

Treatment of Epilepsy



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약물 치료에 있어 중요한 이슈

- ▶ 치료를 해야 하는 이유
- ▶ 치료 방법과 치료 계획
- ▶ 약물 치료에 고려해 보아야 하는 요소들
 - : 부작용, 상호작용, 동반질환, 특별한 상황(임신..)
- ▶ 치료 기간
- ▶ 치료 중단

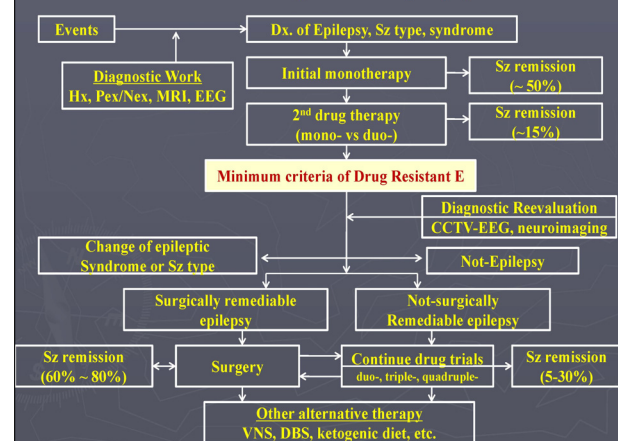
약물 복용이 왜 필요한지

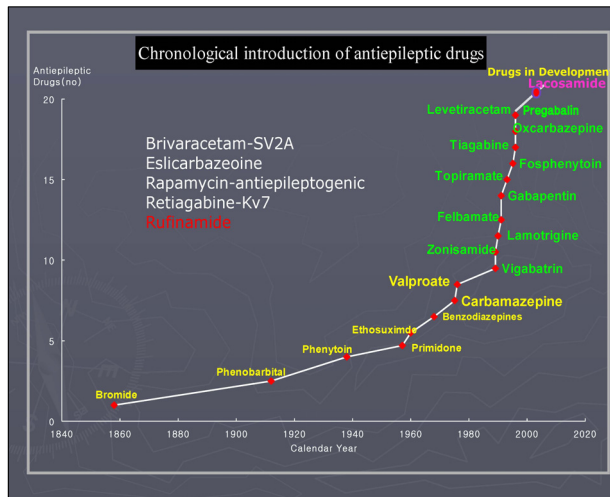
- ▶ 첫 비유발발작 (unprovoked seizure) 후 발작이 재발할 가능성
 - : 27%-81%
 - : 첫 발작이 있은 후 60%가 6개월 이내에, 3년 내에는 78%가 재발 → morbidity, social problems...
- ▶ 재발을 잘 초래하는 인자
 - (1) 부분발작이 있는 경우
 - (2) 중추신경계에 병터가 있는 경우
 - (3) 뇌파검사에 이상이 있는 경우 (2-3배)
 - (4) 가족력이 있는 경우

뇌전증의 치료

- ▶ 약물 치료
- ▶ 수술 치료
 - 국소 절제술, 뇌량 절제술...
 - 미주신경자극술
 - 심부뇌자극(시상하핵)
- ▶ 보조적 치료
 - 케톤생성식 (ketogenic diet)
 - Biofeed back...

Treatment Options of Epilepsy





항뇌전증약 선택시 고려해야 하는 사항들

▶ Type of epilepsy

First sz
Newly diagnosed
Localization-related, Generalized, Doubtful
Idiopathic or Syndromic
Refractory

▶ Patient factors

Special populations
Weight status
Comorbidities
Concomitant dz
Compliance
Cost

▶ Drug-related factors

Efficacy
Mechanism
Pharmacokinetics : Interactions
Toxicity :
Teratogenicity
Dosing schedule

Efficacy
Tolerability

발작, 뇌전증증후군에 따른
약물 선택 지침

1. Broad spectrum AEDs에 속하지 않는 것은?

1. TPM
2. LTG
3. ZNS
4. VPA
5. LEV

Evidence-based Recommendations

Sz type/ Epi. syndrome	1 st choice	2 nd choice	Drug to avoid
partial/mixed	CBZ, TPM, LTG, OCBZ	PHT, VPA, GBP, ZNS, LEV, PB, LCS	
absence	VPA, ESM	LTG, TPM	CBZ, PHT, TGB, GBP
JME	VPA	LEV, TPM, ZNS, LTG, FBM	CBZ, PHT
LGS	VPA, LTG	TPM, Rufinamide, LTG, CBZ (ZNS, FBM, LEV)	
West syndrome	ACTH, VGB	TPM, ZNS, LTG, VPA, CLZ	
PME	VPA, ZNS, LEV	TPM, CLZ	
undetermined	broad spectrum AEDs : TPM, LTG, VPA, ZNS, LEV		
	3rd line drugs		

부작용과 유해 효과

: maintenance, compliance에 지장을 줄 수 있는...

Major Adverse Reactions

- ▶ **Early** : skin eruptions, dizziness, hepatotoxicity, headache, nausea/vomiting...
- ▶ **Long-term** : weight gain or loss, hair loss, hirsutism, nephrolithiasis, dysmorphic figures, polycystic ovarian syndrome, hyponatremia...
- ▶ **Early and long-term** : cognitive dysfunction, calculation difficulty, sleep disturbances

머리 주의 환기, 의무기록에 기재

환자에 따라

- ▶ 어지럼, 실조, 배뇨장애
- ▶ 임신과 선천 기형
- ▶ 간과 신장 기능
- ▶ 난소 등 생식 관련
- ▶ 체중
- ▶ 계산장애
- ▶ 얼굴 털, 녹내장, 결석...

Considering Drug Interaction

Epileptic patients - potential for Drug Interaction

- ▶ Population-based studies: 20-30% received AED polytherapy.
- ▶ 35 % of the adults suffered from CNS-related comorbid conditions.
- ▶ the elderly is the largest group with new-onset epilepsy having a considerable risk of interactions with commonly prescribed drugs

2 types of DI

▶ Pharmacokinetic interaction

: change in serum concentration

Absorption, Distribution, Metabolism, Excretion

Protein binding

Hepatic metabolism: most common

Cyp450 system
Other enzyme

▶ Pharmacodynamic interaction

: no change in serum concentration

: interaction with binding site, other physiological mechanism...

: difficult to identify

The older AEDs are susceptible to cause

► Inducer

: carbamazepine (CBZ), phenobarbital (PB), phenytoin (PHT), primidone

► Inhibitor

: **valproic acid (VPA)**

Newer AEDS

- Topiramate, oxcarbazepine, eslicarbazepine are mild inducers and may affect the disposition of oral contraceptives with a risk of failure of contraception.
- Felbamate, rufinamide, stiripentol are inhibitors.
- Felbamate, tiagabine, topiramate and zonisamide **are sensitive to induction** by known anticonvulsants with inducing effects, **but are less vulnerable** to inhibition by common drug inhibitors.
- Lamotrigine, vulnerable to both induction and inhibition

► AEDs with the least potential of interaction

: **gabapentin, vigabatrin, pregabalin, levetiracetam, and lacosamide**

(Johannessen, 2010)

The most clinically significant DI between AEDs

Lamotrigine on Valproate

- LTG clearance is delayed. Must require slow titration of LTG (**vs. VPA on LTG**).
- Antiepileptic effects is augmented and wider spectrum, compared to monotherapy of each drug.

PDD/DDD ratio concept

- (Prescribed Daily Dose) / (Defined Daily Dose) + + + ...
= Total drug load
- Same total drug load
= 750mg VA (0.5) + 500mg CBZ (0.5)
= 1500mg VA (1.0) or 1000mg CBZ (1.0)
(DDD: VPA 1500mg/day, CBZ 1000mg/day)

- Prospective, randomized study comparing CBZ alone to CBZ plus VPA, using comparable drug loads, **found no difference in tolerability or efficacy** between the two groups - **특정 약물의 용량의존 부작용이 염려되는 경우**

Low dose polytherapy

- 개념 - 부작용의 합은 각 약물의 용량에 따름
- 실제 적용 -initial target dose (=DDD) 혹은 therapeutic range 내에 있을 때 중량할 경우: 부작용 위험 대비 효과?
- 빨리 용량을 증가하기 쉽지 않은 경우

라믹탈을 꼭 쓰고 싶을 때

발작이 잦은 환자에게 라모트리진 단독요법을 꼭 쓰고 싶을 때

- ▶ 라모트리진+다른 약(VPA, LEV, TPM..) half dose, and LTG 서서히 증량 후 다른 약 중단
- ▶ VPA... Mono target dose, and then LTG add on, increase gradually and tapering VPA and stop

특별한 경우의 약물 선택

Pediatrics : **avoid** Barbiturates, BDZs, TPM, ZNS
 Woman planning for pregnancy : newer drugs
 Elderly with multiple medicines : **PHT, CBZ, VPA**
 Hepatic Dysfunction : **GBP, LEV, VGB, TPM**
 Cardiac arrhythmia : **CBZ**
 Hx of nephrolithiasis : **TPM, ZNS**
 Parkinson dz, Essential tremor : **VPA**

Comorbidities

GBP, Pregabalin - *neuropathic pain*
VPA, TPM, ZNS - *migraine*
LTG - *bipolar depression*
Pregabalin - *generalized anxiety disorder*

Body Weight

VPA, CBZ, GBP, Pregabalin-증가
TPM, ZNS-감소

치료 기간과 치료 중단

Epileptic Syndromes and Prognosis

(Sander JW, 2003)

- 1) Excellent prognosis : ~20-30%
- 2) Good prognosis : ~30-40%
- 3) AED-dependent prognosis : ~10-20%
- 4) Bad prognosis : <20%

1) Excellent prognosis : ~20-30%

- ▶ Self-limiting, very benign
 - ▶ Only a few seizures
 - ▶ Commonly do not require AEDs
- Ex) **Benign epileptic syndromes**
Fifth-day seizures
Epilepsy with acute symptomatic seizures

2) Good prognosis : ~30-40%

- ▶ Usually benign, short-lived
- ▶ Easily controlled with AEDs
- ▶ Once remission, permanent and successfully tapered
- ▶ AEDs: curative? suppressant until spontaneous remission?

Ex) **CAE, GTCs, nonspecific GTCs, some of LRE** (증상성부분뇌전증)

3) AED-dependent prognosis : ~10-20%

- ▶ Long-term tendency
- ▶ AEDs are suppressive of seizures rather than curative
- ▶ Remit but may relapse after discontinuation
- ▶ Treatment is usually lifetime project

Ex) **JME, bulk of LRE**

→ Surgery, new AEDs, and new treatment modalities

4) Bad prognosis : <20%

- ▶ AEDs are palliative rather than suppressive
- ▶ Recur despite intensive treatments
- ▶ Seizure associated with deficit from birth

Ex) **EPC, PME, West, LGS, LRE with gross lesions, some LRE**

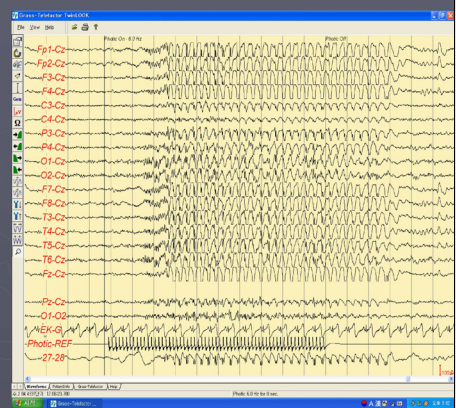
→ Surgery, new AEDs, and new treatment modalities

약물 중단 (1~5년 free?)

- ▶ 충분히 상의, 동의를 얻고...
- ▶ 주의 사항 전달과 기록
위험한 곳, 수면 부족, 과음, 다시 복용 상황
- ▶ 효과가 적었다고 판단하는 AED 부터...
- ▶ 약물상호작용도 고려하면서...
- ▶ 25% rule ?
- ▶ 다음 AED 중단 시- 주의 사항 전달과 기록을 반복...

Case Discussion

- ▶ 2 GTC Seizure
- ▶ 여자 18세, 162cm/65kg
- ▶ 고교 2년생
- ▶ 자연계 우등생
- ▶ fatty liver, 간효소 수치 증가



- ① 측두엽뇌전증 (temporal lobe epilepsy)
- ② 전두엽뇌전증 (frontal lobe epilepsy)
- ③ 소아소발작뇌전증 (childhood absence epilepsy)
- ④ 청소년근간대뇌전증 (juvenile myoclonic epilepsy)
- ⑤ 레녹스-가스토증후군 (Lennox-Gastaut syndrome)

- ① valproate
- ② topiramate
- ③ pregabalin
- ④ levetiracetam
- ⑤ carbamazepine

VGB, TGB, FBM, ZNS, TPM,
LTG, LEV, **PGB**, LCS

Tip

- ▶ 적극적인 치료에도 불구하고 발작이 지속하고, 발작으로 인해 일상생활에 장애가 있는 경우
- ▶ 2년 이상 지속적인 치료 병력
- ▶ 발급 직전 6개월 이상 진료한 전문의
- ▶ 장애진단서, 소견서
- ▶ 경과 기록, 처방 기록
- ▶ 배경과 다른 장애와 차이점

Treatment Options of Epilepsy

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graph TD; Events[Events] --> Dx[Dx. Of Epilepsy, Sz type, syndrome]; Dx --> Mono[Initial monotherapy]; Mono --> R1[Sz remission (~50%)]; Mono --> Duo[2nd drug therapy (mono- vs duo-)]; Duo --> R2[Sz remission (~15%)]; Duo --> MCR[Minimum criteria of Drug Resistant E]; MCR --> R3[Diagnostic Reevaluation CCTV-EEG, neuroimaging]; MCR --> NE[Not-Epilepsy]; MCR --> CS[Change of epileptic Syndrome or Sz type]; MCR --> SR[Surgically remediable epilepsy]; MCR --> NSR[Not-surgically Remediable epilepsy]; SR --> S[Surgery]; NSR --> CRT[Continue drug trials duo-, triple-, quadruple-]; S --> R4[Sz remission (60% ~ 80%)]; CRT --> R5[Sz remission (5-30%)]; S <--> CRT; CRT --> OAT[Other alternative therapy VNS, DBS, ketogenic diet, etc.];
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The flowchart illustrates the treatment options for epilepsy, starting with 'Events' leading to 'Dx. Of Epilepsy, Sz type, syndrome'. This leads to 'Initial monotherapy', which results in 'Sz remission (~50%)'. If not remitted, '2nd drug therapy (mono- vs duo-)' is initiated, leading to 'Sz remission (~15%)'. If still not remitted, the patient meets the 'Minimum criteria of Drug Resistant E'. This leads to 'Diagnostic Reevaluation CCTV-EEG, neuroimaging', 'Not-Epilepsy', 'Change of epileptic Syndrome or Sz type', 'Surgically remediable epilepsy', and 'Not-surgically Remediable epilepsy'. 'Surgically remediable epilepsy' leads to 'Surgery', which results in 'Sz remission (60% ~ 80%)'. 'Not-surgically Remediable epilepsy' leads to 'Continue drug trials duo-, triple-, quadruple-', which results in 'Sz remission (5-30%)'. There is a bidirectional arrow between 'Surgery' and 'Continue drug trials duo-, triple-, quadruple-'. Both 'Surgery' and 'Continue drug trials duo-, triple-, quadruple-' lead to 'Other alternative therapy VNS, DBS, ketogenic diet, etc.'.

뇌전증 장애진단 서류 작성에 대한 팁

- ▶ 적극적인 치료의 기준??
 똑같은 약, 장기간 repeat 처방
 한, 두 개 약물만 사용
 저용량, 저용량 두 개=한 개 치료 용량 NS, NP
- ▶ 장애 정도
 불명확한 발작 유형 GTCS, CPS, SPS (...)
 일상생활 지장 여부- 사고, 부상, ...
- ▶ 재심사 대상 - 일부 약물만 사용, 질환의 초기, 변동이 심한 경우, 다른 치료 계획이 있는 경우...
- ▶ 중복장애에 대한 배려: 뇌병변, 지적장애, 언어장애 ...