LeBonheur Children’s Hospital
Pediatric Surgery Grand Rounds

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Outline

- Volatile Anesthetics: History and modern compounds
- Malignant Hyperthermia: Causes, treatments & prevention
- Neuromuscular Blocking Drugs
  - Atypical Pseudocholinesterase
- Pain Management
  - Opioids
  - Regional
Volatile Anesthetics

- Methyl Ether Basis:

Isoflurane (Forane):

Desflurane (Suprane):
Volatile Anesthetics

- Methyl Isopropyl Basis:
- Sevoflurane (Ultane):

\[
\begin{align*}
F_3C & \quad O \quad F \\
& \quad CF_3
\end{align*}
\]
Volatile Anesthetics

- Solubility:
  - blood/gas partition coefficient:
  - Isoflurane >> sevoflurane >> desflurane

- Vapor Pressure:
  - Desflurane (near atmospheric pressure) >> isoflurane >> sevoflurane
Volatile Anesthetics

- Nitrous Oxide:
  - MAC 104%
  - Least soluble of all volatile anesthetics
  - Nitrous is 34x more soluble in the blood than nitrogen:
    - Pneumothorax
    - Pneumocephalus
    - Placement of IOL
    - Bowel obstruction
Volatile Anesthetics
Volatile Anesthetics

- MAC (Minimum Alveolar Concentration)
  - Defined as the expiratory concentration at which 50% of people do not respond to noxious stimuli
  - Potency varies inversely to the lipid solubility of the volatile agent
  - In general, MAC increases as the age of the patient decreases
Malignant Hyperthermia

- First described in 1960 by Denborough & Lovell.
- Classically linked to an autosomal dominant pattern with variable penetrance. RyR1 gene implicated.
- Incidence: 1:50,000 in adults, 1:20,000 in children; when succinylcholine is added the risk is somewhat greater.
## Malignant Hyperthermia

### TABLE 40-1 Clinical and Laboratory Findings Associated with Malignant Hyperthermia

<table>
<thead>
<tr>
<th>Clinical Findings</th>
<th>Laboratory Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tachycardia, tachypnea and hypertension</td>
<td>Increased PaCO₂</td>
</tr>
<tr>
<td>Hypercarbia (increased CO₂)</td>
<td>Acidosis (mixed respiratory and metabolic)</td>
</tr>
<tr>
<td>Greatly increased minute ventilation</td>
<td>Relative hypoxia, increased alveolar to arterial partial pressure gradient for oxygen</td>
</tr>
<tr>
<td>Generalized muscle rigidity (unresponsive to nondepolarizing muscle relaxants)</td>
<td>Hyperkalemia</td>
</tr>
<tr>
<td>Skin mottling</td>
<td>Elevated plasma lactate concentration</td>
</tr>
<tr>
<td>Hyperthermia (late sign)</td>
<td>Abnormal coagulation studies (late sign)</td>
</tr>
<tr>
<td>Cardiac arrhythmias (hyperkalemia-induced: PVC, VT, VF)</td>
<td>Myoglobinuria, myoglobinemia</td>
</tr>
<tr>
<td>Cola-colored urine (late sign)</td>
<td>Increased CPK level (usually a late sign)</td>
</tr>
<tr>
<td>Disseminated intravascular coagulation (late)</td>
<td></td>
</tr>
</tbody>
</table>

CPK, Creatine phosphokinase; CO₂, carbon dioxide; PaCO₂, arterial partial pressure of carbon dioxide; 
PVC, premature ventricular contraction; VT, ventricular tachycardia; VF, ventricular fibrillation.

Malignant Hyperthermia

- Mortality rate: decreased from 80% in the 1960’s to 1.5% today.
  - Early recognition (use of capnography) as well as precise temperature monitoring have contributed to the decrease in MH.
  - More accurate family history & recordkeeping.
Malignant Hyperthermia Treatment

- Dantrolene:
  - Hydantoin derivative originally developed as a muscle relaxant.
  - Decreases the amount of intracellular calcium released from the sarcoplasmic reticulum without completely blocking it.
  - Works in two ways:
    - Binds to the RyR1 channel attenuating efflux of calcium from the sarcoplasmic reticulum
    - Store operated calcium entry (SOCE) is inhibited, thus reducing the amount of calcium that is replenished into the sarcoplasmic reticulum
Malignant Hyperthermia Treatment

- **Dantrolene:**
  - At LBCH, dantrolene is available as a powder that is pre-mixed with mannitol.
  - Per vial there is 20mg dantrolene and 3g of mannitol; this must be diluted with 60ml of sterile water.
  - Starting dose of 2.5mg/kg, repeated every 3-5 minutes until clinical symptoms abate.
Diagnosis:

- Clinical criteria vs. Laboratory findings vs. Genetic testing
<table>
<thead>
<tr>
<th>Process</th>
<th>Indicator</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rigidity</td>
<td>Generalized muscular rigidity</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Masseter spasm</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Creatine kinase &gt; 20,000 IU after succinylcholine</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Creatine kinase &gt; 10,000 IU with no succinylcholine</td>
<td>15</td>
</tr>
</tbody>
</table>

**Muscle breakdown**

<table>
<thead>
<tr>
<th></th>
<th>Cola-colored urine in perioperative period</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Myoglobin in urine &gt; 60 μg/L</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Myoglobin in serum &gt; 170 μg/L</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Blood, plasma, or serum K⁺ &gt; 6 mEq/L, no renal illness</td>
<td>3</td>
</tr>
</tbody>
</table>

**Respiratory acidosis**

<table>
<thead>
<tr>
<th></th>
<th>Perco₂ &gt; 55 mm Hg with controlled ventilation</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterial Paco₂ &gt; 65 mm Hg with controlled ventilation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Perco₂ &gt; 80 mm Hg with spontaneous ventilation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Arterial Paco₂ &gt; 85 mm Hg with spontaneous ventilation</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Inappropriate hypercarbia, anesthesiologist’s call</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>Inappropriate tachypnea</td>
<td>10</td>
</tr>
</tbody>
</table>

**Temperature increase**

<table>
<thead>
<tr>
<th></th>
<th>Inappropriately rapid increase</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Inappropriately increased temperature &gt; 38.8°C (101.8°F)</td>
<td>10</td>
</tr>
</tbody>
</table>

**Cardiac involvement**

<table>
<thead>
<tr>
<th></th>
<th>Inappropriate sinus tachycardia</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ventricular tachycardia or fibrillation</td>
<td>3</td>
</tr>
</tbody>
</table>

**Family history**

<table>
<thead>
<tr>
<th></th>
<th>Positive family history for first-degree relative</th>
<th>15</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive family history for more distant relative</td>
<td>5</td>
</tr>
</tbody>
</table>

**Others**

<table>
<thead>
<tr>
<th></th>
<th>Arterial base excess more negative than ±8 mEq/L</th>
<th>10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Arterial pH &lt; 7.25</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Rapid reversal of malignant hyperthermia (MH) signs after intravenous administration of dantrolene</td>
<td>5</td>
</tr>
<tr>
<td></td>
<td>Positive MH family history with another indicator from the patient’s anesthesia experience other than increased creatine kinase level</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>Elevated creatine kinase level and a family history of MH</td>
<td>10</td>
</tr>
</tbody>
</table>
# Malignant Hyperthermia Diagnosis

<table>
<thead>
<tr>
<th>Score</th>
<th>Likelihood</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Almost never</td>
</tr>
<tr>
<td>3-9</td>
<td>Unlikely</td>
</tr>
<tr>
<td>10-19</td>
<td>Somewhat less than likely</td>
</tr>
<tr>
<td>20-34</td>
<td>Somewhat greater than likely</td>
</tr>
<tr>
<td>35-49</td>
<td>Very likely</td>
</tr>
<tr>
<td>≥50</td>
<td>Almost certain</td>
</tr>
</tbody>
</table>
Malignant Hyperthermia Diagnosis

- Muscle biopsy:
  - Fresh muscle is harvested from a patient
  - This muscle is then placed on a strain gauge
  - Its response to caffeine in various doses & 3% Halothane are recorded
  - The value must be abnormal for either test in order for the patient to have MH
  - False negatives with the available protocol are virtually zero
Malignant Hyperthermia Diagnosis

- Testing for RyR calcium channel mutations are available
- Any physician can write a prescription for these tests
- Unfortunately only about 60% of those with a positive muscle biopsy test also have a positive genetic test
Malignant Hyperthermia Diagnosis

- Post-MH episode testing:
  - Ideally the patient and first degree relatives would all be referred to a center for a muscle biopsy and caffeine-halothane contracture testing
  - If the muscle biopsy is positive, they should also be genetically tested
  - Unfortunately, if the patient is pre-pubescent (<10y), there are no muscle standards and so they must wait until the start of puberty to be tested
  - The costs (~$5,000) are normally covered by insurance
Malignant Hyperthermia Management

- If there is known disease in the patient or a close relative with known disease a total intravenous anesthetic is recommended.

- The anesthesia machine must also be flushed of residual anesthetic:
  - Our Drager machines take ~120 minutes to flush.
  - Charcoal filters are available at LBCH to reduce this time to 5 minutes.
  - Remember also to replace the absorbent canister and anesthesia circuit.
Neuromuscular Blocking Drugs

- Depolarizing:
  - Succinylcholine (Anectine)
  - Depolarizes the neuromuscular junction receptor
  - Onset time in ~30s for 2-3mg/kg.
  - Duration of 5-10 minutes total
  - Significant side effects resulted in a black box warning
Atypical Pseudocholinesterase

- Pseudocholinesterase or plasma esterase or butyrylcholinesterase is the primary way that succinylcholine is metabolized.

- Numerous other drugs e.g. remifentanil, ester type local anesthetics are also metabolized in this way.

- Two mutations of the gene that codes for pseudocholinesterase identified.
Atypical Pseudochocholinesterase

- Heterozygous atypical pseudochocholinesterase
  - This causes the duration of succinylcholine to increase by 50-100%; it is largely not clinically relevant. Present in 1:30 individuals

- Homozygous atypical pseudochocholinesterase
  - The duration of succinylcholine is greatly increased; total duration of action is 6-8 hours. Present in 1:10,000 individuals
Neuromuscular Blocking Drugs

- Non-depolarizing:
  - Benzylisoquinolinium: cisatracurium
    - One of 10 stereoisomers of atracurium
    - Elimination by Hoffmann elimination
    - Concern for laudanosine accumulation in renal failure (metabolite that can cause seizures) has proven unfounded in clinical use
  - Intubating dose of 200mcg/kg
Neuromuscular Blocking Drugs

- Aminosteroid: rocuronium
  - A derivative of pancuronium, much less potent than vecuronium
  - Intubating dose of 0.6-1.2mg/kg.
  - High dose is the “rapid sequence dose”; it allows for intubating conditions in approximately 45s to 1 min.
  - Most common reason for allergic reaction to anesthesia worldwide
Neuromuscular Blocking Reversal

- Sugammadex (Bridion):
  - Indicated for reversal of steroid based neuromuscular blocking drugs (rocuronium specifically)
  - Dosages vary from 2mg/kg-16mg/kg
  - Concern in Europe for anaphylaxis to sugammadex have resulted in only the recent approval by the FDA in the U.S. of this drug
  - Vials are 200mg each; will be available at LBCH soon
Traditionally the management of post-operative pain has been via opioid medications:

- Morphine: dose of 100mcg/kg divided normally provides sufficient post op pain control for most surgeries

- Hydromorphone: differs from morphine only in the 6th position of the molecule. Nominally it is 5x more potent than morphine. Questionable lower incidence of side effects secondary to lack of build-up of morphine metabolites.
Fentanyl: 100x more potent than morphine. Short apparent effects of initial bolus dose are secondary to redistribution, not metabolism or elimination. After an 8 hour infusion, half life can stretch to 8 hours.

Demerol: A weak mu agonist with 1/10 the potency of morphine. It is not routinely used in children except to treat post-op shivering. It is metabolized to normeperidine which, especially in patients with renal failure, will precipitate seizures.
Pain Management

- Ketamine: NMDA receptor antagonist causing dissociation of the cerebral cortex. Induction dose of 2-3 mg/kg in children. Post operative doses of 0.5-1 mg/dose or 0.5 to 1 mg/kg/h. Side effects include increased ICP, increased secretions and possibly seizures in susceptible individuals.

- Dexmedetomidine: α2 agonist; net effect is a reduction of sympathetic outflow and anxiolysis, sedation and analgesia. Bolus dose of 0.5 to 1 mcg/kg/h given over 10 min and continuous rates of 0.5-1.2 mcg/kg/h at LBCH. Side effects include hypotension & bradycardia.
Regional Anesthesia

- Thoracic and lumbar epidurals:
  - Provide excellent analgesia for a variety of surgical procedures in the thoracic space and abdomen.

- Caudal epidural:
  - Can be single shot or continuous via a catheter...provide excellent lower extremity analgesia and perineal analgesia.
Regional Anesthesia

- **Paravertebral blocks:**
  - The paravertebral space is a plane between the lateral border of the vertebral body and the anterior surface of the transverse process.
  - Ultrasound guidance can help prevent the dreaded complication of pneumothorax while performing this block.
  - Useful for pectus repairs and unilateral analgesia from the T1-T12 dermatomes.

- **TAP (Transversus Abdominus Plane) blocks:**
  - Reasonable choice for abdominal cases including those that are laparoscopic. Pain control is similar to or slightly better than local infiltration around laparoscopic ports. Does not help with visceral analgesia.
Questions?