Pharmacology of Anesthetics II

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Importance of Quantifying Dosage & Potency: MAC

- General anesthetics have low therapeutic indices, ranging from 2 to 4
- Depth of anesthesia depends upon anesthetic concentration in brain; cannot be measured routinely
- Can accurately measure anesthetic concentration in lung
Minimum Alveolar Concentration

MAC is the minimum alveolar concentration of an inhaled anesthetic at 1 atmosphere that prevents gross and purposeful movement in 50% of subjects exposed to a noxious stimulus.
### MAC for various agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>MAC</th>
<th>Induction Concentration (Vol%)</th>
<th>Maintenance Concentration (Vol%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethyl ether</td>
<td>1.92</td>
<td>10-30</td>
<td>4-15</td>
</tr>
<tr>
<td>Halothane</td>
<td>0.76</td>
<td>2-4</td>
<td>0.5-2.0</td>
</tr>
<tr>
<td>Isoflurane</td>
<td>1.12</td>
<td>2-4</td>
<td>1.0-3.0</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.68</td>
<td>2-5</td>
<td>1.5-3.0</td>
</tr>
<tr>
<td>N₂O</td>
<td>105.0</td>
<td>Up to 80</td>
<td>Up to 80</td>
</tr>
</tbody>
</table>

Dripps et al., 1988
<table>
<thead>
<tr>
<th>Agent</th>
<th>λ</th>
<th>MAC</th>
<th>Vapor Pressure</th>
<th>% Recovered as Metabolite</th>
</tr>
</thead>
<tbody>
<tr>
<td>Desflurane</td>
<td>0.45</td>
<td>6.0</td>
<td>669</td>
<td>0.02</td>
</tr>
<tr>
<td>Sevoflurane</td>
<td>0.65</td>
<td>2.0</td>
<td>170</td>
<td>3.0</td>
</tr>
<tr>
<td>N₂O</td>
<td>0.47</td>
<td>105.0</td>
<td>gas</td>
<td>0.0004</td>
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<tr>
<td>Isoflurane</td>
<td>1.4</td>
<td>1.15</td>
<td>240</td>
<td>0.2</td>
</tr>
<tr>
<td>Enflurane</td>
<td>1.8</td>
<td>2.0</td>
<td>172</td>
<td>2.4</td>
</tr>
<tr>
<td>Halothane</td>
<td>2.4</td>
<td>0.75</td>
<td>224</td>
<td>15-20</td>
</tr>
</tbody>
</table>

Eger et al., *Anesthesiology* 80:906-922, 1994
MAC is a Useful Index of Anesthetic Potency

- MAC values can be used to quantitatively compare the potencies of different anesthetics
- MAC values are additive
- MAC can be used to quantify the effects of adjuvant agents on anesthetic requirement
- MAC values are relatively invariant with a variety of supra-maximal noxious stimuli
MAC is a Useful Index of Anesthetic Potency

- MAC is not significantly altered by sex, weight, and duration of anesthesia
- MAC is not altered by changes in metabolic acid-base balance, PaO2, or blood pressure
Cautionary Notes about MAC

- MAC measures only one point on a continuum of responses that represent a graded dose-response curve for the production of anesthesia
- The slopes of dose-response curves for inhalation anesthetics are very steep
Eger El. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 4
Cautionary Notes about MAC

- MAC values decrease with pregnancy
- MAC values decrease with age
- MAC values decrease with hypothermia
Eger EI. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 14
U.S. Population Age 65 Years and Over

from: U.S. Department of Commerce, Issued February 1996
Eger EJ. Anesthetic Uptake and Action, Williams & Wilkins, Baltimore, 1974, p. 12
<table>
<thead>
<tr>
<th>Reflexes</th>
<th>Stage 1</th>
<th>Stage 2</th>
<th>Stage 3</th>
<th>Stage 4</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>i</td>
<td>ii</td>
<td>iii</td>
<td>iv</td>
</tr>
<tr>
<td>Consciousness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Excitement</td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Respiration</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Abdominal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Thoracic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Eye movement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lid or wink</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting</td>
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</tr>
<tr>
<td>Swallowing</td>
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</tr>
<tr>
<td>Laryngeal</td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Corneal and peritoneal</td>
<td></td>
<td></td>
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<tr>
<td>Pupil dilatation</td>
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</tr>
<tr>
<td>Tachycardia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated blood pressure</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lowered blood pressure</td>
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</tbody>
</table>
Balanced Anesthesia

the concept that no single anesthetic can produce all the desired effects, thus anesthetics must be given in combination
Balanced Anesthesia

Goals of modern anesthesia:

• to produce analgesia, amnesia, loss of consciousness, inhibition of sensory and autonomic reflexes, and skeletal muscle relaxation
• to ensure a smooth, rapid onset of anesthesia, and a rapid recovery from anesthesia
Balanced Anesthesia

involves the use of drug combinations:

• preoperative sedatives and/or anxiolytics
• anesthetic induction with an i.v. agent
• intra-operative neuromuscular blockers
• inhalation and i.v. agents for maintenance of anesthesia
## Balanced Anesthesia

<table>
<thead>
<tr>
<th></th>
<th>Thiopental</th>
<th>Fentanyl</th>
<th>Vercuronium</th>
<th>Isoflurane</th>
<th>N₂O</th>
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</thead>
<tbody>
<tr>
<td>Unconsciousness</td>
<td>*</td>
<td></td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>Muscle relaxation</td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amnesia</td>
<td></td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
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<tr>
<td>Analgesia</td>
<td>*</td>
<td></td>
<td>*</td>
<td>*</td>
<td></td>
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<tr>
<td>Reduced autonomic</td>
<td></td>
<td>*</td>
<td></td>
<td>*</td>
<td></td>
</tr>
<tr>
<td>responses</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>
Methods for Evaluating Anesthetic Depth

- measure end tidal concentrations of CO2, N2, O2, N2O, potent agent
- look or ask for movement
- monitor vital signs
- look for sympathetic activity
Methods for Evaluating Anesthetic Depth

- nerve conduction tests
- evoked potentials
- Bispectral Index Scale (BIS)
Bispectral Index Scale (BIS)

- used as a measure of depth of anesthesia or sedation analgesia
- provides a sedation score ranging from 100 (awake) to 0 (isoelectric EEG) values range from 40 to 55 during general anesthesia

Johansen and Sebel, *Anesthesiology* 93:1336-1344, 2000
Integrated cortical output
(arbitrary units)

INTEGRATED CORTICAL OUTPUT

Complex
Burst suppression (early)
Burst suppression (late)
Suppression

INCREASING ANESTHETIC DEPTH

Martin et al., Anesthesiology 20:359, 1959
Graph of Bispectral index

Commonly used IV Agents

- **Barbiturates**: sodium thiopental
- **Benzodiazepines**: midazolam, diazepam, lorazepam
- **Opioids**: morphine, fentanyl, remifentanil, sufentanil
- **Dissociative anesthetic**: ketamine
- **Alkyl phenol**: propofol
Ketamine and Phencyclidine

Ketamine

Phencyclidine
Ketamine: Major Clinical Uses

- Induction of anesthesia in patients in hemodynamic shock or with active asthmatic disease
- IM sedation of uncooperative patients, particularly children
- Supplementation of incomplete regional or local anesthesia
Ketamine: Major Clinical Uses

• Sedation in the ICU
• Short, painful procedures, i.e., dressing changes in burn patients

Ketamine: Clinical Pharmacology

- A racemic mixture consisting of two optical enantiomers R(-) and S(+) and the preservative benzethonium chloride
- Short half-life (2-3 hrs)
- Extensive metabolism by the hepatic cytochrome p450 system
- Primary metabolite is norketamine; 1/3 to 1/5 as potent as ketamine

Kohrs and Durieux, *Anesth Analg* 87:118
Ketamine: Clinical Pharmacology

- Produces a dissociative state characterized by profound analgesia and amnesia but not necessarily a loss of consciousness
- Patients receiving ketamine appear completely unaware of the environment
- Emergence can be complicated by psychotomimetic reactions, such as hallucinations or vivid dreams
Ketamine: Mechanism of Action

- Interacts with multiple binding sites
- Antagonism of the N-methyl-D-aspartate (NMDA) glutamate receptor accounts for most of the analgesic, amnestic, psychotomimetic, and neuroprotective effects
- Ketamine binds to the phencyclidine (PCP) binding site in the NMDA receptor channel
Propofol

2,6-diisopropylphenol
Propofol: Major Clinical Uses

• Induction and maintenance agent
• Neurosurgical and pediatric anesthesia
• ICU sedation
• Outpatient ambulatory procedures
Propofol: Clinical Pharmacology

- rapid onset of action (22-125 sec)
- rapid metabolic clearance - 10 x faster than thiopental
- metabolic clearance exceeds hepatic blood flow, suggesting extra-hepatic metabolism
- antiemetic properties
Propofol: Clinical Pharmacology

• recovery is characterized by a rapid return to an alert state
• patients report feeling in a “good mood” upon recovery
Propofol: Mechanism of Action

- decreases the rate of dissociation of GABA from the GABA_A receptor
- this increases the duration of GABA-activated chloride ion conductance
- results in increased hyperpolarization of neuronal membranes
- may produce a loss of consciousness, in part, by reducing central cholinergic neurotransmission at muscarinic receptors