Antiseizure medication adverse effects and drug interactions

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January 19, 2023

Alberta Health Services

Would like to review:

- Risks of uncontrolled seizures
- Medication adverse effects
  - Idiosyncratic and dose related
- Drug interactions

Antiseizure medications: the *risk* of uncontrolled seizures is *much greater* than the *risk* of the medications

Risks of uncontrolled seizures

- Cognitive and behavioural delay, risk of worsening of epilepsy related comorbidity
- Injury, status epilepticus, SUDEP

Important to understand antiseizure medications chosen in a systematic manner

Medication Adverse Effects Primer

- Idiosyncratic
- Dose related-what you see is what you get
- Not cut and dry idiosyncratic or dose related
- Not exclusive to antiseizure medications

Idiosyncratic Adverse Effects

- Rash, Stevens Johnson syndrome (SJS)/Drug Reaction with Eosinophilia and Systemic Symptoms (DRESS)/Toxic Epidermal Necrolysis (TEN)
- Most commonly occur in 1st 12 weeks after antiseizure medication introduction
- Monitor for rash appearing on mucus membrane areas OR rash associated with fever (feeling very unwell)

Idiosyncratic Adverse Reactions

- History of previous antiseizure medication allergic drug reactions
- Cross sensitivity amongst “aromatic” antiseizure medications: carbamazepine, eslicarbazepine, oxcarbazepine, lamotrigine, phenytoin, phenobarbital

Idiosyncratic Adverse Reactions

- Isolated hematologic/heart/kidney/liver reactions rare especially without associated rash or fever

Idiosyncratic Adverse Drug Reactions

- Generally *not* dose related
- May occur up to 1 year after medication introduction
- May be reduced by gradual titration to target dose of antiseizure medication
  - e.g. reduce likelihood of rash with lamotrigine

Idiosyncratic Adverse Drug Reactions

- Generally speaking the are no studies that support regular laboratory monitoring to detect adverse effects in advance
- Best approach is to monitor for clinical signs and symptoms of potential adverse effects and do labwork when concerning symptoms arise

Idiosyncratic Adverse Effects

- Do baseline bloodwork especially in those at risk
  - CBC, ALT/AST, ammonia, creatinine, carnitine in children less than 3-4 years of age with possible pre existing metabolic and developmental concerns, MRI changes, and on multiple antiseizure medications at once (polytherapy)

Idiosyncratic Adverse Effects

- Genetic predisposition
- People of Han Chinese, Thai and Malaysian descent and **SJS/TEN** secondary to carbamazepine, oxcarbazepine, eslicarbazepine with positive tissue typing for the HLA-B*1502 allele
- People of Japanese or northern European descent and **less severe cutaneous adverse** reactions if positive for HLA-A*3101 allele

Dose Related Adverse Reactions

- Rapid increase in dose may increase risk…there are clinical situations where need rapid increase in dose
- Reversibility mostly dependent on half life (t ½)

Dose Related Adverse Effects

- Central Nervous System (CNS), gastrointestinal system (GI)
- GI→nausea/vomiting, anorexia, ?constipation/diarrhea
- CNS→cognition (sedation, concentration challenges, insomnia), behaviour (irritability, depression, psychosis, suicidal ideation).
  - all functions that the brain is responsible for

Dose Related Adverse Effects

- Paresthesia (tingling of extremities), reduced sweating, stones, secondary to topiramate, acetazolamide, zonisamide
- Reduced platelets and valproic acid (Depakene®, Epival®)
- MRI abnormalities and vigabatrin (Sabril®)

Dose Related Adverse Effects

- Increased risk if on more than 1 antiseizure medication at once (polytherapy) because of overlapping adverse effects, especially impact on cognitive and behavioural functioning OR
- Because of pharmacokinetic drug interactions e.g. rifampin reduces lamotrigine levels by 50% so when stop rifampin lamotrigine levels double
- Increase risk with faster dose escalation

table 3

Range of AED-induced Adverse Effects[6,7,16,22,30-32]

ADVERSE EFFECT	PATIENT COUNSELLING	RISK FACTORS
Suicide	Increased risk with epilepsy alone. Benefits of AEDs outweigh suicide risks but monitor for s/s suicidality/depression. Discuss feeling of self harm with neurology team.	Epilepsy; some AEDs, although this is controversial.
Cutaneous	Contact healthcare provider if any rash develops; rash is potentially severe if it occurs on mucous membranes or is associated with fever.	Lamotrigine -young age (<13 years), co-treatment with valproic acid, rapid dose escalation. Topiramate, gabapentin, pregabalin, levetiracetam have low risk of rash.
Reproduction and sexuality	If s/s of impaired libido/potency/arousal or reproductive dysfunction occur, see physician for relevant lab work (e.g., sex hormone levels). PCOS s/s→changes in weight, hair pattern, irregular or absent menstruation→follow up with physician and relevant lab work	EIAEDs + valproic acid. Valproic acid in addition to a diagnosis of epilepsy increases risk of PCOS.
Bone health	Some suggest bone density assessment after >5 years AED use and before AED treatment in postmenopausal women; ensure receiving RDA of calcium/vitamin D.	Treatment with EIAEDs; likely all AEDs are a risk.
Thyroid	If s/s of hypothyroidism (e.g., excessive tiredness, cold intolerance, constipation) see physician for relevant lab work. Occurs rarely.	Treatment with EIAEDs.
Liver	Baseline liver function tests recommended in high-risk patients; if s/s liver dysfunction (e.g., unexplained n/v, yellowing of skin) see physician. Otherwise these effects occur rarely.	With valproic acid: < 2 years, AED polytherapy, metabolic disorder, organic brain disease, mental retardation, co-treatment with other aromatic AEDs.
Hematologic (e.g. aplastic anemia,agranulocytosis, thrombocytopenia)	Baseline CBC beneficial. See physician if s/s suggestive of hematologic changes (e.g., abnormal bruising, blood in urine, lethargy). Outside of valproic acid-induced thrombocytopenia, hematologic adverse effects only occur rarely.	With felbamate: female gender, post-pubertal, history of cytopenia/immune disorder, Caucasian. Also rare with ethosuximide, phenytoin, zonisamide, phenobarbital, carbamazepine, phenytoin and lamotrigine. Valproic acid-induced thrombocytopenia is dose-related adverse effect.
Hyperammonemia	Baseline ammonia recommended for higher-risk patients prescribed valproic acid (e.g., those with metabolic disorders or less than 2 years of age). See physician if s/s suggestive of encephalopathy (e.g., drowsy, fatigued, confused).	Valproic acid (risk may be further increased with topiramate co-treatment).
Body weight	Monitor monthly.	Weight gain caused by valproic acid and carbamazepine. Weight loss caused by topiramate and zonisamide. Weight-neutral AEDs are phenytoin, lamotrigine and levetiracetam.
Pancreatitis	Baseline amylase/lipase recommended in high-risk patients (i.e., those with a history of pancreatitis). See physician ASAP if s/s of pancreatitis (e.g., significant abdominal pain, n/v). Occurs rarely.	With valproic acid: <1 yr treatment, shortly after dose increase, <20 years of age, AED polytherapy, chronic encephalopathy, receiving hemodialysis.
Seizures	Monitor for worsening of seizures particularly around dose changes or addition of new AEDs.	Generally avoid use of carbamazepine, phenytoin, oxcarbazepine for juvenile myoclonic epilepsy and absence seizures.
SUDEP (sudden unexplained death in epilepsy patients)	This subject is receiving increasing attention, but is not routinely discussed in epilepsy clinic settings; therefore, it is important to redirect patients to their neurology team.	Patients on AED polytherapy and who have uncontrolled seizures.
Teratogenicity	Ideally this concern should be discussed with the patient's neurology team.	All AEDs.

AED = anticonvulsant drugs, AHS = anticonvulsant hypersensitivity syndrome, ASAP = as soon as possible, CBC = complete blood count, EIAED = enzyme-inducing anticonvulsant drug, N/V = nausea and vomiting, PCOS = polycystic ovary syndrome, RDA = recommended daily amount, s/s = signs and symptoms.

Drug Interactions

- Either pharmacokinetic or pharmacodynamic
- Pharmacokinetic results in ↑↓ drug levels and pharmacodynamic is a result of overlapping adverse effects
- Pharmacokinetic interactions often secondary to overlapping metabolic pathways ie. mechanisms wherein the body breaks down or metabolizes the medication

Drug Interactions

- Is a growing evidence base available describing how the antiseizure medications are metabolized which allows for a “theoretical” assessment of drug interactions
- Most drug interaction software relies on those interactions reported in the literature and much less on overlapping metabolic pathways which limits the reporting

Drug Interactions

- Metabolic pathways most commonly include the cytochrome P450 group of enzymes
- Consequently ensure your healthcare provider assessing for drug interactions for you or your child is confident in their assessment

Summary

- Risks of uncontrolled seizures outweighs potential risks of antiseizure medications
- Little to no value in regular bloodwork to “predict” idiosyncratic adverse antiseizure medication reactions, best is clinical monitoring
- Valproic acid may cause adverse liver effects however epilepsy experts would consider it the most effective antiseizure medication commercially available in Canada.

Summary

- When valproic acid is chosen its benefits far outweigh its risks especially with appropriate clinical monitoring
- Levetiracetam may infrequently cause behavioural adverse effects and maybe prolonged QTc interval however it is otherwise devoid of adverse effects and very unlikely to interact with other medications therefore a very appropriate first line antiseizure medication

Issue	Monitoring	Management
Weight gain	Periodic (every 1-2 weeks) weight measurements	Consider modified diet although likely insignificant as reversible upon discontinuation and short duration of treatment.
Behavioral changes/sleep changes	Appreciate baseline behavior/sleep patterns to understand what is new.	Medications are available to assist with sleep/irritability problems should they become a significant issue.
Immune system	Monitor signs and symptoms of infection (fever, lethargy, cough, sore throat).	Promptly seek medical attention if any indication of infection appears.
Adrenal suppression	Infection, surgical procedures, dehydration all increase risk of bodily stress	Stress steroid doses (given IV or by mouth) may be needed for a period of ~1 year after last prednisolone dose.
High blood pressure	Check BP weekly.	Consider reduced salt intake however a high blood pressure medication may be required; discuss with paediatrician.

Issue	Monitoring	Management
Glucose (sugar) intolerance	Signs and symptoms of high blood sugar (significantly elevated thirst and urination, fatigue).	Blood glucose and urine glucose monitored by paediatrician every two weeks and once weekly respectively.
Gastroesophageal reflux	Assess for heartburn and associated symptoms (irritability).	Medications like ranitidine may be used to treat and such will be prescribed for duration of prednisolone treatment.
Peptic ulcer disease	Signs and symptoms of stomach upset, stool color change (to black), lethargy, anemia.	There is a very low risk of prednisolone causing an ulcer therefore this is very unlikely.
Bone changes	→	Ensure recommended daily amount of calcium and vitamin D administered although there is a only low risk of bone problems with short courses of treatment
Vaccinations	→	Discuss with neurologist prior to starting prednisolone and prior to administering vaccinations.