

# Chapter 7

## Adverse Effects of Antiepileptic Drugs

### CQ 7-1

## What are the adverse effects of antiepileptic drugs?

### Summary

Adverse effects of antiepileptic drugs comprise idiosyncratic drug reactions, dose-dependent adverse effects, and adverse effects after long-term usage.

### Comment

Adverse effects of antiepileptic drugs are roughly divided into acute early idiosyncratic reactions to drugs associated with allergic mechanisms, dose-dependent inhibitory action on the nervous system, and chronic phase adverse effects seen after long-term usage.

For idiosyncratic reactions to drugs, skin rash is a representative adverse effect occurring at a relatively high frequency. Rare but serious adverse effects include Stevens-Johnson syndrome (SJS), drug-induced hypersensitivity syndrome (DIHS), and toxic epidermal necrolysis (TEN). When these conditions are suspected, the suspected drug should be discontinued, and a dermatologist should be consulted. Pancytopenia, myelosuppression, and hepatic dysfunction may also be observed as adverse effects with allergic mechanisms. Most of the adverse effects due to these idiosyncratic reactions occur from 1–2 weeks to 2–3 months after the start of treatment. Therefore, attention should be given during the early stage of administration.

Adverse effects due to suppression of the nervous system (neurotoxic side effects) include many adverse effects such as dizziness, nystagmus, diplopia, drowsiness, nausea, anorexia, cerebellar ataxia, and psychiatric symptoms. Many of these adverse effects are dose-dependent.

Some adverse effects are accompanied by long-term use of antiepileptic drugs, such as weight gain, hypertrichosis or hair loss, urolithiasis, cerebellar atrophy, and gingival hyperplasia. Enzyme inducers (phenytoin, carbamazepine, phenobarbital, and primidone) and valproate are risk factors of osteoporosis.

To identify adverse effects of antiepileptic drugs, systematic adverse effect screening has been reported to be useful<sup>1)</sup>. Representative adverse effects of major antiepileptic drugs are summarized in **Table 1**.

### ■ References

- 1) Gilliam FG, Fessler AJ, Baker G, et al. Systematic screening allows reduction of adverse antiepileptic drug effects: a randomized trial. *Neurology*. 2004; 62(1): 23-27.

### ■ Search formula and secondary reference sources

PubMed search: June 26, 2015

((("Epilepsy/drug therapy" [Majr]) AND "adverse effects" [Subheading])) OR "Anticonvulsants/adverse effects" [Majr] Filters: Randomized Controlled Trial; Publication date from 2008/01/01 to 2015/12/31; Humans; English; Japanese = 119

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(((((epilepsy/TH or epilepsy/AL)) and (SH = drug therapy)) and (adverse effects/AB or adverse effects/TI)) and (DT = 2008:2015 and PT = excluding proceedings))) and (PT = Comment, review) = 94

**Table 1. Typical adverse effects of major antiepileptic drugs.**

<b>Drug</b>	<b>Idiosyncratic adverse effects</b>	<b>Dose-dependent adverse effects</b>	<b>Adverse effects after long-term use</b>
Carbamazepine	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	diplopia, nystagmus, dizziness, ataxia, drowsiness, nausea, hyponatremia, cardiac conduction disturbance or cardiac failure, reduced cognitive function, hearing abnormality	osteoporosis
Clobazam	rare	drowsiness, ataxia, behavioral disorder, salvation	
Clonazepam	rare	drowsiness, ataxia, behavioral disorder, salvation	
Ethosuximide	rash, pancytopenia	drowsiness, abnormal behavior	
Gabapentin	rare	dizziness, ataxia, drowsiness, myoclonus	weight gain
Lamotrigine	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	drowsiness, dizziness, diplopia, excitability	
Levetiracetam	rare	drowsiness, abnormal behavior, bad mood	
Phenobarbital	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	dizziness, ataxia, drowsiness, reduced cognitive function	osteoporosis
Phenytoin	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	diplopia, nystagmus, dizziness, ataxia, drowsiness, peripheral neuropathy, cardiac conduction disturbance or cardiac failure, asterixis	cerebellar atrophy, hypertrichosis, gingival hyperplasia, osteoporosis
Primidone	rash, liver injury, pancytopenia, thrombocytopenia, SJS, TEN, DIHS	dizziness, ataxia, drowsiness	osteoporosis
Valproate	pancreatitis, liver injury	thrombocytopenia, tremor, hyponatremia, increased ammonia, Parkinson syndrome	weight gain, hair loss, osteoporosis
Topiramate	rare	anorexia, psychotic symptom, drowsiness, speech symptom, metabolic acidosis, hypohidrosis	urolithiasis, weight loss
Zonisamide	rare	anorexia, psychotic symptom, drowsiness, speech symptom, metabolic acidosis, hypohidrosis, reduced cognitive function	urolithiasis
Rufinamide	drug-induced hypersensitivity syndrome, SJS, status epilepticus, aggressiveness, QT interval shortening	anorexia, drowsiness	
Stiripentol	attention deficit, hyperactivity disorder, talkativeness, sleeping disorder, aggressiveness, prolonged QT	somnolence, insomnia, anorexia, ataxia	
Sultiame	rash, leukocytopenia, tachypnea, paresthesia	anorexia, drowsiness	

SJS: Stevens-Johnson syndrome, TEN: toxic epidermal necrolysis, DIHS: drug-induced hypersensitivity syndrome  
 [Before prescription, read the package inserts of individual drugs]