Medication Management of Epilepsy

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Overview

- Acute or rescue management of seizures
- Chronic treatment of epilepsy
- Status epilepticus (discussed in a separate session)
Acute (rescue) Management of Seizures
Abortive Agents – Overview

• Benzodiazepines for a prolonged seizure
  • Mechanism of action of benzodiazepines
    • Binds to GABA receptor and reduces the excessive excitation in the brain
  • Administration routes
    • Oral, intravenous, intramuscular, rectal, intranasal, buccal

Sources:
• [http://www.sec.gov/Archives/edgar/data/946840/000119312512399193/d414342dex991.htm](http://www.sec.gov/Archives/edgar/data/946840/000119312512399193/d414342dex991.htm)
• [http://online.lexi.com.libproxy.unm.edu/lco/action/home](http://online.lexi.com.libproxy.unm.edu/lco/action/home)
Abortive Agents – Overview

• Benzodiazepines for a prolonged seizure
  • FDA-approved medications among benzodiazepines

<table>
<thead>
<tr>
<th>Benzodiazepine</th>
<th>FDA approved for status epilepticus</th>
<th>FDA approved for treatment of seizures</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clonazepam</td>
<td>No – off-label use</td>
<td>Yes</td>
</tr>
<tr>
<td>Diazepam</td>
<td>Yes (rectal gel)</td>
<td>Yes</td>
</tr>
<tr>
<td>Lorazepam</td>
<td>Yes; parenteral only</td>
<td>No – off-label use (focal seizures)</td>
</tr>
<tr>
<td>Midazolam</td>
<td>No – off-label use</td>
<td>No – only for sedation</td>
</tr>
</tbody>
</table>

Source: [http://online.lexi.com.libproxy.unm.edu/lco/action/home](http://online.lexi.com.libproxy.unm.edu/lco/action/home)
Abortive Agents – Overview

• **Commercially** available formulations at outpatient setting
  • Diazepam – rectal gel
  • Clonazepam – tablet (wafer, disintegrating tablet [ODT])

• **Conditionally** available formulations at outpatient setting
  • Midazolam – intranasal or buccal
    • May be available at compounding pharmacy
    • Need a special devise to make mist (atomizer) for intranasal formulation
Diazepam

- Administration route: rectal
- Formulation: gel
- Dose – dose may be repeated if needed
  - Children <2 years: Safety and efficacy have not been studied
  - Children 2-5 years: 0.5 mg/kg
  - Children 6-11 years: 0.3 mg/kg
  - Children 12 years or above: 0.2 mg/kg
Midazolam

• Administration route: IM or IN
• Formulation
  • Solution for IV, IM, IN, buccal
  • Syrup
  • Buccal (UK, not available in the US)
• Dose for prehospital treatment
  • 13 - 40 kg: 5 mg once
  • >40 kg: 10 mg once

Sources
• http://www.hospira.com/products_and_services/drugs/MIDAZOLAM HYDROCHLORIDE
• http://www.mims.co.uk/news/1106012/Buccolam-licensed-buccal-midazolam-product/
• http://online.lexi.com.libproxy.unm.edu/lco/action/doc/retrieve/docid/patch_f/7296
IN midazolam

• Gerrit-Jan de Haan et al. (2010)
  • Primary outcome: comparisons between diazepam (rectal) and midazolam (intranasal) in efficacy, safety, and preference

• Study population
  • Adults (N = 21)
    • Male: 13 (61.9%)

• Dose
  • Diazepam (DZP): 10 mg
  • Midazolam (MDZ): 2.5 mg

Source:
IN midazolam

• Gerrit-Jan de Haan et al. (2010)
  • Results
    • Success rate
      • DZP 89% vs. MDZ 82% (NS)
    • Time to stop seizures: NS
  • ADRs
    • No severe ADRs were observed
    • More CNS ADRs in DZP group; more local irritation in MDZ group
  • Preference (easy to use)
    • MDZ > DZP ($p<0.001$)

<table>
<thead>
<tr>
<th>Table 2. Efficacy of DZP-r and MDZ-n in suppressing seizure exacerbations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Success</td>
</tr>
<tr>
<td>---------</td>
</tr>
<tr>
<td>DZP-r</td>
</tr>
<tr>
<td>MDZ-n</td>
</tr>
<tr>
<td>Total</td>
</tr>
</tbody>
</table>

* $p = 0.57$ (not significant); ** $p = 0.6$ (not significant). min., minutes; SD, standard deviation. DZP-r, diazepam rectal solution; MDZ-n, midazolam nasal spray.

Source:
Clonazepam

- High potency benzodiazepine
- Administration route
  - Oral
- Formulation
  - Disintegrating tablet (wafer)
    - Dissolve in oral cavity
Clonazepam

• Onset (adult data)
  • Rapid; peak plasma concentrations in one to four hours

• Bioavailability (adult data): 90%

• Half-life
  • Children: 22-33 hours
  • Adults: 17-60 hours

• Available strength (Clonazepam Wafers)
  • 0.125 mg, 0.25 mg, 0.5 mg, 1 mg, 2 mg

Sources:
• http://online.lexi.com.libproxy.unm.edu/lco/action/doc/retrieve/docid/patch_f/6642#f_pharmacology-and-pharmacokinetics
Summary

• Three benzodiazepine drugs have been used to stop prolonged seizures at outpatient setting

• Each benzodiazepine and its formulation are different in pharmacokinetics and caregiver’s preference

• Select appropriate rescue medicine in accordance with patient’s needs, such as social factors (e.g., patient’s or caregiver’s preference)
Suggested Rational Use:

• What abortive agent would you recommend for this situation? **Diazepam rectal**
  • Appropriate for younger children when a seizure lasts three to five minutes
• What if the patient has multiple seizures within a short period (cluster)? **Clonazepam ODT**
  • Appropriate for clusters of seizures
• What if he is a teenager? **Intranasal midazolam**
  • Appropriate for older children
  • May become the drug of choice for all rescue
    • Exception: short half-life may not help with clusters
Chronic Treatment of Epilepsy

Anti-seizure medications
To Treat or Not To Treat

- Risk factors for seizure recurrence
  - Remote symptomatic etiology
  - Abnormal EEG
  - Seizure occurring while asleep
  - History of prior febrile seizures
  - Todd’s paresis
Risk of Seizure Recurrence After a Single, Unprovoked Seizure; 2 yr f/u

<table>
<thead>
<tr>
<th>Seizure type</th>
<th>EEG normal</th>
<th>EEG epileptiform, or exam abnormal</th>
<th>Both abnormal</th>
</tr>
</thead>
<tbody>
<tr>
<td>Generalized</td>
<td>25%</td>
<td>50%</td>
<td>75%</td>
</tr>
<tr>
<td>Partial</td>
<td>50%</td>
<td>75%</td>
<td>&gt;90%</td>
</tr>
</tbody>
</table>

~90% of recurrences are within 2 years

Data from Camfield & Camfield 1985.
The Ideal Medicine For Epilepsy

- Effective
- Safe
- Few side effects
- Easily absorbed
- Few daily doses
- No drug interactions
- Inexpensive
- Kid friendly formulation

NONE EXISTS
Choice of AEDs

• Based on
  • Seizure type/epilepsy syndrome
  • Age:
    • Valproate not the preferred drug <2 years
    • Phenobarbital still the drug of choice in neonatal seizures, although other drugs like topiramate/levetiracetam can be used
  • Co-morbidities
    • Weight, other medical conditions (e.g: hepatic or renal disease), other medications

• The most effective Rx is with a single drug, chosen on the basis of epilepsy syndrome (and type of seizure) and titrated to the seizure control or side effects

• Problems with polytherapy
  • Additive side effects
  • Drug interactions
Choice of AEDs

• Common choices
  • Generalized epilepsy:
    • ethosuximide, valproate, lamotrigine, topiramate, zonisamide, levetiracetam.
    • Carbamazepine/oxcarbazepine not preferred in generalized epilepsies for risk of absence status
  • Focal epilepsy:
    • Oxcarbazepine often preferred, other drugs such as levetiracetam, lamotrigine, topiramate, zonisamide, valproate, lacosamide can also be used
Traditional Drugs of Choice for Seizures

FOCAL ONSET

GENERALIZED ONSET
Absence
Tonic-clonic

{ Oxcarbazepine
  Carbamazepine
  Phenytoin (esp acutely)
}

{ Ethosuximide
  Levetiracetam
}

Valproate
Lamotrigine
Topiramate
Zonisamide
Lacosamide
Ethosuximide

• Commonly used for treating absence epilepsy
• Inexpensive
• Main Side Effects
  • Dizzy / unsteady
  • GI upset
  • Sedation
  • Can cause mild lowering of WBC counts
Phenytoin/Fosphenytoin

- Phenytoin is the most used medication since 1938
- Can be once-a-day, available in IV form
- Main Side Effects
  - Dizzy / unsteady
  - Gingival hypertrophy
  - Cosmetic (long term use associated with coarsening of features)
  - Rash
  - Long-term: Osteomalacia, Neuropathy
Oxcarbazepine

- Preferred drug for focal seizures
- Structurally similar to carbamazepine, with an oxygen molecule, fewer drug interactions
- Better tolerated than carbamazepine
- May stabilize mood
- Can be taken BID
- Main Side Effects:
  - Blurry vision
  - Dizzy / Uncoordinated/ Fatigue
  - Stomach upset
  - Low blood sodium
Valproic Acid

- Broad spectrum, including generalized
- May stabilize mood problems, help headaches
- Main Side Effects:
  - Weight gain
  - Hair loss
  - Tremor
  - Rare blood or liver injury, pancreatitis
  - Menstrual irregularities, PCOS
  - Higher risk of fetal neural tube defects
  - AVOID in children under 2 and with suspected mitochondrial (POLG) disorder
Lamotrigine

- Broad spectrum against seizures: used in absence epilepsy, JME, LGS, focal epilepsies
- Can be once (or twice) a day
- Can stabilize mood
- Main Side Effects:
  - Rash, including Steven Johnson syndrome
  - Fatigue
  - Unsteadiness
  - AVOID in Sodium channel defects (Dravet syndrome): can make epilepsy worse
Topiramate

• Broad spectrum action
• Can also help migraines
• Main Side Effects:
  • Slow / Fuzzy thinking/Speech difficulties
  • Kidney stones in ~ 2%
  • Weight loss/anorexia
  • Anhydrosis
  • Rarely glaucoma
  • Rare psychiatric problems
Levetiracetam

- Broad spectrum
- Commonly used for treating JME
- Few drug interactions
- Main Side Effects
  - Dizzy / Uncoordinated
  - Fatigue
  - Rare psychiatric effects: aggression, irritability
Zonisamide

• Broad spectrum action
• Good for myoclonic seizures
• Can be once-a-day
• Structurally related to sulfa drugs: need to check for sulfa allergy
• Main Side Effects:
  • Slow / Fuzzy thinking
  • Kidney stones in ~ 2%
  • Anorexia
  • Anhydrosis
  • Rare psychiatric problems
New Anti-Seizure Drugs

• Lacosamide
• Rufinamide
• Ezogabine
• Perampanel
• Clobazam
• Stiripentol (not freely available in the US)
Lacosamide

- FDA approved in Europe in August 2008, USA in October 2008
- Indication: Adjunctive treatment for focal seizures in patients $\geq 17$ years of age.
- Mechanism of Action
  - Enhancement of slow inactivation of Voltage Gated Sodium channels (VGSC)
  - Binds to collapsin response mediator protein (not clear if this contributes to the anti-seizure action).
  - Postulated to contribute to neuroprotective effects vs apoptosis and glutamate
Lacosamide

Mechanism of Action

• Enhancement of slow inactivation of Voltage Gated Sodium channels (VGSC)

• It also binds to collapsin response mediator protein (not clear if this contributes to the anti-seizure action). Postulated to contribute to neuroprotective effects vs apoptosis and glutamate
Lacosamide

- Adult Dose: up to 200 mg/day
- Pediatric doses 1-5 mg/kg/day (can go higher)
- Formulation
  - Tablets, oral solution, IV infusion
- Covered by insurance
Lacosamide: Side effects

- Side effects similar to other Anti-seizure drugs: somnolence, fatigue, dizziness, nausea, blurred vision
- Cardiac effects:
  - Related to dose dependent enhancement of slow inactivation of cardiac sodium channels
  - Prolongation of PR interval, second degree AV block, atrial fibrillation/flutter (at high doses)
  - Transient 3rd degree AV block reported after IV Lacosamide use for status epilepticus
Rufinamide

- FDA approved in November 2008 as adjunctive treatment in LGS for children over 4 and adults
- Structurally unrelated to other Anti-seizure drugs
- Mechanism of action not fully understood
- Prolongation of the inactivated state of Sodium channels, limiting the firing of Sodium dependent action potentials
- Probably has broader spectrum of action than the typical Na-channel blockers (PHT, LMT, CBZ, OXC)
Rufinamide

- Dose: 5-45 mg/kg/day
- Formulation
  - Tablets: 200, 400 mg
  - Oral solution: 200 mg/5 ml
- Covered by insurance (may need LGS as diagnosis for prior authorization)
Rufinamide

- Double blind randomized placebo controlled trial of Rufinamide in LGS (Glauser et al 2008)
- 138 patients randomized to Rufinamide or placebo
- Median % reduction in seizures: 32.7% vs 11.7%
- Improvements in seizure severity and improvements in tonic-atonic seizures
Rufinamide

• Side effects
  • Somnolence, vomiting, headache
  • Rash
• Interaction with valproate, requiring a lower daily dose
• Cardiac effects: can shorten QT interval
• Not clear if clinically significant (Schimpf et al, Heart Rhythm 2012)
Clobazam

- Newly approved by the US FDA for LGS in children ≥ 2 years of age
- 1,5 benzodiazepine, which is structurally different from the traditional ones (1,4 benzos) such as diazepam
- Less acidophilic and less lipophilic than the 1,4’s; so may be less sedating and less likely to cause tolerance
Clobazam

- Benzodiazepine
- 1,5 benzodiazepine, which is structurally different from the traditional ones (1,4 benzos) such as diazepam
- Less acidophilic and less lipophilic than the 1,4’s; so may be less sedating and less likely to cause tolerance
Clobazam

- **Dose:** 0.5-1 mg/kg (higher doses have been used)
- **Formulation:** 10, 20 mg tabs (can be crushed, but not dissolvable), 2.5 mg/ml oral solution
- **Insurance:** covered, may needs prior auth. May be more of a problem if diagnosis is not LGS
- **Side effects**
  - Sedation, inco-ordination, agitation
  - Weight gain
Treatment of Common Childhood Epilepsies
Childhood Absence Epilepsy

- Drug of choice = ethosuximide

- Randomized-controlled trial:
  - Ethosuximide = valproic acid for efficacy
  - Lamotrigine lower efficacy
  - Lamotrigine > ethosuximide > valproic acid for cognitive side effects

Juvenile Myoclonic Epilepsy

Traditionally, **valproate** has been the treatment of choice for JME.

Side effects: tremor, weight gain, menstrual irregularity, teratogenic (neural tube) defects, pancreatitis.

Drugs used in preference over valproate: **Levetiracetam**, lamotrigine, topiramate, zonisamide, clobazam.

Source: Crespel et al, Epilepsy Behav. 2013
Focal Epilepsies

• Focal epilepsies
  • Carbamazepine, oxcarbazepine

• Rolandic Epilepsy (BECTS)
  • Carbamazepine, oxcarbazepine
  • Gabapentin (Bougeois et al)
Lennox Gastaut Syndrome

- Generally anti-seizure drugs with a broad spectrum are preferred
  - Sodium valproate
  - Lamotrigine
  - Topiramate
  - Felbamatate
  - Benzodiazepines such as clobazam
  - Rufinamide
Infantile Spasms

- ACTH (adrenocorticotropic hormone), prednisolone
- Vigabatrin (drug of choice in tuberous sclerosis)
- Ketogenic diet (discussed in another session)
- Less commonly used treatments:
  - Sodium valproate, topiramate, benzodiazepines