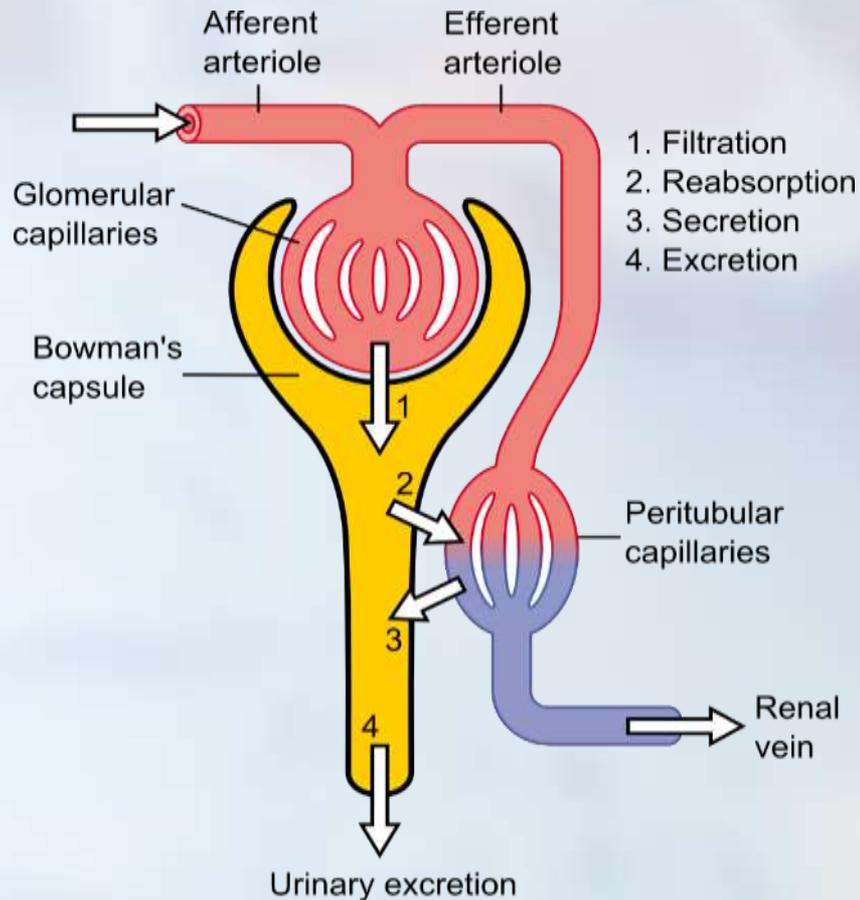




Hepatic extraction ratios (ER) for intravenous anesthetic drugs

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

Renal excretion



$$\text{Excretion} = \text{Filtration} - \text{Reabsorption} + \text{Secretion}$$



Pharmacological properties of intravenous induction agents

Intravenous induction agent	Effector site equilibration and $t_{1/2Keo}$	Haemodynamic effects in vivo	Comments
Ketamine	$\cong 2$ min	\uparrow CO, \uparrow HR, \uparrow ABP Sympathomimetic	\uparrow CPP and ICP
Thiopental	1.5 min	\uparrow HR, \rightarrow CO, \downarrow ABP \rightarrow laryngeal reflexes, \downarrow inotropism vasodilatation	unlikely to tolerate induction dose $> 3 \text{ mg.kg}^{-1}$
Propofol	≤ 20 min	\rightarrow HR, \downarrow CO, \downarrow ABP Vagotonic, \downarrow laryngeal reflexes	elderly, ASA 3 or more or hypovolaemic patients



Pharmacological properties of intravenous induction agents

Intravenous induction agent	Effector site equilibration and t _{1/2} Keo	Haemodynamic effects in vivo	Comments
Etomidate	~2.5 min	→CO, →ABP Minimal dose adjustment in shock	Prolonged inhibition of steroid synthesis in the critically ill
Opioide	6 min (fentanyl)	↓CO, ↓HR, ↓ABP ↓laryngeal reflexes Vagotonic	Potent vagally mediated bradycardia
Benzodiazepenes	~9 min (e.g. lorazepam)	→CO, →HR	Induction time of anaesthesia incompatible with RSI



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
- $t_{1/2Keo}$ of ~2 min
- intact autonomic nervous system -
sympathomimetic \uparrow heart rate, arterial pressure,
and cardiac output
- \downarrow inotropism in heart failure

Pagel PS, Kampine JP, Schmeling WT, Wartier 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 $t_{1/2Keo} \sim 1.5$ 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 $\frac{1}{4}$ of cases



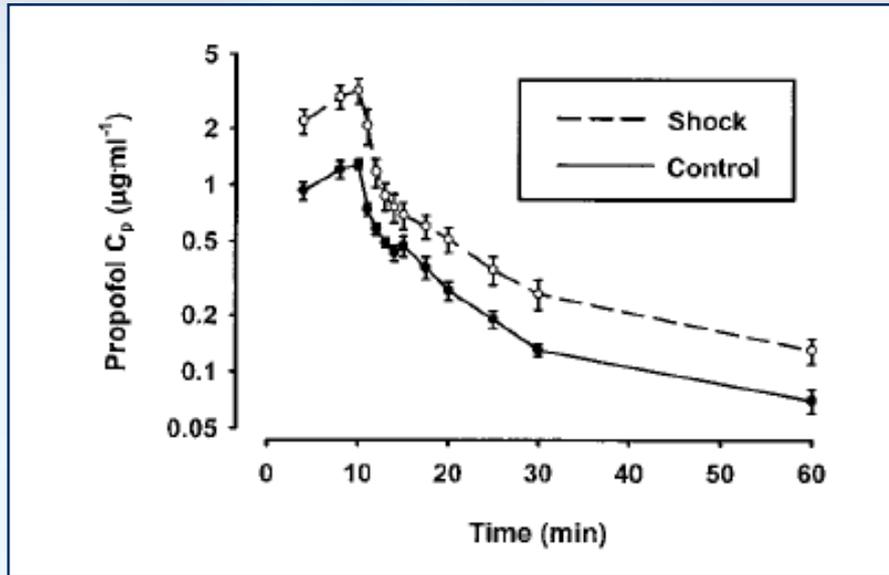
Propofol

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

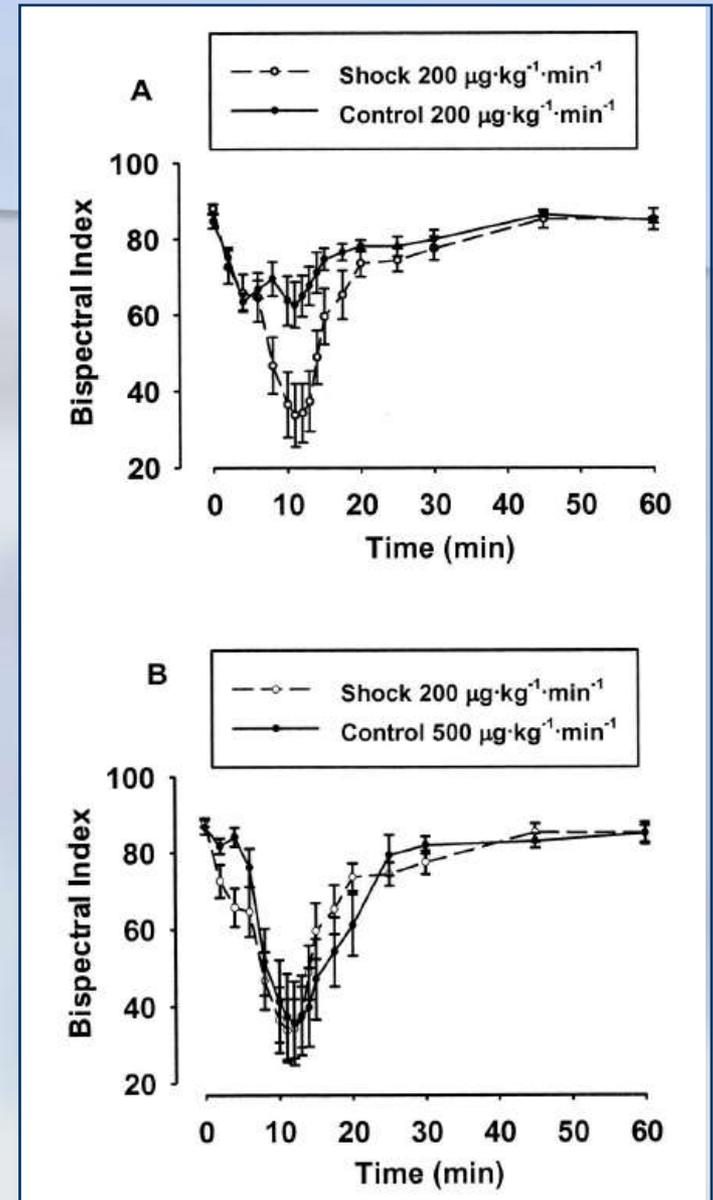




Propofol



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.





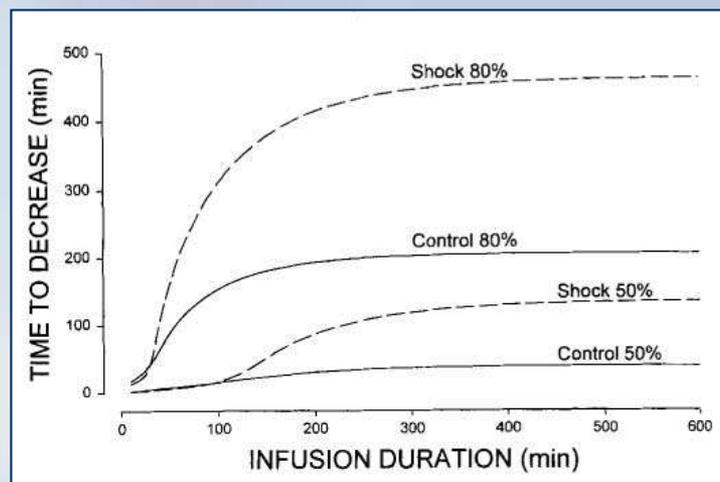
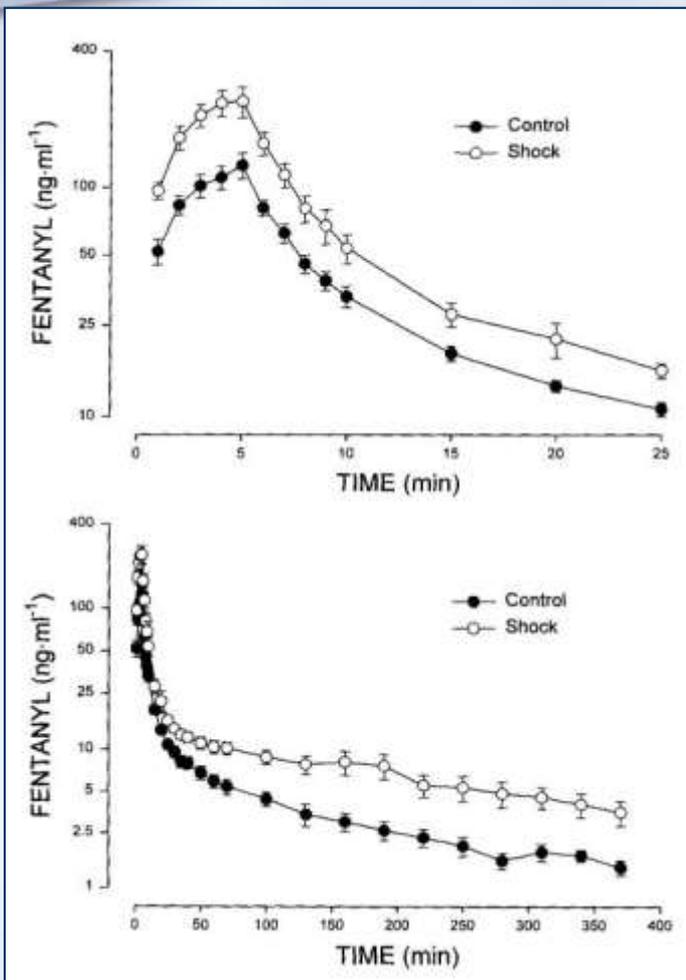
Propofol

- Avoid propofol if $SBP \leq 70$ mmHg or hypovolemic pts



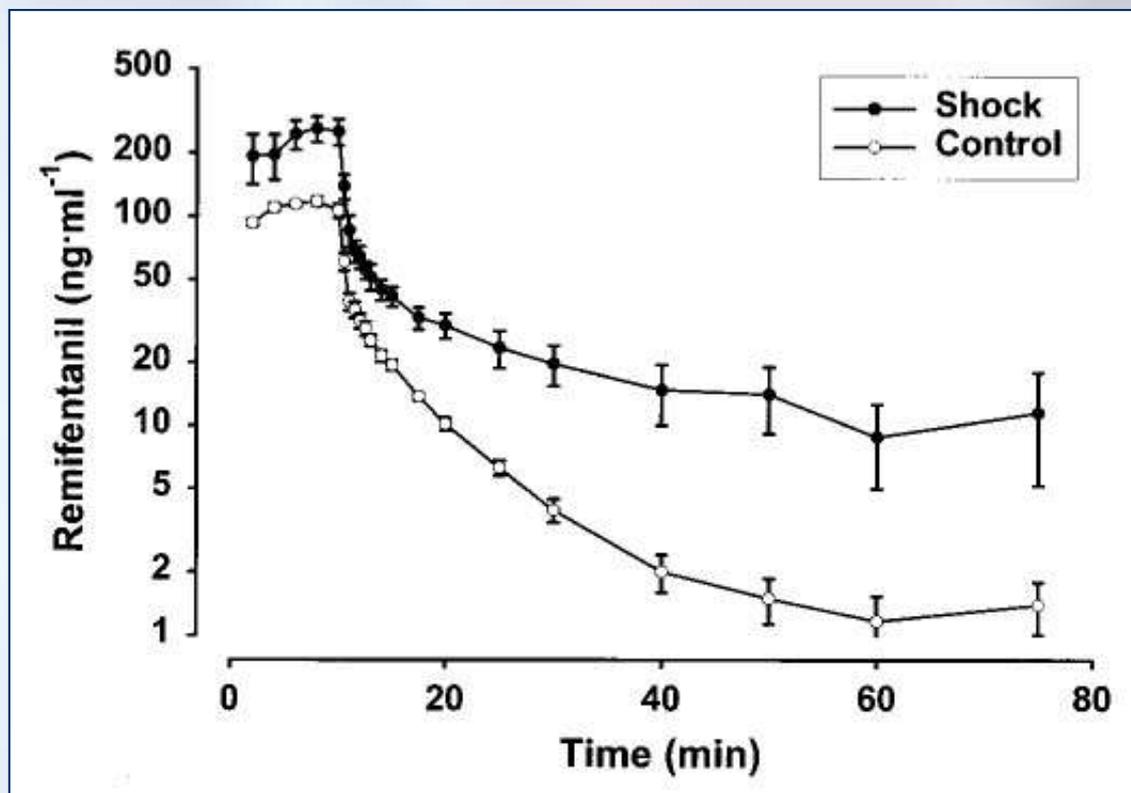
Fentanyl

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.





Remifentanyl



Hemorrhagic shock altered the pharmacokinetics of remifentanyl, suggesting that less remifentanyl 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 remifentanyl after termination of the infusion was minimal. Hemorrhagic shock did not alter the pharmacodynamics of remifentanyl.



Influence of blood loss on opioids behavior

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



Etomidate

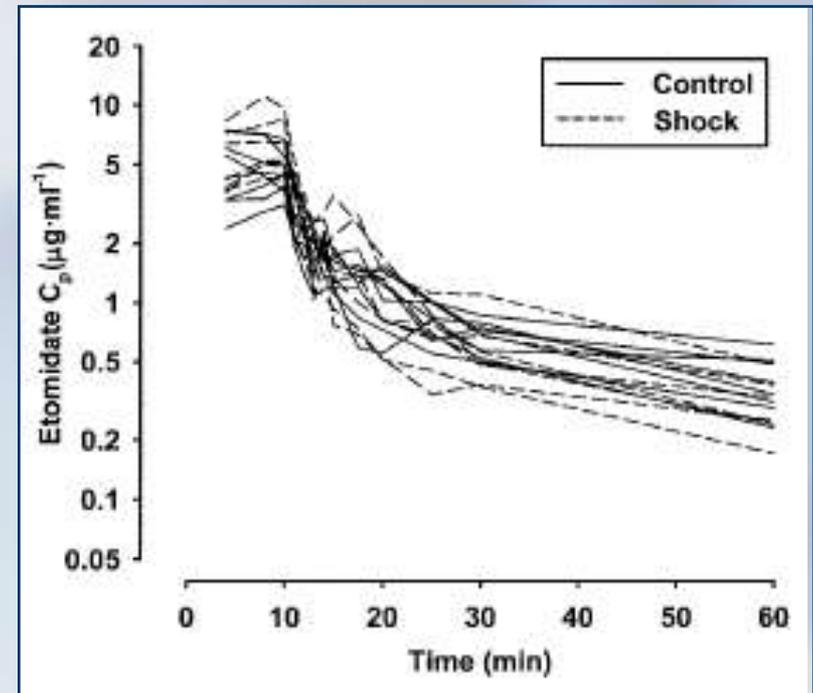
- a very popular choice for haemodynamically compromised patients
- preserve the pressor response to laryngoscopy

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.





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

Influence of blood loss on intravenous drug behavior



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



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!