Clinical Use of Antiepileptic Drugs and Epileptic Syndrome

Scope

- New classification of seizures and epilepsies
- How correct diagnosis is important!
- Indication for starting antiepileptic drug
- AED selection
- Maintenance therapy
- Strategies when treatment fails

NEW CLASSIFICATION OF SEIZURES AND EPILEPSIES

ILAE classification_old version

- ILAE classification of epileptic seizures 1981

- ILAE classification of epilepsies and epileptic syndromes 1989

ILAE classification_new version

Epilepsia 2010;51:676–685

SPECIAL REPORT


Seizures are categorized into 3 main types:
- Generalized seizures
- Focal seizures
- Unknown seizure type

Generalized seizures:
- Originate at some point within, and rapidly engage, bilaterally distributed networks
- Individual seizure onsets can appear localized.
- The location and lateralization are not consistent from one seizure to another.
- Bilateral networks:
  - Include cortical and subcortical structures
  - Not necessarily include the entire cortex
- Generalized seizures can be asymmetric.

Absence:
- Subtype
  - Typical absence
  - Atypical absence
  - Absence with special features:
    - Myoclonic absence
    - Eyelid myoclonia

Myoclonic seizure:
- Subtype
  - Myoclonic seizure
  - Myoclonic atonic seizure
  - Myoclonic tonic seizure
FOCAL SEIZURE

Focal seizure
- Originate within networks limited to one hemisphere
  - may originate in subcortical structures
- In some cases, there is more than one network,
  - more than one seizure type
- For each seizure type
  - have a consistent site of onset
  - ictal onset is consistent from one seizure to another

Descriptors of focal seizures
- Without impairment of consciousness or awareness
  - With observable motor or autonomic components
  - Involving subjective sensory or psychic phenomena only
- With impairment of consciousness or awareness
  - Evolving to a bilateral, convulsive seizure

Unknown seizure type
- Epileptic spasm
  - inadequate knowledge to classify epileptic spasm as focal, generalized, or both

EPILEPSY SYNDROMES AND OTHER EPILEPSIES

Electroclinical syndromes and other epilepsies
- Electroclinical syndromes arranged by age at onset
- Distinctive constellations
- Epilepsies attributed to and organized by structural-metabolic causes
- Epilepsies of unknown cause
- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
Electroclinical syndromes arranged by age at onset

- Neonatal period
- Infancy
- Childhood
- Adolescence – Adult
- Less specific age relationship

Electroclinical syndromes
Onset at adolescence – adult

- Juvenile absence epilepsy (JAE)
- Juvenile myoclonic epilepsy (JME)
- Epilepsy with generalized tonic–clonic seizures alone
- Progressive myoclonus epilepsies (PME)
- Autosomal dominant epilepsy with auditory features (ADEAF)
- Other familial temporal lobe epilepsies

Distinctive constellations

- Mesial temporal lobe epilepsy with hippocampal sclerosis
- Rasmussen syndrome
- Gelastic seizures with hypothalamic hamartoma
- Hemiconvulsion–hemiplegia–epilepsy

Seizures not diagnosed as epilepsy

- Conditions with epileptic seizures that are traditionally not diagnosed as a form of epilepsy per se
  - Febrile seizure
  - Benign neonatal seizures (BNS)

Example

- ชาย อายุ 52 ปี มีอาการระคายกันจนหน้าฝ้าขวาแข็ง ต่อมากระตุกทั้งตัว หมดสติขณะกระตุกทั้งตัว CT scan of brain พบ right frontal lobe tumor
- Seizure type
  - Focal motor seizure at right face evolving to a bilateral, convulsive seizure
- Epilepsy type
  - Epilepsy attributed to right frontal lobe tumor
Clinical use of AEDs

- How correct diagnosis is important!
- Indication for starting antiepileptic drug
- AED selection
- Maintenance therapy
- Strategies when treatment fails

Why correct diagnosis is important?

- Etiology management
- Prognosis
- AED selection
- AED-induced seizure
- Non-epileptic attack disorders

AED choice according to epilepsy syndrome

- Infantile spasm
  - Vigabatrin, nitrazepam, valproate, B6, adrenocorticotropic hormone, surgery
- Juvenile myoclonic epilepsy
  - Valproate, lamotrigine, topiramate, levetiracetam

AED choice according to epilepsy type

- Epilepsy with focal seizure
  - Many AEDs
- Epilepsy with generalized seizure
  - Many AEDs
  - Epilepsy syndrome with generalized seizure prefer valproate, phenobarbital, lamotrigine, topiramate, levetiracetam, zonisamide
  - Some AEDs may induce seizure !!!

AED choice according to seizure type

- Generalized tonic-clonic seizure
  - Any AED
- Focal seizure
  - Any AED
- Absence
  - Valproate, lamotrigine, topiramate, levetiracetam
- Myoclonic seizure
  - Phenobarbital, valproate, lamotrigine, topiramate, levetiracetam
AEDs induce seizure

- AEDs induce absence
  - phenytoin, carbamazepine, phenobarbital
- AEDs induce myoclonic seizure
  - phenytoin, carbamazepine

INDICATION FOR STARTING ANTIEPILEPTIC DRUG

Indication for starting AED

- Based on assessing consequence of epilepsy versus consequence of AED
- Consider
  - How seizures interfere with
    - ability to function
    - quality of life
  - Perspective view of patient, family, society

Consequence of epilepsy depend on

- Seizure type
- Timing and frequency of attack
- Age and condition of patients
- Type of employment
- Response of patient, family and society
- Driving license

All patients with epilepsy need Rx?

- Average risk of having further seizure after a first unprovoked seizure = 46% (Berg and Shinnar, Neurology 1991)
- Risk of subsequent seizures after a second seizure = more than 70% (Hauser et al, N Engl J Med 1998)

Recurrence risk factors after first seizure

- With recurrence risk factor, risk of recurrence after a first seizure might be similar to the average risk after two unprovoked seizure (Berg and Shinnar, Neurology 1991)
  - Known etiology ++
  - Epileptiform EEG ++
  - Family history: first degree relatives +
  - Time elapsed from seizure +
  - Todd’s paresis +
Indication for starting AED

- In conclusion
  - No single guideline applicable to all!!
  - Individually interactive decision-making among patient, family and doctor

AED SELECTION

Why AED selection important

- Goal of epilepsy treatment:
  - Achieve seizure freedom
  - No or tolerated side effects
  - Affordable cost
  - Comply to local guideline
- Different AED choices must be informed!!

Beneficial characteristics for AED selection

- Epilepsy syndrome / epilepsy type
- Age
- Gender
- Co-morbidities
- Co-medication

Key factors to maximized AEDs’ benefit

- Initial therapy
- Efficacy
- Safety and tolerability
- Initiation/dose
- Hepatic enzyme induction
- Drug-drug interaction
- Evidence for Rx of newly diagnosed epilepsy
- Co-morbidities
- Special groups

Initial therapy

- 40% of newly diagnosed epilepsy will be seizure free on first AED
- However, some patients suffer from AED side effects
- Some patients remain on troublesome AED with a fear of seizure attack.
- These patients may have better life with other AED.
Sample case

Unwanted adverse effect

**Unwanted adverse effect**

- **EEG:** generalized multiple spikes and slow wave complex on a normal background activity
- **Diagnosis:** Juvenile myoclonic epilepsy (Generalized epilepsy)
- **Antiepileptic drug:**
  - First gen AED: sodium valproate

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**AED Efficacy**

- Despite great hopes, no new AED proven to be more efficacious than standard AED in newly-diagnosed epilepsy

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**AEDs recommendation as first-line therapy for adults with focal seizures**

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</table>
Sample case

Efficacy

Dx: Focal epilepsy of unknown cause
Rx:
- Start with phenytoin 300 mg/d
- Another seizure attack
- Titrate up to 350 mg/d
- Another seizure attack and dizziness

Adverse effect

<table>
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<th>Antiepileptic drug</th>
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<tbody>
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<td>Drug rash</td>
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<td>Over weight</td>
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<tr>
<td>Drowsiness</td>
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<tr>
<td>Cognitive impairment</td>
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Carbamazepine, oxcarbazepine, lamotrigine
Valproate, gabapentin, pregabalin
Phenobarbital, gabapentin, pregabalin
Phenobarbital, topiramate

She is well at 1,000 mg bid of levetiracetam.
Safety and tolerability

- New generation AED proved to have better side effect profile
- However, new generation AED still carry some significant side effect, for example
  - Topiramate:
    - glaucoma, renal calculi, cognitive impairment

Initiation/dose

- Patients remain at risk for another seizures until reaching therapeutic level
- Favorable AED:
  - Initiation at therapeutic dose
  - Rapid titration
  - Linear relationships pharmacokinetics

AEDs initiated at therapeutic dose (minimum effective dose)

1st generation AEDs
- Sodium valproate 500-750 mg/d

2nd generation AEDs
- Levetiracetam 250 mg, bid
- If necessary, 500 mg, bid

AEDs initiated at therapeutic dose (minimum effective dose)

Phenytoin & Phenobarbital
- Despite of starting with therapeutic dose, steady state of serum drug level need a week (5-half life period)
- Phenytoin: 3-5 mg/kg/d (300 mg/d)
- Phenobarbital: grain 1/d

Rapid titration

1st gen AEDs
- Sodium valproate
  - If necessary, 250-500 mg/d
  - every few days

2nd gen AEDs
- Levetiracetam
  - If necessary, 500 mg/d
  - every day

Hepatic enzyme induction

- Most 1st gen AEDs except valproate strongly induce cytochrome P450 system
- Most new generation AED have no or minimal enzyme inducing effect
- Many intrinsic substances such as vitamins and hormones are subjected to induced metabolism
- Several drugs are metabolized via cytochrome P450 system
Drug-drug interaction

- Better knowledge on pharmacokinetics and pharmacodynamics help to select proper AED particular in patients who need polytherapy AED and polypharmacy
- New generation AEDs have better pharmacokinetics such as lower or non protein binding property, no liver metabolism etc.

Sample case

Drug interaction

Co-morbidities

- New generation AEDs have better pharmacokinetics such as non liver metabolism
- The more suitable drug profile may be needed in epileptic patient with other co-morbidity such as liver cirrhosis

Sample case

Co-morbidities
● Dilated cardiomyopathy
● Chronic atrial fibrillation
● Cardiac liver cirrhosis
● Epilepsy attributed to old cerebral embolism

He needs AED with better pharmacokinetic profile
- No liver toxicity
- Not induce hepatic coma
- Not metabolized by liver
- Not induce cyp 450 enzyme that metabolize warfarin
Therefore, all 1st gen AEDs not suitable

2nd gen AED that has suitable profile are
- Levetiracetam
- Pregabalin
- Gabapentin
- Topiramate > 200 mg/d may have liver toxicity.
- Lamotrigine is glucuronidated by liver.

Special groups
- Children
- Women
- The elderly

AED in women
- Women with childbearing potential
  - Hormonal contraception
  - Pregnancy
  - Breast feeding
- Bone health particularly in post menopausal period

Valproate in pregnancy
- Several observational studies reported
  - higher rates of major congenital malformations with use of valproate Vs other AEDs such as carbamazepine or lamotrigine
  
Valproate in pregnancy

- Compared with other AEDs, valproate carries an increased risk of teratogenicity
  - significantly lower IQ (although within the normal range)

Valproate in pregnancy

- The teratogenic effects of valproate seem to be
  - dose-dependent
  - more prominent at doses of 800 mg per day or more
    (Perucca and Tomson, Lancet Neurol 2011)

AED in the elderly

- Physiologic changes of aging needed to be more concern
- The elderly tend to have lower threshold of side effects such as sedation, cognitive dysfunction, unsteady gait
- New generation AEDs with superior pharmacokinetics may be necessary in some older patients

Other key factors on appropriate use of new generation AEDs

- Current health economic status in Thailand, other two factors are vital:
  - Cost
  - Drug availability

Maintenance AED therapy

- Start with small dose
  - to minimize risk of initial side effects and allergic reaction
- Gradually increase to minimum effective dose
- Allow sufficient time between dose or drug changes for efficacy evaluation
### Maintenance AED therapy

#### Principles of adding a second drug

- After reaching un-tolerable level of first AED
- Adjust un-tolerable level of 1st AED
- Sufficient drug titration time
- If seizures not under control, switch to another combination

#### Rational poly-therapy AEDs

- Polytherapy
  - Efficacy: less than additive
  - Side effects: supra-additive
- Two or not more than three AEDs!
- Consider
  - Modes of action
  - Drug to drug interaction (metabolism induction, protein binding, etc.)
  - Adverse effect profiles

#### Strategies when treatment fails

- About 50% will achieve seizure freedom without intolerable side effects on the initially prescribed AED.
- If idiosyncratic reaction, avoid, if possible, AED that are likely to show cross reactivity.
- Carbamazepine has cross reaction of rash with
  - Phenytoin for 58%
  - Phenobarbital for 27%
  - Oxcarbazepine for 33%
  - Lamotrigine for 20%.
**Strategies when treatment fails**

- If lack of efficacy with highest tolerated dose,
  - Check drug compliance
  - Re-evaluate diagnosis
  - Re-evaluate AED (choice and dosage)
  - Switch to other monotherapy
  - Consider rational polytherapy