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Confidential

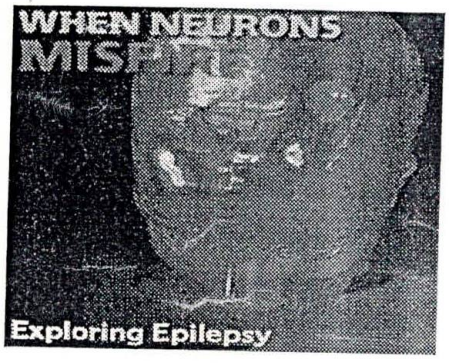
TRAINING MANUAL

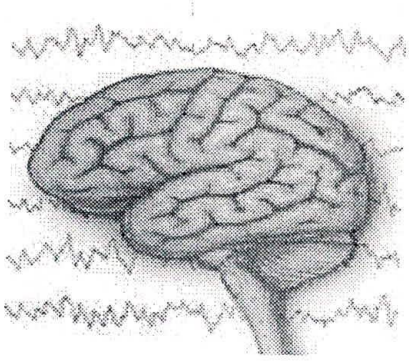
Neurology

Cipla protec

Module 1 - Epilepsy

Definition





Epilepsy is defined as a chronic neurological disorder characterized by recurrent seizures. Seizure or convulsion is a surge in the brain's electrical activity (abnormal and excessive), which manifests as a disturbance in body movements or consciousness or behavior.

Types of Epilepsy

Classifying epilepsies is a difficult task. It is useful for neurologists to group epilepsies into different types, but the reality is more complex. Each epilepsy is a malfunction of a particular area of the brain and is different for each patient.

- Epilepsy
  - Partial epilepsy
    - a. Simple partial
    - b. Complex partial
    - c. Partial with secondary generalization
  - Generalized epilepsy
    - a. Generalized tonic clonic
    - b. Absence
    - c. Atonic
    - d. Myoclonic
    - e. Tonic
    - f. Clonic
  - Unclassified
    - a. Neonatal
    - b. Infantile

Partial Epilepsy

These are epilepsies with a clearly defined focal area within the brain.

Simple partial seizures

The person is fully conscious and may exhibit symptoms depending upon the area of brain involved, like disturbances in the motor cortex can cause motor disturbances in the face, limbs or other parts of the body; those in the sensory regions of brain can produce auditory, olfactory or visual hallucinations.

Complex partial seizures

Complex partial seizures are one of the most common forms of seizure. They always involve impairment of consciousness. The attack may begin as a partial seizure, which may act as an 'aura' that warns the patient of the impending seizure. During the seizure, there may be altered behavior or automatisms, in which the patient engages in repetitive movements such as lip-smacking or chewing, facial grimacing, plucking at clothing, or wanders aimlessly or even undresses.

Partial with secondary generalization

The seizure starts as partial seizure (localized to one part of brain), but gradually spreads to both sides of brain.

Generalized Epilepsy

Generalized epilepsies are those, which have no defined focal area within the brain; as a result they have generalized symptoms as the whole brain becomes affected. The most common types of generalized seizures are -

Clinical features of the main types of generalized epileptic seizures

Tonic-clonic seizures (Grand mal)	• The patient falls suddenly to the ground. There is continuous forceful contraction and relaxation of muscles • Tonic phase: stiffness (the tongue may be bitten), increased heart rate and blood pressure, sweating • Clonic phase: clonic movements, labored breathing, excessive salivation. • Deep sleep often follows the attack.
Absence seizures (Petit mal)	• Most common in children. • Short intervals of loss of consciousness; look of blankness and staring. • Last only a few seconds and may not be recognized until other problems (e.g. learning difficulties) arise
Myoclonic seizures	• Sudden, brief muscle contractions (jerky movements) occurring singly or in clusters, involve peripheral parts of limbs
Atonic seizures	• Sudden loss of body tone followed by falling to the ground.(drop attack) • Severe injury often occurs.
Tonic seizures	• More contractions of muscles
Clonic seizures	• More relaxation of muscles

Unclassified Epilepsy

This, of course, is the grouping for epilepsies, which do not fit the classification.

- Neonatal seizures: Brief episodes of eye deviation, eye blinking, repetitive movements of arms, legs
- Infantile seizures: Sudden jerky movements of different body parts, like sudden flexion of neck etc.

Febrile fits: A common trigger factor for seizures in young children (up to 5 years of age) is high fever (38°C and above). About 4-5% of children have 'febrile seizures' or 'febrile convulsions

Epilepsy Syndromes

Syndrome consists of cluster of symptoms.

Lennox-Gastaut syndrome:

- Age group 1-8 years
- Multiple types of seizures
- Mental retardation

West syndrome (Infantile spasm)

- Age group <1 year
- Multiple types of seizures

Juvenile myoclonic epilepsy

- Appears in early adolescence
- Predominantly myoclonic seizures, GTC or absence are also seen

Causes of Epilepsy

Seizures are a result of a shift in the normal balance of excitation and inhibition within the Central Nervous System.

- Brain injury to the fetus during pregnancy
- Birth trauma, such as a lack of oxygen
- Poisoning from substance abuse or environmental contaminants, eg lead poisoning
- Aftermath of infection, e.g. meningitis
- Head trauma, e.g. car accident
- Metabolic disorders- e.g. hypoglycemia, hepatic failure
- Brain tumour or stroke
- Genetic defect
- Idiopathic: unknown cause

Basic Pathophysiology

Initiation Of Seizure

A] Sodium channels:

Action potential burst

Open of Na+ voltage dependent channels

Excess Na+ entry, K+ exit across the cell

Depolarization of cell membrane

B] Other channels thought to be involved in the development of seizures:

1. High voltage calcium channels
2. Potassium channels

Spread Of Seizure

The abnormal discharge may remain localized around the epileptic focus, or spread to adjacent areas or generalize throughout the brain via cortical or subcortical routes including callosal and thalamocortical pathways. Spread of discharge occur via

- Excess of K+ outside the cell - depolarizes the neighbouring neurons
- Accumulation of Ca++ in presynaptic terminal lead to release of glutamate.

Neurotransmitters

Gamma-amino-butyric Acid (GABA)

GABA is the most important known inhibitory neurotransmitter. Experiments at a cellular level have indicated that decreased GABA inhibition can result in electrical activity typical of epilepsy in experimental foci. It has also been shown that some people with epilepsy have low levels of GABA in their brains, and that drugs that increase the concentration of GABA in the brain can control some types of epilepsy.

Glutamate

There is some evidence that excessive activity or increased sensitivity in the excitatory amino acid neurotransmitter systems may be involved in the genesis of epileptic seizures. Substances to block the release of the amino acid neurotransmitters, glutamate, have been another focus of research on drug treatments for epilepsy.

Summary of Pathogenesis of Epilepsy

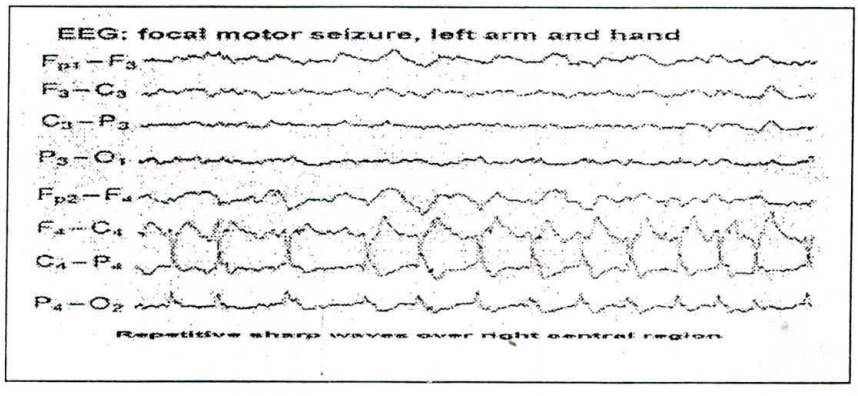
1. Excess Na+ entry
2. Increase Glutamate
3. Decrease GABA

Electro-encephalography (EEG)

An electroencephalograph (EEG) measures the electrical activity occurring in the cerebral cortex.

A set of electrodes is attached to the scalp. The electrodes pick up the electrical discharges in the cortex, amplify and then record them. The whole procedure usually takes about 30 to 40 minutes.

EEG Recordings



EEG is useful to -

- Confirm the clinical diagnosis of epilepsy
- Support classification of partial-onset or generalized seizures
- Monitoring drug therapy
- Discontinuing drug therapy

Clinical Diagnosis
Classification of Types of epilepsy
. Monitoring Drug Therapy
+ discontinuing drug Therapy

Management of Epilepsy

Therapy for a patient with a seizure disorder is almost always multimodal.

1. *Treatment of underlying conditions*

- Metabolic disturbance such as an abnormality of serum electrolytes or glucose, then treatment is aimed at reversing the metabolic problem and preventing its recurrence.

- Seizures caused by a structural CNS lesion such as a brain tumor or blood vessels abnormality or brain abscess may not recur after appropriate treatment of the underlying lesion.

2. *Avoidance of precipitating factors*

- Precipitants such as stress, sleep deprivations, exposure to toxic substances and certain medications, should be avoided.

3. *Anti-epileptic drug therapy (AED)*

Goals of anti-epileptic drug therapy

- To prevent the occurrence of seizures
- To help the patient accept his / her disease state & improve the quality of life

Antiepileptic Drugs

Conventional Antiepileptic Drugs

Carbamazepine, phenytoin, valproic acid, phenobarbitone

Newer Antiepileptic Drugs

Lamotrigine, topiramate, oxcarbazepine, gabapentine, clobazam, clonazepam, vigabatrin

The limitations of the conventional anti-epileptic drugs

- These drugs are not effective in the treatment of all types of epilepsy and hence are said to have narrow therapeutic indices.
- Despite their efficacy, the agents fail to produce complete seizure control in about 30% of treated cases

- Short half-lives pose problems for some AEDS since it may be difficult to maintain a stable concentration of the drug in the blood over 24 hours which is essential for the efficacy of some AEDs e.g. carbamazepine. Due to this, the increase in number of daily doses would however, adversely affect compliance

- Enzyme induction and inhibition

  - Enzyme Inducers: Carbamazepine, phenytoin and phenobarbitone induce the cytochrome P450 isoenzymes hence, the concomitant drugs are metabolised faster.

  - Enzyme Inhibitor: Sodium valproate is an enzyme inhibitor hence, concomitant drugs are slowly metabolised and remain in circulation for long time causing side-effects.

- Close monitoring of plasma concentrations is generally necessary.

- The pharmacokinetics of Phenytoin are non-linear (serum-concentration increases disproportionately to an increase in the dose) and carbamazepine induces its own metabolism (auto induction).

- Adverse effects caused by the traditional AEDs limits their use in many situations.

5. *Limitations of conventional antiepileptic agents*

Aed	Limitations
Carbamazepine	• Neurological: Carbamazepine affects cognition, sedation, ataxia, vertigo • Systemic: Aplastic anemia, bone marrow suppression, neutropenia • Allergic rash • Drug-drug interactions • Pharmacokinetic disadvantages, like enzyme induction and auto induction • 3-4 times daily dosing due to autoinduction, decreased patient compliance

Phenytoin	• Long term phenytoin therapy can cause gum hyperplasia, hirsutism (hairy face), acne, hypertrophy of subcutaneous facial tissue • Osteoporosis • Teratogenic – 30% of infants exposed to phenytoin in utero can develop severe anomalies such as cleft lip, cleft palate, microcephaly, heart defect known as 'fetal anticonvulsant syndrome' • Drug-drug interactions due to interference with cytochrome P450 liver enzymes. Increases clearance of oral contraceptives and can lead to oral contraceptive failure
Phenobarbital / Phenobarbitone	• Vitamin K depletion in foetus leading to bleeding disorders • Hyperactivity in children • Sedation in adults, megaloblastic anaemia, osteopenia • Increases chances of developing tolerance due to sedation • Doubled risk of congenital malformations in foetus
Sodium Valproate	• GI side-effects • Transient Alopecia • Hepatotoxicity • 2% of children develop spina bifida / before birth exposed to valproic acid • Weight gain
Clobazam	• Initially it is highly effective, but within a few days to few weeks efficacy decreases in approximately one third of patients • Cannot be used for long term therapy • Increased risk of breakthrough seizures
Clonazepam	• Patients develop tolerance to therapeutic effects of benzodiazepines • Not good choices for long term treatment • Increase risk of seizure recurrence • Sudden withdrawal leads to status epilepticus

SELF-ASSESSMENT 1

1) Define

Epilepsy _____

_____

_____

Seizure _____

_____

_____

2) Types of partial seizures are

a) _____

b) _____

c) _____

3) Match the following

Absence seizure	Patient falls down on the ground
GTC	Staring at one point
Atonic seizure	Brief contraction at peripheral parts of limbs
Myoclonic seizure	Forceful contraction or relaxation of muscles throughout the body

4) Name the 3 important reasons in pathogenesis of epilepsy

a) _____

b) _____

c) _____

5) Match the following

Phenobarbitone	Allergic rash
Phenytoin	Weight gain
Sodium valproate	Cleft lip and cleft palate
Carbamazepine	Osteopenia

Module 2 - Antiepileptics drugs

Valtec / Valtec CR

Brand Name : Valtec / Valtec CR

Molecule : Sodium Valproate

Class : Conventional anti-epileptic drug

Mechanism of action : Reduces Na+ entry, improves GABA synthesis & release

Valtec is our brand of sodium valproate. Valtec is available as Valtec 200, Valtec 300, Valtec 500 containing sodium valproate 200 mg, 300 mg and 500 mg respectively.

Valtec CR is our brand of controlled release sodium valproate. Valtec CR is combination of sodium valproate and valproic acid. Valtec CR is available as Valtec CR 200, Valtec CR 300 and Valtec CR 500.

Advantages of Valtec CR

Sr. No.	Feature	Benefit
1.	Valtec CR is a combination of sodium valproate plus valproic acid	Results in greater amount of valproic acid to be available for action
2.	Sustained release preparation	Ensures sustained concentrations of valproic acid. No wide fluctuations
3.	Long elimination half-life	Convenient daily dosing hence better patient compliance
4.	Sustained release of valproic acid in GI tract	Less gastrointestinal side effects hence better tolerability profile

Indications

I. Epilepsy

Valtec/Valtec CR is indicated as monotherapy and add-on therapy in adults and children for the treatment of all types of seizures.

II. Bipolar disorder

III. Migraine Prophylaxis

Dosage

In Epilepsy

Monotherapy (initial therapy)

Patients should initiate therapy at 10 to 15mg/kg/day. The dose should be increased by 5 to 10mg/kg/week to achieve optimal clinical response.

No recommendation regarding the safety of sodium valproate for use at doses above 60mg/kg/day can be made.

Conversion to monotherapy

Patients should initiate therapy at 10 to 15mg/kg/day. The dosage should be increased by 5 to 10mg/kg/week to achieve optimal clinical response. No recommendation regarding the safety of sodium valproate for use at dose above 60mg/kg/day can be made.

If satisfactory clinical response has not been achieved, plasma levels should be measured to determine whether or not they are in the usually accepted therapeutic range (50-100mcg/mL).

Concomitant anti-epileptic drug (AED) dosage can ordinarily be reduced by approximately 25% every 2 weeks. This reduction may be started at initiation of Valtec therapy, or delayed by 1 or 2 weeks if there is concern that seizures are likely to occur with a reduction.

Adjunctive therapy

Valtec/Valtec CR may be added to the patient's regimen at a dosage of 10 to 15 mg/kg/day. The dosage may be increased by 5 to 10 mg/kg/week to achieve optimal clinical response. If the total daily dose exceeds 250 mg, it should be given in divided doses.

Migraine

The recommended starting dose is 250mg twice daily. Some patients may benefit from doses up to 1000mg/day.

Highlights

- Valtec/Valtec CR is recognized as a broad-spectrum anti-epileptic drug highly effective against all types of seizures.
- Valtec/Valtec CR is the only conventional drug used in absence and myoclonic seizures.
- Synergism between Lamotrigine & Valproate

  Lamotrigine and valproate show synergism in clinical studies. This is due to multiple reasons

  - Different mechanisms of action
  - Well documented combination in epilepsy
  - Less drug interactions
  - Greater efficacy
  - Minimal side effects
  - Cost effective
- Effective in childhood epilepsy
- less incidence of allergy rash than carbamazepine

Lametec

Brand Name	:	Lametec
Molecule	:	Lamotrigine
Class	:	Newer antiepileptic drug
Mechanism of action	:	Reduces excess Na+ entry, reduces glutamate release

Lametec is out brand of lamotrigine and available as Lametec 5 DT containing lamotrigine 5 mg in dispersible tablet form, Lametec 25 containing lamotrigine 25 mg, Lametec 50 containing 50 mg lamotrigine and Lametec 100 containing 100 mg lamotrigine

Indications

- As add-on therapy in the treatment of all types of epilepsy. In UK it is recommended as a monotherapy in the treatment of epilepsy
- As add-on therapy in Lennox-Gastaut Syndrome
- Neuralgias
- Childhood epilepsy

Dosage

Dose recommendations for Lametec (mg/day) for adults (over 16 years)

AEDs	Weeks 1 and 2 Maintenance Dose	Week 3 and 4	Usual
With carbamazepine, Phenytoin, Phenobarbitone with or without sodium valproate	50 mg/day (once a day)	100 mg/day (two divided doses)	300-500 mg/day (two divided). To achieve maintenance, doses may be increased by 100 mg/day every 1 or 2 weeks
Valproic acid with or without other AEDs	25mg every other day	25mg (once a day)	100-400mg/day (two divided doses). To achieve maintenance, doses may be increased by 25-50 mg/day every 1or 2 weeks.

Below 16 years

Anti-epilepti drugs (AEDs)	Weeks 1 and 2	Week 3 and 4	Maintenance Dose
With carbamazapine, phenytoin, phenobarbitone with or without sodium valproate	0.6mg/kg/day in two divided doses	1.2mg/kg/day in two divided doses, rounded down to the nearest 5 mg	5 to 15mg/kg/day (maximum 400 mg/ day in two divided doses). Increments every 1 to 2 weeks as follows: Calculate 1.2mg/kg/day round this amount down to the nearest 5mg and add this amount to the previously administered daily dose.
Valproic acid with or without other AEDs	0.15mg/kg.day in one or two divided doses, rounded down to the nearest 5mg.	0.3mg/kg/day in one or two divided doses, rounded down to the nearest 5mg.	1 to 5mg/kg/day (maximum 200 mg/day in one or two divided doses). Increments every 1 to 2 weeks as follows: calculate 0.3 mg/kg/day, round this amount down to the nearest 5 mgand add this amount to the previously administered daily dose.

Highlights

Pharmacokinetics

- 98% oral bioavailability
- Linear pharmacokinetics in adults as well as children
- No enzyme inducing or inhibiting properties
- Routine therapeutic monitoring of plasma concentrations not required
- Convenient dosing due to long elimination half life

Efficacy & Tolerability

- Effective against all types of seizures and syndromes
- Approved by US FDA as add-on therapy for partial and secondarily generalised tonic-clonic seizures
- In UK approved additionally as monotherapy
- Highly effective against a wide range of seizures in children and in Lennox Gastaut Syndrome
- No interaction with oral contraceptive drugs
- Lower withdrawal rates
- As effective as Carbamazepine but displays superior tolerability profile
- Treatment withdrawal due to CNS related effects was lower in patients receiving lamotrigine (2.5%) as compared to CBZ (7.7%) or PHE (7.4%)
- Lametec is ideal antiepileptic drug for use in epilepsy in females.
  - Does not alter steroid hormones, hence less menstrual abnormalities
  - Does not interfere with effectiveness of hormonal contraceptives
  - Does not lead to appreciable weight gain, hair loss or gum disorders
  - Prevents development of PCOS symptoms in epilepsy patients & improves fertility rates in patients with epilepsy & PCOS.
  - Less chances of teratogenicity

Topamate 25 - 40/-
Topamate 100 = 138/-

Topamate

(Topex old name)

Brand Name	:	Topamate
Molecule	:	Topiramate
Class	:	Newer antiepileptic drug
Mechanism of action	:	Reduces excess Na entry, blocks glutamate receptors and increases release of GABA

TOPAZ
Topiramate

Topamate is our brand of topiramate. Available as Topamate 25, Topamate 100 containing topiramate 25 mg and 100 mg respectively

Indications

- As adjunctive treatment for adults with partial onset and primary generalized tonic-clonic seizures

Dosage

Initiate therapy with Topamate (Topiramate) at 25-50mg/day followed by titration to an effective dose in increments of 25-50mg/week. The recommended total daily dose of Topamate (Topiramate) as adjunctive therapy is 400mg/day in two divided doses. Daily doses above 1600 mg have not been studied. The recommended titration rate for Topiramate is:

* Start with PM Dose 25-50mg
1st week
2ND AM PM

	AM Dose	PM Dose
Week 1	None	25-50 mg
Week 2	25-50 mg	25-50 mg
Week 3	25-50 mg	50-100 mg
Week 4	50-100 mg	50-100 mg
Week 5	50-100 mg	100-150 mg
Week 6	100-150 mg	100-150 mg
Week 7	100-150 mg	150-200 mg
Week 8	150-200 mg	150-200 mg

BN
Increment 25-50mg from PM dose / week

(8)
Paediatric patient :-
5 - 9 mg/kg/day in two divided dose

Highlights

- Multidimensional approach to seizure control attributed to multiple mechanisms of action
- Blocks Na+ channels, enhances GABA activity, antagonizes glutamate receptors
- Topamate has a high neuroprotective index. Due to multiple modes of action, Topamate effectively controls imbalance of ions and chemicals in epilepsy and protects against the neuronal damage secondary to ion-chemical imbalance and antioxidants.
- Wide spectrum of antiseizure activity hence effective against all types of seizures and syndromes in adults as well as children
- Linear kinetics in adults as well as children
- Routine monitoring of plasma concentrations not required
- Convenient twice daily dosing due to long elimination half-life of 21 hours
- Favourable safety and tolerability profile
- Topiramate causes weight loss unlike some conventional antiepileptic drugs like Sodium Valproate

Topiramate Doesnot cause ↓ weight loss
Sodium valproate weight gains.

Oxcarb

Brand Name	:	Oxcarb
Molecule	:	Oxcarbazepine
Class	:	Newer antiepileptic drug
Mechanism of action	:	Blocks voltage-sensitive sodium channels, increases potassium conductance, modulates high-voltage activated calcium channel

Oxcarb is our brand of oxcarbazepine and available as Oxcarb 150, Oxcarb 300, Oxcarb 600 containing oxcarbazepine 150 mg, 300 mg and 600 mg respectively

Pharmacokinetics

Superior Pharmacokinetics Over Carbamazepine

OXCARBAZEPINE ——— MHD
REDUCTION

- No autoinduction
- Less enzyme induction (Cyt P 450) – Less drug-drug interactions
- Less side effects

CARBAMAZEPINE ——— 10, 11 EPOXIDE
OXIDATION

- Autoinduction
- Enzyme induction (Cyt P 450) – More drug- drug interactions
- More side effects

Indications

1. Epilepsy

Oxcarbazepine is indicated for use as monotherapy or adjunctive therapy in the treatment of partial seizures in adults with epilepsy and as adjunctive therapy in the treatment of partial seizures in children ages 4-16 with epilepsy. In clinical studies, Oxcarbazepine has been proven to control partial and generalized tonic clonic seizures.

2. ***Trigeminal neuralgia***

Oxcarbazepine may be a useful alternative to carbamazepine in the management of trigeminal neuralgia. In clinical studies, Oxcarbazepine appears to have equivalent analgesic effects compared with carbamazepine.

3. ***Acute mania of bipolar disorder***

Dosage & Administration

Monotherapy and adjunctive therapy with Oxcarbazepine

- Start with 600 mg/day given 300 mg BID
- Add 600 mg/day in approximately one week
- Effective daily dose: 1200 mg/day
- If needed, continue further titration at weekly intervals (600 mg/day increments) to a maximum daily dose of 2400 mg/day
- A lower starting dose and slower titration may be considered for more sensitive patients

For pediatric patients aged 4 to 16 as an Adjunctive therapy with Oxcarbazepine

- Start Oxcarbazepine at 8 to 10 mg/kg given BID (not to exceed 600 mg/day)
- Titrate to target dose over two weeks
- Recommended daily dose according to weight

  20-29 kg - 900 mg/day

  29.1-39 kg - 1200 mg/day

  Over 39 kg - 1800 mg/day

Highlights

Highlights of Oxcarb

Pharmacokinetic Highlights

- OXCARB is not oxidatively metabolized, therefore causing minimal induction of hepatic enzymes.
- OXCARB does not undergo autoinduction.
- Oxcarbazepine exhibits *linear pharmacokinetics.*
- The plasma concentration half-life of the active metabolite (monohydroxy derivative: MHD) makes it possible to administer OXCARB twice daily.

Highlights In Efficacy

- OXCARB has similar efficacy to carbamazepine in patients with partial seizures with or without secondary generalization, or tonic-clonic seizures
- OXCARB has similar efficacy to other conventional drugs like valproate or phenytoin.
- Many patients who are hypersensitive to carbamazepine can be treated with OXCARB.
- The usually administered dosage of OXCARB is approximately 50% higher than that of carbamazepine. However, better tolerability of OXCARB makes it possible to give higher dosage.
- In patients with refractory seizures, substitution of oxcarbazepine for carbamazepine may be associated with reduced seizure frequency and an improved mental state.
- No changes in dosage are necessary in patients with impaired renal function unless creatinine clearance is below 30 ml/min.
- Oxcarb is easy to start, titrate, and manage – important for patients and physicians

Highlights In Tolerability

- Rash leading to discontinuation of OXCARB seems to be less frequent than with CBZ, but resolution of carbamazepine-associated skin rashes after substitution with oxcarbazepine has also been reported.
- Oxcarbazapine cause less ocular side effects as compared to carbamazepine.

- OXCARB may be less sedating and may cause less cognitive impairment and other CNS side effects (e.g.headache) than most marketed AEDs.
- Less drug-drug interactions with concomitant medications than most marketed antiepileptic drugs.
- No drug interaction with warferin
- No need of monitoring of WBC count
- Less sexual side effects as compared to carbamazepine

SELF ASSESSMENT 2

Fill the columns

	Valtec CR	Lametec
1. Composition		
2. Class		
3. Mechanism of action		
4. Indication & dosage		
5. Highlights		

Fill the columns

	Topamate	Oxcarb
1. Composition		
2. Class		
3. Mechanism of action		
4. Indication & dosage		
5. Highlights		

Module 3 - Alzheimer's disease and Acetylcholinesterase Inhibitor

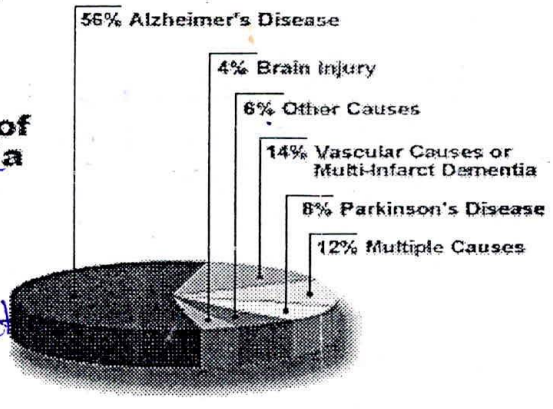
Dementia

- Dementia is an acquired complex of intellectual deterioration, which affects areas of cognitive functions.
- The cognitive functions can be memory, orientation (time and place), ability to speak and understand language, ability of proper judgement (to differentiate between right and wrong, good or bad), perception (of any of the 5 senses), attention, ability to perform simple tasks, etc.

Types of Dementia

Reversible dementia: those types of dementias, which can be reversed or which can be corrected

- Toxicity due to drugs like anti-epileptics, anti-psychotics, etc
- Infections of the blood or Central Nervous System
- Metabolic disorders like thyroid disorders, Chronic kidney or liver failure
- Brain tumors or brain injury



Causes of Dementia

Irreversible dementia: those types of dementias, which can't be reversed or which can be corrected

Types of irreversible Dementia

- Alzheimer's disease
- Multi-infarct dementia (vascular dementia)
- Parkinson's disease
- Lewy body dementia
- AIDS – dementia complex

Alzheimer's disease

- Type of irreversible dementia
- It is the most common cause of the loss of mental function known broadly as dementia
- It is a neurodegenerative disease (Neurodegenerative: Where the nerve cells / neurons degenerate or get destroyed) neuroDeg.
- It proceeds in stages (slow progression) gradually destroys the memory, reasoning ability, judgement, language skills
- In the last stages, a patient of AD becomes totally dependent on the family members (care-givers / care-providers) to do even the simplest of tasks

ABCs of Alzheimer's Disease

A. Activities of daily living

B. Behaviour

C. Cognition – that operation of the mind Process by which we become aware of objects of thought & perception including all aspects of Perceiving, Thinking & Remembering

Stages of AD

To define the various stages of AD, a standard was set, using two scales: CDR (Clinical Dementia Rating), GDR (Global Dementia Rating)

Early Stage	Middle Stage (Self-care difficulty)
• Routine loss of "recent" memory (working memory / immediate memory)	• Chronic loss of "recent" memory
• Mild aphasia (word-finding difficulty)	• Moderate aphasia
• Seeks the familiar (people, objects, places) home	• May get lost at times, even inside the
• Avoids the unfamiliar	• Repetitive actions (forgotten they had done the same thing before – e.g.: Combing of hair)
• Some difficulty in writing and using objects (pen, spoon, comb)	• Apraxia (Difficulty or inability of movement)
• Apathy (no emotions expressed or inappropriate emotions), depression	• Possible mood and behavioral disturbances (aggression, violence, shouting, agitation)
• Needs reminder with some Activities of Daily Living (ADLs)	• Need reminders and help with most ADLs

Last Stage (Completely dependent)	Terminal Stage
• Mixes up past and present	• No link to past or present
• Expressive aphasia (inability to express in words)	• Remains mute (doesn't speak) or speaks senselessly
• Misidentifies familiar persons and places	• Unaware of surroundings
• Bradykinesia (slowing down of movement)	• Very little spontaneous movement
• At risk for falls	• Completely passive mood and behavior
• Greater incidence of mood and behavioral disturbances	• Can't swallow food or drink
• Need reminders with all ADLs	• Lose control over bladder and spincter muscles
	• Urinary incontinence, defecation
	• Co-existing medical problems can aggravate symptoms and hasten decline
	• Death from Pneumonia or sepsis

Inside the brain in Alzhiemer's disease

I) Neurotransmitters

- ACh is responsible for learning and memory. ACh is found abundantly in Hippocampus (memory store) and cerebral cortex
- It was thought at that time that AD might disrupt the synthesis of ACh
  Or
- AD might trigger the over-production of the enzyme that destroys ACh – Acetylcholinesterase Enzyme

2) Neurofibrillary Tangles

Loss of tau protein
↓
Loss of microtubules (give shape to neuron)
↓
Neurones shrink and die

3) Neuritic Plaques

Amyloid precursor proteins
↓
A-Beta protein
↓ In AD
Insoluble
↓
Fibrils formation
↓
Neuritic plaques

Strategies for medical treatment of AD

a) Prevention of disease (e.g. with a vaccine)

b) Delay onset of symptoms for 5-10 years

c) Slow down progression of the disease – thus maintaining individual at their highest possible level of functioning

d) Treat the secondary symptoms (behavioral) symptoms of AD – like agitation aggression, hallucinations, delusions, insomnia

Donecept

Brand	:	Donecept
Molecule	:	Donepezil
Class	:	Acetylcholinesterases inhibitor
Mechanism of action	:	Non-competitive, reversible inhibitor of acetylcholinesterase and thereby increase Ach levels, at synapse

Donecept is our brand of Donepezil and available as Donecept-5, Donecept-10 containing Donepezil 5mg, 10mg respectively

Indications

- Alzheimer's disease
- Vascular dementia
- Lewy-body dementia

Dosage

- Starting dose : 5 mg/day
- Can be increased to 10 mg/day after 6 weeks
- OD as compared to QID of Tacrine and BID of Rivastigmine

Highlights

- Donepezil is considered as a first – line therapy for mild to moderate AD
- Improves symptoms of cognition and global clinical function
- Significantly delays loss of function and disease deterioration
- Reduces care-giver stress
- Well-tolerated
- Once-daily dosing convenience
- Effect of Donepezil in moderate to severe AD - Evidences support that Donepezil is effective in moderate-severe AD. Donepezil improves cognitive measures and day-to-day function in persons with moderate to severe AD.

Notes

SELF-ASSESSMENT 3

1) What is ABC of Alzheimer's disease

A Activities of daily living

B Behaviour

C Cognition

2) Which neurotransmitter is reduced in Alzheimer's disease?

a) Serotonin

b) Noradrenaline

c) Aspartate

d) Acetylcholine

3) What happens to memory, speech and activities of daily living in all stages of Alzheimer's disease

	Early stage	Middle stage	Last stage	Terminal stage
Memory				
Speech				
Activities of daily living				

4) Match the following

Reversible dementia	Insoluble A-beta protein
Irreversible dementia	Loss of TAU-protein
Neurofibrillary tangles	Lewy-body dementia
Neuritic plaques	Dementia due to renal failure

5) Primary line of treatment for AD is _____.

Fill the columns

	Donecept
1. Composition	
2. Class	
3. Mechanism of action	
4. Indication & dosage	
5. Highlights	

Module 5 - Migraine, Parkinson's disease, haemorrheogical disorders

Migraine

Definition

Migraine is defined as a familial disorder characterized by recurrent attacks of throbbing headache, generally felt on one side of the head usually followed by pain free intervals and often provoked by stereo-typed stimuli.

Clinically, migraine can be defined as a syndrome (group of symptoms that occur together in a similar pattern, time after time) characterized by periodic, throbbing headache affecting one side of the head (unilateral) accompanied with nausea and sometimes vomiting. Migraine usually begins in early childhood, adolescence or young adult life.

Prodrome
↓
Aura
↓
Migraine

- Prodrome - The prodrome refers to vague yawning, excitation, or depression and lethargy, sometimes with a craving or distaste for various foods, in the 24 hours before the headache and lasts for 15 to 20 mins.
- Aura - The aura is usually visual. Flashing lights, zig-zag lines or balls of light may appear in the visual field peripherally and spread centrally or start centrally and spread to the periphery. There may be loss of one half of visual field (scotoma) or

Idiopathic – unknown

Idiopathic – Unknown

appearance of bright, simmering stars in front of the eyes. The aura typically lasts for 30 minutes and is succeeded by headache. The change in vision is often followed by numbness and tingling of the lips, hands and face.

- Migraine – Unilateral headache

Unilateral – one side

Types

Migraine is classified as follows:

1. Common Migraine (Migraine without aura)
2. Classic Migraine (Migraine with aura)

Causes

Aetiology of Migraine includes stress, emotions, hormonal changes, dietary factors, medications, disturbances in sleep pattern, hunger, atmospheric conditions and hypoglycemia.

The various migraine triggers

1. Food Items: Cheese dairy products, citrus fruits, chocolates, seafood, onions
2. Food additives: Aspartame, nitrates, caffeine
3. Alcohol: Red wine, beer
4. Hormonal changes: Menstruation, pregnancy, ovulation
5. Medications: Nitroglycerin, oral contraceptive, H_2 –receptor antagonist
6. Physical Exertion : Excessive exercise, fatigue
7. Visual stimuli: Bright lights, glare
8. Auditory stimuli: Loud noise or music
9. Olfactory stimuli: Perfumes and certain odours
10. Sleep: Too much or too little
11. Weather
12. Hunger
13. Stress and Anxiety

Pathogenesis of Migraine

The brain is supplied by the paired carotid and vertebral arteries, through an extensive system of branches. The carotid arteries further branch out into the cerebral arteries, which supply the cerebrum. The vertebral arteries unite at the base of the brain to form basilar artery, which supplies the brain stem cerebellum and spinal cord. The vascular theory proposes that the constriction of blood vessels supplying the cerebrum (intracerebral) accounts for aura / prodrome of migraine and dilation of blood vessels inside the skull (intracranial) and those, which are outside the skull (extracranial) are probably responsible for headache. This constriction occurs due to excessive calcium entry, which may be triggered by any of the migraine trigger factors.

Management

Acute migraine

Acute migraine: Treatment (Abortive therapy) to treat isolated mild to moderate migraine attacks, an analgesic together with an anti-nauseant may be adequate.

Analgesics – Aspirin, Paracetamol , Ibuprofen , Diclofenac, Naproxen, Acetaminophen + Caffeine, Acetaminophen + Aspirin + Caffeine

Anti-nauseant drugs – Antiemetics, Promethazine, Chlorpromazine, Metoclopramide, Domperidone

Analgesic is to be given along with anti-nauseant drugs 15-20 minutes before onset of headache or during the headache. Anti-nauseant drugs can be repeated 4-6 hourly as per the patient's response.

Other drugs used in acute migraine are :

Ergotamine and Sumtatriptan

Prophylactic therapy

This is employed to lessen the frequency and severity of migraine attacks.

Preventive therapy is indicated in the following situations

1. When attacks occur at a frequency of more than 2 per month
2. When attacks are refractory to abortive therapy.
3. When their pattern is predictable like a Menstrual Migraine.

Preventive Therapy for Migraine

	Drugs	Dose (mg)
I	**Beta-blockers**	
	Propranolol	40-320mg/day
	Atenolol	50-120mg/day
II	**Calcium Channel Blockers**	
	Flunarizine	10-20mg/day
	Verapamil	120-480mg/day
	Nimodipine	60-120mg/day
	Diltiazem	120-360mg/day
III	**Serotonin antagonist**	
	Methysergide	4-8mg/day
IV	**Tricyclic Antidepressant**	
	Amitriptyline	10-20mg/day
V	**Serotonin reuptake inhibitors**	
	Fluoxetine	20-60 mg/day
VI	**Anticonvulsant**	
	Sodium valproate	600-1200 mg/day
VII	**Adrenergic Blocker**	
	Clonidine	0.2-0.3 mg/day
VIII	**Anti-histaminics**	
	Cyproheptadine	4-8 mg/day

Parkinson's disease

Introduction

The Triad of Hypokinesia, Tremor and Rigidity producing a typical syndrome was first described by James Parkinsons in 1871.

This disease is also called as 'Paralysis Agitans' a disorder of the extrapyramidal system that becomes evident in the fifth and sixth decades of life.

Epidemiology

PD usually occurs in the middle or late life between 50 and 70 years, though it rarely is seen in young people. The prevalence of this disease is estimated to be between 59 and 353 cases per 1,00,000.

Clinical symptoms

Tremor

Rigidity

Gait hesitation

Diminished levels of Dopamine causes unnecessary skeletal muscle movements, that often interfere with voluntary movement therefore causing TREMOR, the most common symptom of PD. Some muscles may contract continuously causing RIGIDITY of the involved body part. Rigidity of the facial muscles gives the face a mask like appearance (the expression is characterized by a wide unblinking stare and a slightly open mouth with uncontrolled drooling). As the disease progresses patient develops GAIT HESITATION (Freeze on initiating gait-start hesitation or when approaching a target terminal hesitation).

Some more signs are: decreased swallowing resulting in drooling of saliva, soft voice (hypophonia), loss of speech modulation, impaired handwriting with micrographia, decreased amplitude in performing repetitive movements (such as opening and closing the hand or tapping the foot). The cause of these abnormal motor effects is almost unknown.

Etiology

PD results from relative imbalance between the neurotransmitters as a result of depletion of dopamine in the presence of normal amount of acetylcholine. In effect, in PD there is degeneration of dopamine-producing neurons in the substantia nigra and thus severe reduction of dopamine in the basal ganglia, which bring about most of the symptoms of PD.

Management

Commonly used drugs for the management of PD are

1) Levodopa
2) Levodopa + Carbidopa
3) Bromcriptine
4) Anticholinergic Drugs — Procyclidine, Trihexyphenidyl & Benzexol
5) Amantidine

Levodopa

Levodopa remains the most effective drug in Parkinsons disease. Unfortunately the side effects associated with long-term levodopa treatment constitute an important cause of functional disability.

Side effects of levodopa:

- Involuntary movements
- Psychiatric disorders, which result from increase in dopamine levels
- Other important side effects of levodopa are agranulocytosis and postural hypotension.
- Another problem with levodopa is fluctuations in clinical response with passage of time. More than 50% of patients experience these fluctuations which is called as ***on and off phenomenon*** where certain doses fail to cause a response and there is increasing variation in the latency period for taking the drug to clinical response.

Haemorrheological Disorders

Haemorrheology

Haemorrheology is the study of behaviour of blood flow.

Haemorrheological disorders

Haemorheological disorders include

- Peripheral vascular disease (diseases of arteries / veins)
- Diabetic vascular disease (diabetic neuropathy, diabetic nephropathy)
- Cerebral vascular disease

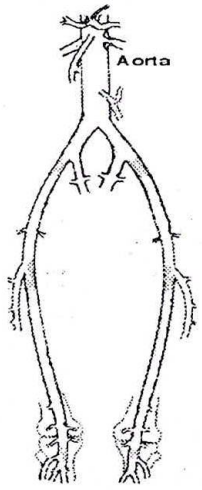
Peripheral vascular disease (PVD)

PVD is usually classified as vasospastic or occlusive. In vasospastic disorder, such as Raynaud's disease, blood flow to the skin is reduced by reversible vasoconstriction and there is little or no organic involvement in chronic occlusive peripheral vascular disorders, blood flow is reduced by organic obstruction.

I. Diseases of Arteries

a. Chronic arterial occlusive diseases

These are slowly progressive disorders characterized by chronic ischaemia of the limb. Risk factors include smoking, diabetes, mellitus, hyperlipidaemia, hypertension, obesity and atherosclerosis



Clinical manifestation

a. Men: women = 5:1

b. Intermittent claudication: This consists of a cramp-like pain in the calf-muscles produced by a constant amount of exercise and relieved by rest. As the disease progresses, effort pain is characteristically brought on by diminishing amounts of exercise.

c. Rest pain: It is a continuous pain affecting the distal portion of the feet and toes. The pain is severe, usually occurring at night when the patient is in bed. Relief is obtained by handing the foot off the bed.

d. Colour changes such as pallor or cyanosis

e. Absence of pulse

f. Trophic changes

b. Burger's Disease (Thromboangitis Obliterans)

This is an uncommon disease of unknown origin, which usually affects young men. It is confined to males who smokes heavily and usually begins after the age of 40. Clinical signs and symptoms are similar to (a) above. There is no specific treatment, but it is imperative that they stop smoking at once.

c. Acute (sudden) arterial occlusion

The two most common causes of sudden obstruction of a peripheral artery are thrombosis and embolism, the other causes being trauma or spasm of the vessel secondary to inadvertent intra-arterial injection of drugs.

II. Diseases of The Veins

i. Deep vein thrombosis

Thrombosis of the deep veins of the lower extremities. The predisposing factors are stasis of blood flow, injury to the vein wall and hypercoagulability of the blood.

The common underlying conditions responsible are bed rest, surgical procedures, obesity, pregnancy, C.C.F., oral contraceptives etc.

The symptoms are variable, complications mainly being pulmonary embolism and chronic venous hypertension.

ii. Varicose veins

These are defined as abnormally dilated, tortuous, superficial veins of the lower

iii. Superficial Thrombophlebitis

It is a self-limiting disease of the superficial veins most commonly caused by indwelling catheters / needles.

Cerebrovascular Diseases

Transient ischemic attacks (TIA):

This is a temporary period during which blood supply to the brain is reduced either due to block of an artery or rupture of blood vessel.

Thrombosis:

Clotting of blood is called thrombosis, which occurs inside a blood vessel.

Embolism:

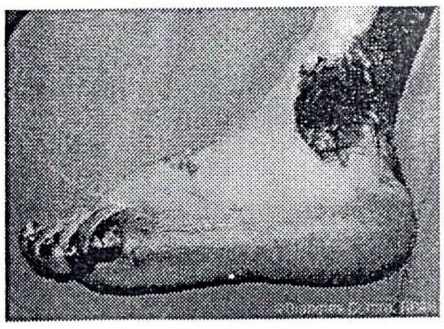
Embolus is a mass of bacteria or blood clot, which is carried by blood flow to a blood vessel and blocks the blood vessel.

Subarachnoid haemorrhage/bleeding

Rupture of blood vessel in the subarachnoid space (space below arachnoid layer of brain).

Diabetic Vascular Disease

Diabetes presents with multiple microvascular and macrovascular complications.



Notes

SELF ASSESSMENT 4

1) Migraine is characterized by ____ (Say yes / no)

- ☐ Bilateral headache
- ☐ Unilateral headache
- ☐ Nausea, vomiting
- ☐ Diarrhoea

2) Match the following

Common migraine	Lethargy and yawning
Classic migraine	Flashing lights
Prodrome	Migraine with aura
Aura	Migraine without aura

3) Vascular theory of migraine consists of

Vaso _____ of intraceretral and

Vaso _____ of exracrenial blood vessel

4) Prophylactic therapy of migraine is necessary in

a) _____

b) _____

c) _____

5) Drugs used for prophylaxis of miraine are.....,except

- ☐ Propranolol
- ☐ Venlafaxine
- ☐ Sodium Valproate
- ☐ Azithromycin

6) Key features of Parkinson"s disease are

T _____

R _____

H _____

7) _____ neurotransmitter is reduced in Parkinson's disease in basal ganglion.

8) Define Haemorrheology

_____

_____

_____

9) Following are the arterial diseases, except

- ☐ Varicose veins
- ☐ Smoker's arteritis
- ☐ Arterial thrombosis
- ☐ Burger's disease

10) Causes of cerebral vascular diseases are

I _____

T _____

E _____

B _____

Module 5 - Anti-migraine drugs, Anti-Parkinsonian drug, Haemorrheological gent

Migarid

Brand	:	Migarid
Molecule	:	Flunarizine
Class	:	Selective calcium entry blocker
Mechanism of action	:	Selective class IV calcium entry blocker.

Migraid is our brand of flunarizine and available as migarid 5, migarid 10 containing flunarizine 5mg and 10mg

Indications

1. Prophylaxis of classic (with aura) or common (without aura) migraine
2. Treatment of vertigo
3. 'Add-On' therapy in the treatment of epilepsy resistant to conventional antilepileptic medication.

Dosage and Administration

The recommended maximum daily dose of Flunarizine in the prophylaxis of migraine, and treatment of vertigo is 10mg/day in adults and 5mg/day in children weighing less than 40kg.

An optimal therapeutic dosage in epileptic patients receiving other anti-epileptic drugs is 15 to 20mg/day in adults and 5 to 10mg/day in children.

Highlight

1. Flunarizine is a 'selective' calcium antagonist. It appears to selectively block calcium entry when calcium is stimulated to enter cells in excess and thus prevents vasoconstriction. Thus it prevents cell damage caused by 'calcium overload' in various tissues.

2. It inhibits contraction of vascular smooth muscle mediated by the entry of extracellular calcium, and protects.

   a. endothelial cells against damage from calcium overload

   b. red blood cells from membrane rigidity induced by calcium ion loading, and

   c. brain cells from the effects of hypoxia

   3. It also demonstrates vestibular depressive effects, as well as antihistaminic and anticonvulsant properties.

Domcet

Brand	:	Domcet
Molecule	:	Domperidone + Paracetamol
Class	:	Domperidone is Antiemetic and paracetamol is Analgesic and Antipyretic
Mech. of action	:	Domperidone is peripheral dopamine receptor antagonists while paracetamol is centrally acting analgesic

Domcet is our brand of domperidone and paracetamol combination available as domcent tablet containing domperidone 10 mg and paracetamol 500 mg per tablet.

Advantages of domperidone

- Domperidone is a very widely used anti-emetic drug, which possesses prokinetic properties.

  Anti-emetic: drug that prevents vomiting.

  Prokinetic: enhancing the movement of contents of gastro-intestinal tract Domperidone has the potential to enhance gastrointestinal tract motility and produce relief from stagnation of contents in the GIT, which is seen in vomiting

- Domperidone enhances the absorption of paracetamol so it can work on the pain
- Domperidone does not penetrate well into the central nervous system (CNS), therefore rarely causes CNS side effects like movement disorders unlike metoclopramide.

Advantages of paracetamol

- Paracetamol is an analgesic (it produces relief from pain) and antipyretic agent (produces relief from fever)
- Paracetamol is a safe and effective analgesic, widely used for the last 30 years

The rationale for combining domperidone and paracetamol

- Domperidone is a time tested anti-emetic drug which possesses prokinetic properties
- It has the potential to enhance gastrointestinal motility and produce relief from stagnation of contents in the GIT which is seen in vomiting
- Domperidone enhances the absorption of paracetamol so it can work on the pain.
- Domperidone does not penetrate well into the central nervous system (CNS), therefore rarely causes extrapyramidal side effects unlike metoclopromide.
- Paracetamol is a time tested analgesic and antipyretic
- Paracetamol is a safe and highly effective analgesic
- Repeated administration of paracetamol does not have any effects on the cardiovascular and respiratory systems
- It does not produce gastric irritation, erosion or bleeding after administration
- No effects on platelets, bleeding time or the excretion of uric acid.

This is an effective combination which produces relief from both headache / other pain / fever / nausea and vomiting associated with the above conditions.

Indications of Domcet

This effective combination produces relief from both headache / other pain/ fever / nausea and vomiting associated with migraine, viral fever, diabetic gastroparesis, post-operative nausea and vomiting + pain, PID, Dyspepsia, infections of GIT and the nausea / vomiting headache associated with oral contraceptives / hormone replacement therapy.

Dosage of Domcet

1-2 tablets not frequently than every 4 hours upto maximum of 8 tablets in 24 hours.

Amantrel

Brand	:	Amantrel
Molecule	:	Amantadine
Class	:	Anti-viral drug
Mech. of action	:	Augment synthesis and release of dopamine from dopaminergic presynaptic neurons of the extrapyramidal system.

Amantrel is our brand of amantadine and available as Amantrel 100 containing amantadine 100mg.

Indications

- Initial therapy of Parkinson's disease
- As a Add-on therapy with Levodopa in later stages of Parkinson's Disease
- Amantadine has also been useful in the prophylaxis and treatment of Influenza- A virus infections.

Dosage and Administration

Amantidine is administered orally. If insomnia occurs the daily last dose should be taken several hours before retiring.

- The usual dosage in all forms of parkinsonian syndrome is 100mg twice daily. When patients are receiving other anti-parkinsonian drugs or have other serious illness the dosage should be started with 100mg daily for 1 week and then gradually increased to 100mg B.D. up to 400mg of Amantadine has been used in divided doses, However patients, receiving more than 200mg daily, should be supervised closely by their physicians.

Highlights

- Amantidine, Hydrochloride (Amantrel) is used in the symptomatic treatment of all types of Parkinsons disease including the post encephalitic, idiopathic types and for relief from parkinsonian signs and symptoms of carbon-monoxide poisoning and drug – induced extrapyramidal effects.

- Amantidine may be especially useful in the treatment of drug – induced extrapyramidal symptoms when drugs with anticholinergic properties should be avoided e.g. in patients with glaucoma or urinary retention.

- Amantrel produces improvement in all symptoms of akinesia, rigidity, tremor, salivation, gait disturbance and total functional disability.

- Subjective responses such as sense of all well being and elevation of mood have also been reported. Improvement in extrapyramidal symptoms is apparent within 40-80 hours of initiation of therapy. However some patients experience a reduction in the benefit which may by regained by increasing the dosage or by discontinuing the drug for few weeks and then resuming the therapy.

- Combined therapy with amantidine (Amantrel) and levodopa has been found to be more effective than levodopa which will result in less side effects.

Kinetal

Brand : Kinetal

Molecule : Pentoxifylline

Class : Haemorrheological agent

Kinetal is our brand of pentoxifylline in sustained form and available as Kinetal-400 containing pentoxifylline 400mg.

The mode of action of Kinetal

The primary mechanism by which it increases blood flow appears to relate to an overall improvement in haemorheological characteristics such as:

i. erythrocytic deformability

ii. blood viscosity

iii. platelet aggregation

iv. plasma fibrinogen concentration

Indications of Kinetal

1. Peripheral vascular disease
2. Diabetic vascular disease
3. Cerebrovascular disorders

Dosage of Kinetal

The usual adult oral dosage of Kinetal 400 in peripheral vascular disorders is 1200mg/ day in three divided doses. Therapy should be maintained for atleast 8 weeks.

In cerebrovascular diseases, the currently recommended dosage is 600-1200mg daily in divided doses.

The tablets should preferably be taken after meals with some liquid to minimize gastrointestinal complications.

Notes

SELF ASSESSMENT - 5

Fill the columns

	Migarid	Domcet
1. Composition		
2. Class		
3. Mechanism of action		
4. Indication & dosage		
5. Highlights		

Fill the columns

	Amantrel	Kinetal
1. Composition		
2. Class		
3. Mechanism of action		
4. Indication & dosage		
5. Highlights		