Chapter 30 | Antiepileptic Drugs

Epilepsies These are a group of disorders of the CNS characterized by paroxysmal cerebral dysrhythmia, manifesting as brief episodes (seizures) of loss or disturbance of consciousness, with or without characteristic body movements (convulsions), sensory or psychiatric phenomena. These episodes are unpredictable and their frequency is highly variable. Epilepsy has a focal origin in the brain, manifestations depend on the site of the focus, regions into which the discharges spread and postictal depression of these regions. Recognised from the dawn of history as 'disease of lightening', it was correctly described by JH Jackson little over a century ago. Epilepsies have been classified variously; major types are described below.

I. Generalised seizures

They have a diffuse origin involving both hemispheres of the brain; manifestations and EEG abnormalities are bilateral.

1. *Generalised tonic-clonic seizures* (GTCS, major epilepsy, grand mal): lasts 1–2 min.

The usual sequence is aura—cry—unconsciousness and patient falls—tonic spasm of all body muscles—clonic jerking followed by prolonged sleep and depression of all CNS functions.

2. *Absence seizures* (minor epilepsy, petit mal): prevalent in children, lasts about 1/2 min.

No or only momentary loss of consciousness, no fall, patient apparently freezes and stares in one direction, no muscular component or minimal bilateral jerking or blinking of eyes, EEG shows characteristic 3 cycles per second spike and wave pattern. Multiple episodes may occur each day. Seizures may remit spontaneously in adolescence.

3. *Atonic seizures* (Akinetic epilepsy): Brief loss of consciousness with relaxation of all muscles due to excessive inhibitory discharges. Patient may fall.

4. *Myoclonic seizures* Shock-like momentary contraction of muscles of a limb or the whole body. Myoclonic jerking may accompany any type of generalised or partial seizures.

5. *Infantile spasms (Hypsarrhythmia)* Seen in infants. Probably not a form of epilepsy. Intermittent muscle spasm and progressive mental deterioration. Diffuse changes in the interseizure EEG are noted.

II. Partial seizures

They have a unilateral localized origin in the brain, but may spread to small or large area, or to the whole brain. Focal origin may be evident clinically, or may be detected in the EEG.

1. *Simple partial seizures* (SPS): There is sudden onset unilateral clonic jerking of a group of muscles or a limb lasting 30–90 sec, or localized sensory disturbances such as pin pricks, visual/auditory hallucinations, etc. depending on the area of the cortex involved. The patient remains conscious and aware of the attack.

2. *Complex partial seizures* (CPS, temporal lobe epilepsy, psychomotor): attacks of bizarre and confused behaviour, dream-like state and purposeless movements, or even walking unaware, emotional changes lasting 1–2 min along with impairment of consciousness. The patient has no recollection of the attack. An aura often precedes. The seizure focus is located in the temporal lobe.

3. *Simple partial or complex partial seizures secondarily generalized* The partial seizure occurs first and evolves into generalized tonic-clonic seizures with loss of consciousness.

Most of the cases of epilepsy are primary (idiopathic), some may be secondary to trauma/surgery on the head, intracranial tumour,

tuberculoma, cysticercosis, cerebral ischaemia, etc. Treatment is symptomatic, depends mostly on the seizure type, but not on the etiology of seizure or whether it is primary or secondary.

Experimental models These models for testing antiepileptic drugs have also shed light on the etiopathogenesis of epilepsy.

1. *Maximal electroshock seizures* Brief high intensity shock is applied to the head of a rodent (just as in ECT): produces tonic flexion—tonic extension—clonic convulsions. The tonic phase (especially extensor) is selectively abolished by drugs effective in GTCS and complex partial seizures. Activity in this model represents action on spread of seizure discharge.

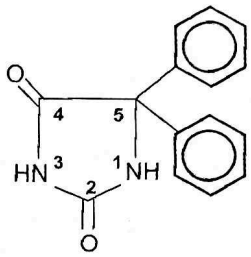
2. *Pentylenetetrazol (PTZ) clonic seizures* Injection of PTZ in rats or mice produces clonic convulsions which are prevented by drugs effective in absence and myoclonic seizures. Activity in this model represents action on seizure focus itself.

3. *Chronic focal seizures* Produced by application of alumina cream on the motor cortex of monkey.

4. *Kindled seizures* Brief bursts of weak electrical impulses are applied to the brain (especially amygdala) intermittently over days. After-discharges increase progressively and tonic-clonic seizures are produced after 10–15 shocks. With time spontaneous seizures set in, usually after >100 shocks. This indicates that seizures have a self perpetuating and reinforcing effect: more neuronal circuits are facilitated and recruited in the seizure process. Kindling is probably involved in the genesis of complex partial seizures and GTCS.

Phenytoin (Diphenylhydantoin)

It was synthesized in 1908 as a barbiturate analogue, but shelved due to poor sedative property. Its anticonvulsant activity was specifically tested in 1938 in the newly developed electroshock seizure model, and till recently it was a major antiepileptic drug.



PHENYTOIN

Phenytoin is not a global CNS depressant; only mild sedation occurs at therapeutic doses. The most prominent action is abolition of tonic phase of maximal electroshock seizures, with no effect on or prolongation of clonic phase. It limits spread of seizure activity. Threshold for PTZ convulsions is not raised.

Mechanism of action Phenytoin prevents repetitive detonation of normal brain cells. This

ANTIEPILEPTIC DRUGS

- **Barbiturate**: Phenobarbitone
- **Hydantoin**: Phenytoin, Fosphenytoin
- **Succinimide**: Ethosuximide
- **Benzodiazepines**: Clonazepam, Diazepam, Lorazepam, Clobazam
- **Newer drugs**: Topiramate, Levetiracetam, Zonisamide, Vigabatrin, Tiagabine, Lacosamide
- **Deoxybarbiturate**: Primidone
- **Iminostilbene**: Carbamazepine, Oxcarbazepine, Eslicarbazepine
- **Aliphatic carboxylic acid**: Valproate sod (Valproic acid), Divalproex
- **Phenyltriazine**: Lamotrigine
- **Cyclic GABA analogues**: Gabapentin, Pregabalin

Perampanel, retigabine, stiripentol, rufinamide and few other newer antiseizure drugs have been introduced in some countries as second line/add-on drugs for refractory partial seizures.

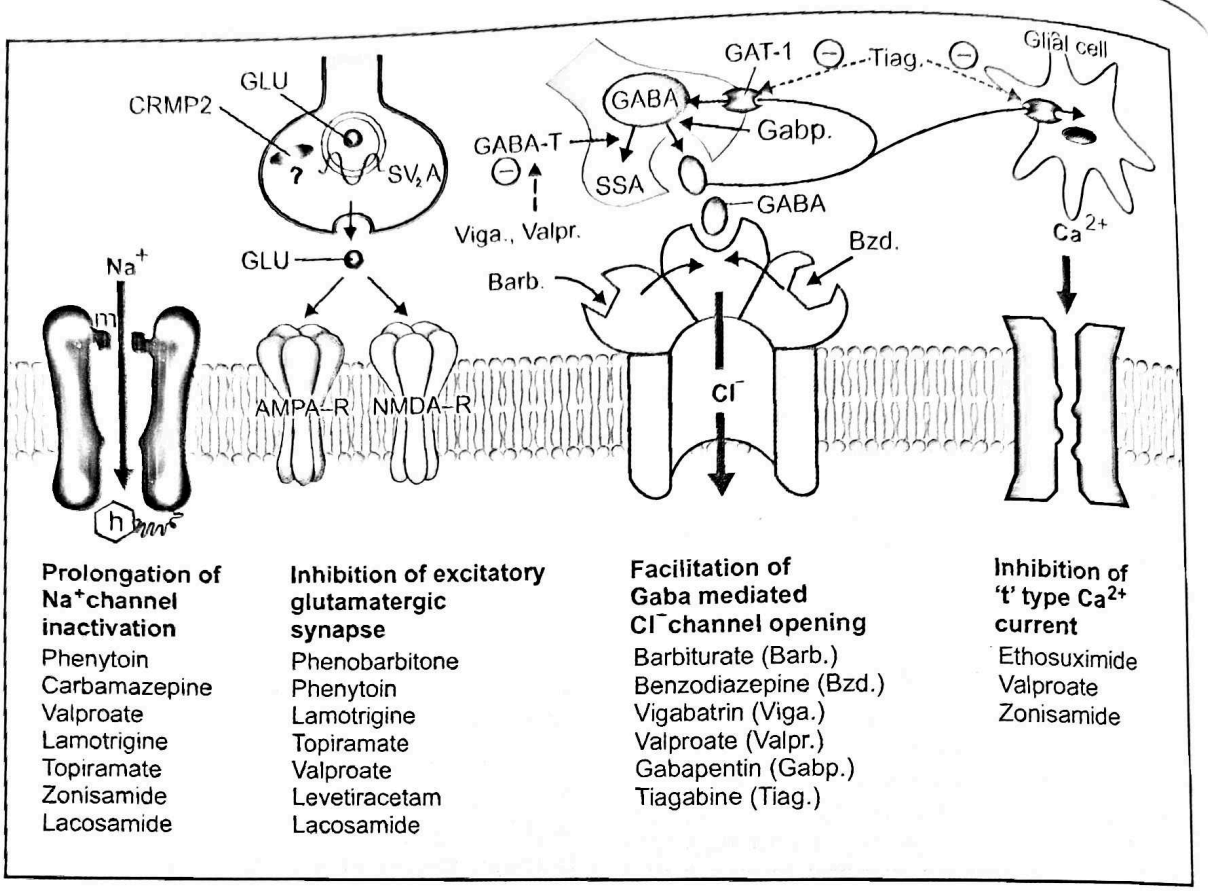


Fig. 30.1: Major mechanisms of anticonvulsant action
m—Activation gate; h—Inactivation gate; GABA-T—GABA transaminase; SSA—Succinic semialdehyde; GAT-1—GABA transporter; GLU—Glutamate; SV_2A—Synaptic vesicular protein 2A; CRMP2—collapsin-response mediator protein; NMDA-R—N-methyl D-aspartate receptor; AMPA-R—α aminohydroxy methyl isoxazole propionic acid receptor

is achieved by prolonging the inactivated state of voltage sensitive neuronal Na^+ channel (Fig. 30.1) that governs the refractory period of the neurone. As a result high frequency discharges are inhibited with little effect on normal low frequency discharges. This effect has been noted at therapeutic concentration of phenytoin. It also depresses presynaptic release of glutamate (excitatory transmitter), facilitates GABA (inhibitory transmitter) release and reduces Ca^{2+} influx. However, these actions require higher concentration and their contribution to the therapeutic response is uncertain. Intracellular accumulation of Na^+ that occurs during repetitive firing is also prevented.

Therapeutic concentrations of phenytoin have no effect on resting membrane potential: normal synaptic transmission is not impaired. Phenytoin, in contrast to phenobarbitone and valproate, does not interfere with kindling. Its ability to selectively suppress high frequency firing confers efficacy in trigeminal neuralgia and cardiac arrhythmias as well.

Pharmacokinetics Absorption of phenytoin by oral route is slow, mainly because of its poor aqueous solubility. Bioavailability of different market preparations may differ. Phenytoin is metabolized in liver by hydroxylation involving CYP2C9 and 2C19 as well as by glucuronide conjugation. The kinetics of metabolism is *capacity limited*; changes from first order to zero order over the therapeutic range. As a result small increments in dose produce disproportionately high plasma concentrations. The t½ (12–24 hours at therapeutic levels), progressively increases (upto 60 hr) when plasma concentration rises above 10 μg/ml because metabolizing enzymes get saturated. Monitoring of plasma concentration is very helpful in adjusting dosage.

Adverse effects After prolonged use numerous side effects are produced at therapeutic plasma concentration:

- Gum hypertrophy: Commonest (20% incidence), more in younger patients. It is due to overgrowth of gingival collagen fibres. This can be minimized by maintaining oral hygiene.
- Hirsutism, coarsening of facial features (troublesome in young girls), acne.
- Hypersensitivity reactions are—rashes, DLE, lymphadenopathy; neutropenia is rare but requires discontinuation of therapy.
- Megaloblastic anaemia and osteomalacia can occur on long term use due to interference with folate absorption and vit. D activation respectively.
- Administered during pregnancy, phenytoin can produce *'foetal hydantoin syndrome'* (hypoplastic phalanges, cleft palate, harelip, microcephaly), which is probably caused by its arene-oxide metabolite.

Over dose toxicity due to higher plasma concentration of phenytoin produces:

(a) Cerebellar and vestibular manifestations: ataxia, vertigo, diplopia, nystagmus.
(b) Drowsiness, behavioural alterations, mental confusion, hallucinations, disorientation and rigidity.
(c) Epigastric pain, nausea and vomiting.
(d) Intravenous injection of phenytoin sodium can cause local vascular injury → intimal damage and thrombosis of the vein → edema and discolouration of the injected limb. Tissue necrosis occurs if the solution extravasates.
(e) Fall in BP and cardiac arrhythmias occur only on i.v. injection which, therefore, must be given under continuous ECG monitoring.

Interactions Phenytoin is a potent inducer of CYP2C8/9, CYP3A4/5 isoenzymes. It competitively inhibits CYP2C9/19.

- Phenobarbitone competitively inhibits phenytoin metabolism, while by enzyme induction both enhance each other's degradation—unpredictable overall interaction.
- Carbamazepine and phenytoin induce each other's metabolism.
- Valproate displaces protein bound phenytoin and decreases its metabolism: plasma level of unbound phenytoin increases.
- Chloramphenicol, isoniazid, cimetidine and warfarin inhibit phenytoin metabolism—can precipitate its toxicity.
- Phenytoin competitively inhibits warfarin metabolism.
- Phenytoin induces microsomal enzymes and increases degradation of steroids (failure of oral contraceptives), doxycycline, theophylline.
- Sucralfate binds phenytoin in g.i. tract and decreases its absorption.

Uses Phenytoin has been the standard drug for GTCS and partial seizures, but is now used only when better tolerated newer drugs cannot be used. It produces frequent side effects and numerous drug interactions. Due to nonlinear clearance, small increase in dose causes marked rise in plasma concentration and toxicity. It can exacerbate absence and myoclonic seizures. For status epilepticus, phenytoin sod. i.v. is used only when fosphenytoin is not available.

In trigeminal neuralgia, it is a second choice drug to carbamazepine.

Dose: Start with 100 mg BD, maximum 400 mg/day. Children 5–8 mg/kg/day.

DILANTIN 25 mg, 100 mg cap., 100 mg/4 ml oral suspension, 100 mg/2 ml inj; EPSOLIN 100 mg tab, 100 mg/2 ml inj; EPTOIN 50, 100 mg tab, 25 mg/ml syr; FENTOIN-ER 100 mg extended release cap.

Fosphenytoin This water soluble prodrug of phenytoin has been introduced to overcome the difficulties in i.v. administration of phenytoin, which it has replaced for use in status epilepticus. In the body, it is rapidly converted to phenytoin; its doses are expressed as phenytoin equivalents (PE). On i.v. injection it is less damaging to the intima; only minor vascular complications are produced and it can be injected at a faster rate (150 mg/min), but like phenytoin sod., it requires ECG monitoring. While phenytoin cannot be injected in a drip of glucose solution (because it gets precipitated), fosphenytoin can be injected with both saline and glucose.

FOSOLIN 50 mg/ml in 2 ml, 10 ml inj.

Carbamazepine

Chemically related to imipramine, it was introduced in the 1960s for trigeminal neuralgia, but soon became a first line drug for partial seizures as well as GTCS. Its pharmacological actions resemble those of phenytoin, but important differences have been noted in experimental studies. Carbamazepine modifies maximal electroshock seizures as well as raises threshold to PTZ and electroshock convulsions. High frequency neuronal discharges are inhibited, and presynaptic action may decrease transmitter release. It also inhibits kindling. Action on Na^+ channels (prolongation of inactivated state) is similar to phenytoin.

Carbamazepine exerts a lithium-like therapeutic effect in mania and bipolar mood disorder. It also has antidiuretic action, probably by enhancing ADH action on renal tubules.

Pharmacokinetics Oral absorption of carbamazepine is slow and variable because of poor water solubility. It is 75% bound to plasma proteins and metabolized in liver by oxidation to an active metabolite (10–11 epoxy carbamazepine), as well as by hydroxylation and conjugation to inactive ones. It is a substrate as well as inducer of CYP3A4 and CYP2C9. Initially its plasma t½ is 20–40 hours but, decreases to 10–20 hr on chronic medication due to autoinduction of metabolism.

Adverse effects Carbamazepine produces dose-related neurotoxicity—sedation, dizziness, vertigo, diplopia and ataxia. Use of extended release oral tablets helps to avoid high peaks in plasma concentration and the resultant neurologic symptoms. Vomiting, diarrhoea, worsening of seizures are also seen with higher doses. Acute intoxication causes coma, convulsions and cardiovascular collapse.

Hypersensitivity reactions are rashes, photosensitivity, hepatitis, lupus like syndrome, rarely agranulocytosis and aplastic anaemia. Mild leucopenia due to hypersensitivity is more common.

Water retention and hyponatremia can occur in the elderly because carbamazepine enhances ADH action.

Increased incidence of minor foetal malformations has been reported. Its combination with valproate doubles teratogenic frequency.

Interactions Carbamazepine is an enzyme inducer; can reduce efficacy of haloperidol, oral contraceptives, lamotrigine, valproate and topiramate. Metabolism of carbamazepine is induced by phenobarbitone, phenytoin, and *vice versa*. Erythromycin, fluoxetine, isoniazid inhibit metabolism of carbamazepine.

Uses Carbamazepine is the most effective drug for CPS and is very commonly used for GTCS and SPS. However, it can exacerbate myoclonic, absence and atonic seizures.

Trigeminal and related neuralgias: Carbamazepine is the drug of choice. These neuralgias are characterized by attacks of high intensity electric shock-like or stabbing pain set off by even trivial stimulation of certain trigger zones in the mouth or on the face. Drugs benefit by interrupting temporal summation of afferent impulses (by a selective action on high frequency nerve impulses). Carbamazepine is not an analgesic, but has a specific action (almost diagnostic) in these neuralgias. About 60% patients respond well. Phenytoin, lamotrigine and baclofen are less efficacious alternatives. Gabapentin can be tried in nonresponders.

Carbamazepine is not useful in diabetic, traumatic and other forms of neuropathic pain.

Manic depressive illness and acute mania: as an alternative to lithium (*see* Ch. 32).

Dose: 200–400 mg TDS; Children 15–30 mg/kg/day.

TEGRETOL, MAZETOL 100, 200, 400 mg tab, 100 mg/5 ml syr; CARBATOL 100, 200, 400 mg tab.

MAZETOL SR, TEGRITAL CR 200, 400 mg sustained release/continuous release tabs. to avoid high peaks and low troughs in plasma concentration. These are the preferred formulations.

Oxcarbazepine This newer congener of carbamazepine is rapidly converted to an active metabolite that is only glucuronide conjugated but not oxidized. Toxic effects due to the epoxide metabolite are avoided. Drug interactions and autoinduction of own metabolism are less marked, because it is a weak enzyme inducer. Risk of hepatotoxicity is estimated to be lower than with carbamazepine; but that of hyponatraemia is more. Indications are the same as for carbamazepine, but it may be better tolerated. Dose to dose it is 1½ times less potent.

OXETOL, OXCARB, OXEP 150, 300, 600 mg tabs.

Eslicarbazepine This (S)+ enantiomer prodrug is very rapidly converted in liver to the same active metabolite as is oxcarbazepine. As such, it has the same range of therapeutic and toxic effects, but is suitable for once daily dosing. It is approved as add-on drug for partial seizure with or without generalization only in adults.
Dose: Initially 400 mg/day; increase if needed upto 1200 mg OD.
ESLIFY 200, 400, 600, 800 mg tabs; NORMICTAL, ZEFRETOL 400, 800 mg tabs.

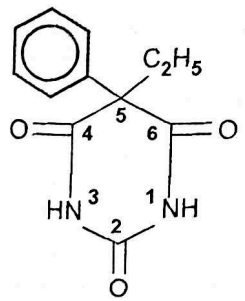
Phenobarbitone (*see* Ch. 29)

Phenobarbitone was the first efficacious antiepileptic introduced in 1912. The mechanism of CNS depressant action of barbiturates is described on p. 426. The same may apply to anticonvulsant action. Enhancement of $GABA_A$ receptor mediated synaptic inhibition appears to be most important mechanism. However, conferred probably by its 5-phenyl substitution, phenobarbitone has specific anticonvulsant activity which is not entirely dependent on general CNS depression. Quantitative differences in the different facets of action (GABA-facilitatory, GABA-mimetic, antiglutamate, Ca^{2+} entry reduction) have been noted for phenobarbitone compared to the hypnotic barbiturates. The higher anticonvulsant: hypnotic activity ratio of phenobarbitone may be due to its minimal effect on Ca^{2+} channels and glutamate release compared to hypnotic barbiturates. With continued use of phenobarbitone sedation wanes off but not anticonvulsant action. It has a wide spectrum of anticonvulsant property—raises seizure threshold as well as limits spread and suppresses kindled seizures.

Phenobarbitone has slow oral absorption and a long plasma t½ (80–120 hours), is metabolized in liver as well as excreted unchanged by kidney. Steady-state concentrations are reached after 2–3 weeks.

Phenobarbitone competitively inhibits as well as induces phenytoin and imipramine metabolism; effect on their plasma concentration is unpredictable. Sod. valproate tends to raise phenobarbitone levels when given concurrently.

The major drawback of phenobarbitone as an antiepileptic is its sedative action. Long term administration (as needed in epilepsy) may produce additional side effects like—behavioural abnormalities, diminution of intelligence, impairment of learning and memory, hyperactivity in children, mental confusion in older people.



PHENOBARBITONE

Uses Phenobarbitone is effective in generalized tonic-clonic (GTC), simple partial (SP) and complex partial (CP) seizures in a dose of 60 mg 1–3 times a day in adults; in children (3–5 mg/kg/day). However, it is infrequently used now because of its dulling and behavioural side effects.
Status epilepticus: Phenobarbitone sod. may be injected i.m. or i.v. but response is slow to develop.
It is not effective in absence and atonic seizures.
GARDENAL 30, 60 mg tabs, 20 mg/5 ml syr; LUMINAL 30 mg tab, PHENOBARBITONE SODIUM 200 mg/ml inj.

Primidone A deoxybarbiturate, which is converted by liver to phenobarbitone and phenylethyl malonamide (PEMA). Its antiepileptic activity is mainly due to these active metabolites because t½ of primidone (6–14 hr) is less than that of its active metabolites. About 1/3 primidone is excreted unchanged by kidney. Dose to dose primidone is less potent, but antiepileptic efficacy is similar to phenobarbitone. It is seldom used now in GTCS and partial epilepsy, mainly as an adjuvant to phenytoin or carbamazepine.

Adverse effects are similar to phenobarbitone. In addition, anaemia, leukopenia, psychotic reaction and lymph node enlargement occur rarely.
Dose: Start with 250 mg OD, then 250–500 mg BD, children 10–20 mg/kg/day.
MYSOLINE 250 mg tab.

Ethosuximide

The most prominent action of ethosuximide is suppression of PTZ induced clonic seizures at doses which produce no other discernable effect. It raises seizure threshold but does not modify maximal electroshock seizures or inhibit kindling. Clinically it is effective only in absence seizures.

The primary action appears to be exerted on the thalamocortical system which is involved in the generation of absence seizures. The EEG in absence seizures shows characteristic bilaterally synchronous 3 Hz spike and wave rhythm generated by reciprocal activation and oscillation of impulses between thalamus and neocortex through reverberatory synaptic connections. Thalamic neurones exhibit prominent 'T' (transient) current which is low threshold Ca^{2+} current (due to inward flow of Ca^{2+} through T type Ca^{2+} channels) that acts as the pacemaker and amplifies repetitive spikes. Ethosuximide selectively suppresses T current without affecting other types of Ca^{2+} or Na^+ currents. This correlates well with its selective action in absence seizures.

Ethosuximide is rather slowly absorbed, largely metabolized in liver and excreted in urine. Plasma t½ averages 48 hours in adults and 32 hours in children.

Adverse effects Dose-related side effects are gastrointestinal intolerance, tiredness, mood changes, agitation, headache, drowsiness and inability to concentrate.

Hypersensitivity reactions like rashes, DLE and blood dyscrasias occur rarely.

Use The primary indication for ethosuximide is absence seizures; but valproate is more commonly used. Ethosuximide is also approved for use in myoclonic seizures.

Dose: 20–30 mg/kg/day; ZARONTIN, ETHOSUXIMIDE 250 mg/5 ml syr.

Valproic acid (Sodium valproate)

It is a branched chain aliphatic carboxylic acid with a broad spectrum anticonvulsant action. Valproate is more potent in blocking PTZ seizures than in modifying maximal electroshock, but phenytoin-like suppression of high frequency neuronal firing has been demonstrated at therapeutic concentrations. Establishment of chronic experimental seizure foci and kindling are also prevented. Remarkably, at anticonvulsant doses, valproate produces little sedation or other central effects. Likewise, it is effective in partial seizures and GTCS, as well as in absence, myoclonic and atonic seizures.

Valproate appears to act by multiple mechanisms:

- A phenytoin-like frequency-dependent prolongation of Na^+ channel inactivation.
- Weak attenuation of Ca^{2+} mediated 'T' current (ethosuximide like).
- Enhanced release of inhibitory transmitter GABA due to inhibition of its degradation (by GABA-transaminase) as well as probably by increasing its synthesis from glutamic acid.
- Blockade of excitatory NMDA glutamate receptors.

Pharmacokinetics Oral absorption of valproic acid is good. It is 90% bound to plasma proteins; completely metabolized in liver by oxidation, mainly by CYP2C9 and 2C19 (some metabolites are active) and glucuronide conjugation, and then excreted in urine. Plasma t½ is 10–15 hours; but anticonvulsant effects are longer lasting.

Adverse effects The toxicity of valproate is relatively low.

Anorexia, vomiting, loose motions and heart burn are common but mild. Drowsiness, ataxia and tremor occur at high doses. However, cognitive and behavioural effects are not prominent. Alopecia, curling of hair, weight gain and increased bleeding tendency have been observed. Rashes and thrombocytopenia are infrequent hypersensitivity phenomena.

Asymptomatic rise in serum transaminase is often noted; monitoring of liver function is advised.

A rare but serious adverse effect is fulminant hepatitis; occurs only in children (especially below 3 yr). Those with hepatic disease or who receive other anticonvulsant or hepatotoxic drug are at greater risk.

Administered during pregnancy, it has produced spina bifida and other neural tube defects in the offspring; should be avoided.

Dose: Adults—start with 200 mg TDS, maximum 600 mg TDS; children—15–30 mg/kg/day.

VALPARIN CHRONO 100, 200, 300, 500 mg tabs, 200 mg/5 ml syr; ENCORATE 200, 300, 500 mg regular and controlled release tabs, 200 mg/5 ml syr, 100 mg/ml inj.

VALPROL-CR 200, 300, 500 mg controlled release tab, 200 mg/5 ml syrup, 100 mg/ml inj.

Uses Valproic acid is the drug of choice for absence seizures. Because of good tolerability it is also one of the Ist line drugs for partial seizures and GTCS.

Valproate is the most effective drug for myoclonic seizures. It is also useful in atonic seizures, in which control is often incomplete, but valproate is the drug of choice.

Mania and bipolar illness: Very commonly used as alternative to lithium (*see* Ch. 32). It has also been used for panic attacks.

Valproate has some prophylactic efficacy in migraine.

Interactions

- Valproate increases plasma levels of phenobarbitone and lamotrigine by inhibiting their metabolism.
- It displaces phenytoin from protein binding site and decreases its metabolism; phenytoin toxicity may occur.
- Valproate inhibits hydrolysis of active epoxide metabolite of carbamazepine.
- Concurrent administration of clonazepam and valproate is contraindicated because absence status may be precipitated.

- Foetal abnormalities are more common if valproate and carbamazepine are given concurrently.

Divalproex (Semisodium valproate) It is the coordination compound of valproic acid with sodium valproate (1:1). Oral absorption is slower, but bioavailability is the same. Gastric tolerance may be better. Divalproex is primarily used in mania and bipolar illness, but may be employed in epilepsy in the same way as valproic acid.
DIPROEX, VALANCE, 125, 250, 500 mg tabs; DEPAKOTE 250, 500 mg tabs.

Clonazepam

It is a benzodiazepine with prominent anticonvulsant properties: blocks PTZ seizures at doses which produce mild sedation. Efficacy in modifying maximal electroshock seizures is low and it is singularly ineffective in GTCS. Production of generalized seizures by kindling is suppressed, but local after-discharges persist.

Benzodiazepines potentiate GABA induced Cl^- influx to produce sedation and the same mechanism has been held responsible for the anticonvulsant property, but the locus of action in the brain may be different. At large doses, high frequency discharges are inhibited akin to phenytoin.

Pharmacokinetics Oral absorption of clonazepam is good. It is 85% bound to plasma proteins, completely metabolized in liver and excreted in urine; t½ averages 24 hours confering long duration of action. It does not produce any active metabolite.

Adverse effects The most important side effect of clonazepam is sedation and dullness. This can be minimized by starting at low dose; some tolerance develops with chronic therapy. Lack of concentration, irritability, temper and other behavioural abnormalities may occur in children. Motor disturbances and ataxia are dose-related adverse effects. Salivation and increased respiratory secretions may be complained of.

Uses Clonazepam has been primarily employed in absence seizures. It is also useful as an adjuvant in myoclonic and akinetic epilepsy and may afford some benefit in infantile spasms. However, its value is limited by development of tolerance to the therapeutic effect within six months or so. Clonazepam is also used to suppress acute mania.
Dose: adults 0.5–5 mg TDS, children 0.02–0.2 mg/kg/day.
LONAZEP, CLONAPAX, RIVOTRIL 0.5, 1.0, 2.0 mg tab.

Clobazam It is a 1,5 benzodiazepine (diazepam and others are 1,4 benzodiazepines), found to possess useful antiepileptic efficacy in partial, secondarily generalized tonic-clonic as well as in absence and atonic seizures, including some refractory cases. Sedation and psychomotor retardation are less prominent, but side effect profile is similar to other BZDs. It appears to act by facilitating GABA action.

Oral bioavailability of clobazam is ~90% and elimination t½ 18 hrs, but an active metabolite is produced which has longer t½ (>35 hr). It is generally used as adjuvant to other antiepileptic drugs like carbamazepine or valproate or lamotrigine when monotherapy is inadequate.
Dose: start with 10–20 mg at bedtime, can be increased upto 40 mg/day;
FRISIUM, LOBAZAM, CLOZAM, 5, 10, 20 mg cap.

Diazepam (*see* Ch. 29)

It has anticonvulsant activity in a variety of models, including maximal electroshock, but is not used for long term therapy of epilepsy because of prominent sedative action and rapid development of tolerance to the antiepileptic effect. However, it is a first line drug for emergency control of convulsions, e.g. status epilepticus, tetanus, eclampsia, convulsant drug poisoning, etc.

For this purpose 0.2–0.3 mg/kg slow i.v. injection is followed by small repeated doses as required; maximum 100 mg/day. However, thrombophlebitis of the injected vein is common. Marked fall in BP and respiratory depression can occur; resuscitative measures should be at hand before the drug is injected.

Rectal instillation of diazepam is now the preferred therapy for febrile convulsions in children.

Lorazepam 0.1 mg/kg injected i.v. at a rate not exceeding 2 mg/min is better suited than diazepam in status epilepticus or for emergency control of convulsions of other etiology, because of lesser local thrombophlebitic complications and more sustained action than that of diazepam which is rapidly redistributed.

Lamotrigine A newer anticonvulsant having carbamazepine-like action profile: modifies maximal electroshock and decreases electrically

evoked as well as photic after-discharge duration. Prolongation of Na^+ channel inactivation and suppression of high frequency firing has been demonstrated. In addition, it may directly block voltage sensitive Na^+ channels, thus stabilizing the presynaptic membrane and preventing release of excitatory neurotransmitters, mainly glutamate and aspartate. This may account for its broader-spectrum of antiseizure efficacy. However, it does not antagonize PTZ seizures or block NMDA type of glutamate receptors.

Lamotrigine is a broad-spectrum antiepileptic. Initially found useful as add-on therapy in refractory cases of partial seizures and GTCS, it has now been shown effective as monotherapy as well. It is a first line drug now for these types of epilepsy. Absence and myoclonic or akinetic epilepsy cases have also been successfully treated. Reduction in seizure frequency or complete control is obtained as frequently as with carbamazepine. Some cases of neuralgic pain also respond.

Lamotrigine is well absorbed orally and metabolized completely in liver. Its t½ is 24 hr, but is reduced to ~16 hrs in patients receiving phenytoin, carbamazepine or phenobarbitone. On the contrary valproate inhibits glucuronidation of lamotrigine and doubles its blood level, but valproate levels are lowered by lamotrigine. The dose of lamotrigine should be reduced to half in patients taking valproate. However, metabolism of other anticonvulsants and oral contraceptives is not altered.

Side effects are sleepiness, dizziness, diplopia, ataxia and vomiting. In some comparative trials lamotrigine has been found to be better tolerated than carbamazepine or phenytoin. Negative effect on cognitive function is not reported. Rash may be a severe reaction, particularly in children, requiring withdrawal.

Dose: 50 mg/day initially, increase upto 300 mg/day as needed; not to be used in children.

LAMETEC, LAMITOR, LAMIDUS 25, 50, 100 mg tabs.

Gabapentin This lipophilic GABA derivative crosses to the brain and enhances GABA release, but does not act as agonist at $GABA_A$ receptor. It modifies maximal electroshock as well as inhibits PTZ induced clonic seizures.

Gabapentin and its newer congener pregabalin exert a specific analgesic effect in neuropathic pain. Recently they have been found to modulate a subset of neuronal voltage sensitive Ca^{2+} channels which contain $\alpha2\delta$-1 subunits. It is postulated that decreased entry of Ca^{2+} into the presynaptic neurone through these channels could reduce glutamate release, lowering neuronal excitability. However, whether $\alpha2\delta$-1 Ca^{2+} channel modulation or the GABA enhancing action, or both are responsible for the anticonvulsant/analgesic effect of gabapentin and pregabalin, is not known.

Added to a first line drug, gabapentin reduces seizure frequency in refractory partial seizures with or without generalization. Though gabapentin monotherapy is also effective in SPS and CPS, it is mostly employed as add-on drug. Gabapentin is considered to be a first line drug for neuralgic pain due to diabetic neuropathy and postherpetic neuralgia. It has some prophylactic effect in migraine and is an alternative drug for phobic states.

Gabapentin is well absorbed orally and excreted unchanged in urine with a t½ of 6 hrs. No drug interactions have been noted, and no change in dose of primary antiepileptic drug is required when gabapentin is added. Side effects are mild sedation, tiredness, dizziness, tremor and unsteadiness.

Dose: Start with 300 mg OD, increase to 300–600 mg TDS as required; NEURONTIN 300 mg, 400 mg cap, GABANTIN, GABAPIN 100, 300, 400 mg cap.

Pregabalin This newer congener of gabapentin has similar pharmacodynamic, pharmacokinetic properties and clinical indications in seizure disorders. It has been particularly used for neuropathic pain, such as diabetic neuropathy, postherpetic neuralgia, complex regional pain syndrome (CRPS) and certain other types of chronic pain. Sedative side effects are claimed to be less prominent, but poor concentration, rashes and allergic reactions have been complained.

Dose: 75–150 mg BD, max 600 mg/day

PREGABA, NEUGABA, TRUEGABA 75, 150 mg caps. PREGALIN-X-SR 75 mg SR tab.

Levetiracetam A unique anticonvulsant which suppresses kindled seizures, but is ineffective against maximal electroshock or PTZ. Clinical efficacy has been demonstrated both as adjuvant medication as well as monotherapy in refractory partial seizures with or without generalization. The mechanism of action is not known. None of the major anticonvulsant mechanisms appear to be applicable. However, levetiracetam binds selectively to a synaptic vesicular protein 'SV_2A', and this may alter release of glutamate and/or GABA across the synapse, thereby exerting anti-seizure effect (*see* Fig. 30.1). It also inhibits N-type calcium channels which may affect intracellular Ca^{2+} release.

Levetiracetam is completely absorbed orally, partly hydrolysed, but mainly excreted unchanged in urine with a t½ of 6–8 hours. It is neither oxidized by CYP enzymes nor induces or inhibits them. As such, it is free of drug interactions. Few side effects like sleepiness, dizziness, weakness and rarely behavioural changes are reported. Driving may be impaired. Because of good tolerability, levetiracetam is being increasingly used in partial seizures, and myoclonic epilepsy, mainly as add-on drug. For GTCS and absence seizures it is a second-line adjunctive drug. It is not approved for use in children below 4 years.

Dose: 0.5 g BD, increase upto 1.0 g BD (max 3 g/day), children 4-15 year *10–30 mg/kg/day.*

LEVOREXA, TORLEVA, LEVTAM 0.25, 0.5, 1.0 g tabs.

Topiramate This weak carbonic anhydrase inhibitor has broad spectrum anticonvulsant activity in maximal electroshock, PTZ induced clonic seizures and in kindling model. It appears to act by multiple mechanisms, *viz.* phenytoin like prolongation of Na^+ channel inactivation, suppression of repetitive neuronal firing, GABA potentiation by a postsynaptic effect, antagonism of certain glutamate receptors and neuronal hyperpolarization through K^+ channels.

Topiramate is indicated as monotherapy as well as for supplementing primary antiepileptic drug in refractory SPS, CPS and GTCS. Promising results have been obtained in myoclonic epilepsy and as add-on drug in absence seizures. Topiramate is readily absorbed orally and mainly excreted unchanged in urine with an average t½ of 24 hours. Adverse effects are impairment of attention, sedation, ataxia, word finding difficulties, poor memory, weight loss, paresthesias and renal stones.

Topiramate has been approved for prophylaxis of migraine; may be used when β blockers/ other prophylactics are contraindicated or are not effective.

Dose: Initially 25 mg OD or BD; increase weekly upto 100–200 mg BD as required.

TOPEX, EPITOP, TOPAMATE, NEXTOP 25, 50, 100 mg tabs.

Zonisamide Another newer anticonvulsant with weak carbonic anhydrase inhibitory action that modifies maximal electroshock seizures and inhibits kindled seizures, but does not antagonize PTZ. Prolongation of Na^+ channel inactivation resulting in suppression of repetitive neuronal firing has been observed. It has also been found to suppress T-type of Ca^{2+} currents in certain neurones.

Zonisamide is well absorbed orally and mainly excreted unchanged in urine with a t½ of > 60 hours. A small fraction is oxidized and conjugated with glucuronic acid. It is indicated both as monotherapy and as add-on drug in refractory partial seizures with or without generalization, and has been tried in absence seizures. Side effects are somnolence, dizziness, headache, irritability and anorexia. Metabolic acidosis and renal stones can occur. Zonisamide is to be avoided in patients sensitive to sulfonamides. No drug interactions have been observed.

Dose: 25–100 mg BD. Not to be given to children.

ZONISEP, ZONICARE, ZONIT 50, 100 mg cap.

Lacosamide This recently introduced antiseizure drug is indicated in adults only for add-on therapy of partial seizures with or without generalization. It acts by enhancing Na^+ channel inactivation and suppressing repetitive firing of neurones. Lacosamide is metabolized by CYP2C19 and excreted in urine with t½ ~ 12 hours. No alteration in dose of companion antiepileptic drug is needed, because it neither

induces nor inhibits drug metabolizing enzymes. Adverse effects are ataxia, vertigo, diplopia, tremor, depression and cardiac arrhythmia.
Dose: Initially 50 mg BD, increase upto 200 mg BD.
LACASA 50, 100, 150, 200 mg tabs, LACOSAM, LACOPSY 50, 100 mg tab.

Tiagabine This newer anticonvulsant potentiates GABA mediated neuronal inhibition by blocking GABA transporter GAT-1 which removes synaptically released GABA into neurones and glial cells (*see* Fig. 30.1). Kindled seizures are suppressed with less marked effect on maximal electroshock. Currently it is approved only for add-on therapy of partial seizures with or without secondary generalization, when not adequately controlled by standard antiepileptic drugs alone. Side effects are mild sedation, nervousness, asthenia, amnesia, dermatitis and abdominal pain.

Tiagabine is well absorbed, partly metabolized and excreted mainly in faeces. The t½ is 6 hours.
Dose: 4–16 mg TDS

TIGATEL 2,4,12,16 mg tabs.

Vigabatrin (γ vinyl GABA) It is an inhibitor of GABA-transaminase, the enzyme which degrades GABA. Anticonvulsant action may be due to increase in synaptic GABA concentration. It is effective in many patients with refractory epilepsy, especially CPS with or without generalization, and in infantile spasms. It is approved only for adjuvant medication.

Visual field contraction, alteration of colour vision, paresthesias and production of behavioural changes, depression or psychosis has restricted its use to only as a reserve drug.
Dose: Adults 0.5–1.5 g BD, for infantile spasms 50–150 mg/kg/day in divided doses.
SABNIL 0.5 g tab.

TREATMENT OF EPILEPSIES

Antiepileptic drugs suppress seizures, but do not cure the disorder; the disease may fadeout though after years of successful control. The aim of drugs is to control and totally prevent all seizure activity at an acceptable level of side effects. With the currently available drugs, this can be achieved in about half of the patients. Another 20–30% attain partial control, while the rest remain refractory. The cause of epilepsy should be searched in the patient; if found and treatable, an attempt to remove it should be made. Some general principles of symptomatic treatment with antiepileptic drugs are:

1. Choice of drug (Table 30.1) and dose is according to the seizure type(s) and need of the individual patient. There is a trend to prefer the newer antiepileptic drugs, because they are less sedating, produce few side effects and drug interactions are insignificant. However, the newer drugs are less well studied.
2. Initiate treatment early, because each seizure episode increases the propensity to further attacks, probably by a process akin to kindling. Start with a single drug, preferably at low dose—gradually increase dose till full control of seizures or side effects appear. If full control is not obtained at maximum tolerated dose of one drug, substitute another drug. For changing one antiepileptic drug to another, dose of the first drug should be gradually reduced and that of the second drug gradually increased till the second drug regimen is fully established.
3. Use combinations only when all reasonable monotherapy fails. Combining drugs with different mechanisms of action, such as those which prolong Na^+ channel inactivation with those facilitating GABA appears more appropriate. Pharmacokinetic interactions among anticonvulsants are common; dose adjustment guided by therapeutic drug monitoring is warranted.
4. When therapy with two drugs fails to achieve adequate control, addition of a third drug generally does not improve the response, unless the patient suffers from more than one seizure types.
5. A single tonic-clonic seizure in a subject with no predisposing factor for development of epilepsy (history of head injury, family history of epilepsy, neurological abnormality, abnormal EEG or brain scan) may not merit initiation of antiepileptic therapy.
6. Therapeutic regimen should be as simple as possible. A seizure diary should be maintained.
7. All drug withdrawals should be gradual (except in case of toxicity). Abrupt stoppage of therapy without introducing another effective drug can precipitate status epilepticus.

Table 30.1: Choice of antiseizure drugs

Type of seizure	*First line drugs*	*Alternative/Add-on drugs*	*Reserve/Add-on drugs*
1. *Partial seizures* (SPS, CPS) with or without generalization	Carbamazepine, Lamotrigine, Valproate, Oxcarbazepine	Levetiracetam, Clobazam, Phenytoin Gabapentin, Topiramate	Lacosamide, Phenobarbitone, Zonisamide, Tiagabine
2. *Generalized seizures* • Tonic-clonic	Valproate, Lamotrigine, Carbamazepine	Clobazam, Oxcarbazepine Phenytoin	Levetiracetam, Topiramate Phenobarbitone
• Absence	Valproate, Ethosuximide	Lamotrigine, Clobazam, Clonazepam	Levetiracetam Topiramate Zonisamide
• Myoclonic	Valproate	Topiramate Levetiracetam	Clobazam, Clonazepam
• Atonic	Valproate	Lamotrigine	Topiramate Clonazepam
3. *Febrile seizures*	Diazepam (rectal)	–	–
4. *Status epilepticus*	Lorazepam (i.v.) Diazepam (i.v.)	Fosphenytoin (i.v.)	Phenobarbitone (i.m.)

Prolonged therapy (may be life-long, or at least 3 years after the last seizure) is needed. Stoppage of therapy may be attempted in selected cases. Features favourable to withdrawal are:
- childhood epilepsy,
- absence of family history,
- primary generalized tonic-clonic epilepsy,
- recent onset at start of treatment,
- absence of cerebral disorder and normal inter-seizure EEG.

Even with these features recurrence rates of 12–40% have been reported.

8. Dose regulation may be facilitated by monitoring of steadystate plasma drug levels. Monitoring is useful because:
   (a) Therapeutic range of concentrations has been defined for many drugs.
   (b) There is marked individual variation in the plasma concentration attained with the same daily dose.
   (c) Compliance among epileptic patients is often poor.

Plasma levels given in Table 30.2 are to serve as rough guides.

9. When women on antiepileptic therapy conceive, antiepileptic drugs should not be stopped. Though, most antiseizure drugs increase the incidence of birth defects, discontinuation of therapy carries a high risk of status epilepticus. Fits occurring during pregnancy themselves increase birth defects and may cause mental retardation in the offspring (anoxia occurs during seizures). An attempt to reduce the dose of drugs should be cautiously made. It may be advisable to substitute valproate by another drug.

   Prophylactic folic acid supplementation in 2nd and 3rd trimester along with vit. K in the last month of pregnancy is recommended, particularly in women receiving antiepileptic drugs to minimise neural tube defects and bleeding disorder respectively in the neonate.

10. A seizure episode does not require any drug treatment. During an attack of tonic-clonic seizures, the first priority is to prevent injury due to fall or biting. The patient should be put in prone or lateral position. The head should be turned and patency of airway ensured. The attack usually passes off in 2–3 min, but the patient may not be roadworthy for a couple of hours.

Table 30.2: Plasma half life, therapeutic and toxic plasma concentration range of some important antiepileptic drugs

Drug	Half life (hr)	Plasma concentration (μg/ml)	
		Therapeutic	Toxic
Phenobarbitone	80–120	10–30	> 30 mild, > 60 severe
Phenytoin	12–36	10–20	> 20 mild, > 35 severe
Carbamazepine	10–40	5–10	> 12
Ethosuximide	30–50	50–100*	>200
Valproate	10–15	40–100*	–
Clonazepam	20–40	0.01–0.1*	–

* Poorly correlated with response.

Febrile convulsions Some children, especially under 5 years age, develop convulsions during fever. Seizures may recur every time with fever and few may become chronic epileptics. Every attempt should be made to see that they do not develop fever, but when they do, temperature should not be allowed to rise by using paracetamol and external cooling.

The best treatment of febrile convulsions is rectal diazepam 0.5 mg/kg given at the onset of convulsions. The i.v. preparation can be used where the rectal formulation is not available. A rectal solution (5 mg in 2.5 ml) in tubes is available in the UK and some other countries. Seizures generally stop in 5 min; if not, another dose may be given. The drug is repeated 12 hourly for 4 doses. If fever is prolonged a gap of 24–48 hr is given before starting next series of doses.

In recurrent cases or those at particular risk of developing epilepsy—intermittent prophylaxis with diazepam (oral or rectal) started at the onset of fever is recommended. Chronic prophylaxis with phenobarbitone advocated earlier has been abandoned, because of poor efficacy and behavioural side effects.

Infantile spasms (hypsarrhythmia) Therapy of this condition is unsatisfactory, antiepileptic drugs are generally useless. Corticosteroids afford symptomatic relief but cannot be used for long-term due to adverse effects. Clonazepam, valproate and vigabatrin may afford some relief.

Status epilepticus When seizure activity occurs for >30 min, or two or more seizures occur without recovery of consciousness, the condition is called *status epilepticus*. Recurrent tonic-clonic convulsions without recovery of consciousness in between is an emergency; fits have to be controlled as quickly as possible to prevent death and permanent brain damage.

- The first priority is to maintain patient airway. This is followed by 20–50 ml of 50% dextrose injected i.v. to correct hypoglycaemia, in case that is responsible for the seizures.
- *Lorazepam* 4 mg (0.1 mg/kg in children) injected i.v. at the rate of 2 mg/min, repeated once after 10 min if required, is the first choice drug now. It is effective in 75–90% cases and produces a more sustained anticonvulsant effect (lasting 6–12 hours) than diazepam, because of lower lipid solubility and slower redistribution. Moreover, thrombophlebitis of injected vein is less likely with lorazepam.
- *Diazepam* 10 mg (0.2–0.3 mg/kg) injected i.v. at 2 mg/min, repeated once after 10 min if required, has been the standard therapy till recently. However, its anticonvulsant effect starts fading after 20 min, and many supplemental doses may be required. It is also more damaging to the injected vein.
- *Fosphenytoin* 100–150 mg/min i.v. infusion to a maximum of 1000 mg (15–20 mg/kg) under continuous ECG monitoring is a slower acting drug which should be given

subsequently irrespective of response to lorazepam. This may suppress seizures that have not responded to lorazepam, and pave the way for long-term seizure treatment.

- *Phenytoin sod.* It should be used only when fosphenytoin is not available, because it can be injected only at the rate of 25–50 mg/min and causes more marked local vascular complications.
- *Phenobarbitone sod.* 50–100 mg/min i.v. injection to a maximum of 10 mg/kg is another slower acting drug which can be used as alternative to fosphenytoin or when the latter is ineffective. It is also employed to maintain seizure free state over short term before definitive oral therapy is instituted.
- Refractory cases who fail to respond to lorazepam and fosphenytoin within 40 min of seizure onset may be treated with i.v. midazolam/propofol/thiopentone anaesthesia, with or without curarization and full intensive care.
- General measures, including maintenance of airway (intubation if required), oxygenation, fluid and electrolyte balance, BP, normal cardiac rhythm, euglycaemia and care of the unconscious must be taken.

PROBLEM DIRECTED STUDY

30.1 A young lady aged 25 years comes for consultation along with her husband for having suffered two episodes of fits lasting 2–3 min each over the past one week. Just before each fit, she experienced flickering in her right arm. Description of the fit given by the husband corresponds to tonic-clonic seizures. She gave the history of having met a car accident about one year back in which she received head injury. There is no family history of epilepsy. General physical and neurological examination revealed no abnormality. Investigations, including EEG and MRI scan of the brain, were ordered.

(a) What instructions should be given to the husband regarding care to be taken, if and when, the next fit occurs?

(b) Should antiepileptic drug/drugs be started right away, or therapy be delayed till findings of the investigations become available or till more fits occur?

(c) In case antiseizure therapy has to be started right away, should a single drug or a combination of drugs be given? Which drug(s) would be the most appropriate for this patient?

(see Appendix-1 for solution)