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:
- (-)inotropism and vasodilatation (hTA)
- cardiorespiratory depression

in patients who are already hemodynamically compromised
Compartment changes

Intravascular fluid:
280 mOsm/L
(Total = 980 mOsm)
Fluid volume 3500 ml
- 700 ml
Total volume 5000 ml
- 1000 ml

Interstitial fluid:
280 mOsm/L
(total = 2940 mOsm)
10,500 ml

Intracellular fluid:
280 mOsm/L
(Total = 7840 mOsm)
28,000 ml

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
  - $\uparrow \alpha_1$–acid glycoprotein (alfentanil), $\downarrow$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
Cytochrome P-450 enzyme system
Hepatic extraction ratios (ER) for intravenous anesthetic drugs

<table>
<thead>
<tr>
<th>Low hepatic ER (ER &lt; 0.3)</th>
<th>Intermediate hepatic ER (ER 0.3-0.7)</th>
<th>High hepatic ER (ER &gt; 0.7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlordiazepoxide</td>
<td>Alfentanil</td>
<td>Fentanyl</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Chlorpromazine</td>
<td>Flumazenil</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Diphenhydramine</td>
<td>Ketamine</td>
</tr>
<tr>
<td>Methadone</td>
<td>Droperidol</td>
<td>Morphine</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>Etomidate</td>
<td>Nalmefene</td>
</tr>
<tr>
<td></td>
<td>Haloperidol</td>
<td>Naloxone</td>
</tr>
<tr>
<td></td>
<td>Hydromorphone</td>
<td>Propofol</td>
</tr>
<tr>
<td></td>
<td>Pethidine (meperidine)</td>
<td>Sufentanil</td>
</tr>
<tr>
<td></td>
<td>Midazolam</td>
<td></td>
</tr>
</tbody>
</table>

Renal excretion

Excretion = Filtration – Reabsorption + Secretion
<table>
<thead>
<tr>
<th>Intravenous induction agent</th>
<th>Effector site equilibration and t1/2Keo</th>
<th>Haemodynamic effects in vivo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ketamine</td>
<td>≈ 2 min</td>
<td>↑CO, ↑HR, ↑ABP</td>
<td>↑CPP and ICP</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Sympathomimetic</td>
<td></td>
</tr>
<tr>
<td>Thiopental</td>
<td>1.5 min</td>
<td>↑HR, →CO, ↓ABP, →laryngeal reflexes, ↓inotropism, ↓vasodilatation</td>
<td>unlikely to tolerate induction dose &gt; 3 mg.kg(^{-1})</td>
</tr>
<tr>
<td>Propofol</td>
<td>≤20 min</td>
<td>→HR, ↓CO, ↓ABP Vagotonic, ↓laryngeal reflexes</td>
<td>elderly, ASA 3 or more or hypovolaemic patients</td>
</tr>
</tbody>
</table>

Pandit JJ. Anaesthesia and Intensive Care Medicine 2008; 9: 154–9
# Pharmacological properties of intravenous induction agents

<table>
<thead>
<tr>
<th>Intravenous induction agent</th>
<th>Effector site equilibration and ( t_{1/2}^{Keo} )</th>
<th>Haemodynamic effects in vivo</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Etomidate</strong></td>
<td>(~2.5) min</td>
<td>(\rightarrow CO, \rightarrow ABP) Minimal dose adjustment in shock</td>
<td>Prolonged inhibition of steroid synthesis in the critically ill</td>
</tr>
<tr>
<td><strong>Opioide</strong></td>
<td>(~6) min (fentanyl)</td>
<td>(\downarrow CO, \downarrow HR, \downarrow ABP) (\downarrow) laryngeal reflexes Vagotonic</td>
<td>Potent vagally mediated bradycardia</td>
</tr>
<tr>
<td><strong>Benzodiazepenes</strong></td>
<td>(~9) min (e.g. lorazepam)</td>
<td>(\rightarrow CO, \rightarrow HR)</td>
<td>Induction time of anaesthesia incompatible with RSI</td>
</tr>
</tbody>
</table>

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

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

Himmelseher S, Durieux ME. *Anesthesia and Analgesia* 2005; 101: 524–34
Thiopental

- a short t1/2Keo \(\sim 1.5\) 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 ¼ of cases

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

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 ≤ 70 mmHg or hypovolemic pts

Shafer SL. *Anesthesiology* 2004; 101: 567–8
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.
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.
## Influence of blood loss on opioids behavior

<table>
<thead>
<tr>
<th>Drug</th>
<th>PK changes with BL</th>
<th>PD changes with BL</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Opioids</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morphine</td>
<td>++</td>
<td>-</td>
<td>DePaepe et al., 1998</td>
</tr>
<tr>
<td>Fentanyl</td>
<td>+++</td>
<td>-</td>
<td>Egan et al., 1999</td>
</tr>
<tr>
<td>Remifentanil</td>
<td>+++</td>
<td>0</td>
<td>Johnson et al., 2001</td>
</tr>
</tbody>
</table>

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

Walz JM, Zayaruzny M, Heard SO. *Chest* 2007, 131: 608-620
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

[www.ccmjournal.org](http://www.ccmjournal.org)
# Influence of blood loss on intravenous drug behavior

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

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**Induction doses and characteristics**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose [mg/kg]</th>
<th>Onset [s]</th>
<th>Duration [min]</th>
<th>Excitation</th>
<th>Pain</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiopental</td>
<td>3 - 5</td>
<td>30</td>
<td>5 - 8</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td></td>
<td>(less in suspec. hypovolemia)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Etomidate</td>
<td>0.2 - 0.4</td>
<td>15 - 45</td>
<td>3 - 12</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Propofol</td>
<td>1.5 - 3.0</td>
<td>15 - 45</td>
<td>5 - 10</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Midazolam</td>
<td>0.2 - 0.4</td>
<td>30 - 60</td>
<td>15 - 30</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Ketamine</td>
<td>1 - 3</td>
<td>45</td>
<td>10 - 20</td>
<td>+</td>
<td>0</td>
</tr>
</tbody>
</table>
Thank you!