

## INTRODUCTION

Epilepsy poses a great challenge to physicians in its management when it is associated with special situations. In these special situations, epilepsy can occur either as an index disease with other diseases or there can be concurrent occurrence of several chronic disorders requiring treatment. Furthermore it has been suggested that prevalence of cardiovascular disorders, infections, pulmonary disease and gastrointestinal hemorrhage is increased in people with epilepsy. Here, we review the management of epilepsy in these various situations where epilepsy is either as an index disease or present concurrently with other chronic diseases. The recognition and treatment in such situations strengthen the comprehensive care of epilepsy.

## ORGAN DYSFUNCTION AND EPILEPSY

Epilepsy can occur concomitantly with organ (e.g., hepatic, renal or endocrine) dysfunction and it may or may not be related to the latter. The presence of concurrent organ dysfunction in epilepsy has various implications in its management, which are as follows:

1. Organ dysfunction may occur as a complication of epilepsy or its treatment.
2. Organ dysfunction may have an effect on treatment.
3. Seizures may occur as a manifestation of organ dysfunction or as a manifestation of a disorder that affects the brain as well as the body organ.
4. Epilepsy may impact treatment of the organ disorder.

## HEPATIC AND RENAL DISEASE

Antiepileptic drug (AED) metabolism occurs largely in the liver while elimination of drugs usually occurs via either the liver or the kidney or both. Besides, the liver and kidney are involved in synthesis and regulation of plasma proteins and many AEDs are extensively protein-bound. Hence, both hepatic and renal dysfunction may affect AED pharmacokinetics through a variety of mechanisms.

Hepatic dysfunction can be divided into acute and chronic. On the basis of previous data, acute hepatic dysfunction (due to toxins and viral hepatitis) does not significantly alter AED pharmacokinetics. Midazolam, in view of its short duration of action, can be used for aborting the seizures and phenytoin (with a loading dose), phenobarbital, gabapentin and levetiracetam may be used for status epilepticus or recurrent seizures in the setting of acute hepatic dysfunction. However, dosage adjustments

are required in chronic liver disease (i.e., cirrhosis), mainly due to the proportion of AED being metabolized or eliminated in the liver or the degree of protein binding. Most of the available AEDs have low hepatic extraction ratios, except conventional AEDs, including phenytoin, valproate, carbamazepine, phenobarbital and primidone, which are chiefly metabolized in the liver. In many liver disorders, impaired protein synthesis results in reduced fraction of the protein-bound drug and elevated free levels of the drug. Hence, dosage considerations in chronic hepatic dysfunction should be based on clinical response to AED (i.e., degree of seizure control) and estimation of free drug levels, along with slower titrations and lower maintenance doses of AEDs.

In renal dysfunction, reduced glomerular filtration and tubular secretion may result in reduced drug elimination. To add to this, there are both quantitative (i.e., protein loss in nephrotic syndrome) and qualitative changes in plasma proteins. This may result in elevated free drug levels. Furthermore, the need of dialysis in both acute and chronic renal dysfunction, may also lead to loss of AED from the body. For certain AEDs, dosage guidelines have been reviewed regarding supplemental doses in immediate post-dialysis period. (Table 1)

## CARDIAC DISEASE

A variety of life-threatening cardiac arrhythmias have been described in epilepsy. They may be present either as effects of seizures on cardiac rhythm or various cardiac disorders associated with epilepsy. Ictal tachycardia is seen with intense sympathetic discharge during seizures, while excessive parasympathetic discharge results in ictal asystole. For various cardiac rhythm disorders with epilepsy, a genetic basis involving sodium and potassium ion channel disorders has been suggested. The most common cardiac rhythm disorder seen is atrio-ventricular heart block (AV block) associated with carbamazepine and lacosamide. QT interval abnormalities inherited or as a consequence of AED (such as carbamazepine and phenytoin), may account for a proportion of cases of sudden unexpected death in epilepsy (SUDEP).

A baseline electrocardiogram should be ordered, for QT interval abnormalities and AV blocks, before commencing AED treatment. Barbiturates, valproate and most of newer AEDs are safer in such situations.

## PULMONARY DISEASE

Obstructive sleep apnoea has been encountered in people with epilepsy (PWE). The high frequency of sleep apnoea

**Table 1: Dosage Adjustments for Newer Antiepileptic Drugs in Patients with Reduced Kidney Function**

AED	Total Daily Dose (GFR, in mL/min)				Supplementary Dose After Hemodialysis
	60-89	30-59	15-29	<15	
Gabapentin	400-600 mg TID	200-300 mg BID	200-300 mg/day	100-150 mg/day or 300 mg every other day	125-250 mg
Levetiracetam	500-1000 mg BID	250-750 mg BID	250-500 mg BID	250-500 mg BID	250-500 mg
Topiramate	100-200 mg BID	50-100 mg BID	50-100 mg BID	50-100 mg BID	50-100 mg
Oxcarbazepine	300- 600 mg BID	300- 600 mg BID	50% of original dose	Insufficient data; use with caution	NA
Zonisamide	100-400 mg	100-400 mg	Insufficient data; use with caution		Supplement 50% dose if seizure occurs after hemodialysis

in people with epilepsy has been attributed to depressive effect of nocturnal seizures and AEDs on airway muscle tone. Treatment of sleep apnoea with continuous positive airway pressure (CPAP) ventilation has been shown to improve seizure control.

Bronchodilator treatment with theophylline in pulmonary airway disease can result in seizures, usually in extremes of age and with over-dosages. Theophylline therefore should be used cautiously in PWE.

A rare complication of seizures and status epilepticus is neurogenic pulmonary edema, occurring within a few hours of the seizure and may present with dyspnea, breathing difficulty and hemoptysis, leading to cardiovascular collapse and SUDEP. Intensive cardiopulmonary support is the mainstay of this emergency.

### THYROID DISEASE AND EPILEPSY

Subclinical hypothyroidism due to carbamazepine, phenytoin and valproate has been reported. These effects have been attributed to enzyme inducing effects of AEDs or effects on the hypothalamic centers regulating thyroid function. However, the abnormalities revert upon withdrawal of the AED. In individuals with pre-existing thyroid dysfunction, such AEDs with demonstrated effects on thyroid function should best be avoided.

### CANCER AND EPILEPSY

Limited data is available regarding the incidence of seizures in people with cancer. However there appear to be some differences between adults and children for the etiology of seizures. In children, the myelo-ablative therapy (busulphan for leukemia) has been related with high frequency of seizures, and in adults, intracranial metastasis is mostly the culprit.

Anti-cancer drug induced seizures and metabolic disturbances are the other common causes, and such seizures do not require long term AED treatment. In the treatment of such acute seizures, a drug with rapid onset

**Table 2: Cancer Chemotherapeutic Agents that are Substrates for Enzyme-Inducing Action of Aeds**

Agent	Reference
Methotrexate	Relling et al., 2000
Busulfan	Hassan et al., 1993
Cyclophosphamide	Alberts et al., 1976, 1978
Ifosfamide	Lu et al., 1998
Vincristine	Villikka et al., 1999
Doxorubicin	Cusack et al., 1988; Sturgill et al., 2000
Paclitaxel	Fetell et al., 1997; Chang et al., 1998
Tamoxifen	Moorthy et al., 1997

of action is preferred. Oral benzodiazepines (lorazepam or clonazepam) are routinely administered prophylactically before and until 24 hours after high dose busulphan as myelo-ablative treatment.

Many cancer chemotherapeutic agents are substrates for the enzyme inducing action of AEDs. In the presence of conventional AEDs, higher doses of anti-cancer agents (e.g. paclitaxel) are recommended when given concomitantly. Newer AEDs that do not induce hepatic microsomal enzyme systems may be preferred for seizure control in people with cancer (Table 2).

### INFECTIONS AND EPILEPSY

#### Human Immunodeficiency Virus Infection and Seizures

Seizures are common in human immunodeficiency virus (HIV) infection and these typically occur in the later stages of HIV infection. In about half of the HIV-infected individuals, the primary HIV infection itself is considered the cause of seizures and in others, it is attributed to a variety of opportunistic infections.

Due to multiple co-morbidities and concurrent use of several medications for HIV treatment and other

opportunistic infections, several drug-drug and disease-drug interactions should be carefully considered in prescribing the AED.

### CONNECTIVE TISSUE DISORDERS

Systemic lupus erythematosus (SLE) may result in seizures with many underlying mechanisms including anti-neuronal antibodies, vascular infarctions, metabolic disturbances or complicating CNS infections. Newer non-enzyme inducing AEDs may be preferred, in view of long term and multiple classes of medications being required in SLE.

### PREGNANCY & EPILEPSY

#### Pre-Conceptional Care

Very often, determination of pregnancy leads to impulsive revision of AED regimen in seeking a safe AED with low teratogenic potential. All AEDs with exception of valproate have a reasonable teratogenic profile; therefore, there is perhaps no absolutely safe AED during pregnancy. Preconceptional folic acid supplementation reduces risk of major congenital malformations.

#### SEIZURE CONTROL IN PREGNANCY

Hyperventilation, sleep deprivation, pain, emotional stress can increase the risk of seizure during labor. AEDs should be continued during labor and oral clobazam can be added to reduce the risk of seizure as well as to allay anxiety. Convulsive seizures during labor should be treated with intravenous benzodiazepines such as lorazepam and if needed, intravenous phenytoin or levetiracetam be used. Status epilepticus in pregnancy is managed as otherwise. The levels of many AEDs decline by average of 50% during third trimester of pregnancy, and an increase in dosage is recommended during this time. Drug dosage should be reduced to pre-pregnancy dosage within 10 days after delivery.

### OBSTETRIC OUTCOME

The occurrence of seizures during pregnancy have been associated with low birth weight, pre-term labor and increased gestational age. However there is no contraindication to the use of regional anaesthesia including spinal or epidural. A multi-disciplinary approach consisting of anaesthesiologist, obstetrician and neurologist is critical in order to minimize obstetric and perinatal risk in women with epilepsy.

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