Anesthetic Issues in Children with Neurologic Diseases

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Nothing to Declare
Generalities

• Common problems in children with various neurologic diseases:
  • Cortical issues (intelligence, behavior, etc.)
  • Visual or hearing disturbances
  • Oropharyngeal, pulmonary mechanical problems
  • Cervical instability or torticollis
  • Reflux
  • Contractures, weakness/hypotonia
  • Movement disorders
  • Seizures and antiseizure medications
Intubation-related risks
Approach to individuals with epilepsy

• Avoid prolonged preoperative fast

• 18+ ASDs—avoid holding doses pre/post
  • Depends on half-time drug elimination
  • Oral with small sip/rectal/IV
  • Anesthetic choice/dose: consider ASD etc. med

• Care with hyperventilation/hypocarbia
  • Reduction of CBF v worsening metab/EEG
  • Care in interpretation of cause or nature of twitching, tonicity, shivering, confusion
Anesthetics with effects on seizure threshold (sometimes…)

- Enflurane Proconvulsant
- Etomidate Proconvulsant
- Sevoflurane Proconvulsant
- Fentanyl Pro- or anticonvulsant
- Ketamine Pro- or anticonvulsant*
- Lidocaine Pro- or anticonvulsant
- Methohexital Proconvulsant
- Morphine Pro- or anticonvulsant
- Propofol Pro- or anticonvulsant*
- Etc.

* Particularly useful treating BDZ-resistant status epilepticus
Receptor trafficking
Inhalational Anesthetics (1)

- **Enflurane:** proconvulsant
  - Organic/inorganic flourinated metabolites
  - *No Epilepsy:* Facial/appendicular myoclonus
    - No associated convulsive EEG abnormalities
    - Deep levels have been associated with GTC szs
  - *Epilepsy:* concn-related worsening szs + EEG abn
    - HV (to decrease CFB/ICP) worsens enflurane effect
    - DZP, thiopental may *worsen* enflurane effects
    - Nitrous not known to have + or – influence
    - Post-op GTC/myoclonic szs may persist for days
Inhalational Anesthetics (2)

• Isoflurane
  – Little proconvulsive—except co-admin of nitrous?
  – *Valuable anticonvulsant effects* (esp. BDZ-resistant status)
  – Good choice in status epilepticus
  – Concerns re caspase-3 activation/NMDA-r endocytosis
    • Pertinent to Alzheimer (including Down syndrome-associated and…?)

• Desflurane
  – Similar to isoflurane
  – Faster emergence
    • Valuable in individuals with *metabolic diseases* where special dietary frequent accomodations must be made
    • However greater tendency to peri-emergent coughing
Inhalational Anesthetics (3)

• **Sevoflurane**
  – Induction-related movements
    • May be non-epileptic
    • Focal or generalized epileptic seizures may occur
      – Children especially vulnerable, epileptic >> normal
      – Especially with rapid induction, higher doses
      – Rapid + controlled HV may provoke in 80% cf 20% without HV
      – May have associated CNS-related autonomic changes
      – Nitrous or bolus MDZ may suppress sevoflurane-related seizures

• **Nitrous:** Little proconvulsive or *anticonvulsive* activity
  – Extensive experience, valuable in epilepsy surgery

• **Halothane:** *anticonvulsive*
  – Except with co-administered nitrous?
    – Transient post-op vertex sharp waves 2-7 days
Barbiturate Anesthetics (1)

• Phenobarbital
  • Very anticonvulsive, high doses well-tolerated
    – Up to at least 120mg/kg over time well tolerated
    – Long duration of effects
    – Loss of effect with receptor trafficking (as with BDZ)

• Pentobarbital
  • Brainstem in addition to cortical anticonvulsive
    – Shorter duration, cardiopulmonary support early
    – Loss of effect with receptor trafficking (as with BDZ)?
Barbiturate Anesthetics (2)

• Thiopental
  • Powerful anticonvulsive effects in Tx range
    – Valuable for status epilepticus, local anesthetic related szs
    – Probably safe for induction in mitochondrial diseases

• Methohexital
  • Excitatory during induction:
    – Tremor, muscle twitch, hypertonus, hiccough with nl EEG
  • Epilepsy (PC): Szs/EEG abn may occur (IV, IM, rectal admin)
    – Low doses may activate PC (>70% cases?)
    – No such effect in primary generalized epilepsies?
    – High doses—electrocerebral silence possible
  • Methohexital suppression test to find TLE focus
Other Anesthetics(1)

• **Etomidate**
  - Useful in neurological diseases with cardiovascular instability
  - Non-epileptic individuals
    - Longer convulsive phase after electroconvulsive Tx than with propofol
    - Involuntary myoclonic mvts 10-70% of patients
      » May suggest szs, may be violent
      » Co-administration opioid or short acting BDZ avoids problem
      » But: epileptiform in 20% heart valve replacement cases
  - Epileptic individuals
    - Some risk for provocation of focal or secondary GTC szs
      » 0.2mg/kg sz focus activation (<30s onset)
Other Anesthetics (2)

• Ketamine
  • Epilepsy: 37% risk sz/obtundation 2-4mg/kg IV(focal/2° genl)??
    – Treat with BDZ or barb rather than increasing ketamine dose
      » Some studies show little ketamine risk in well-treated epilepsy but given alternative agents may be best to avoid if epilepsy.
  • Dissociative state with delirium possible (may suggest “PC Sz”)
  • With prolonged use cerebellar injury possible
Propofol

• Cortical depressant for anesthesia/treatment of seizure
  – CNS subcortical excitatory phenomena in 10% of patients
  – When used in electroconvulsive Tx shortens convulsive phase
  – Avoid in well-controlled epilepsy (driver’s license risk?)
• Status epilepticus: 5-10 mg/kg/hr infusion
  – May bolus with 1.0-3.0 mg/kg over 5 min; beware hypotension
    • Titrated to achieve suppression-burst or isoelectric EEG
    • Intubation and pressor support required
    • Central arterial blood pressure monitoring recommended
  – Monitor acid-base balance: at risk for severe metabolic acidosis.
    • Children may be particularly subject to this
  – May wish to replace with other agents once control of SE is achieved.
    • Taper at rates no faster than 5% per hour
• Alternatives:
  – Inhalation anesthesia (isoflurane)
Propofol infusion syndrome (1)

- Rare but may be fatal; critically ill children > adults (21/14 as of 2003)
  - Mostly acute neurological or inflammatory illnesses—receiving catecholamines/steroids as well as longterm high dose propofol.
  - Cardiac failure, rhabdomyolysis, severe metabolic acidosis and renal failure.
  - CNS activation with ↑catecholamines and glucocorticoids

Vasile et al., Intensive Care Med. 2003 Sep;29(9):1417-25
Propofol infusion syndrome (2)

- Systemic inflammation / cytokine production priming cardiac/ peripheral muscle dysfunction ± necrosis.
  - Potent inhibitor of Complex I of electron chain
    - Impairs free fatty acid utilization: LCFA transport via CPT as well as beta oxidation
    - Mismatch of energy supply and demand
    - Avoid utilization in mitochondrial neurologic disease
    - Avoid prolonged (>48 h) propofol sedation at doses higher than 5 mg/kg/h especially if acute neurological or inflammatory illnesses.
    - In such cases, alternative sedative agents should be considered. If unsuitable, strict monitoring of signs of muscle necrosis advisable.

*Vasile et al., Intensive Care Med. 2003 Sep;29(9):1417-25*
A few more things about propofol

- Prolonged infusion-related acid-base disturbances
  - Fever, muscle membrane dysfunction, CK>20,000, occ rhabdomyolysis, some fatalities—especially <20yo

- Movement abnormalities especially in induction phase:
  - May provoke myoclonus in myotonic dystrophy
  - Twitches, athetosis, chorea, dystonia, opisthotonus are also described in individuals who do not have myotonic dystrophy
  - May reappear in postoperative period

- Conscious dental sedation:
  - Even with epilepsy not provocative of seizures

- Bolus anesthetic doses may activate epileptic foci
  - Occ seizure recurrence for up to 23 d postop—metabolite?
  - Cardiac surgery with propofol + calcium + MDZ reduces post-op risk of seizures
<table>
<thead>
<tr>
<th>Drug class</th>
<th>Drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alcoholism treatments</td>
<td>Disulfiram</td>
</tr>
<tr>
<td>Analgesic/anti-inflammatory</td>
<td>Aspirin, acetaminophen, diclofenac, fenoprofen, indomethacin</td>
</tr>
<tr>
<td>Anesthetics</td>
<td>Isoflurane, halothane, propofol</td>
</tr>
<tr>
<td>Angina medications</td>
<td>Perhexilene, amiodarone, diethylaminoethoxyhexesterol</td>
</tr>
<tr>
<td>Antiarrhythmic</td>
<td>Amiodarone</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>Tetracycline, antimycin A</td>
</tr>
<tr>
<td>Antidepressants</td>
<td>Amitriptyline, amoxapine, citalopram, fluoxetine</td>
</tr>
<tr>
<td>Antiemetics</td>
<td>Haloperidol</td>
</tr>
<tr>
<td>Antipsychotics</td>
<td>Chlorpromazine, fluphenazine, haloperidol, risperidone, quetiapine, clozapine, olanzapine</td>
</tr>
<tr>
<td>Anxiety medications</td>
<td>Alprazolam, diazepam</td>
</tr>
<tr>
<td>Barbiturates</td>
<td>All barbiturates</td>
</tr>
</tbody>
</table>
Medications said to induce mitochondrial damage (2)

<table>
<thead>
<tr>
<th>Drug Class</th>
<th>Drugs</th>
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<tbody>
<tr>
<td>Cholesterol medications</td>
<td>Statins (atorvastatin, fluvastatin, etc)</td>
</tr>
<tr>
<td>Bile acid medications</td>
<td>Cholestyramine, clofibrate, ciprofibrate, etc</td>
</tr>
<tr>
<td>Cancer chemotherapeutics</td>
<td>Mitomycin C, profiromycin, Adriamycin</td>
</tr>
<tr>
<td>Dementia medications</td>
<td>Tacrine, Galantamine</td>
</tr>
<tr>
<td>Diabetes medications</td>
<td>Metformin, troglitazone, rosiglitazone, etc.</td>
</tr>
<tr>
<td>HIV/AIDS medications</td>
<td>Atripla, Combivirm, Emtrivam, etc.</td>
</tr>
<tr>
<td>Epilepsy/Seizure meds</td>
<td>Valproic acid</td>
</tr>
<tr>
<td>Mood stabilizers</td>
<td>Lithium</td>
</tr>
<tr>
<td>Parkinson's meds</td>
<td>Tolcapone, also Stalevom)</td>
</tr>
</tbody>
</table>
Nitroprusside

- Some cyanide in blood of many individuals:
  - Smoking
  - Industrial exposures
  - Mining wastes
  - Cassava (tapioca)
  - Almonds
  - Apple, apricot pits
  - Spies, wealthy relatives
- Mitochondrial Dx:
  - May wish to use labetolol instead for hypotensive anesthetic approaches
**C. elegans mitochondrial diseases**
(Hartman et al, 2001)

- **Complex I (gas-1 mutation)**
  - Hypersensitive to volatile anesthetics
    - Halothane, diethylether, isoflurane, (propofol?)

- **Complex II (mev-1 mutation)**
  - Hypersensitivity to oxidative damage/hypermutability
    - Paraquat-induced free radicals or hyperoxia

- Either: incr free-radical sensitivity (↓ubiquinone)
Haloperidol v Complex I

[Graph showing concentration vs. effect for Haloperidol and HPP⁺]
Antiemetics

• Haloperidol effects on Complex I
• Movement disorders
  – May resemble seizures
  – Produce wasteful energy expenditure
  – Esp. Dopamine antagonists
    • Extrapyramidal effects, e.g. dystonia
    • Phenothiaazines (prochlorperazine)
    • Butyrophenones (droperidol)
Muscle relaxants

• Hepatic enzyme inducing anti-Sz meds
  – Lower than expected duration of liver-metabolized muscle relaxants
  – The effect may be marked
    • Esp. Aminosteroidal compounds
      – Vecuronium, Pancuronium less so with rocuronium
    • Not benzylisoquinolininium compounds
      – Atracurium, mivacurium
Leigh Disease
(Subacute necrotizing encephalomyelopathy)

- AR: ↓PDH complex and electron chain
- Weakness, Szs, ataxia, ophthalmoplegia
- Progressive symmetric necrosis BG, brainstem, periacqueductal gray
Leigh Disease
Anesthetic Considerations*

• Avoid stress that may ↑energy demand
  • No fasting interval >8 hours
  • Avoid/treat suspected infection, fever, acidemia (no lactated fluids)
  • Avoid ↓glucose, hypoxia, hypercarbia, cardiomyopathy
  • Assure optimal pulmonary function at time of surgery
  • Leigh disease probably not associated with MHyperthermia

• Barbs and volatile anesthetics may compromise mitochondrial respiratory function—thiopental induction may be safe
  • Be cautious with succinylcholine (↑K+?), rocuronium, atracurium
  • Avoid halothane, propofol, nitroprusside, chloral hydrate, BDZs
  • Avoid narcotics--clonazepam for postoperative pain control

*Baum and O’Flaherty 2007; Shear and Tobias Paed Anaesth 14:792, 2004
Malignant Hyperthermia (1)

- Inherited myopathy-related vulnerability
  - Muscle constitutes 40% of body weight!
- Volatile anesthetics or succinylcholine
  - Other stresses may contribute to vulnerability
- MH mortality formerly 70%
  - Dantrolene (RyR1 receptor inhibitor) with supportive care has reduced mortality to 5%
Malignant Hyperthermia (2)

- Classic: AD myopathic ryanodine receptor (RyR1) (30+ mutations)
  - Abnormal caffeine-halothane muscle contraction test (MCT)
    - Cause of trismus/generalized rigidity
  - MCT positive patients tolerate anesthetic challenges
  - Vulnerability to ↑ membrane permeability
  - Sarcoplasmic reticular calcium release
  - Control of Abn calcium fluxes produces
    - Compensatory ↑ metabolic rate/heat, H+ ion release acidemia
    - Differs from myopathic membrane leaks without compensatory response
- Child > adult susceptibility
  - any time during/shortly after anesthetic
Malignant Hyperthermia (3)

• Variant: rhabdomyelitic ↑K+, CK, Myoglobin
  • 50% Co-occurs in setting of RyR1 hyperthermia/abnl MCT
  • 50% occurs in isolation where RyR1 and MCT are normal
    – Fever of later onset than true malignant hyperthermia
    – Especially myopathies with membrane breakdown
    – Rapid occurrence after succinylcholine bolus
      » Contraindicated in myopathic patients
    – May occur with volatile anesthetics (slower onset)
    – Best approach if risk:
      » Nitrous + IV opiates/sedative, propofol maintenance
MH-associated conditions

- **King-Denborough Syndrome**
  - Ptosis, strabismus, kyphosis, cryptorchid, short

- **Succinylcholine induced trismus**
  - Most children have this but subclinical in 95%
  - Small number may manifest “jaws of steel” phenomenon

- **SCN4A-related ↑K+ periodic paralysis (17Q)**
  - Also K+ aggravated myotonia, paramyotonia congenita

- **Central Core Disease**

- **Duchenne / Becker dystrophinopathies**
Central Core Disease
(19q13.1=RyR1 gene locus)

- AD congenital myopathy
  - Mandibular hypoplasia, short neck
  - Contractures
  - Proximal muscle weakness
  - Non- or slowly progressive (19q13.1)
    - Ryanodine receptor-1 Ca channel gene: “true” RyR1 MH
    - Abnl mitochondria/sarcoplasmic reticulum
    - Loss of central skeletal muscle fibers
    - ↑Type 1 muscle fiber calcium
    - Abnl muscle contraction testing
Duchenne dystrophinopathy

- X-linked boys
  - Membrane instability
  - Calcium leakage
  - Inflammatory fibrosis
- ±Congenital adrenal hypoplasia
- Abnl ECG in 90%
  - Tall R to right, deep Q to left
- Dilated cardiomyopathy
  - Severity many differ from striated muscle
  - Cardiomyopathy in adult female carriers
Duchenne dystrophinopathy
Anesthetic considerations

• Acute rhabdomyolysis ± hyperkalemia
  • Not “true” (RyR1-related) malignant hyperthermia
  • May occur after succinylcholine with ↑K+ rhabdomyolysis—sometimes associated with cardiac arrest
    – Pre-Dx occurrence led to succinylcholine warning for children
    – Multilead ECG monitoring important even for biopsy
    – Occasional ↑K+ arrest at or after anesthetic emergence
    – Late DMD: fibrotic heart block
  • Inhalation anesthetics sometimes cause similar problems:
    – Halothane, isoflurane, enflurane, sevoflurane
    – May be latency of several hours for myoglobinuria—especially if muscle very fibrotic;
• Occasionally similar picture seen in Becker’s
• Don’t neglect possible adrenal insufficiency
Myotubular (Centrotubular) Myopathy
Anesthetic considerations

· X-linked (myotubularin)
  Unless ventilated usually fatal in infants
  AR (infantile) or AD (adult) varieties
· Much less MH risk than central core
  • ±hyperkalemia to succinylcholine
  • ↓swallow, aspiration risk
  • Low risk nondepolarizing agents
    – may not need: muscles markedly weak

--Pierson et al, J Neuropathy: 2006
Nemaline Rod Myopathy

- Three clinically similar types:
  - Type 1 (AD: tropomyosin-3)
  - Type 2 (AR: nebulin)
  - Type 3: (AD: alpha-actin 1)
- Subsarcolemmal rods of fast-twitch fibers (Z-disc derived)
- Variable axioproximal weakness
- ± faciopharyngeal/distal limbs
- ± cardiomyopathy (rare)
Nemaline Rod Myopathy
Anesthetic considerations*

- Micrognathia/malocclusion:
  - Laryngoscopy/tracheal intubation difficulties
  - Aspiration risk
- Pulmonary > cardiac risk
  - May require prolonged postoperative ventilation
  - Postoperative pain worsens breathing
  - No reports of malignant hyperthermia or succinylcholine-related hyperkalemia (but little information available)
- High level spinal anesthesia may be risky
- Muscle relaxants may not be necessary (weak)
  - …and may be risky

*Cunliffe and Burrows, Can Anaesth Soc J 1985
Approach to anesthesiological issues in muscle disease (CN)

- Tell your patients to inform the anesthesiologist they have heritable muscle disease
  - Especially important in the emergency room
- Rely on the anesthesiologist to know what to do if a complication (rhabdomyolysis, MH, postoperative weakness) develops
  - Also rely on the ER anesthesiologist to enforce a sensible approach to anesthetic or paralytic medications in order to obtain scans—which are usually beside the point in evaluation and treatment of status epilepticus
Joubert Syndrome

- AR, severe psychomotor delay
- Infantile nystagmus, ataxia
- Tachypnea/panting/apnea
  - Improves with development or caffeine
  - Apnea may entail cardiac arrest
- Various oropharyngeal abnormalities
- Occipital myelomeningocele sometimes
  - May also have caudal epidural deformation
- Characteristic scan:
  - Cerebellar vermal dysplasia/agenesis
  - “Molar tooth” deformity of peduncles
  - Lg 4th ventricle “batwing” or “umbrella”
  - Agenesis corpus callosum
Joubert Syndrome
Anesthetic considerations*

• Direct laryngoscopy may be difficult
  • Micrognathia, large tongue, short/stiff neck, epiglottic deformities, etc.

• Apneas usually 15 secs or so duration:
  • Nitrous oxide, opioids, etc. may prolong these for as much as several hours postoperatively
  • Regional anaesthesia recommended if possible
  • Caudal epidural anesthesia may be challenging but spinal anesthesia may prove useful
  • IV propofol has been used uneventfully

• Improves after infancy or with caffeine

*Vodopich and Gordon, 2004
Central hypoventilation syndrome (Ondine’s Curse)

• AR/AD* (PHOX2B etc. genes)
  • Usually neonatal onset
    – May be have low tone, somnolence
    – Mile to moderate developmental delay
    – Apnea occurs in non-REM sleep
      » Anesthetics, narcotics may ↑ apnea
    – May have cardiac arrhythmias
    – SIADH-related risk for hyponatremic seizures
    – Neuroblastoma or ganglioneuroma in some
    – Hirschsprung disease in 50%: aspiration risk
      » Suggests neural crest migration disorder
  • Tracheostomy, PPV in sleep
    – Low CO2 responsiveness—O₂ may provoke apnea
SMARD1
(SMA with respiratory disease)

• AR (11q13-q21/IGHMBP2 gene defects in some)
  • IGHMBP2 mutation in some—resembles SMN1 protein
• Completely normal CNS function
• May present in infancy resembling infantile GBS
• Progressive untreatable distal → central peripheral and diaphragmatic/respiratory muscle paralysis
• Large myelinated peripheral nerve abns in some
SMARD1
(SMA with respiratory disease: Distal HMN VI)

• Ethical issues resembling those of respiratory failure in Duchenne muscular dystrophy

• Without breathing support death <1yo
  – After intubation total ventilatory dependency, survival for decades possible
Approaches: severe breathing paralysis

- Maintain lung capacity
  - Stack breathing, etc.
- Flu prophylaxis, viral precautions
- Mucolytics, steroids, bronchodilators??
- Incentive spirometry, breath stacking early
- Aerosolized nebulizers
- Cough inexsufflator
- Antibiotics *if secondary* bacterial pneumonia
- BiPAP if VC falls below 40%
Generalities concerning neurometabolic diseases

• Things that may be required:
  – Continuation of dietary restrictions if needed
  – Avoidance of hypoglycemia
  – Avoidance of catabolic state (e.g. PKU)
  – Avoidance of GI protein load (e.g. blood)
  – Avoidance of hemolysis (e.g. PGK deficiency)
  – Awareness of cardiac status (e.g. Pompe, DMD)
  – Avoidance of rhabdomyolysis
  – Fluid titrations if renal disease
Phenylketonuria
Anesthetic considerations

• Must continue PA restriction perioperatively
  – If untreated:
    • Vomiting risk
    • Megaloblastic anemia?
• Avoid prolonged fast
  • Catabolic ↑ phenylalanine
• Anesthetics
  • Avoid proconvulsants
  • Antiseizure meds v anesthetics
  • Nitrous oxide inactivation of b12-dependant methionine synthase→post-op paraparesis?

The enzyme phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine.
Phenylketonuria

- AR chromosome 12
  - ↓phenylalanine hydroxylase or
  - ↓tetrahydrobiopterin in 1-2% *
  - 1/10,000 US / 1/2600 Turkey
  - Heterozygosity v mycotoxins

- Rx: restrict phenylalanine
  - Protein restriction
  - Doesn’t work if BH4 deficiency
  - May develop 2○ ↓B12

- If untreated:
  - Musty odor
  - Blue eyes/light hair/exczema
  - MR, vomiting episodes, szs
  - Spasticity, PD (if ↓BH4)

The enzyme phenylalanine hydroxylase converts the amino acid phenylalanine to tyrosine.
Maple syrup urine disease (AR)

- AR—BCKAD genes, chromosome 19
  - Mitochondrial branched-chain keto acid DH
    - Some thiamine-responsive forms
  - Maple syrup: isoleucine ketoadduct (ear/navel)
  - Untreated: severe encephalopathy (Guthrie patch!)

- Decompensation:
  - Surgical stress / intercurrent illness / fast
  - Ataxia, lethargy, coma, cerebral edema, apnea, opisthotonus
  - Pancreatitis risk
Maple Syrup Urine Disease
Maple Syrup Urine Disease

![MRI comparison of MSUD vs Normal brain scans](image-url)
Maple Syrup Urine Disease

Anesthetic Considerations

• No prolonged fasting (pre-, intra- or postop)
  • Risks of hypoglycemia, ketoacidemia
    – Associated opisthotonus, focal dystonia may occur
    – 1/3 of daily dose dietary AA supplement just prior to surgery—
      post-operatively IV supplementation

• IV fluids with glucose, fat emulsion
  • Hypertonic glucose may $\uparrow$CO$_2$ and provoke NorEpi release

• Risk for cerebral edema if overhydrate
  • Especially in older patients

• Orogastric/throat packs for oral/GI blood
  • Excess protein load→metabolic failure
A UVA Colleague has written:

Anesthesia for Genetic, Metabolic, & Dysmorphic Syndromes of Childhood

Second Edition

Victor C. Baum
Jennifer E. O'Flaherty