ANTI-SEIZURE MEDICATIONS STRIVING FOR NO SEIZURES, NO SIDE EFFECTS

PEDIATRIC PERSPECTIVES

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ANTI-SEIZURE MEDICATIONS: PEDIATRIC PERSPECTIVES

- smooth sailing epilepsy, the 60% rule
- rough riding epilepsy
- drug resistance, medical intractability

ANTI-SEIZURE MEDICATIONS: PEDIATRIC PERSPECTIVES

- the Brodie study; how do we predict intractability
- at least 14 new anti-epilepsy medications
- the age of choice: efficacy verses side-effects
- majority approved for partial seizures
- pediatric challenges

ANTI-SEIZURE MEDICATIONS

- monotherapy the mantra
- combining AED's, rational or obligatory polytherapy

- can one and one make three

- "the combinations of bromides with other drugs are of much value in the treatment of epilepsy. In many cases a greater effect is produced by the combination than by other drugs given alone"

William Gowers, 1881

ANTI-SEIZURE MEDICATIONS CHILDHOOD ABSENCE EPILEPSY

- age related epilepsy syndrome
- neurologically and developmentally normal children between 5 to 10 years of age
- absence seizures, pyknolepsy
- eeg: normal BG, hyperventilation activated H_2 spike and slow wave
- universal tendency to remission
- which medications

ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILEPSY

- double blind, randomized, controlled trial in 453 children
- primary outcome: freedom from treatment failure
- secondary outcome: attentional dysfunction

NEJM 2010; 362: 790-9

ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILESPY

- freedom from treatment failure – combination of efficacy and tolerability
- persistence of absence seizures week 16 or week 20
- generalized tonic clonic seizure at any time
- platelet count <50,000 per mm^3
- moderately severe rash
- Increase in BMI

NEJM 2010; 362: 790-9

ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILEPSY

- free of treatment failure: 209/446 (47%)
- lack of seizure control: 109/446 (24%)
- intolerable side effects: 97/446 (22%)

- lack of seizure control
  - ethosuximide: 22/154 (14%)
  - lamotrigine: 69/146 (47%)
  - valproic acid: 18/146 (12%)

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ETHOSUXIMIDE, VALPROIC ACID AND LAMOTRIGINE IN CHILDHOOD ABSENCE EPILEPSY

- secondary outcome: continuous performance testing (CPT)
- CPT confidence index ≥ 0.6
  - ethosuximide: 35/106 (33%)
  - lamotrigine: 25/104 (24%)
  - valproic acid: 52/106 (48%)
- no differences in the confidence index results between seizure free subjects and those who continued to have seizures
- attentional difficulties not simply a result of the seizures, but a core feature of the syndrome

NEJM; 2010: 362: 790-9

LENNOX GASTAUT SYNDROME

- childhood epileptic encephalopathy with slow spike waves
- 1 to 8 years; cryptogenic or symptomatic

- drops, nods, blinks, jerks
- slow BG; slow (1 ½ to 2 ½ Hz) spike and wave
- generalized paroxysmal fast activity
- typically medically intransigent
- at the onset of seizures, only 30% to 50% have intellectual delay, but after 4 years 78% to 96% will be affected

LENNOX GASTAUT SYNDROME

- no comparative drug studies
- six medications approved by the FDA
- lamotrigine, topiramare, felbamate, rufinamide, clobazam

- majority of practitioners still use valproate as initial treatment
- role of “partial” medications: dilantin, lacosamide, oxcarbazepine (multiple independent spike foci)

DOUBLE BLIND RANDOMIZED, CONTROLLED TRIALS IN LGS

- >50% median seizure reduction rates and side effects
- Lamotrigine: 33%: 9% rash (7% placebo)
- Topamax: 33%: somnolence, behavioral problems, weight loss, dizziness
- Felbamate: 50%: 6/73 seizure free
  - Aplastic anemia, liver toxicity

DOUBLE BLIND RANDOMIZED CONTROLLED TRIALS IN LGS

- Rufinamide: 31%, somnolence, vomiting
- Clobazam
  - high dose: 77%, somnolence, drooling
  - moderate dose: 58%
  - low dose: 43%

LGS: NON-PHARMACOLOGIC TREATMENT

- >50% median seizure reduction rates
- VNS: 21% - 83%
- corpus callosotomy: >80% reduction in drop attacks in 61% to 85%
- ketogenic diet: 51%
  - >23%, a 90% reduction in seizures
  - waning effectiveness after 12 months

DRAVETS SYNDROME

- severe myoclonic epilepsy of infancy
- 1 in 40,000; M:F = 2:1
- prolonged febrile seizures followed by Todd's paresis in infancy
- myoclonic, atypical absence, and partial seizures over time
- cognitive impairment; visual attention, visual motor integration, visual perception and executive function
- SCN1a mutation; affects sodium currents in GABAergic (inhibitory) neurones

DRAVETS SYNDROME

- Topiramate: 3 of 5 had >50% reductions in seizure frequency
- Levetiracetam: 18/28 a positive response to one seizure type
  - 3/28 with tonic clonic seizures, 2/28 with myoclonic seizures, 3/28 with focal seizures and 1/28 with absence seizures became seizure free

DRAVETS SYNDROME

- Stiripentol: 8/37 in one study seizure free
  - 15/21 in another study had 50% drop in seizure frequency
- combination of valproic acid, clobazam and stiripentol especially effective
- levetiracetam also a good option
- topiramate, mixed results

MIXED SEIZURE SYNDROMES OF EARLY CHILDHOOD

- broad spectrum medications
- consider the seizure type
- absence, ethosuximide, lamictal, zonisamide, valproic acid
- myoclonic; levetiracetam, lamotrigine, topiramate, zonisamide, valproic acid
- tonic; lamictal, zonisamide, rufinamide, clobazam, valproic acid
- avoid sodium channel blockers

THE HOLY GRAIL

- the balance between seizure control and side effects
- what is optimal seizure control
- what are acceptable side effects
- rational, methodical trials of effective anti-seizure medications

THE HOLY GRAIL

- obligatory polytherapy
- the cross-over trap
- early consideration of non-pharmacologic options
- the care team, communication and dialogue
- maximise neurodevelopmental outcomes and quality of life