SEDATIVES AND HYPNOTICS

DR PRADNYA ROTITHOR

definitions

- **Sedatives** –drugs that subdue excitement and calm the subject **without inducing sleep, though drowsiness is seen**
- **Hypnotics** **–drugs that induce and/or maintain sleep ---similar to normal sleep**
- **The actions many times overlap**
- **Given drug at lower dose is sedative and at higher dose is hypnotic**

Sleep -NREM AND REM

- Stages of NREM Sleep
- Stage zero awake
- Stage 1 dozing. 5-10 %
- Stage 2 unequivocal sleep 50 %
- Stage 3 deep sleep transition 20 %
- Stage 4 cerebral sleep 20 %
- **NON REM sleep** – real sleep ,subject does not remember dreams
- **NIGHT TERROR** if subject suddenly wakes up from NREM sleep

REM Sleep

- **REM sleep** = paradoxical sleep , dreams during REM are remembered by subject , brain records EEG tracing , **NIGHTMARE** when patient suddenly wakes up from REM
- **Most sedatives suppress REM sleep**
- Stages of NREM Sleep alternate with REM sleep throughout night for brief periods

Sleep waves

Beta 15-35 cps

Alpha 8-14 cps

Theta 4-7 cps

Delta 0.5-3 cps

Slow wave sleep = deep and refreshing sleep
=theta and delta

Sedatives should not be stopped abruptly

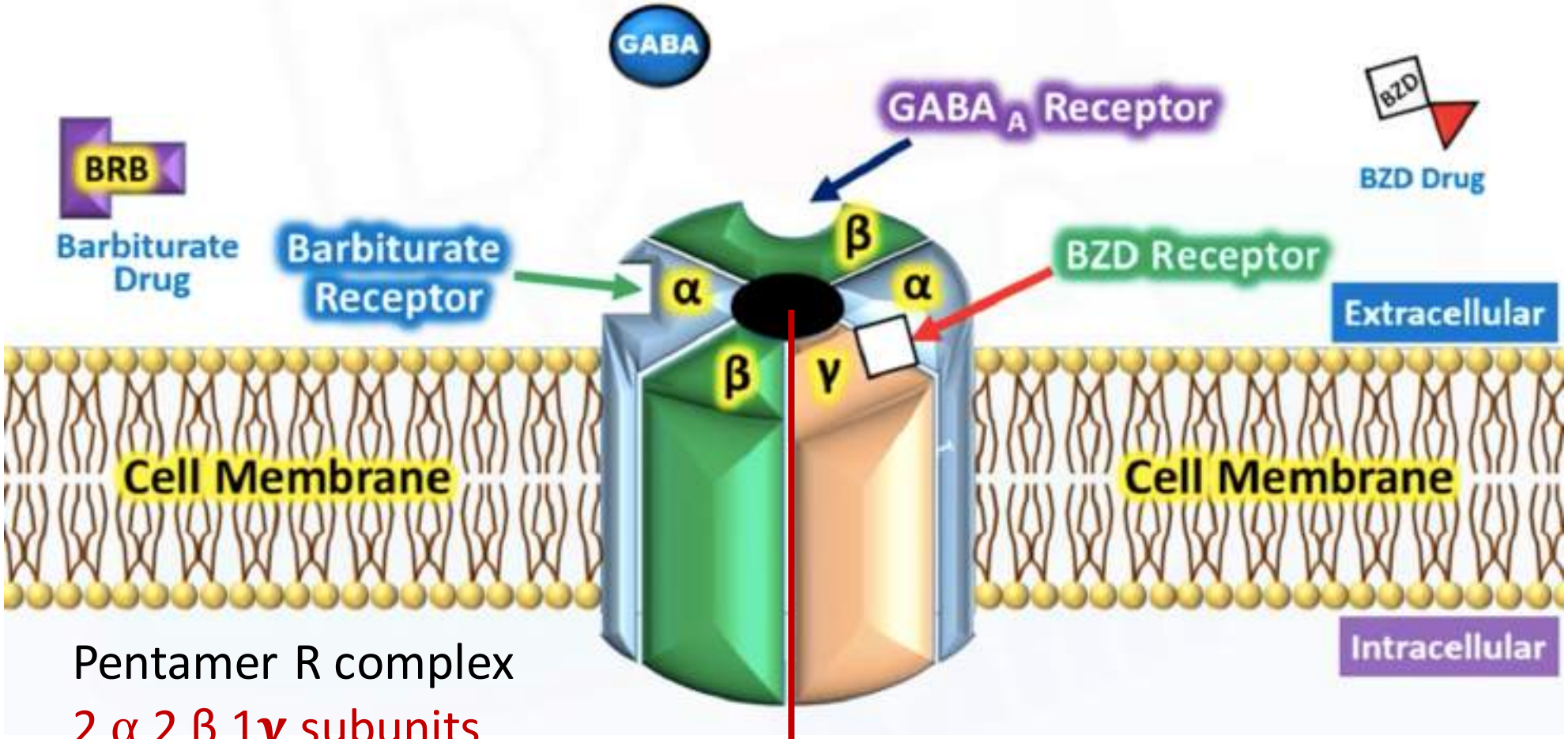
Neither should be continued for long

Stages of CNS depression

- **Dose dependent**
- **Sedation--Calm, quiet**
- **Sleep –deep sleep**
- **Delirium—altered levels of consciousness**
- **Anaesthesia**
- **Stupor**
- **Semi coma**
- **Coma**
- **death**

Classification

- Barbiturates
- Benzodiazepines
- Non BZD hypnotics
- Melatonin , ramelteon
- Others – chloral hydrate
- traditional antihistaminics ,
- alcohol
- narcotic analgesics



Pentamer R complex

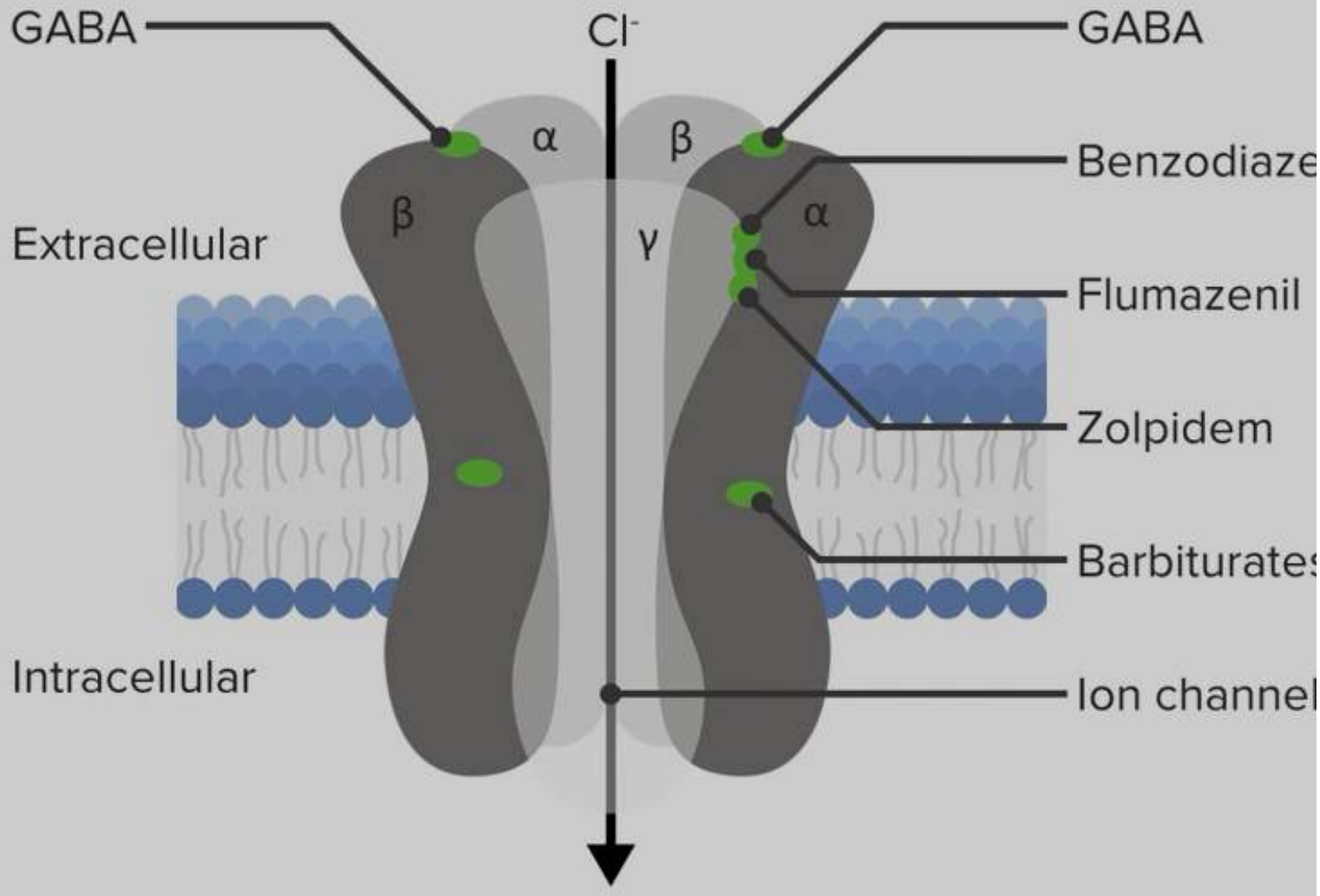
2 α 2 β 1γ subunits

Drugs bind to different sites on R

Binding of agonist to R opens Cl- ion ch

Benzodiazepines

$GABA_A$ receptor-chloride ion channel macromolecular complex.



Barbiturates

1)Long acting

Phenobarbitone

mephobarbitone

2) Ultra short acting

thiopentone

methohexitone

hexobarbitone

3) Short acting

butobarbitone

pentobarbitone

Classification of BZDs

Hypnotic	antianxiety	anticonvulsant
Diazepam	*diazepam*	*diazepam*
Alprazolam	alprazolam	clobazepam
triazolam	lorazepam	lorazepam
Nitrazepam	oxazepam	clonazepam
Temazepam	chlordiazepoxide	

Zopiclone
Zolpidem
Zaleplon

newer non BZD hypnotics

Barbiturates

Commonly used before 1960

Now replaced by BZDs as sedative and hypnotic

Phenobarbitone --Prototype

Currently used barbiturates are ---

1)Phenobarbitone –

2) thiopentone

Phenobarbitone is contraindicated in acute intermittant porphyria (MCQ)

MOA OF BARBITURATES

Phenobarbitone

⇓

Binds to site on GABAa R

⇓

Opens Cl channel –prolongs duration

⇓

Cl^- conductance

Causes Hyperpolarization of neuronal membrane

Raises threshold –thus prevents development of AP

CNS depression –GABA mimetic action

Pharmacological Actions

Depression of all excitable cells –mainly CNS

1)Sedation and hypnosis

Induce and prolong sleep

↓ REM duration ↑NREM

Hangover seen

Euphoria

Impair short term Memory

Hyperalgesia –hence contraindicated in pain

Actions contd

Anaesthesia –

Ultra short acting barbiturate -thiopentone

Anticonvulsant –

Phenobarbitone –specific anticonvulsant property in subhypnotic dose

Respiratory system –significant depression

CVS –toxic doses –hypotension

Pharmacokinetics

- Metabolized in liver
- Redistribution –highly lipid soluble
- HME inducers –drug interactions

- Excreted by kidneys

ADR

- Sleep hangover with N V D Vertigo
- Impaired judgement
- Impaired fine motor skills
- Children –excitement irritability
- Hypersensitivity –skin rash
- Drug abuse liability ++
- Respiratory depression
- Contraindicated in ITP--↑porphyrin synthesis

Acute barbiturate poisoning

- Now not frequently seen due to non availability of barbiturates
- *No specific antidote*
- Gastric lavage
- Haemodialysis
- Supportive treatment
- *Alkaline diuresis with sodium bicarbonate* to hasten renal elimination (MCQ)

Therapeutic Uses

- ✓ Anaesthesia –ultra short acting –**thiopentone**
- ✓ For induction of GA
- ✓ Short procedures
- ✓ Neonatal jaundice and kernicterous- **phenobarbitone** –HME induction of glucuronyl transferase –metabolizes and excretes bilirubin –helps clearance of neonatal jaundice
- ✓ Antiepileptic –**phenobarbitone -**

Ultra-short acting barbiturates

Ultra-short-acting Barbiturate

Rapid Induction 15-20 sec

Recovery 15-20 min

Disorientation many hours— due to redistribution

Patient is awake but can not be discharged

- **Used for Induction,**
- short procedures as sole drug
- Can be used in pregnancy

Advantages of BZD over barbiturates

1) High therapeutic index
2) Lower degree of neuronal depression –GABA facilitatary only Vs both mimetic and facilitatary by barbiturates
3) No loss of consciousness
4) Less or no respiratory depression
5) No action on other systems
6) Less distortion of sleep architecture
7) less rebound insomnia
8) No hepatic microsomal enzyme induction
9) Lower abuse liability
10) Specific antidote Flumazenil is available in poisoning

BENZODIAZEPINE MECHANISMS OF ACTION

Affect neurons that have receptors for the neurotransmitter GABA

BZs potentiate GABA → increase frequency of Cl^- ion channel opening→ causes hyperpolarization→ raise firing threshold→ and thus inhibits the formation of action potentials → inhibitory effect on different sites of the brain especially motor cortex, and limbic system.

GABA—inhibitory transmitter in brain regions

- Limbic system (alter mood)
- RAS (cause drowsiness)
- Motor cortex (relax muscles)

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Zolpidem
Zaleplon

newer non BZD hypnotics

Melatonin and ramelteon

SITE AND RESULT OF ACTION

- Midbrain ascending reticular formation – wakefulness (BZD cause drowsiness)
- Limbic system—thought and mental function (BZD alter mood)
- Cerebellum –ataxia
- Medulla –muscle relaxation

Drugs acting on $GABA_A$ R viva/MCQ

Agonist	antagonist
GABA-natural neurotransmitter **Muscimol-GABA Agonist** **Barbiturates –at beta subunit** **GABA mimetic and facilitating** **BZD –at ά/Y subunit** **GABA facilitatary action** **Alcohol, propofol, inhalational GA – open Cl channel directly**	**Bicuculline –competitive –GABA** **noncometitive –BZD** **No antagonist/antidote for barbiturates** **Flumazenil- competitive antagonist at BZD site** **DMCM –Inverse agonist at BZD site, impedes GABA action** **Picrotoxin- noncompetitive blocker ,direct action on Cl channel at picrotoxin site**

Pentamer R complex

2 α 2 β 1γ subunits

Drugs bind to different sites on R

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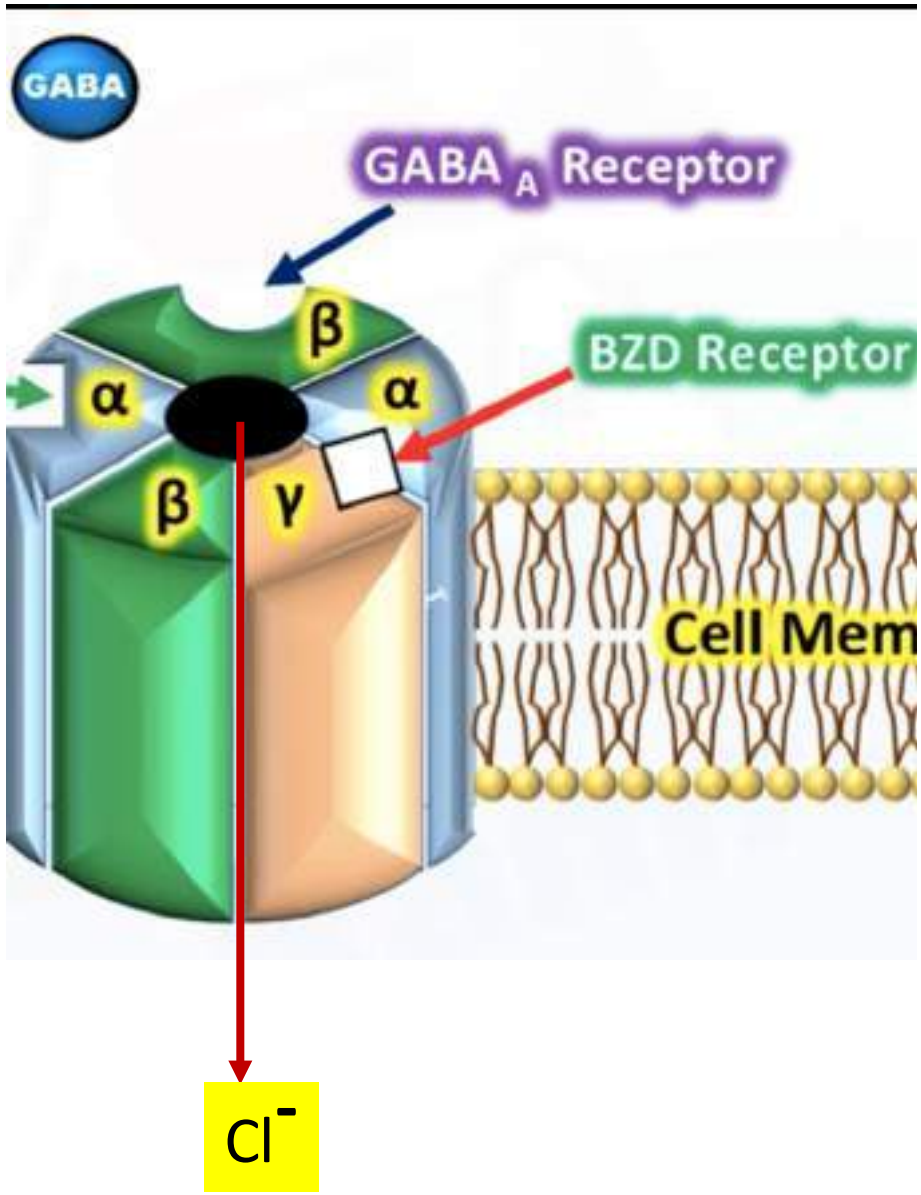

Benzodiazepines

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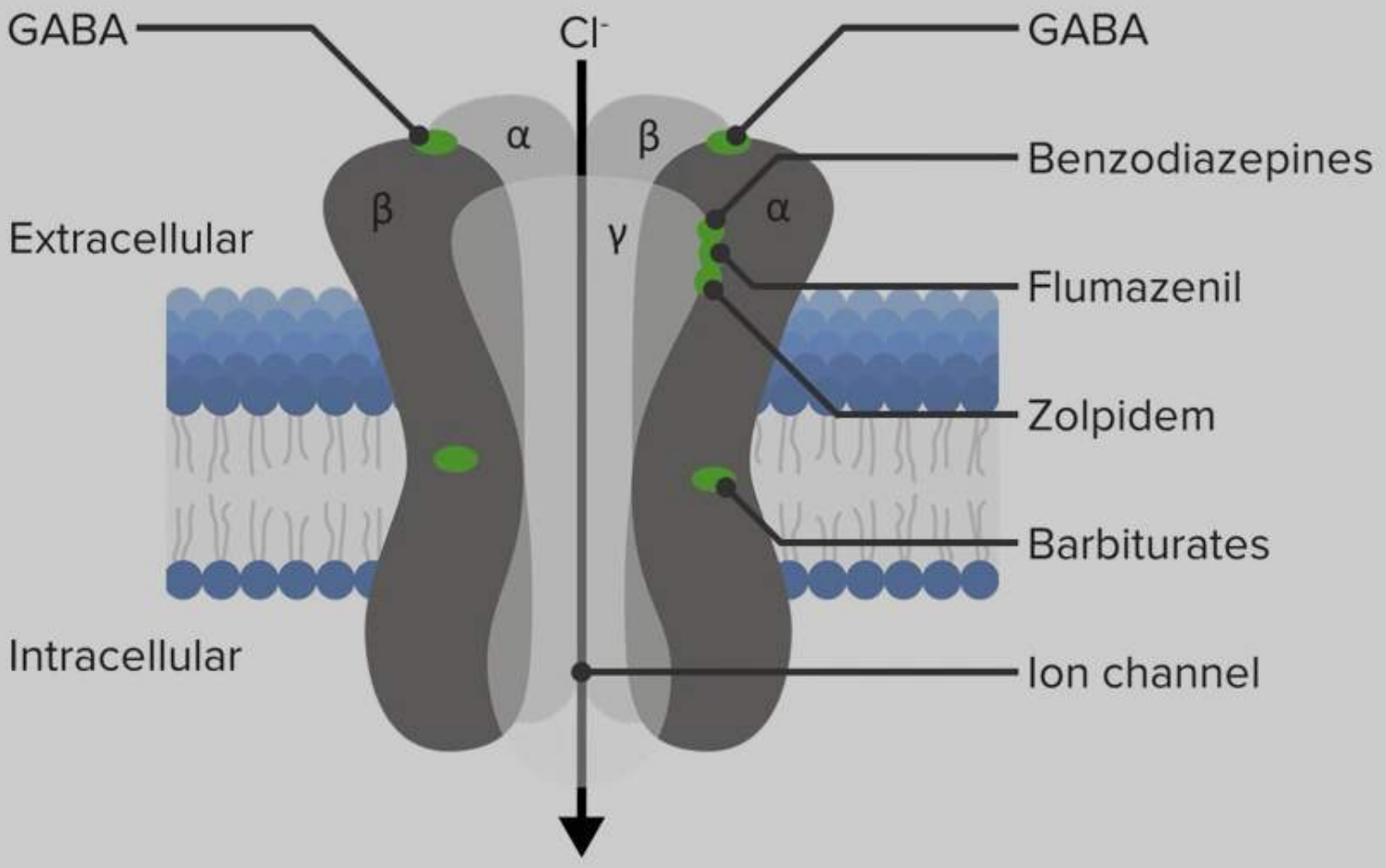


MOA OF BZD

BZD

⇣

Bind to ά/Y subunit of pentameric GABAa R

⇣

Increase the frequency of opening of Cl channel

⇣

Increase in chloride conductance

⇣

Membrane hyperpolarization

⇣

CNS depression -- inhibitory effect at different sites in CNS mainly limbic system and motor cortex

Potentiate inhibitory effect of GABA –GABA facilitating action

No mimetic action

- **Benzodiazepines-**
- **Nonbenzodiazepines**

Increase the ***frequency*** of chloride channel opening

- **Barbiturates –**
- Increase the ***duration (lifetime)*** of chloride channel opening

Newer non BZD hypnotics

zolpidem- high affinity for ά1 subunit of BZD R

selective hypnotic amnesic effect

V little anticonvulsant or muscle relaxant property

BZD inverse agonist [DMCM] inhibit GABA action and is convulsant

competitive BZD antagonist flumazenil blocks both sedative action of BZDs and convulsant action of DMCM

--

Additional MOA of BZD

- At higher concentration BZDs potentiate depressant action of **adenosine** by blocking its uptake
- Some actions of BZDs are countered by adenosine antagonist theophylline
- This suggests that BZDs could be acting through other mechanisms as well

BZD – Pharmacological actions

- **Sedation, hypnosis**
- **↓ sleep latency, ↓ night awakenings, ↑ sleep duration**
- **↑ stage 2, ↓ stage 3,4, ↓ REM**
- **Movements and night terrors reduced**
- **↓ hangover, ↑ refreshing sleep**

- **Less effect on REM (compared with barbiturates)**
- **Less distortion of sleep architecture**

- **Anterograde amnesia**

BZD – Pharmacological actions

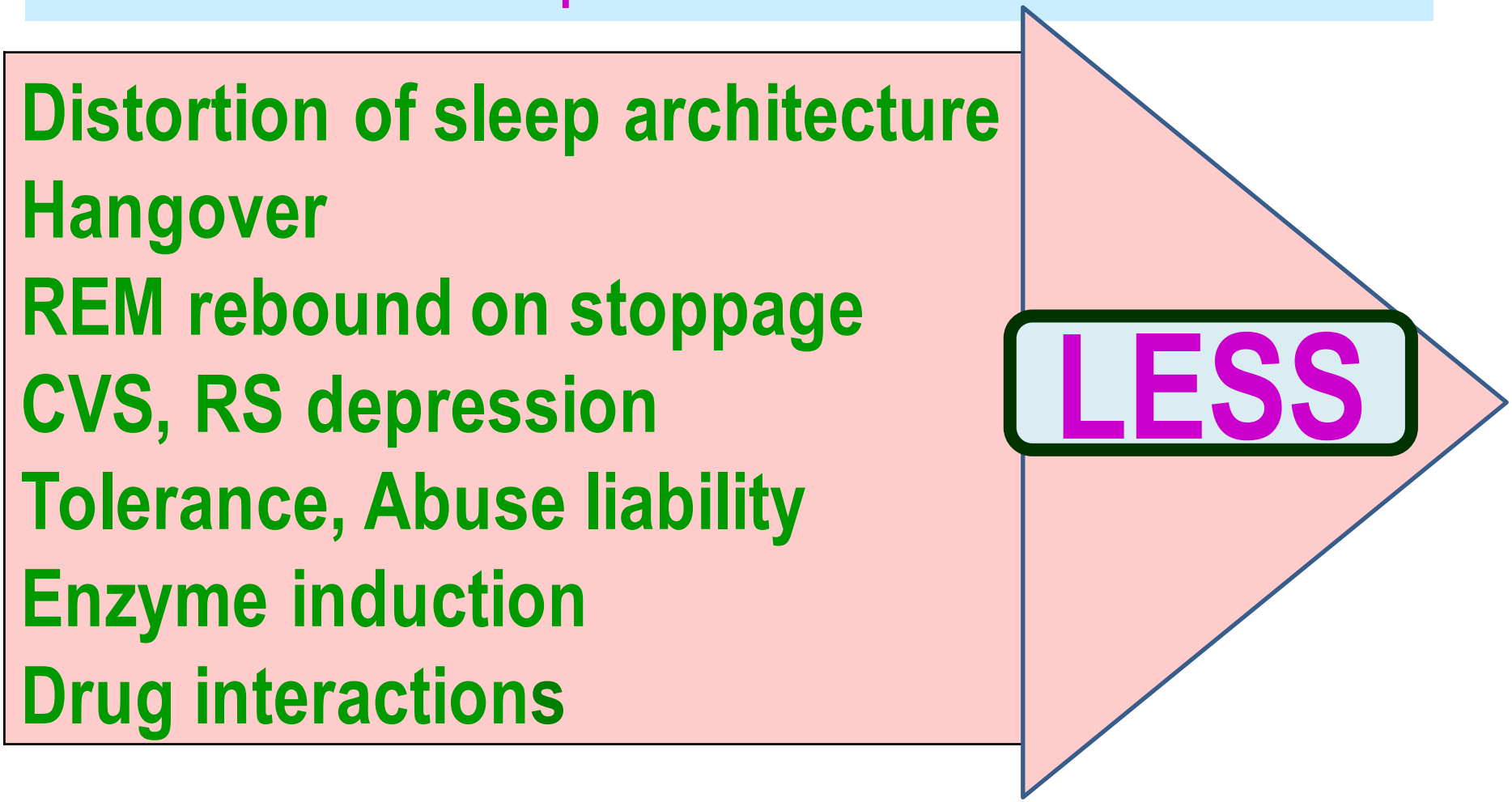
- **Limbic system - Selective anxiolytic action - *independent* of CNS depression**
- **Anticonvulsant – stop convulsions(epilepsy tetanus febrile)**
- **Skeletal muscle relaxation – (central) – clonazepam, diazepam**

- **↓ BP, myocardial suppression**
- **Respiratory depression –much less than barbiturates**

- **Decreases noctural HCl- prevents stress ulcers**

Benzodiazepines – advantages

as compared to barbiturates ---



- Better therapeutic Index - safer
- Competitive antagonist available - FLUMAZENIL

ADR OF BZD

- Relatively safe
- Side effects of hypnotic dose ---
- **Impairment of psychomotor skills –should not drive – older are more prone**
- dizziness vertigo ataxia amnesia weakness
- Sleep apnoea may↑
- Blurring of vision dry mouth urinary incontinence
- Cross tolerance to alcohol and other CNS depressants
- Dependence producing liability –low ,weak re inforcer
- Withdrawal syndrome - mild
- Administration during labour - flaccidity and **resp depression in the neonate --flaccid baby syndrome**
-

BZD ADR

- Old age-↑ forgetfulness
- Parodoxical stimulus –flurazepam
- Flunitrazepam –**date rape drug** . -tasteless BZD having sedative and amnesic action .
- Misused to obliterate memory of events to escape judicial punishment in sexual assaults .

BZD – drug interactions

Additive CNS depression –

Alcohol, Barbiturates, Classical antihistamines, Opioids

Induction – less as compared to barbiturates – don't give with oral contraceptives → contraceptive failure

CYP3A4 INHIBITORS decrease BZD metabolism → INCREASED EFFECTS

Ketoconazole, Erythromycin, Cimetidine, INH

Compare and contrast

barbiturates	benzodiazepines
1)Low therapeutic index Less safe	↑ Relatively safe
2)Abuse liability ↑ physical dependance ↑	< barbiturates low
3) Resp dep more cvs dep seen	less v less
↑ cl ch time	↑ frequency
GABA mimetic	GABAfacilitatory only
4)Disruption of sleep cycle of REM nonREM and Sleep architecture	less ,more like normal sleep
5)↑ sleep duration↓latency ↓awakening	better than barb

Barbiturates	benzodiazepines
↓REM↓ st 3,4	↓REM ↓ST 3,4↑ST2
REM rebound	less severe
More severe	
6)↑hangover	↓hangover
Less refreshing	more refreshing sleep
7)anterograde amnesia	yes but less
--→automation	
8)Skeletal muscle relaxation	better , at low dose

Barbiturates	benzodiazepines
9)Antiepileptic Anticonvulsant	**anticonvulsant - diazepam,lorazepam**
Phenobarb	**petit mal –clonazepam**
Iv anae—thiopental	**insomnia day time sedation,anxiolytic, antidepressant ,iv A conscious sedation preanaesthetic med**
10)No specific anxiolytic	**yes**
Hyperalgesia at higher dose	**not seen**

Barbiturates	benzodiazepines
11) Enzyme induction +	**less**
hence more drug I	
12) No specific antidote	**flumazenil –**
forced alkaline diuresis	**comp antagonist**
and haemodialysis	

BZD Pharmacokinetics

Markedly varied due to different lipid solubility and plasma protein binding

Diazepam 99% bound

Flurazepam 10% bound

Most undergo enterohepatic circulation due to glucuronic conjugation

LONG AND SHORT ACTING BZDs

long acting	t1/2	r'bution	hypnotic dose
Diazepam	30-60	+	5-10 mg
Flurazepam	50-100	_	15-30 mg
Nitrazepam	30	+/-	5 -10 mg
Short acting			
Alprazolam	12	+	0.25 -0.5 mg
Triazolam	2-3	+/-	0.125 -0.25

Midazolam used as iv anaesthesia

Elimination of BZDs

- **Slow – causes day time sedation**
- **produce active metabolite flurazepam**
- **Slow + redistribution –diazepam oxazepam**
- **In hepato toxicity which BZD is safer ---lorazepam**

- **Rapid elimination + marked redistribution**
- **---alprazolam ,temazepam**
- **Anxiety disorder**
- **Ultra rapid elimination –triazolam midazolam**
- **used for iv anaesthesia –banned in some countries due to psychosis**

Therapeutic uses - BZD

- ✓ Sedation for various procedures - Electroversion, catherization, ECT, endoscopies, obstetric and minor procedures
- ✓ Preanesthetic medication
- ✓ Conscious sedation (allowing the person to be receptive to instructions during procedures) (midazolam)
- ✓ Post-operative sedation
- ✓ IV anesthetic

- ✓ Anxiety states (phobia, panic attacks)
- ✓ Daytime sedation
- ✓ Insomnia (flurazepam, temazepam, triazolam), night terrors

Therapeutic uses - BZD

- ✓ **Alcohol / Drug withdrawal, management of addiction (chlordiazepoxide, chlorazepate, diazepam, oxazepam)**

- ✓ **Anticonvulsant (to stop the convulsions) status epilepticus, febrile convulsions, tetanus, drug withdrawal seizures**
- ✓ **-Lorazepam, diazepam (Intravenous)**

- ✓ **Centrally acting muscle relaxant: Spastic disorders, acute muscle spasms, orthopedic procedures**
- ✓ **Absence seizures (Petit mal), myoclonic, infantile spasm: Clonazepam, clobazam, chlorazepate di-K, nitrazepam**
- ✓ **Alongwith analgesics, NSAIDs, spasmolytics, antiulcer agents (decreases HCl, useful in stress ulcers)**

Aims of treatment of insomnia

Evaluate cause and pattern of insomnia

Choice of hypnotic is always patient specific

Aim –

To ↓ sleep latency

To ↑duration of sleep

To ↓ nocturnal awakening

to↓ next morning sedation

Long acting drugs → next morning sedation

Short acting drugs → next morning anxiety

Patient's own assessment of restful sleep and feeling fresh on waking up are important criteria

Classification of BZDs

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Temazepam	chlordiazepoxide	

Zopiclone
Zolpidem
Zaleplon

newer non BZD hypnotics

Newer non BZD hypnotics

Zopiclone bitter / metallic after-taste ↑ stage 3,4, minimal on REM

Zolpidem 5-10 mg hs (commonly used) minimal on slow-wave, ↓ REM,

Zaleplon shortest acting – taken late night mainly latency

Eszopiclone – newer ↑ stage 2

Bind to alpha1 part of BZD R **Flumazenil useful in overdose**

Highly selective hypnotic
Minimal REM suppression, ↑stage 3,4, ↓ sleep latency
Less disturbed sleep architecture, Less hangover
Less abuse potential, Minimal tolerance
Minimal physical dependence (Withdrawal less severe)

Nil or v less muscle relaxant anticonvulsant action

Preferred over BZDs

But long term ADR not yet known

FLUMAZENIL

- BZD receptor Antagonist
- Competitive inhibition of BZD agonist and inverse agonist and also non BZD hypnotics like zolpidem
- Reverses the depressant actions =BZDs and nonBZD
- Reverses stimulant action of DMCM =inverse agonist

flumazenil

- T1/2 = 1-2 hrs
- Used as Iv inj
- Prompt action
- Marketed as 0.1mg/ml 5ml or 10 ml vial

Therapeutic uses of flumazenil

1)Reversal of BZD anaesthesia –patient wakes up within one min

Early discharge possible

2) BZD overdose treatment (and nonBZD)

Iv 0.2mg reverses sedation and patient wakes up within 5 min

incomplete reversal of respiratory depression seen

3)Used for differential diagnosis in mixed CNS depressant poisoning

Sedation NOT abolished by 5 mg of flumazenil should be taken to be due to non BZD , non zolpidem depressants

Melatonin

- Pineal gland hormone
- Nocturnal secretion
- Receptors –MT1 MT2
- Role in body –entraining sleep wakefulness cycle with circadian rhythm

Therapeutic uses of melatonin

1)To ↓ jet lag and hasten re entrainment with day night cycle at new place

To be taken before flight

2) Shift workers—to change sleep pattern

3) Insomnia due to old age –natural secretion of melatonin ↓ with age

tried as ???? Antiageing agent

Perp –3mg tablet dose –one tab bedtime

Ramelteon

SELECTIVE melatonin receptor agonist – MT1 MT2 agonist

New drug but is available in India

Advantages as drug for treatment of insomnia

1) Hastens sleep onset
2) ↑ sleep duration
3) No next morning sedation
4) No rebound insomnia
5) No BZD side effects
6) So far no drug dependence seen

Prep -- 8mg tablet

dose –one tab half an hr before bedtime

Narcotic analgesics

Opioids

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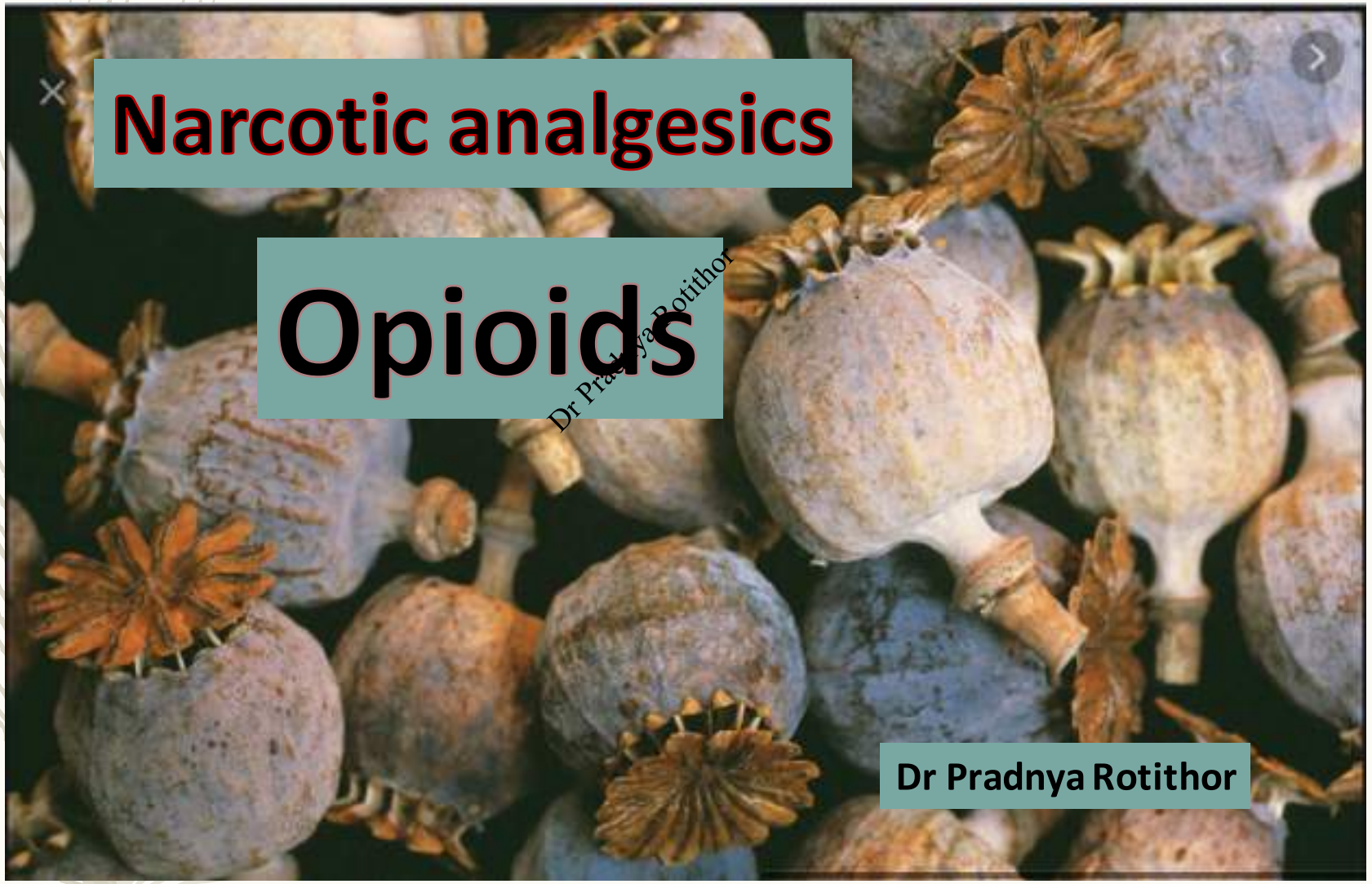

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Terminology

- **Opioid agonist** = activates some or all opioid receptors and do not block any…**Morphine**
- **Partial agonist** = a drug that can activate opioid receptor, but the response is submaximal….**buprenorphine**
- **Mixed agonist-antagonist** = a drug that activates some receptor subtypes and blocks some other subtypes….**pentazocin k agonist and mu weak antagonist**
- **Pure antagonist** = a drug that blocks all receptor subtypes….**naloxone**

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Opos = Greek = juice
Opium –in use since ancient times

Morpheus –Greek God of dreams
Morphine =prototype drug of group
Mu R agonist
Highly potent analgesic
Acting mainly on brain and spinal cord

Dr Pradnya Potithor


Dr Pradnya Rotithor

40 g poppy seeds ≈ 10 mg morphine ≈

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OPIOID/OPIATE RECEPTORS

Mu = μ **Delta = δ**

supraspinal analgesia, euphoria, respiratory depression, physical dependence

μ_1 = mainly analgesia

μ_2 = mainly respiratory depression

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Kappa = κ = spinal analgesia, miosis, sedation

Sigma = σ = Dysphoria, halluci, respiratory depr and vasomotor stimulation

Types of opioid Receptors

μ=δ
K =different and Opposing mu R

Sigma R = dysphoria Mydriasis tachycardia Pentazocin butorphanol

	μ receptor	κ receptor	δ receptor
Q Location	μ1 - supraspinal μ2 - spinal	κ1 - spinal κ3 -supraspinal	Spinal supraspinal
Effects	Analgesia μ1 μ2 Respiratory depression μ2 Sedation Euphoria Miosis Physical dependence Loss of GI motility μ2	Spinal analgesia **Q Dysphoria** Sedation Psychomimetic Physical dependence (nalorphine type)	Spinal analgesia Affective behaviour (Supraspinal) Respiratory depression Reduced GI motility
Agonists	Morphine, Codeine, Fentanyl and pentazocine weakly	Pentazocine	

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Distribution of opioid R in CNS

- Limbic system including amygdaloid nucleus, hypothalamus
- Medial and lateral thalamus, area postrema (CTZ)
- Nucleus of tractus solitarious (cough center)
- Substantia nigra, and spinal cord

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Receptor distribution

High densities of opioid receptors have been identified on peripheral nerve fibers, immune cells and five general areas of the CNS:

1. Brainstem: mediating respiration, cough, nausea & vomiting, maintenance of BP, papillary diameter and control of stomach secretion.
2. Medial thalamus: mediating poorly localized deep pain
3. Spinal cord: receptors located in the substantia gelatinosa are involved in the receipt & integration on sensory input leading to the attenuation of painful afferent stimuli.

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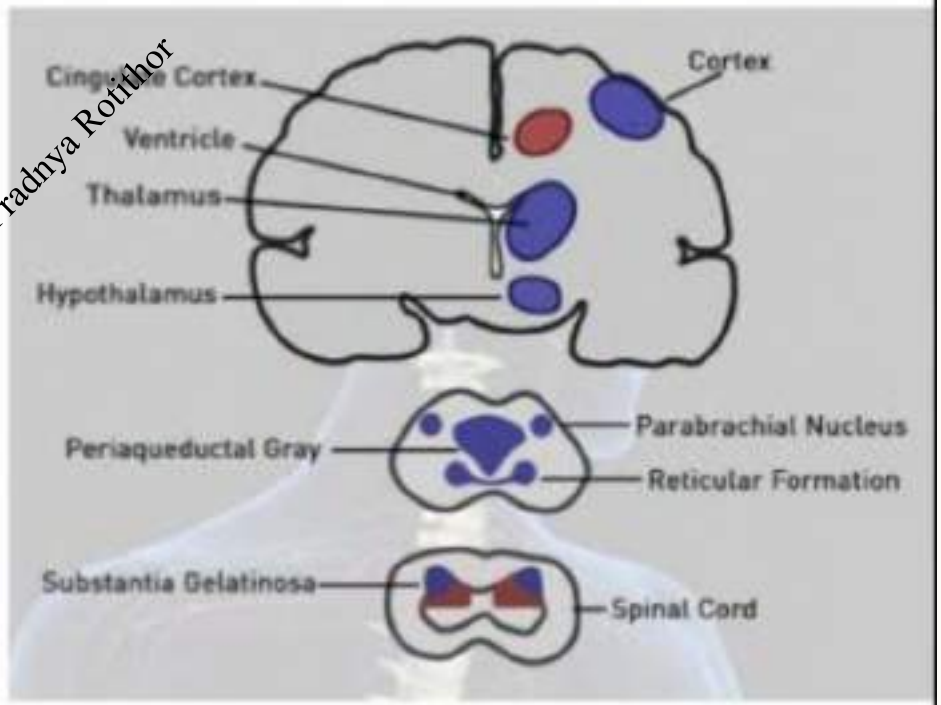

Mechanism of action of opioids

- 1)Receptor activation (ὐ, ð) →
- ↓intracellular cAMP formation
- →opening of K+ channels
- Receptor activation of(k)- suppresses voltage gated N type of Ca++ channels
- Both the actions result in neuronal hyper polarization
- and ↓ availability of intracellular Ca++
- → ↓neurotransmitter release by CNS and myenteric neurones
- Ex --↓glutamate from primary nociceptive afferents

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	Agonist	Antagonist
Mu	Strong: **Morphine, Pethidine, Methadone,** Levorphanol, **fentanyl**, alfentanil, sufentanil, **remifentanil** Moderate: Oxycodone, codeine Weak: Propoxyphene PA: **Buprenorphine-** (long)	**Naloxone** **Naltrexone** **Nalbuphine** **Pentazocine** **Nalorphine** – weak antagonist ***Butorphanol*** *– weak antagonist*
kappa	**Nalbuphine,Pentazocine** ***Butorphanol, Nalorphine***	**Naloxone** **Naltrexone**
Delta		**Naloxone, Naltrexone** **Nalorphine** (weak antagonist) ***Butorphanol*** *– weak antagonist*
Sigma		**Naloxone, Naltrexone**

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no	Opioid ligand	μ	k	delta
1	morphine	Strong agonist	Weak agonist	Weak agonist
2	enkephalin	Moderate agonist	-	Strong agonist
3	Beta endorphin	Strong agonist	-	Strong agonist
4	Dynorphine A B	Weak agonist	Strong agonist	Weak agonist
5	pentazocin	Partial agonist	Moderate agonist	-
6	butorphanol	Partial agonist	Strong agonist	-
7	buprenorphine	Partial agonist	Moderate antagonist	-
8	naloxone	Strong antagonist	Moderate antagonist	Weak antagonist
9	nalorphine	Strong antagonist	Moderate agonist	-
10	naltrexone	Strong antagonist	Strong antagonist	Weak antagonist
11	nalmefene	Strong antagonist	Strong antagonist	

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classification

- 1) Mu **Agonist**—a)naturally growing opium alkaloids—morphine ,codeine
- b) synthetic opioids –pethidine methadone fentanyl loperamide diphenoxylate ,tramadol

- **2)Mixed agonist-antagonist**
- pentazocine butorphanol buprenorphine nalorphine
- 3)Mu **Antagonists** –naloxone naltrexone nalmephene

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- Various other ways to classify –
- sources –natural alkaloids morhine codeine
- semisynthetic –heroin pholcodeine
- synthetic –pethidine fentanyl methadone tramadol dextropropoxyphene

- Based on receptor affinity on all three R

Acute effects

-Analgesia

-Dose dependent CNS depression

-Respiratory depression– medulla

-Histamine release – hypotension, peripheral vasodilation (decreased preload,afterload) bronchospasm

-Cough suppressant

-Decrease GI motility – constipation

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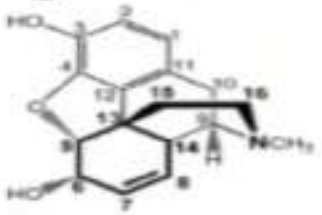
LAQ

MORPHINE (Pharmacological actions) - CNS



- **Analgesia:**
  - Strong analgesic
  - Visceral pain is relieved better than somatic pain
  - Degree of analgesia increases with dose
  - Nociceptive pain is better relieved than Neuretic pain
  - Associated reactions to pain are also relieved – apprehension, fear and autonomic effects
  - Tolerance to pain is better

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Pharmacological actions of Morphine (CNS) – contd.

- **Sedation:**
  - Drowsiness and indifference to surroundings
  - Inability to concentrate and extravagant imagination – colorful day dream
  - Apparent excitement
  - Larger doses produce sleep – EEG resembles normal sleep
- **Mood effects:**
  - In Normal persons calming effect, mental clouding, feeling of detachment, lack of initiative etc. – unpleasant in absence of pain
  - Sometimes DYSHORIA
  - But in persons with pain & addicts sense of wellbeing, pleasurable floating feelings – kick
  - EUPHORIA

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638 × 479

Pharmacological actions of Morphine (CNS) – contd.

- Depression:
  1. Respiratory centre depression – Both rate and depth of respiration are diminished
     - Dangerous in Head injury and asthmatics
  1. Cough Centre – Depressed
  2. Temperature regulating centre – depressed
  3. Vasomotor centre – high doses cause fall in BP

- Stimulation:
  1. CTZ – sensitize CTZ to vestibular and other impulses
  2. Edinger Westphal Nucleus – miosis
  3. Vagal centre – Bradycardia
  4. Hippocampal cells – convulsions (inhibition of GABA release)

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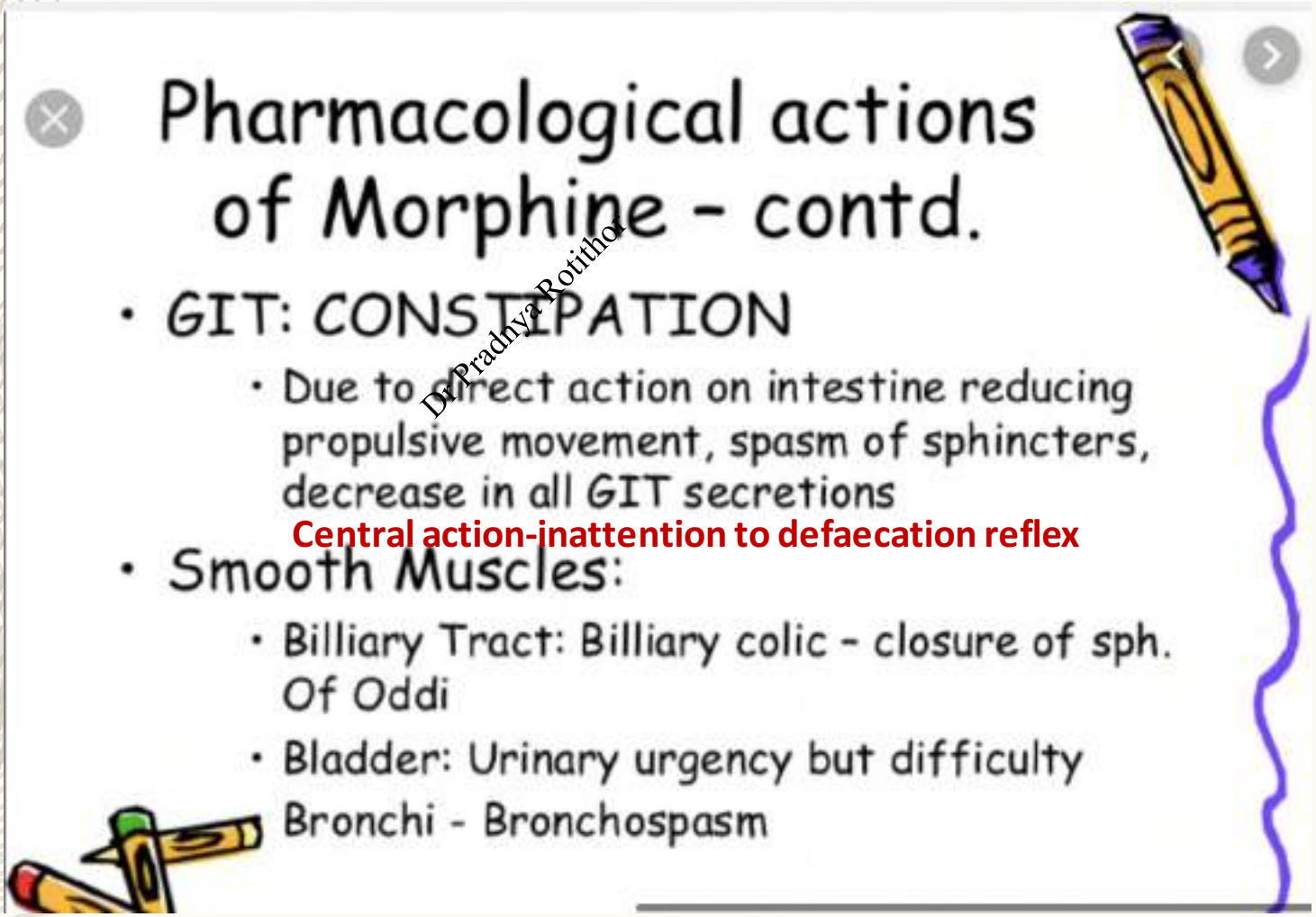
MCQ –**NO tolerance** develops to constipation action
addicts remain chronically constipated



Neuroendocrine actions

- **Hypothalamic influence on pituitary is reduced**
- Hence
- **FSH LH ACTH levels fall**
- Thus
- **sex hormones and cortisol levels are lowered**
- While ---
- **PRL GH levels rise as these are under predominantly inhibitory control**
- **Clinical effects seen in addicts –impotence ,menstrual irregularities ,infertility**

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CVS Actions

- Vasodilatation due to----
- Histamine liberation
- Depression of vasomotor centre
- Direct action decreasing tone of blood vessels

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- Decreased peripheral resistance leading to decreased cardiac workload
- Useful in MI

Contraindications (part of LAQ)

- Head injury
- Acute undiagnosed abdominal pain
- Bronchial asthma ,copd
- Respiratory insufficiency conditions –emphysema, pulm fibrosis, cor pulmonale
- Hypotensive states
- Extremes of age group –infants and elderly –more prone for resp depression
- Elderly male –high urinary retention chances
- Hypothyroidism ,hepatic and renal disorders –caution
- Unstable personalities
-

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- 1)Raises intracranial tension –by retaining CO2 ,
- Which adds to already raised ICT due to head injury

- 2) causes respiratory depression even at therapeutic dose

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- 3) morphine induces vomiting , miosis and altered mentation which interferes with the assessment of progress of head injury cases

SAQ/VIVA

Why is morphine contraindicated in head injury ?

- Morphine causes **spasm of sphincter of Oddi**
- Raises intrabiliary pressure
- **May cause/aggravate biliary colic**
- Bladder sphincter tone increases –urinary urgency
- **Inflamed appendix may rupture**
- Morphine aggravates diverticulitis , pancreatitis, biliary colic
- Atropine does not counter this colic fully
- Naloxone completely counters biliary colic
- ***Morphine can be given AFTER the diagnosis is established.***
- Pentazocin, buprenorphine –less likely to aggravate biliary colic

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viva

Why is morphine contraindicated in acute undiagnosed abdominal pain ?

Acute morphine poisoning

- >50 mg of morphine
- Lethal dose is 250mg
- Stupor, coma, shallow breathing, cyanosis, pinpoint pupil, fall in BP, convulsions
- Death due to respiratory failure

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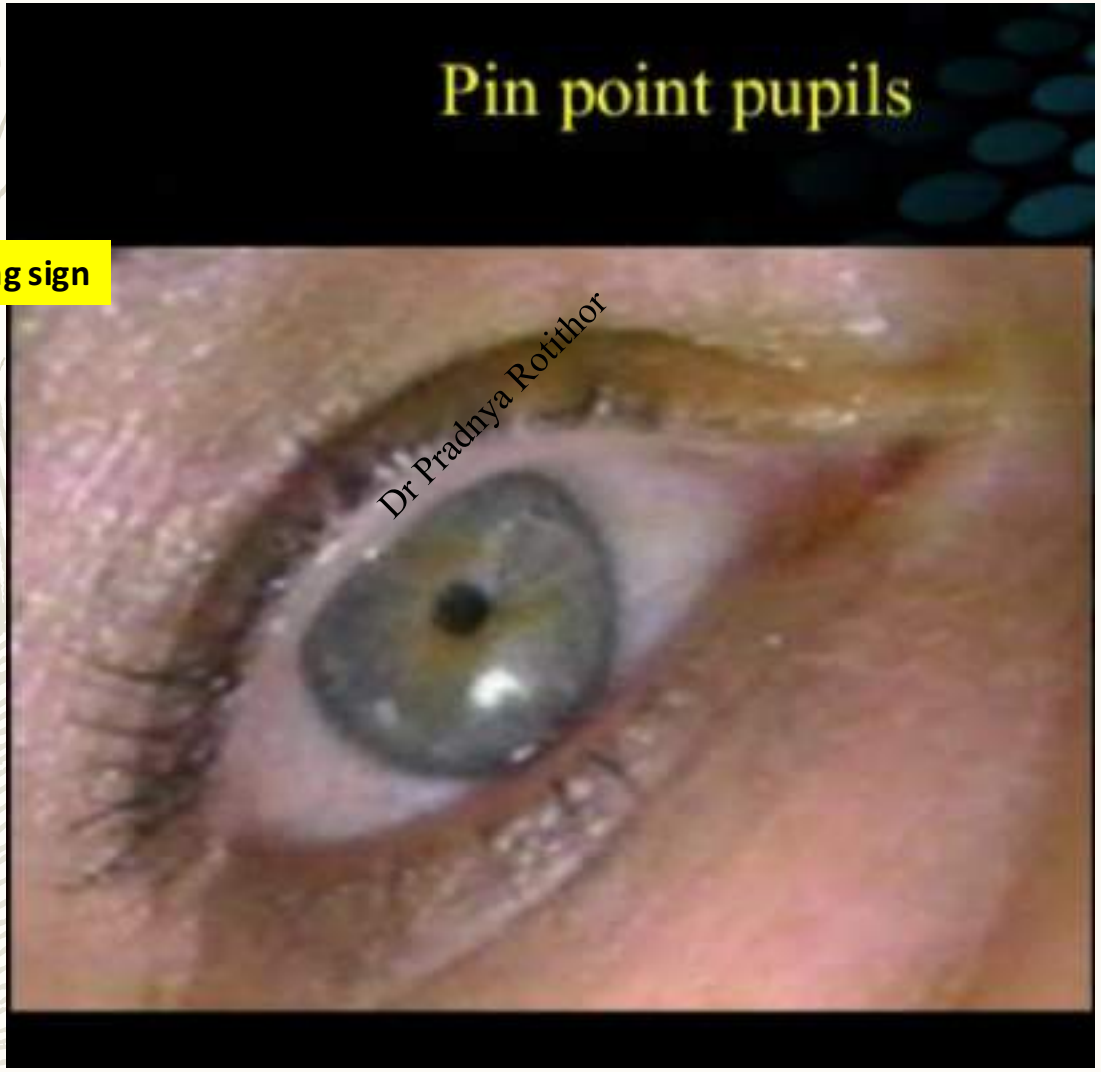
Treatment

- Positive pressure respiration — **Ventilatory support**
- Iv fluids
- Gastric lavage with potassium permagnate
- Naloxone 0.4-0.8 mg/ 2-3 min IV till resp improves — **Specific antidote**

960 × 720

Acute morphine poisoning sign



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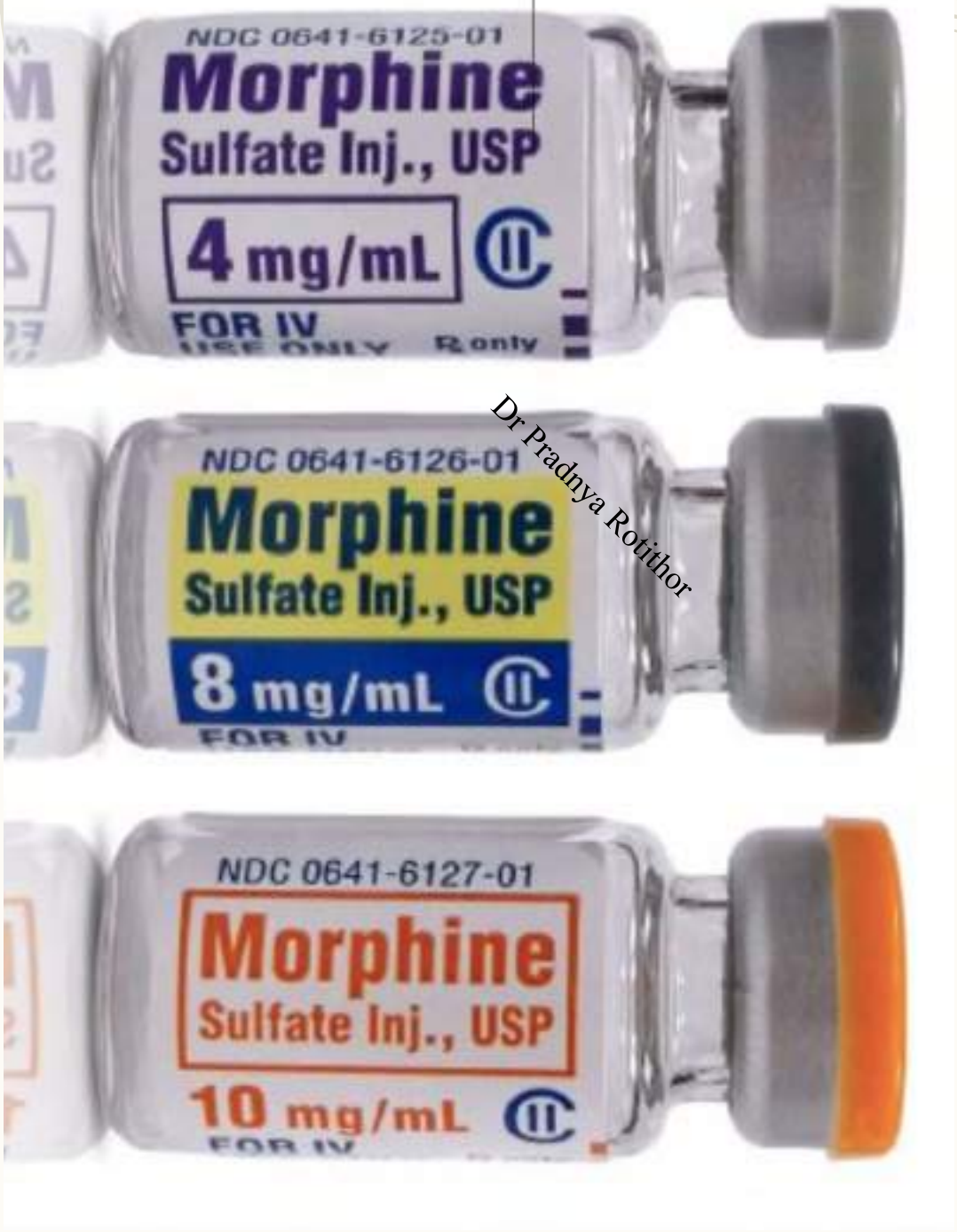

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Therapeutic uses of morphine and other opiates

–Analgesic

- Pre anaesthetic medication
- Balanced anaesthesia and surgical analgesia
- Relief from anxiety and apprehension –eg MI
- Acute LVF-
- Antitussive
- Antimotility for GIT –diarrhoea treatment

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Antimotility Opiates

DIPHENOXYLATE (lomotil)

- Synthetic opioid related to pethidine
- Action similar to codeine
- Low Abuse liability as crosses BBB
- Combined with sub pharmaceutical dose of atropine 0.025 mg to discourage abuse—overdose →disturbing atropinic side effects---

LOPERAMIDE(imodium)

- Opiate analogue—acting on peripheral ὐ R and added weak anti cholinergic property
- More potent than codeine,

  GIT secretion↓

  ↑anal sphinctor tone

  calmodulin action
- CNS entry nigligible
- No drug abuse liability
- --

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ACUTE LVF

- Dramatic relief in Acute LVF on iv morphine

- 1) ↓preload due to vasodilatation and pooling of blood at periphery
- 2)relieves pulmonary congestion and oedema by shifting blood from pulmonary circulation to systemic circulation
- 3)Allays air hunger by depressing respiratory centre
- 4)calming effect

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Individual drugs

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- **Codeine** –natural alkaloid
- less potent than morphine
- selective cough suppressant --dry irritant cough
- orally effective
- used also as antidiarrhoeal

heroin

- Semisynthetic
- More lipid soluble ,enters CNS rapidly
- More euphoriant –highly addictive
- 3 times more potent than morphine
- Hence favoured in illicit drug trafficking
- **Banned in most countries**

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pethidine

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- Synthetic opioid
- 1939 –synthesized as atropine substitute
- **Chemically unrelated to morphine but acts on ụ R and actions are blocked by naloxone**
- Short acting with rapid onset of action
- Miosis and constipation are less marked
- ***Produces tachycardia instead of bradycardia due to atropine like action***
- Uses –postop analgesic and preanaesthetic drug
- Prep –inj pethidine hcl 100mg/2ml tab –100mg

Fentanyl
synthetic ,pethidine congener

- **80 to 100 times more potent than morphine**
- **Highly lipid soluble ,enters CNS rapidly**
- **High redistribution**
- **Analgesia –5 min after iv dose**
- **Iv fentanyl used exclusively in G A**
- **Transdermal patch –**

  Postoperative analgesia

  cancer pain - needs to be changed 2-3 days

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Methadone
synthetic ,similar to morphine

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- Used as ***substitution therapy*** during opioid dependence treatment --**MCQ**
- 1mg of methadone = 4mg M
- = 20 mg of pethidine
- = 2mg of heroin
- Methadone maintenance therapy –
- Oral methadone is given in sufficient dose to produce high degree of tolerance to pleasurable effects of iv opioids and subject gives up habit

Dextropropoxyphene synthetic

- Used as oral analgesic in combination with paracetamol
- Banned in UK but is used in USA and India

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tramadol

- Analgesic –oral and injectable
- Postoperative analgesic and diagnostic procedures
- 50-100mg im or slow iv 6-8 hrly

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Complex relation between opioids and opioid antagonist at different R

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- **1) Agonist at k and antagonist at ụ--**
- Nalorphine
- Pentazocin
- Butorphanol
- **2)partial/weak agonist at ừ and antagonist at k--**
  -buprenorphine
- **3)pure antagonist –**naloxone ,naltroxone ,nalmefene

pentazocin

- **Weak mu antagonist**
- **Marked k agonist**
- Analgesia produced is spinal (k)
- Biliary colic constipation vomiting less than M
- “Drug seeking “ seen but abuse liability is lower than M
- **Tachycardia and ↑ BP at higher dose**
- Uses-postop pain ,burn and trauma ,fracture pain
- Inj fortwin -30mg/ml
- tab fortagesic –pentazocin+pct

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butorphanol

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- **K agonist**
- More potent than pentazocin
- Use –postop pain
- short lasting pain like renal colic
- **Inj butrum** –1mg/ml 2mg/ml
- **Both pentazocin and butorphanol are contraindicated in cardiac asthma**
- **Postaddicts recognize –pentazocine as opiate and butorphanol as barbiturate and mostly dislike it**

buprenorphine

- **Partial agonist –mu R**
- **Antagonist ------- k R**
- 25 times more potent than morphine
- But with low intrinsic activity and ceiling effect
- Shows tissue accumulation
- Terminal t1/2 = 40 hrs
- **Sublingual route possible**
- Prep –0.2 mg tab 0.3 mg /ml inj 1,2 ml amp
- Uses –postop pain ,MI pain ,long lasting pain conditions like cancer

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Pure opioid antagonists
Naloxone naltrexone nalmefene

- **Competitive antagonist at all opioid R and block mu R at lower dose**
- **No agonistic action even at high doses**
- **Uses –reversal of morphine actions –**
- **iv inj 0.4 -0.8 mg**
- **First to go is analgesia**
- **Respiration becomes normal and even stimulated as respiratory centre becomes sensetive to retained CO2**
- **Pupils dilate**
- **Sedation is less completely reversed**
- **At higher doses naloxone antagonises agonistic action of nalorphine ,pentazocin**
- **Hence what is NOT blocked by naloxone is believed to be mediated through delta R**

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NALOXONE contd

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- Naloxone does not effectively reverse buprenorphine which is already bound to R
- Naloxone precipitates morphine withdrawl syn at 0.4 mg iv dose
- And at much higer dose of 5mg precipitates nalorphine and pentazocin withdrawal
- **Naloxone also blocks endogenous opioids and thus blocks placebo ,acupuncture and stress induced analgesia**

naloxone

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- **Ineffective orally**
- **t1/2 –1 hr**
- **Inj narcotan –0.4 mg /ml 1 ml amp**

–Uses-of naloxone

– 1) Drug of choice for M poisoning

0.4-0.8 mg IV max 100 mg

2) Reversal of neonatal asphyxia due to opioid used during labour

10 лg/kg in umbicial cord

3) R_x of overdose of other opioids and agonist, antagonist except buprenophine

4) Other uses-

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Naltrexone

More potent than naloxone orally acting.

Used for

1) " opioids blocked " therapy of post addicts – 50 mg/day ↓ craving for M

2) Alcohol craving ↓hence used to treat relapse

ADR- Hepatotoxic high dose

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Nalmefene – Not hepatotoixic , longer acting orally effective .

Methyl Naltrexone does not cross BBB but blocks л action at periphery hence used to reverse constipation in cancer patient taking M and those on methadone maintenance therapy.

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ETHYL AND METHYL ALCOHOLS

Dr Pradnya Rotithor

DR PRADNYA ROTITHOR

Good morning

PHARMACOLOGICAL ACTIONS

- **1)Local –**Cooling Astringent
- **2) CNS**—**depression**—cortex and reticular activating system are most sensetive
- **3)CVS**-dose dependent effects
- Small –vasodilatation—face ,gastric
- Moderate –tachycardia mild rise in BP
- Large –low BP as VM centre is depressed
- ***Chronic alcoholism contributes to HT ,cardiomyopathy and arrhythmias***

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- 4) blood --↑ HDL ↓ LDL on small regular intake
- Chronic alcoholism –disturbed folate metabolism → megaloblastic anaemia
- 5) **GIT –chronic gastritis**
- **acute pancreatitis**
- 6)liver – impaired gluconeogenesis
- chronic alcoholism→ oxidative stress → cellular necrosis
- This along with inflammation ,↓ glutathione ↑lipid peroxidation coupled with nutritional depletion and vitamin deficiency →**LIVER CIRRHOSIS**

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- 7)Renal --↓ ADH → **diuresis**
- 8) aphrodisiac
- But chr alcoholism →
- impotence ,gynaecomastia
  testicular atrophy infertility

9) endocrine—

acute intoxication →hypoglycaemia

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PK

- Crosses BBB
- Crosses placenta
- Metabolised in liver
- Follows zero order kinetics
- **Concentration in exhaled air is used for medico legal test**
- Subject blows into a balloon and portable analyzer measures alcohol

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metabolism

- Ethyl alcohol
- ↓alcohol dehydrogenase
- (# fomipezole)
- Acetaldehyde
- ↓ aldehyde dehydrogenase
- (# disulfiram)
- Acetate
- ↓
- CO2 + H2O

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Drug interactions

- Potentiates all CNS DEPRESSANT DRUGS
- Opioids
- BZDs
- Antihistaminics
- Reserpine
- Methyldopa
- clonidine

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Drug interactions

- Potentiates adverse effects of ----
- Aspirin and other NSAIDs= GI bleeding

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- Sulfonylureas = hypoglycaemia
- Oral anticoagulants = bleeding
- Isoniazid =hepatic toxicity

Disulfiram like reaction

- Metronidazole and its analogues
- Griseofulvin
- Chlorpropamide
- Tolbutamide
- Cephalosporines
- Phenylbutazone

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contraindications

- Peptic ulcer
- Epilepsy
- Severe hepatic disorder
- Unstable personalities
- pregnancy

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Foetal alcohol syndrome

- IUGR
- microcephaly
- Retarded postnatal growth
- Low IQ
- Low body immunity
- ↑ susceptibility to infections

- ***abortion, stillbirths and LBW babies***

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Acute alcohol intoxication

- Hypotension
- Hypoglycaemia
- Gastritis
- Respiratory depression
- Collapse ----coma ----death

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- Death due to acute poisoning is rare

Treatment

- Gastric lavage –if brought v early
- Prevention of aspiration of vomitus –keeping airway patency
- Correction of hypoglycaemia by iv fluids
- Inj thiamine 100mg in 5% dextrose
- Haemodialysis if needed

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Alcohol withdrawal syndrome

- Signs and symptoms –
- 8 hours tremulous syndrome
- Anxiety N V irritability tremulousness
- 24 hours seizure syndrome
- Hyper excitability
- convulsions
- Disordered perception
- Impaired sleep/insomnia
- 2 to 5 days delirium tremens –rare
- Tremors disorientation Hallucination
- ANS over activity convulsions

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Treatment of withdrawal syndrome

- Symptomatic
- IV Glucose
- Iv thiamine 100mg
- Electrolyte and nutrition balance
- Iv Diazepam –convulsions
- Clonidine- alpha adrenergic agonist } ANS
- Propranolol -Beta blocker } over activity R_X

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Alcohol dependence

- Detoxification
- Safe withdrawal to make patient alcohol free

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- Support therapy
- To prevent relapse

- Rehabilitation
- Psychotherapy institutional therapy

Treatment of alcohol dependence

- Substitution therapy
- with BZDs like diazepam and chlordiazepoxide
- BZDs are later withdrawn gradually
- To prevent relapse –to ↓ craving for alcohol
- naltrexone –long acting opioid antagonist
- Hepatotoxic
- Nalmefene –no hepatotoxicity
- New drugs for relapse prevention --
- Acamprostate ,ondensetron –$5HT_3$ antagonist , topiramate --antiepileptic drug
- Aversion drug -disulfiram

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Therapeutic uses of ethanol

- Metanol poisoning treatment
- Intractable neuralgia –injection around nerve causes permanant loss of transmission –trigeminal neuralgia
- Other than this –restricted to external uses –
- Antiseptic
- Rubifacient
- Prevention of bedsores –
- astringent aftershave lotions antiperspirants
- to lower body temp in fever
- To ward off cold –vasodilatation
- Nasal drops for reflex stimulation in fainting or hysteria

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Aldehyde syndrome

- Ethyl alcohol
- ↓alcohol dehydrogenase
- Acetaldehyde
- ✖ ↓ aldehyde dehydrogenase inhibitor = disulfiram
- acetate
- Irreversible inhibition
- Blood conc of aldehyde ⬆ ➡distressing symptoms

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- aversion technique in motivated patients of chronic alcoholism who are determined to give up addiction

- Due to risk of severe reaction disulfiram is infrequently used
-

disulfiram

- Trade name international –antabuse 250mg tab
- Dose
- 1000 mg ---day1
- 750 mg day2
- 500 mg day 3
- 250 mg day 4 onwards
- Action reaches peak within 12 hrs and lasts for 7 to 14 days after stoppage of drug

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MOA of disulfiram

- Being irreversible inhibitor of enzyme aldehyde dehydrogenase –
- Synthesis of fresh enzyme by the body is essential for alcohol metabolism
- Hence subject's resolve not to drink alcohol is reinforced by distress produced even on low consumption of alcohol
- Disulfiram should not be used if there is physical dependence

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Methyl alcohol
methanol /wood alcohol

- NOT SUITABLE FOR DRINKING
- **Methanol**
- ↓ alcohol dehydrogenase
- **Formaldehyde**
- ↓ aldehyde dehydrogenase
- **Formic acid**

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- But the rate of metabolism is slow
- 1/7 th of ethanol
- Follows zero order kinetics
- ***Toxic effects are due to formic acid and not of methanol***
- Metabolism of formic acid is folate dependent and is slow

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Methanol poisoning
khopadi daru

- Highly fatal
- Symptoms –
- **Retinal damage is specific toxicity of formic acid –(viva Q)**
- Congestion of optic disc
- Blurring of vision
- Blindness almost always preceeds death

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Other symptoms

- Vomiting
- Headache
- Dyspnoea
- Hypotension
- Bradycardia
- Delirium
- Coma
- Acidosis due to formic acid accumulation

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treatment

- *dark quiet room* –to protect eyes from light
- Gastric lavage with soda bi carb if brought within 2 hrs of ingestion
- Iv soda bi carb infusion – to prevent retinal damage
- KCl infusion to counter hypokalemia produced by sodium bicarbonate
- maintenance of respiration and BP

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Ethanol for methanol poisoning viva Q

- Same metabolic pathway and ethanol being 7 times faster
- saturates alcohol dehydrogenase ➡retards methanol metabolism
- ⬇ rate of generation of toxic metabolites
- through ryle's tube if iv prep is not available
- **Disadvantage**
- treatment needs over several days and itself causes intoxication

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fomepizole

- **alcohol dehydrogenase inhibitor**
- Retards methanol metabolism
- Advantageous than ethanol as --

Has longer t1/2

No intoxication

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15 mg /kg iv loading dose

10mg/kg 12 hrly till methanol level < 20mg/dl

BUT not available in India v easily

~~Highly expensive~~

Treatment----

- Haemodialysis-----
- Hastens recovery
- removes both methanol and formates
- Folate therapy –
- To hasten formate metabolism
- Calcium leucovorin –50mg 6 hrly

Dr. Pradnya Rotithor

Thank you

Pre-anaesthetic medication

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DR PRADNYA ROTITHOR

definition

Drugs used before anaesthesia to make it safe and pleasant

and

to counter some of the adverse effects of anaesthetic agents

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Preoperative visit by anaesthetist is essential

Advantages

↓ preoperative apprehension and anxiety facilitate smooth induction .

Amnesia for pre and postoperative events

supplement and potentiate analgesic action of anaesthetic agent leading to dose reduction

Extending antiemetic action to postoperative period ↓N ↓V

↓ volume and acidity of gastric juice so that it is less damaging to lungs if aspirated

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Aims

Antianxiety Amnesia Analgesia

Antiemetic Antisecretory

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combination of drugs is required to achieve different requirements depending upon –

type and duration of anaesthesia

type of surgical procedure

clinical status of the patient

Preoperative evaluation and counseling by anaesthesiologist

Groups of drugs used

Anticholinergics-anti-secretory

atropine glycopyrrolate

Benzodiazepines -Sedatives/antianxiety /amnesia –

diazepam 5mg lorazepam 2mg

midazolam—

Opioids -- narcotic analgesics

morphine pethidine fentanyl pentazocin

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Antihistamines -**promethazine**

H2blockers /PPI – reduce gastric acid

ranitidine /famo tidine

omiprazole/panto prazole

Antiemetic –prokinetic

metoclopramide domperidone

ondensetron

anticholinergics

Atropine –0.6mg im/iv

Glycopyrrolate --0.2mg im/iv

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1) ↓ salivary and respiratory secretions

(caused by ether anaesthesia)

↓↓need with less irritant anaesthetic drugs being used currently.

2) currently used to **↓ vagal bradicardia** and **hypotension** and **prophylaxis of laryngospasm** due to respiratory secretions.

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anticholinergics

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glycopyrrolate vs atropine

Antisecretory	+++	++
Tachycardia	++	+++
CNS effect	-	+
Bronchodilatation	++	++

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Now mostly these drugs are used iv intraop as and when required

Disadvantages of anticholinergics

Pupils dilate –pupillary signs get abolished

↓ tone of lower oesophageal sphinctor hence gastric reflux ↑

Dryness of mouth –both pre and post op may be v distressing

Contraindicated in febrile patient

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Benzodiazepines

Sedative drugs – one hr before surgery

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Diazepam—5 -10mg oral or im

Lorazepam– 2mg /0.05mg/kg im

midazolam iv

Advantages –

- Calms patient
- Smoothens induction of anaesthesia
- Less recall of procedure (amnesia)
- Less respiratory depression
- Less accentuation of post operative vomiting
- Counteract CNS toxicity of Local Anaesthesia drugs
- For minor surgeries and endoscopies these are used with inj pethidine or fentanyl

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antihistamines

promethazine 50 mg im

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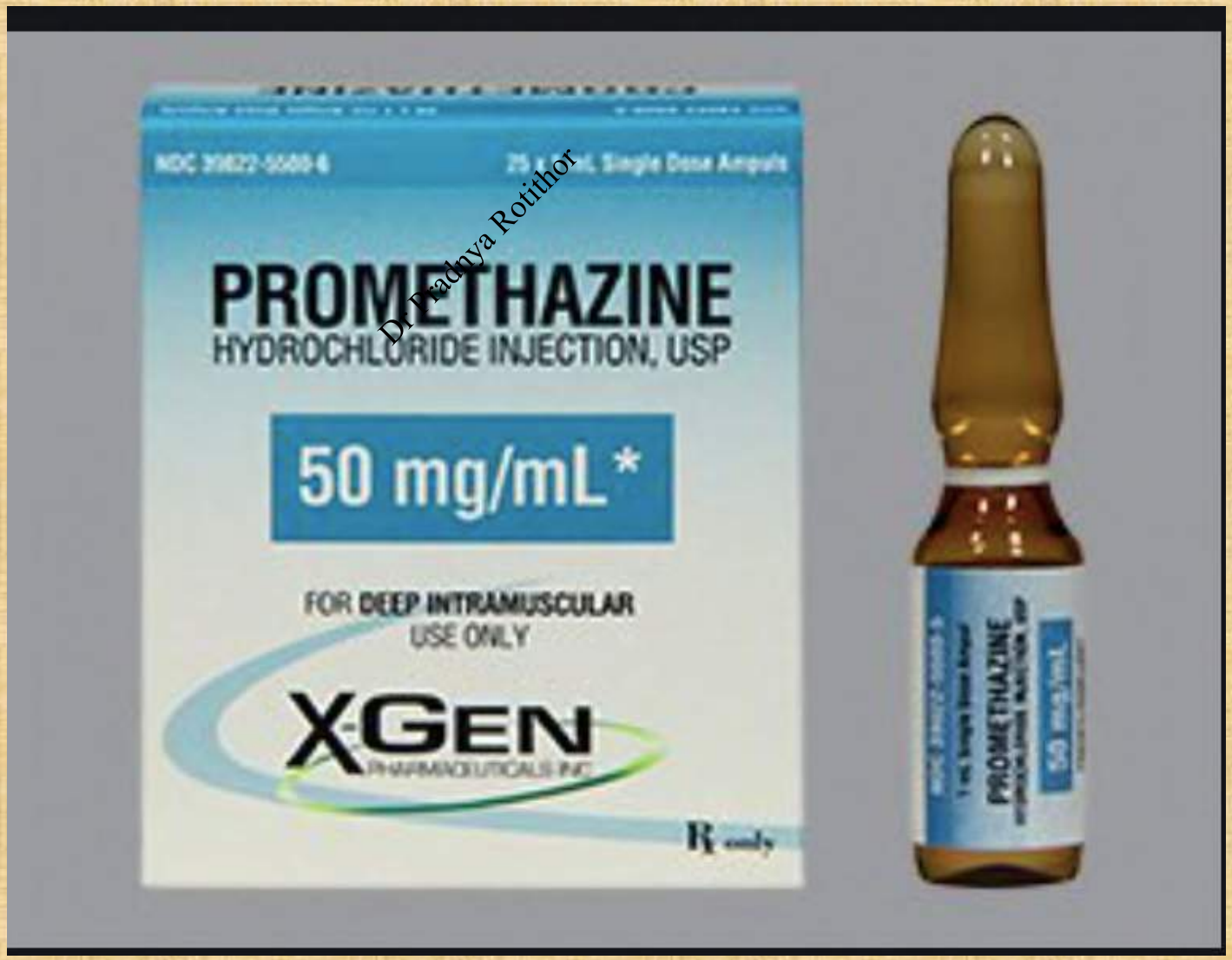
multipurpose drug – anti allergic

sedative antiemetic anticholinergic

and

Minimal respiratory depression



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Opioids –narcotic analgesics

Morphine 10 mg pethidine 50-100 mg

Fentnyl

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Advantages –

Pre and post operative **analgesia**

↓ postoperative restlessness

Smoothens induction of anaesthesia

↓ the dose of anaesthetic drugs

Supplement poor analgesia of thiopental and halothane

Disadvantages of opioids

Respiratory depression **Lowers BP**

Interferes with pupilary signs of anaesthesia

may precipitate asthma

Delays recovery **Lack amnesia**

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↑ biliary spasm and delays gastric emptying

Contributes to postoperative constipation ,vomiting and urine retention

Pethidine –tachycardia

Used selectively --

H2 BLOCKER /PPI

Prolonged surgery ,LSCS ,obesity --↑gastric secretions → regurge →aspiration pneumonia

volume < 25ml and PH is > 3.5=↓ chances of aspiration and less damaging to lungs if aspirated

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Ranitidine 150 mg **Famotidine 20 mg**

Omeprazole 20mg **Pantoprazole 40mg**

Now - **routinely employed**

antiemetics

Preoperative use of

Inj metoclopramide 10-20mg

↑ gastric emptying—prokinetic action

↑ tone of lower oesophageal sphinctor

↓ chances of reflux and aspiration

AND thus

reduces postoperative vomiting

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Disadvantages –motor restlessness

extrapyramidal side effects

Prokinetic action of metoclopramide is handy if patient is not NBM During emergencies

Dr Pradnya Author

NBM =NIL BY MOUTH

**Anaesthetist never forgets to ask –
how long the patient is NBM !!!!!**

Other anti-emetics

Domperidone –equally effective and with less ADR

Ondansetron –selective 5HT3 blocker

No significant ADR

Is now a drug of choice for antiemetic action

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ranitidine

metoclopramide

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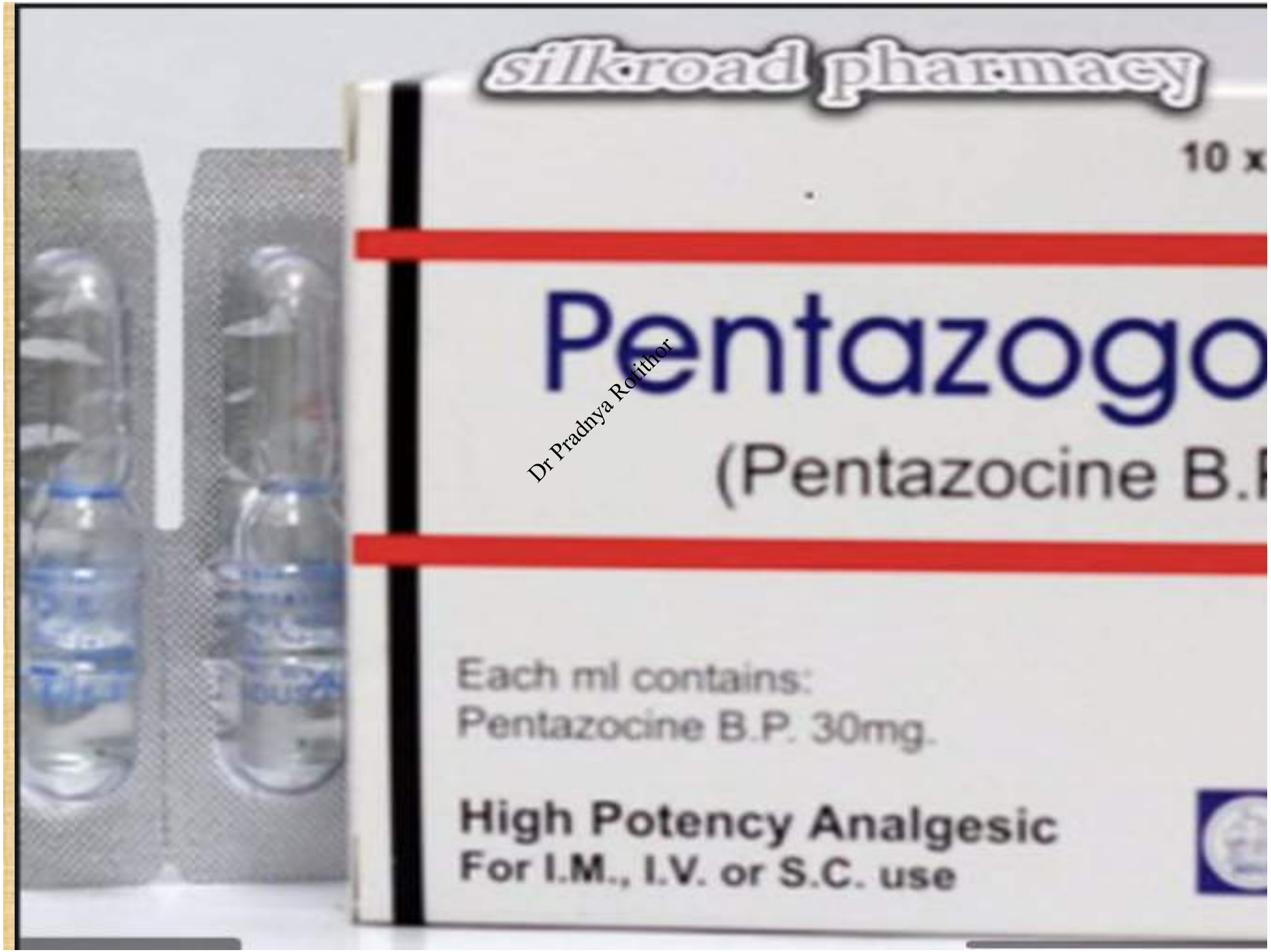
ondansetron

DR P



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Fentanyl TTS patch is also available

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though not required for anaesthesia antibiotic prophylaxis is given along with these drugs

Patients with special problems

Proper pre evaluation and Specific premedication is required for patients with pre existing diseases like

HT ,MI

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DM

Bronchial asthma

Drugs used during anaesthesia

Skeletal muscle relaxants –

For intubation --**succinylcholine**

to provide good muscle relaxation for surgeon to operate –**atracurium**

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--

Drugs administered to counter anaesthesia complications –

Vasopressor agents to counter hypotension

Antiarrhythmics

Anticonvulsants

DRUGS TO BE STOPPED

The risk of stopping the drug for some of the long term illnesses is greater than continuing during surgery

Examples –anti thyroid anti glaucoma

anti parkinsons

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BUT some drugs need to be discontinued –

Aspirin

MAO inhibitors

Warfarin

Oral contraceptive pills

Take home message

Preanesthetic medication:

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It is the use of drugs prior to anesthesia to make it more safe and pleasant.

- To relieve anxiety – benzodiazepines.
- To prevent allergic reactions – antihistaminics.
- To prevent nausea and vomiting – antiemetics.
- To provide analgesia – opioids.
- To prevent bradycardia and secretion – atropine.

MUHS QUESTIONS

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SAQ

What is pre anaesthetic medication and enlist drugs used as pre anaesthesic medication

Glycopyrrolate MCQ

GENERAL ANAESTHESIA

DR PRADNYA ROTITHOR

What is G A ?

A state of **unconsciousness**

achieved mainly **for carrying out a surgery**

with **abolishment of all the peripheral sensations**,

so that the patient **does not get pain** during the procedure plus

easy to **maintain the respiration, cardiovascular functions**,

and keep the patient **out of anxiety** as well as **apprehension**.

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definition

General anaesthetics are the agents that bring about ---

Analgesia

amnesia

Inhibition of autonomic reflexes

Skeletal muscle relaxation

And

Reversible loss of consciousness

First use of nitrous oxide –1844 in USA

Dentist Horace Wells used it for tooth extraction

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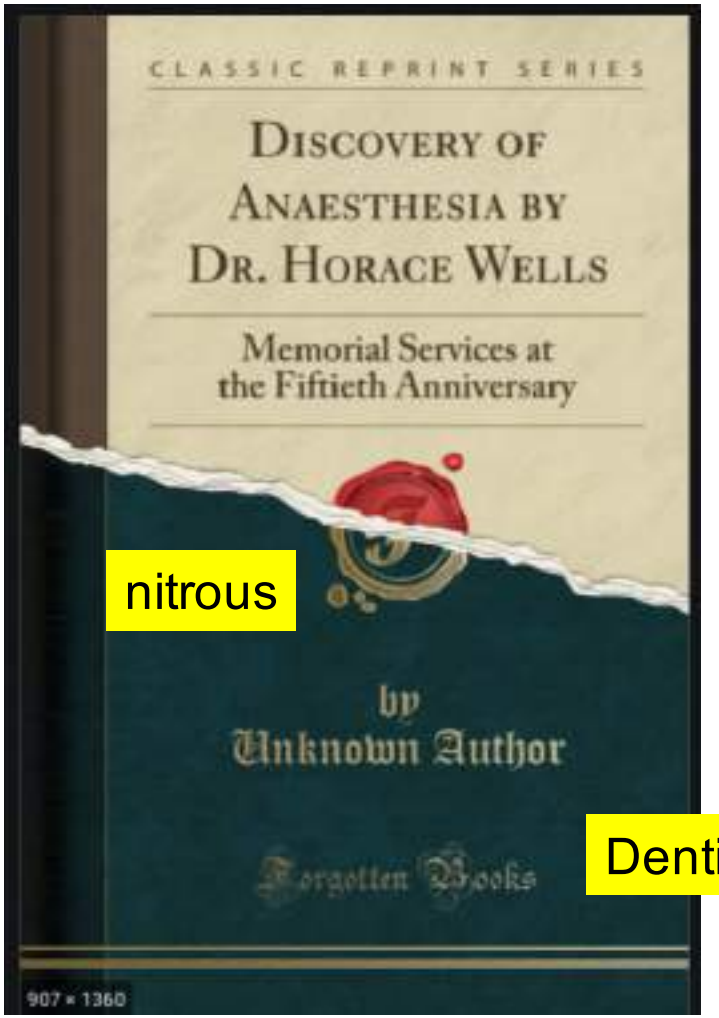
History of anaesthesia discovery



nitrous

Dentistry !!

1844

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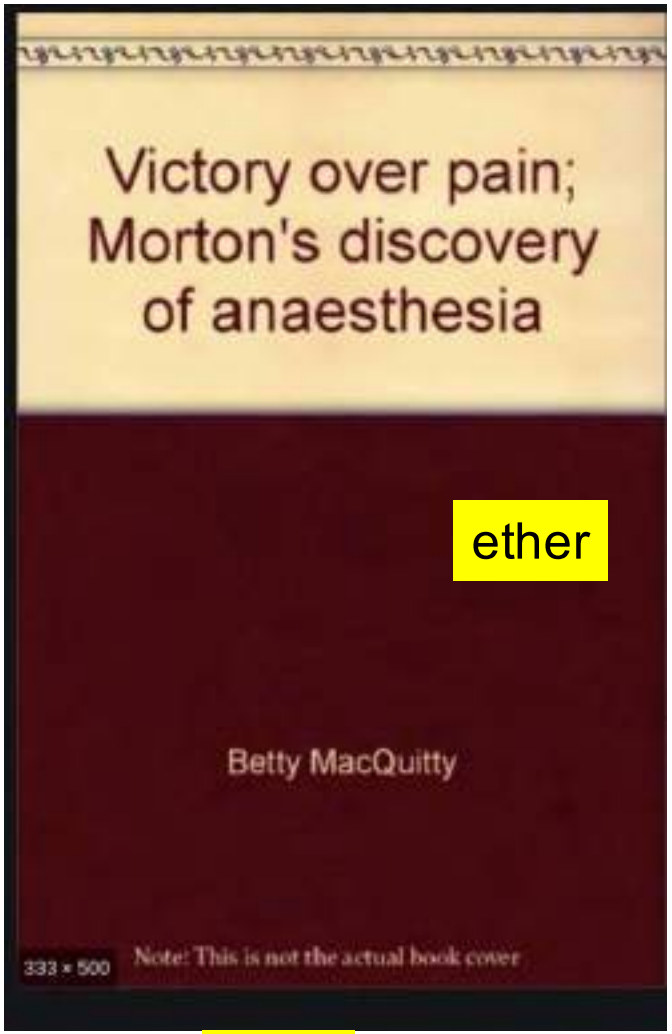

ether

1846

able 1 – Inhalation anesthetic agents (Year available for clinical use).

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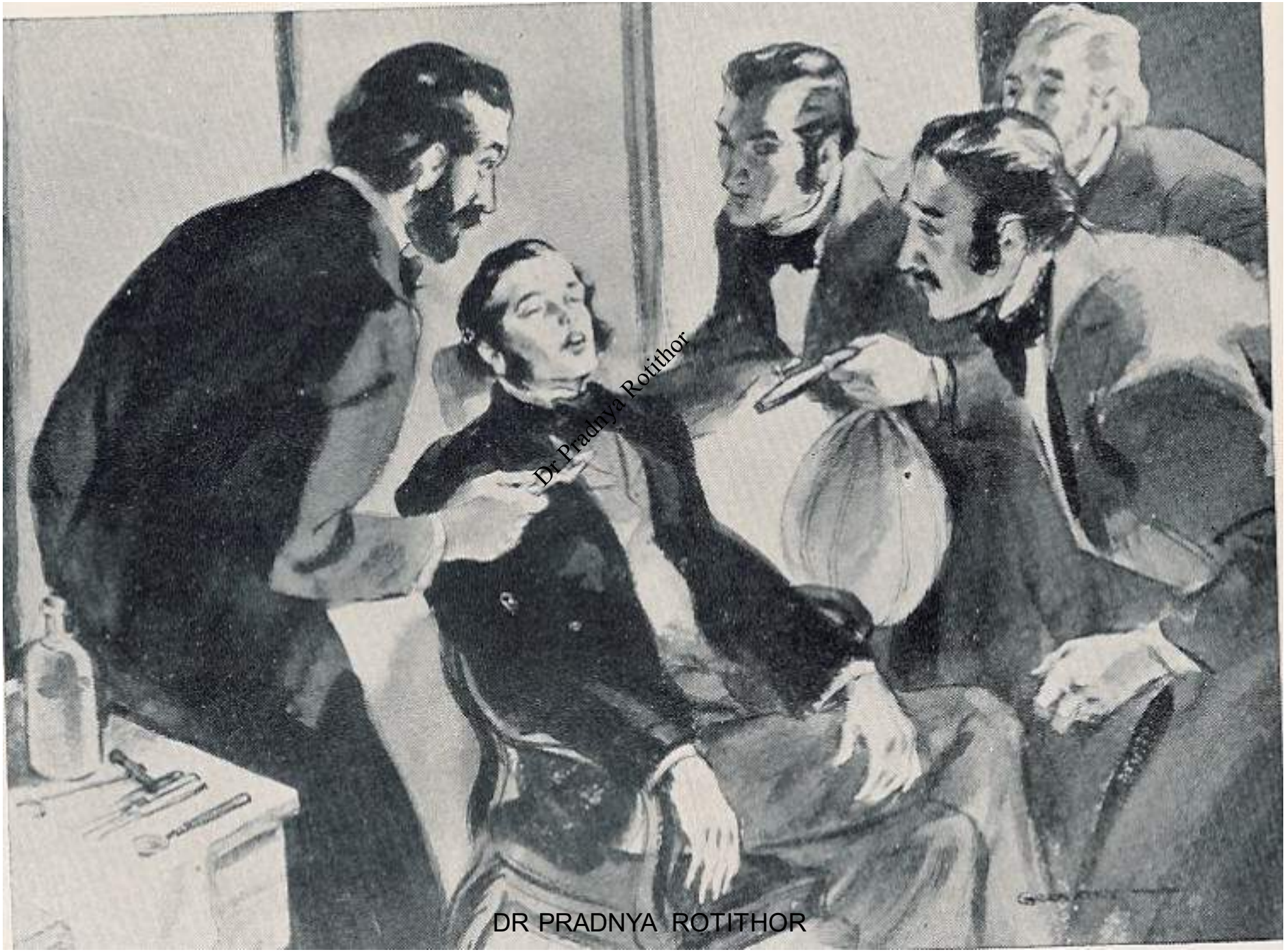
Agents in clinical use	New Agents	Agents of historical interest
Halothane (1956)	Desflurane (1992)	Chloroform (1847)
Isoflurane (1981)	Sevoflurane (1994)	Cyclopropane (1925)
Enflurane (1973)	Xenon (1997)	Diethyl ether (1846)
Methoxyflurane (1960)		Fluroxene (1951)
Nitrous Oxide (1844)		Trichlorethylene (1930)



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STAGES OF ANESTHESIA

based on ether anaesthesia

Stage 1: Stage of analgesia

(Inhalation -→ loss of consciousness)

Stage 2: Stage of excitement or delirium, dysinhibition

(Loss of consciousness -→ beginning of surgical anesthesia) – combative, rowdy, hyperventilation, increased blood pressure

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Stage 3: Stage of surgical anesthesia: 4 Planes

PLANE II

(Regular resp, **sk m relax, decreased eye movements, pupils fixed, loss of reflexes: corneal**, light, laryngeal)

Stage 4: Stage of respiratory paralysis (medullary depression)—seen only on overdose

General anesthetics

Most are halogenated hydrocarbons and may release --

fluoride, bromide, other metabolic products

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Potentially toxic to liver / kidneys

SAQ—classify GA drugs with examples

G A -Agents

1)Inhalational anaesthetics

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2)Intravenous anaesthetics

Inhalation anesthetics

Volatile LIQUIDS:

Halothane

enflurane, isoflurane,

desflurane, sevoflurane ,

Di-ethyl-ether

GASES: Nitrous oxide (N2O)

Xenon *–latest*

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Intravenous anesthetics

Fast acting: (induction, short procedures)

Barbiturate:Thiopental sodium

Nonbarbiturate: propofol, etomidate

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Slow acting:

Diazepam, lorazepam

Midazolam (conscious sedation)

Intravenous anaesthesia – special types

Dissociative anaesthesia: Ketamine

Short procedures – 30-40 min.

The patient appears conscious, can cooperate.

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Neurolept-analgesia:

Droperidol + fentanyl

Classification (SAQ)

1)Inhalation anesthetics

a)Volatile liquids b)gaseous- Nitrous oxide (N2O)

↓ **xenon**

Halothane, enflurane, isoflurane, desflurane, sevoflurane *Di-ethyl-ether*

2)Intravenous anesthetics

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a)Fast acting –

ultra short acting barbiturate ---thiopentone mcq

nonbarbiturate—propofol(mcq) **etomidate**

b)Slow acting –diazepam lorazepam midazolam

c)Special types of IV anesthesia—

Dissociative anesthesia: Ketamine (mcq)

Neurolept-analgesia: Droperidol + fentanyl

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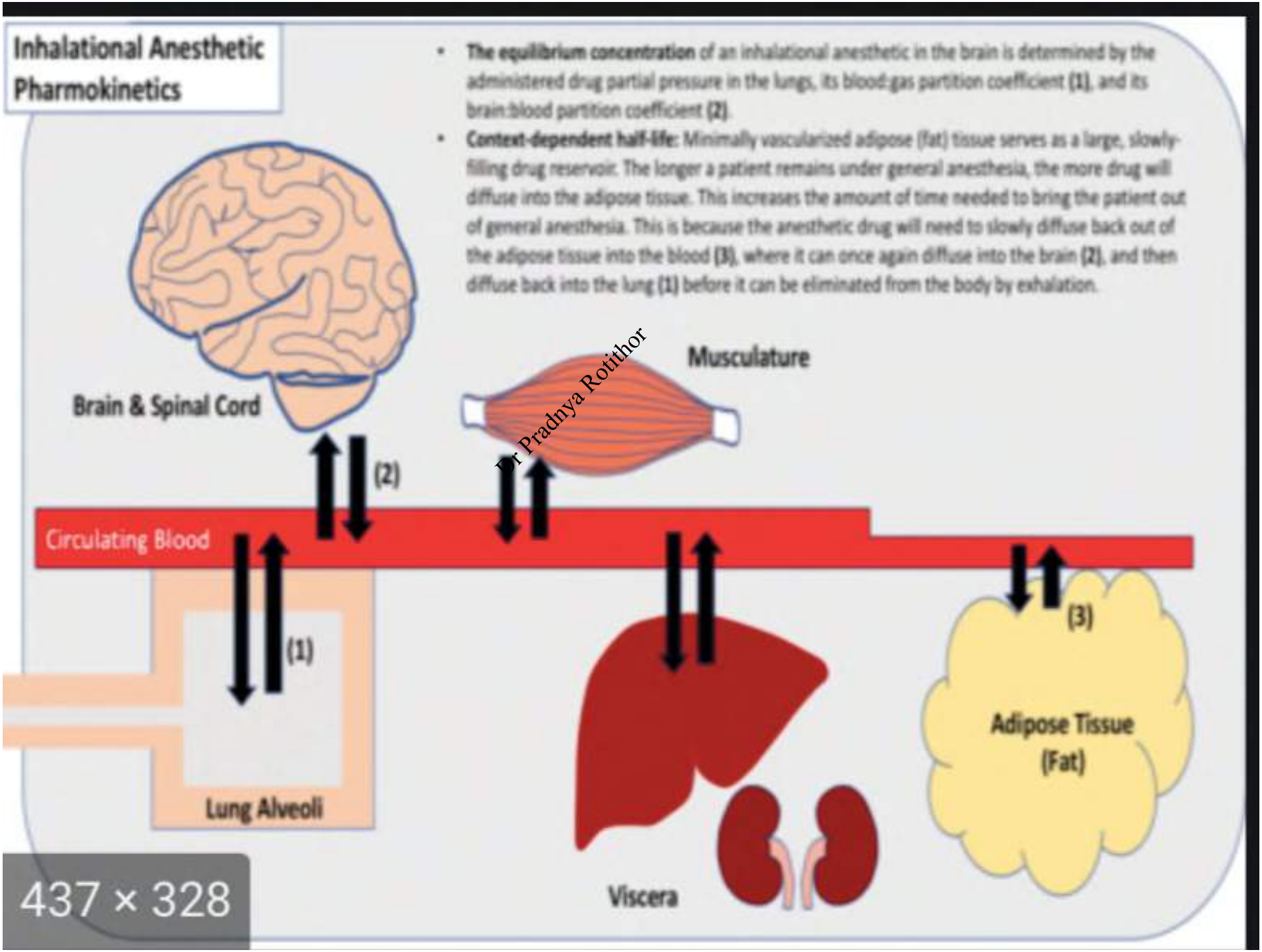
Inhalational Anesthetic Pharmokinetics
The equilibrium concentration of an inhalational anesthetic in the brain is determined by the administered drug partial pressure in the lungs, its blood:gas partition coefficient (1), and its brain:blood partition coefficient (2).
Context-dependent half-life: Minimally vascularized adipose (fat) tissue serves as a large, slowly-filling drug reservoir. The longer a patient remains under general anesthesia, the more drug will diffuse into the adipose tissue. This increases the amount of time needed to bring the patient out of general anesthesia. This is because the anesthetic drug will need to slowly diffuse back out of the adipose tissue into the blood (3), where it can once again diffuse into the brain (2), and then diffuse back into the lung (1) before it can be eliminated from the body by exhalation.
Brain & Spinal Cord
Musculature
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(2)
Circulating Blood
(1)
(3)
Lung Alveoli
Adipose Tissue (Fat)
Viscera
437 × 328

Inhalational GA Drugs

Inhaled gas → alveoli → blood →brain

Factors controlling this transfer

1)Solubility in blood-highly soluble are slow acting

2)Density –lighter gas diffuses in and out of tissues faster

3)Partial pressure –

in anaesthetic mixture

in arterial and mixed venous blood

In the tissues

4) Rate of blood flow through lungs and other tissues

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Potency and onset of action

Minimal alveolar concentration

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Blood : Gas partition coefficient

Lower the value better the drug

MAC

it is the lowest concentration of the anaesthetic agent in the alveoli that immobilizes 50% of the subjects in response to a painful surgical skin incision.

ED5O

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It indicates potency

Less MAC more potent

More MAC less potent

AGENT	MAC	POTENCY
Methoxy-flurane	0.16%	Most potent
Halothane	0.74%	
Isoflurane	1.17%	
Enflurane	1.7%	
Sevoflurane	2.05%	
Desflurane	6.0%	
Nitrous oxide	104%	Least potent

The lower the MAC– the more potent the agent!

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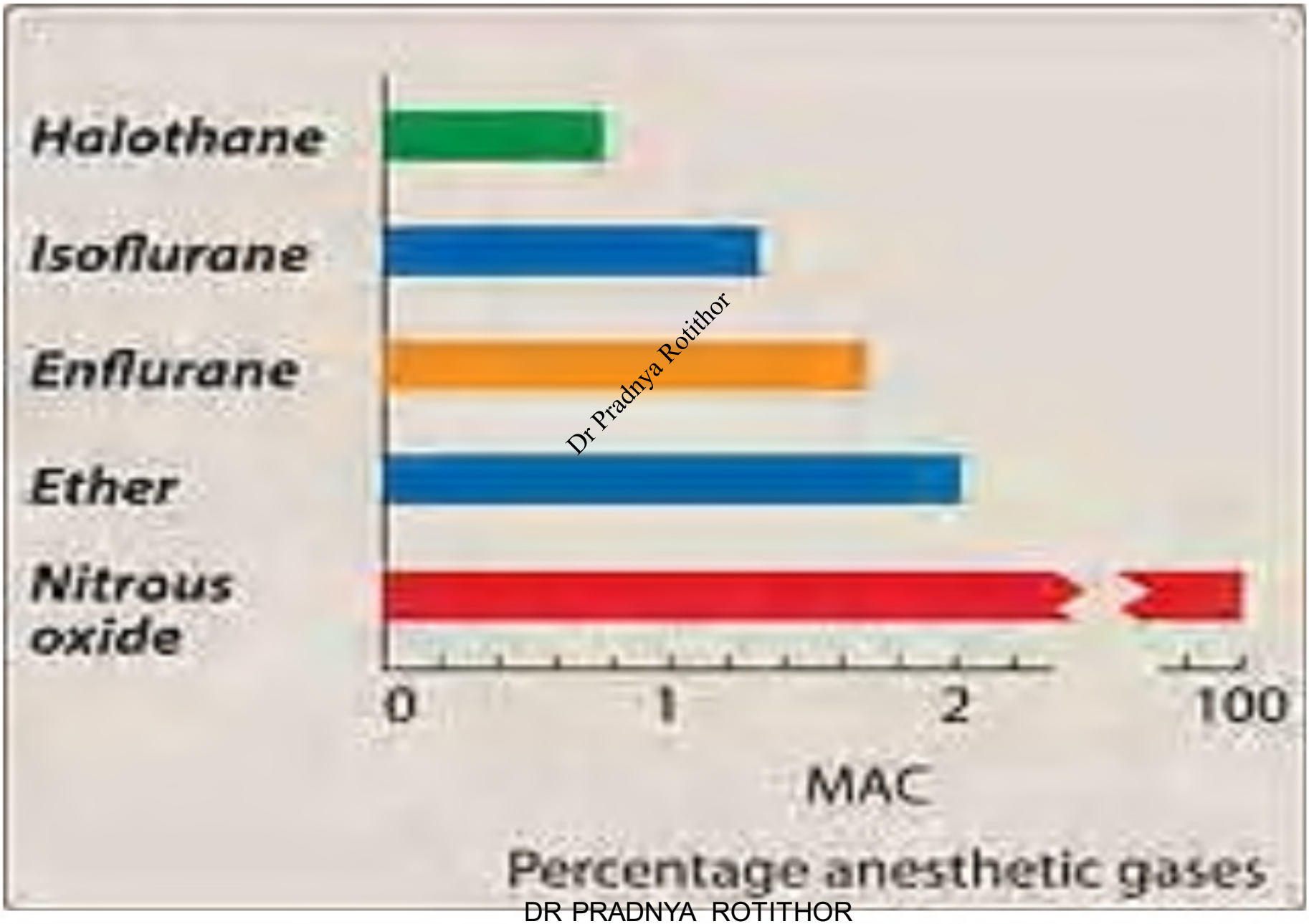

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Blood : Gas partition coefficient

↑value → ↑ water sol → (↓ less lipid sol) equilibrates with blood slowly → Distributes peripherally → Passes slowly to brain →

Slow induction, slow recovery

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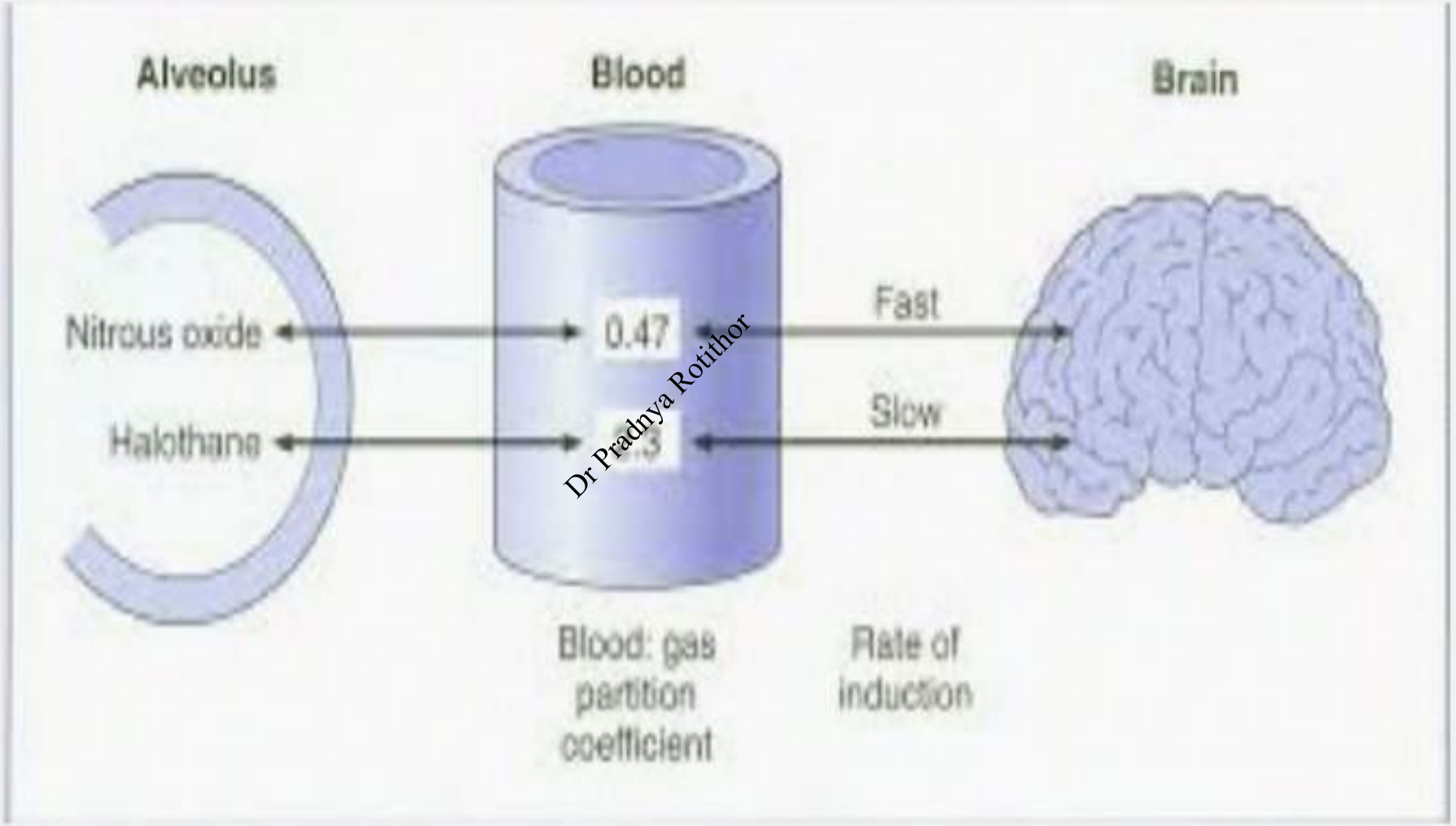
↓ value → ↓ water sol → equilibrates with blood quickly (↑ More lipid sol) → Passes quickly to brain→

Rapid induction, rapid recovery



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Inhalation anesthesia

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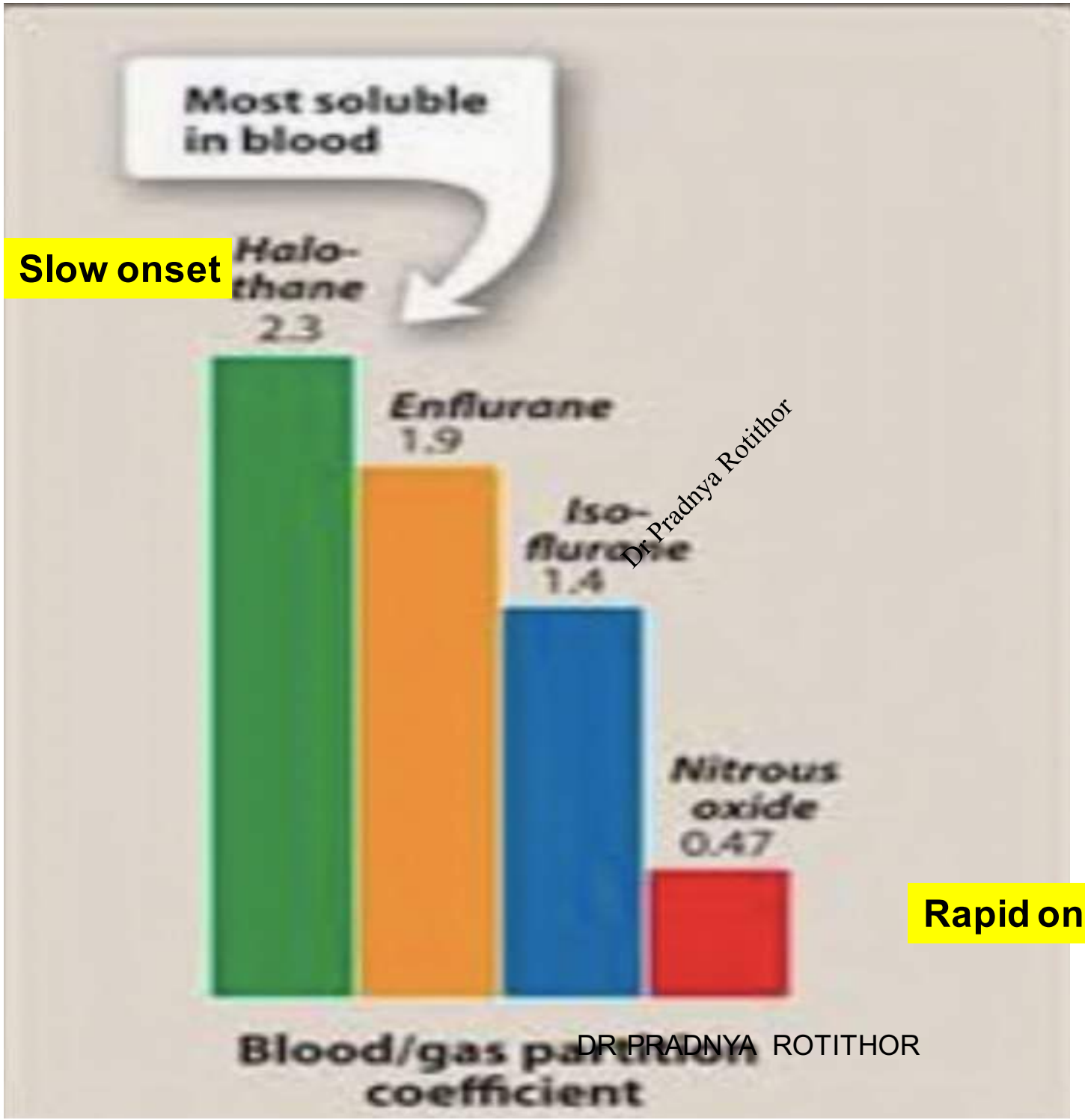

Slow onset

Rapid onset of action

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Blood:Gas coefficient at 37°C

- Methoxyflurane -**15(slowest induction & recovery)**
- Halothane- 2.4
- Enflurane -1.8
- Isoflurane -1.4
- Sevoflurane- 0.69
- Desflurane - 0.42
- Nitrous Oxide- 0.47
- Xenon-0.14 (**earliest induction & recovery)**

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A. Blood gas partition coefficient:

- Inhaled anesthetics that are relatively insoluble in blood (low blood:gas partition coefficient) and brain are eliminated at faster rates than more soluble anesthetics.
- The "washout" of nitrogen oxide, which leads to rapid recovery from there anesthetic effects. Halothane is almost twice as soluble in brain tissue and five times more soluble in blood than nitrous oxide; its elimination therefore takes place more slowly, and recovery from halothane anesthesia is less rapid.

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1024 × 768

Inhalation anaesthetics: solubility in blood

High solubility in blood	Low solubility in blood
High blood/gas partition coefficient	Low blood/gas partition coefficient
- Slow induction and recovery - Slow adjustment of depth of anaesthesia	- Rapid induction and recovery - Rapid adjustment of depth of anaesthesia
(Blood acts as a reservoir (store) for the drug so it doesn't enter or leave the brain readily until the blood reservoir is filled)	(Because the blood reservoir is small the anaesthetic is available to pass into/out of the brain quicker)

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ANESTHETIC	BLOOD:GAS	MAC %
xenon	**0.14**	**63-71**
Nitrous oxide	**0.47**	**100-105**
Desflurane	**0.42**	**6.5**
Sevoflurane	**0.69**	**2**
Isoflurane	**1.40**	**1.4**
Enflurane	**1.80**	**1.7**
Halothane	**2.30**	**0.75**
Methoxyflurane	12	0.16
Ether	**12**	1.9

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Balanced anesthesia

- **Anesthesia balanced by a MIXTURE OF DRUGS**

1 intravenous agent (Thiopental) (induction)-rapid action

1 inhalational (Halothane) (maintenance)

-or-

Both inhalational – one is rapidly acting (Nitrous oxide), the other maintaining (halothane/ether)

PLUS

- Muscle relaxants (facilitate intubation and optimal surgical condition), plus
- an opioid, and a
- cardiovascular agent to control autonomic responses

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General anaesthetic drug regimen for balanced anaesthesia:

Thiopental + Opioid analgesic(pethidine or fentanyl/ benzodiazepine) + Skeletal muscle relaxant (pancuronium) & Nitrous oxide along with inhalation anaesthetic(Halothane/other newer agents)

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Signs of inadequate anaesthesia

Tachycardia

↑ BP

Sweating

Lacrimation

Grimacing

and other muscle activity

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These are indicative of ANS over activity

ETHER

volatile liquid anaesthetic agent

Potent MAC 1.9

SAFE -wide margin of safety

Respiration well maintained –bronchodilator

No Special apparatus

Air used as O2 supply

No special expertise Economical

Excellent analgesia

Good skeletal muscle relaxation –curare-mimetic

LESS ADR : HEART, LIVER, kidney

Can be used during delivery

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Ether - DISADVANTAGES

1)IRRITANT INFLAMMABLE, EXPLOSIVE

Cautery can not be used

2)High BG partition coefficient: 12

Slow stormy INDUCTION with **struggling, breath-holding, excess salivation and respiratory secretions**

3)SLOW UNPLEASANT RECOVERY with **more incidence of post-op N, V**, retching

4)Remember : curarimimetic action

5)convulsions in children

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Forms irritant fumes on exposure to air
Hence marketed in sealed containers

Non-ether agents

Nonirritant, noninflammable

Rapid to medium, smooth induction

Rapid, smooth, pleasant recovery

Less post-op N, V

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ANALGESIA IS MEDIUM

TOXICITY

COST

Equipment / Technique

Expertise

BOYLE'S Anaesthesia machine


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vaporizer

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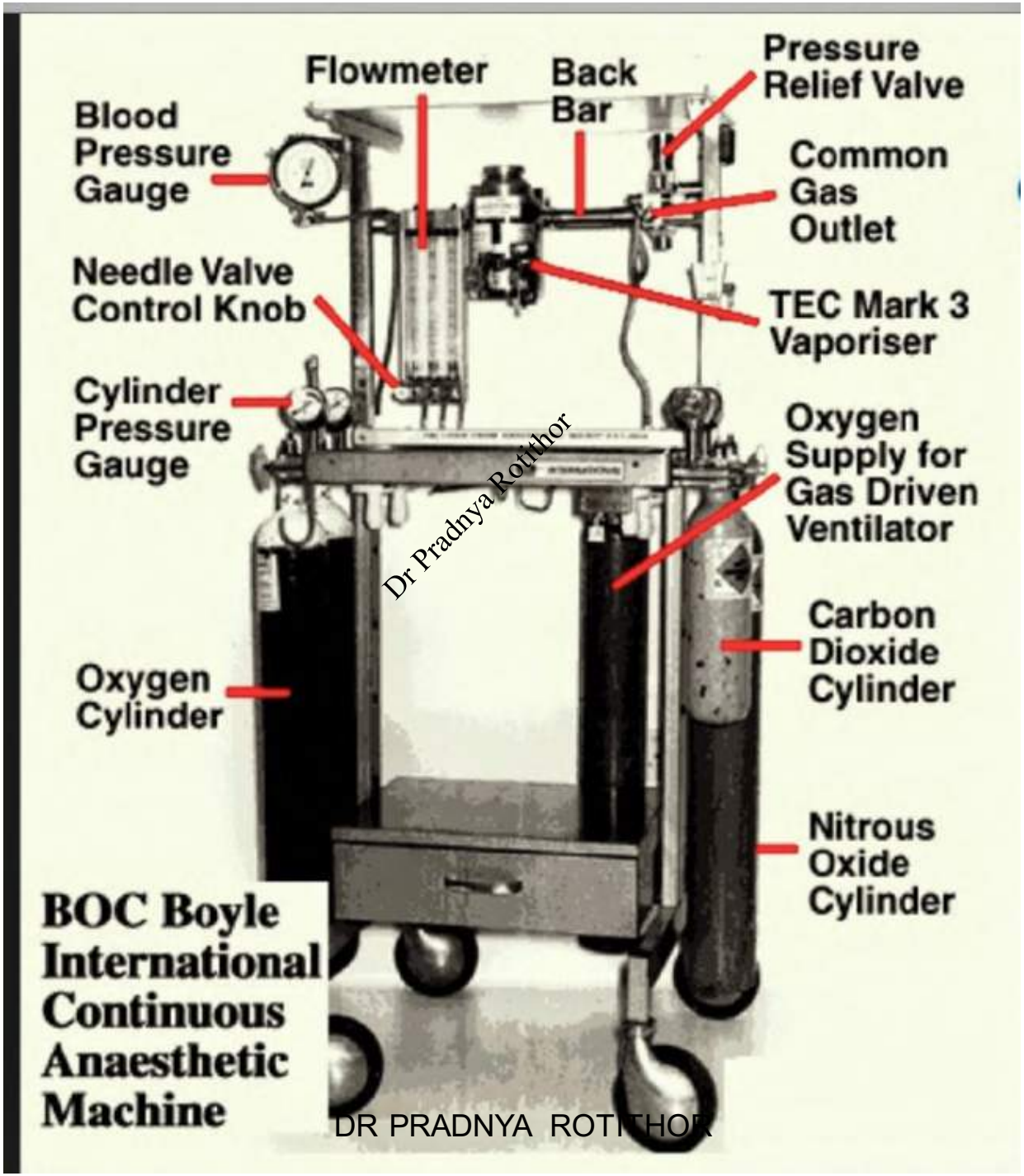

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General anesthesia

- **Inhalation anesthetics:**
- **Volatile LIQUIDS:**
- **Halothane, enflurane, isoflurane, desflurane, sevoflurane** *(Induction, maintenance)*, Di-ethyl-ether

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- **GASES: Nitrous oxide (N2O)** *(Induction, short procedures, less potent)*

Halothane	*Enflurane*	*Isoflurane*
Apparatus, expertise, cost	Apparatus, expertise, cost	Apparatus, expertise, cost
Bronchodilation	Bronchodilation	Bronchodilation
Volatile liquid	Volatile liquid	Volatile liquid
Potent 0.75	Potent 1.7	Potent 1.4
coefficient: 2.3	1.8	1.4
rapid-medium	Rapid-medium	Rapid
Nonirritant Noninflammable	Nonirritant noninflammable	Nonirritant noninflammable

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Halothane	*Enflurane*	*Isoflurane*
Quick, pleasant	Quick, pleasant	Quick, pleasant
LESS post-op N V	LESS post-op N V	LESS post-op N V
Analgesia: poor	Medium	Medium
M relaxation: poor	+++(curare-like)	++ Better
Hepatitis1:10,000	Much less	Rare 1:500,000

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Halothane	Enflurane	Isoflurane
Malignant hyperthermia *(Treat with Dantrolene)*	----------	----------
----------	Clonic seizure Epilepsy?, ICT	NIL - preferred Neurosurgery, (mcq) Epilepsy
Arrhythmia +++ catecholamines (Heart)	Less ++	NIL
---------	C/I: Renal damage	--------
		Vasodiln,coronary blood flow, prefer in IHD(mcq)

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Desflurane	Sevoflurane
Newer, expensive	Newer , expensive
Potent: MAC 6.5	Potent: MAC 2
B:G coefficient 0.42, Rapid, Smooth induction - 5 min	B:G coefficient 0.69, Rapid Smooth induction - 5 min
No tissue toxicity	Nephrotoxic (mcq)
Pungent odor, cough Laryngeal irritation, spasm	Non-pungent, Pleasant No irritation
Sympathetic stimulation	-----no sympathetic stim-------
Pleasant, smooth, rapid recovery	Pleasant, smooth, rapid recovery
Least disorientation, least cognitive motor impairment (Mcq) OUTPATIENT SURGERY	Pleasant (Mcq) PREFERRED IN CHILDREN

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Nitrous oxide – laughing gas

Inorganic inert gas: MAC: 105.2%.--- Less potent – Not sole agent for major procedures

B:G coefficient: 0.47 – Rapid induction and recovery: → INDUCTION, dental OPD procedures as a sole anesthetic

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80% N2O with 20% O2

Good ANALGESIA

poor muscle relaxation

Safe CVS/RS/Liver/Kidney – least hepatotoxic

Second gas effect

- When N_20 is given in high conc 70-80% with another potent inhalational anaesthetic like halothane, it facilitates delivery of halothane to blood at *higher rate* and *induction* is achieved *faster*
- This effect is called as second gas effect

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Diffusion hypoxia

- When N2O is discontinued, large amount of N2O rapidly diffuses into alveoli from blood owing to its low blood solubility .
- This dilutes alveolar air →
- ↓ PP of O2 in alveoli
- Dilutes CO2 as well → ↓drive for ventilation
- Breathing room air at such times → hypoxia
- This hypoxia is called as ***diffusion hypoxia***

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Nitrous oxide …..

- **Diffusion hypoxia**: produces less O2 uptake during recovery
- **2nd gas effect:** N2O has a fast uptake from alveolar gas → It concentrates halogenated anesthetics (other anesthetics) in the alveoli
- Post op N, V, fetotoxic, bone marrow suppression
- Replaces nitrogen in various air spaces, increases volume of closed spaces (can cause pneumothorax)

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Intravenous Anesthetics

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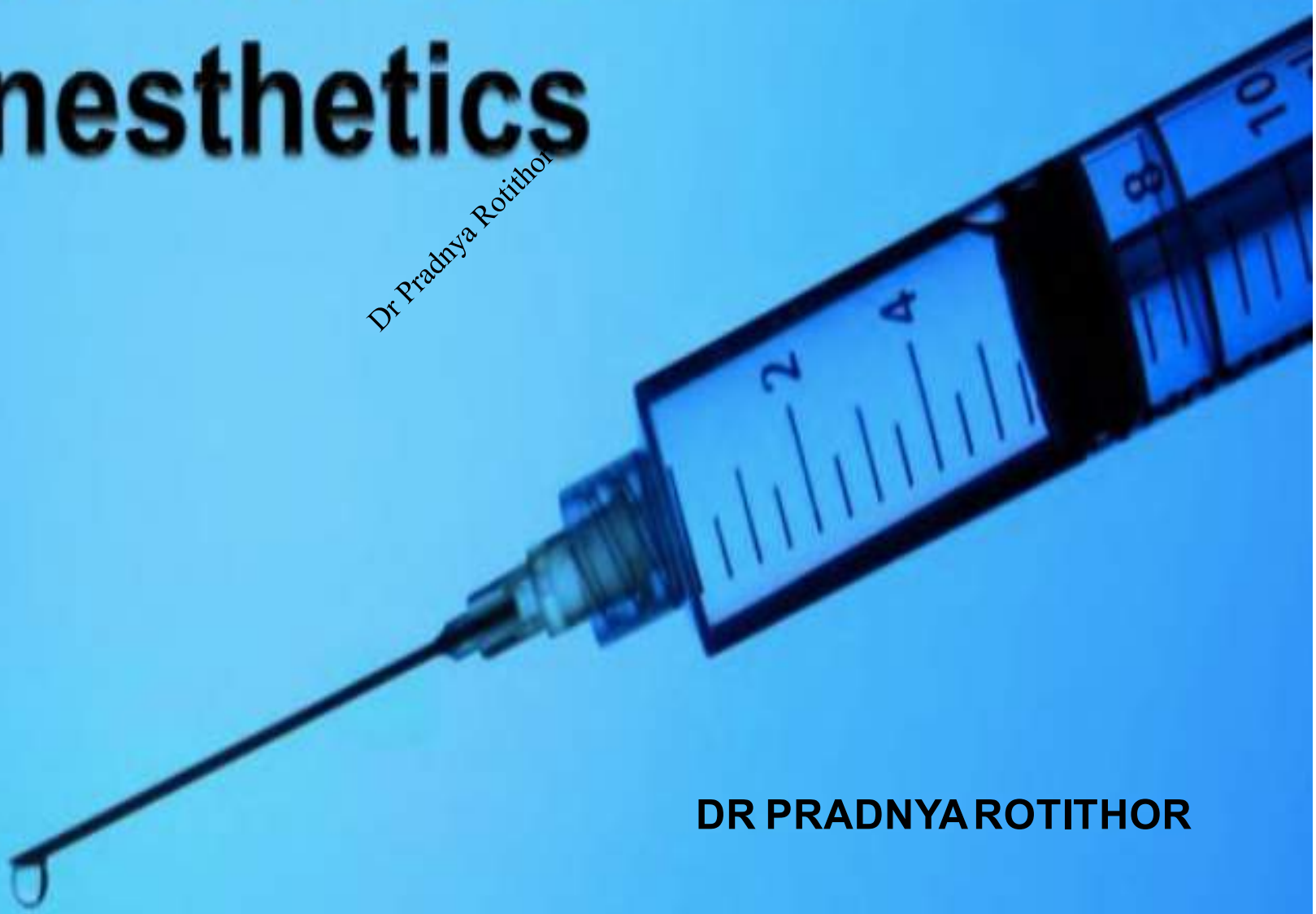

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Iv anaesthetics

Allow extremely rapid induction as their blood concentration can be rapidly raised

One arm brain circulation time -11 sec-

Quick loss of consciousness

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But no channel like lungs for elimination

Can not be hastened by hyperventilation

Yet another reason why *iv is for induction* and *inhalation for maintenance*

Classification (SAQ)

1)Inhalation anesthetics

a)Volatile liquids b)gaseous-

2)Intravenous anesthetics

a)Fast acting –

ultra short acting barbiturate --thiopentone mcq

methohexital

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nonbarbiturate—propofol(mcq) **etomidate**

b)Slow acting –diazepam lorazepam midazolam

c)Special types of IV anesthesia—

Dissociative anesthesia: Ketamine (mcq)

Neurolept-analgesia: Droperidol + fentanyl

Intravenous anesthetics

- **Fast acting:** (induction, short procedures)
- **Rapid distribution and redistribution**
- **Barbiturate:Thiopental sodium(3-5 mg/kg (2.5%)**
- **Nonbarbiturate: Propofol (2 mg/kg), (maintain 9 mg/kg/hr), Etomidate**
- **Slow acting:**
- **Diazepam, lorazepam**
- **Midazolam (conscious sedation)**

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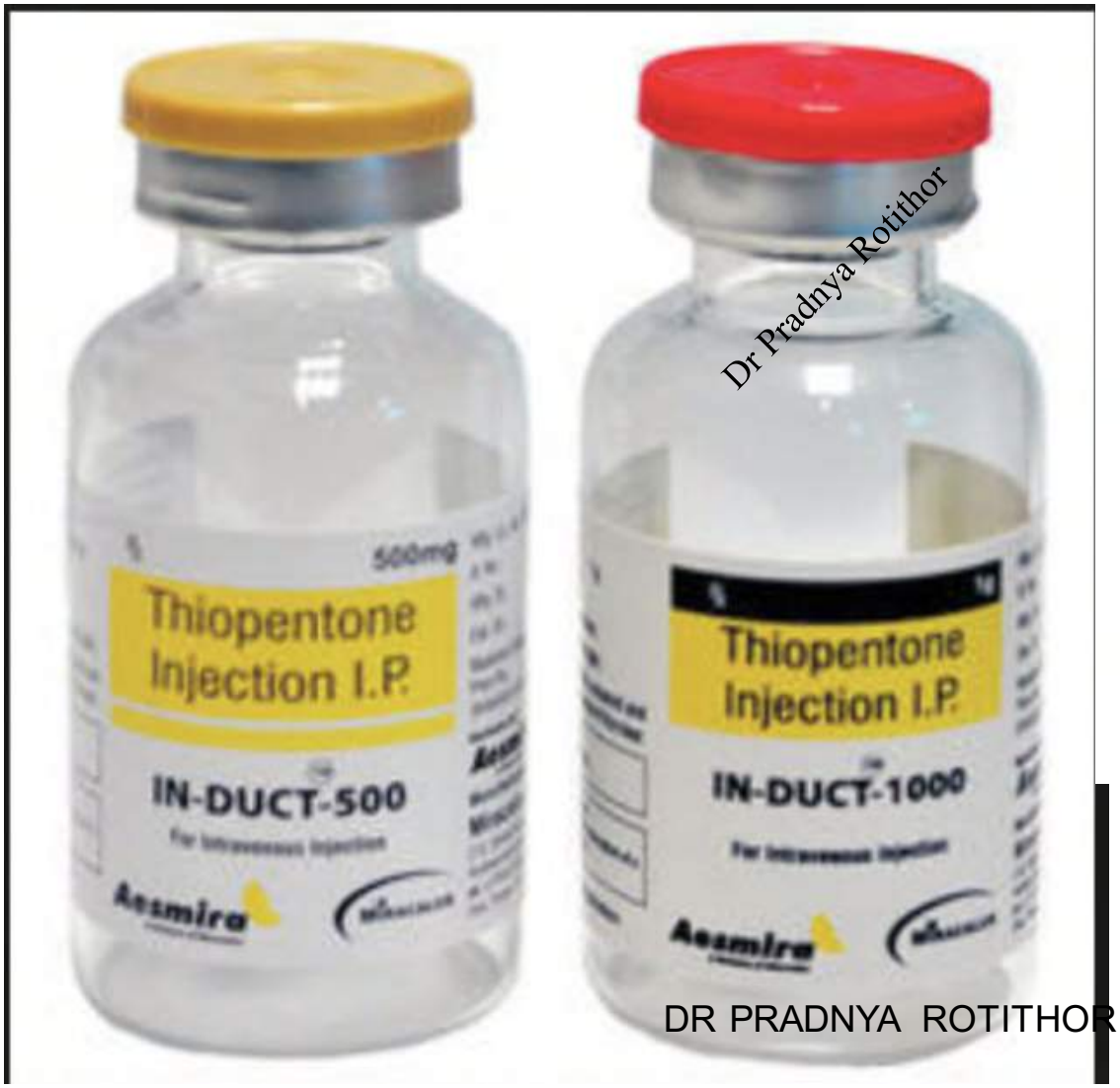
Ultra-short acting barbiturates



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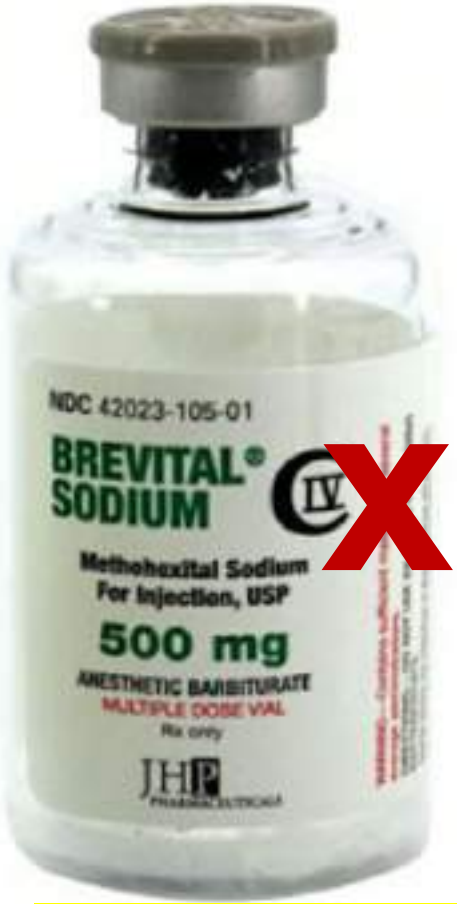

XX

Methohexitone--
Not used now
Due to toxicity

Thiopentone sodium

Ultra-short-acting Barbiturate

Rapid Induction 15-20 sec

Recovery 15-20 min

Disorientation many hours— due to redistribution

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Patient is awake but can not be discharged

No analgesia, no muscle relaxation

Therapeutic uses

- ✓ **Used for Induction,**
- ✓ **short procedures as sole drug**
- ✓ **Can be used in pregnancy**
- ✓ **Treats Convulsions- status epilepticus**
- ✓ **Used for verbal communication{truth serum}—medico-legal cases-suspect interrogation**

No ↓ cerebral blood flow

- ✓ **No ↑ ICT: Preferred Neurosurgery, head trauma, brain tumors**

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Adverse effects

- **hypotension, ↓ myocardium**
- **accidental extravasation– Irritation local necrosis**
- **Accidental entry into artery –intense vasospasm**
- **Shivering**
- **Transient apnea - characteristic feature**
- **laryngospasm—intubation facility is a must**
- **Post –op - N, V, cough**
- **----------**
- **C/I:Acute Intermittant Porphyria (as it is barbiturate)**
- **Don't mix with Sch**

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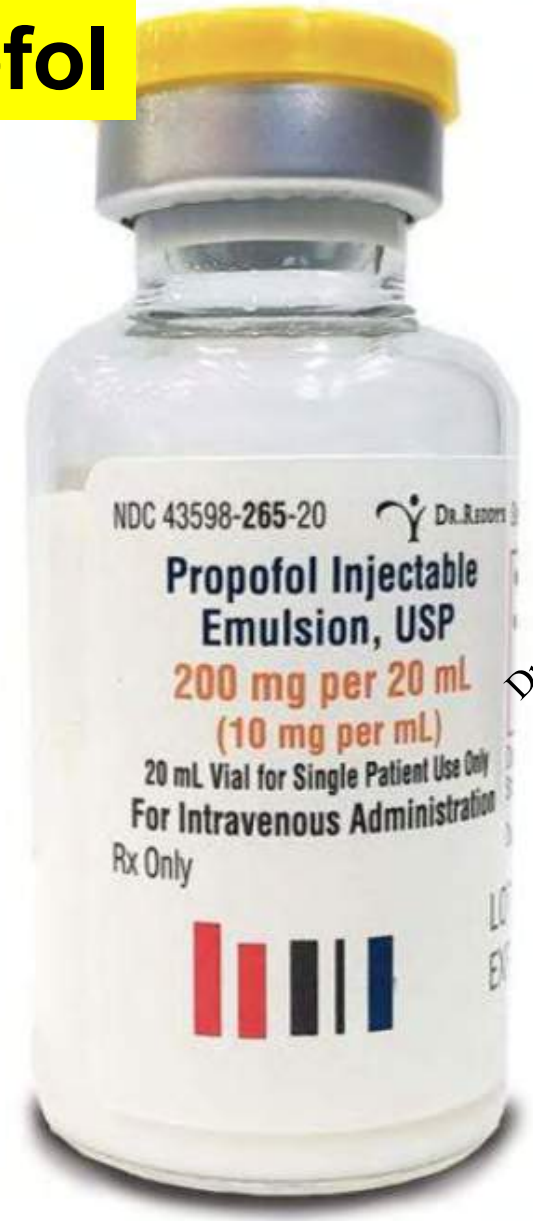
Propofol



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Non barbiturate

Rapidly acting 15-45sec

Smooth recovery

Early ambulation 3-15min

<u>Most Suitable for OPD procedures</u>

Antiemetic
antipruritic
Good analgesia
Bronchodilator
Safe in pregnancy

Propofol-uses

- ✓ Induction and maintanance
- ✓ **For sedation in ICU: 2.4 mg/kg/hr –**
- ✓ **Most Preferred drug for OPD – many day care procedures –(MCQ)**
- ✓ **ambulatory surgical procedures,**
- ✓ **Burn dressing**
- ✓ **spinal tumors**

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disadvantages

- hypotension Bradycardia
- Negative inotropic effect on heart- depression of cardiac contractility
- Irritation on IV administration
- ***V painful –mixed with xylocard to reduce pain (xylocaine without preservative)***
- excitement, involuntary movements
- Post-op N, V less than pentothal

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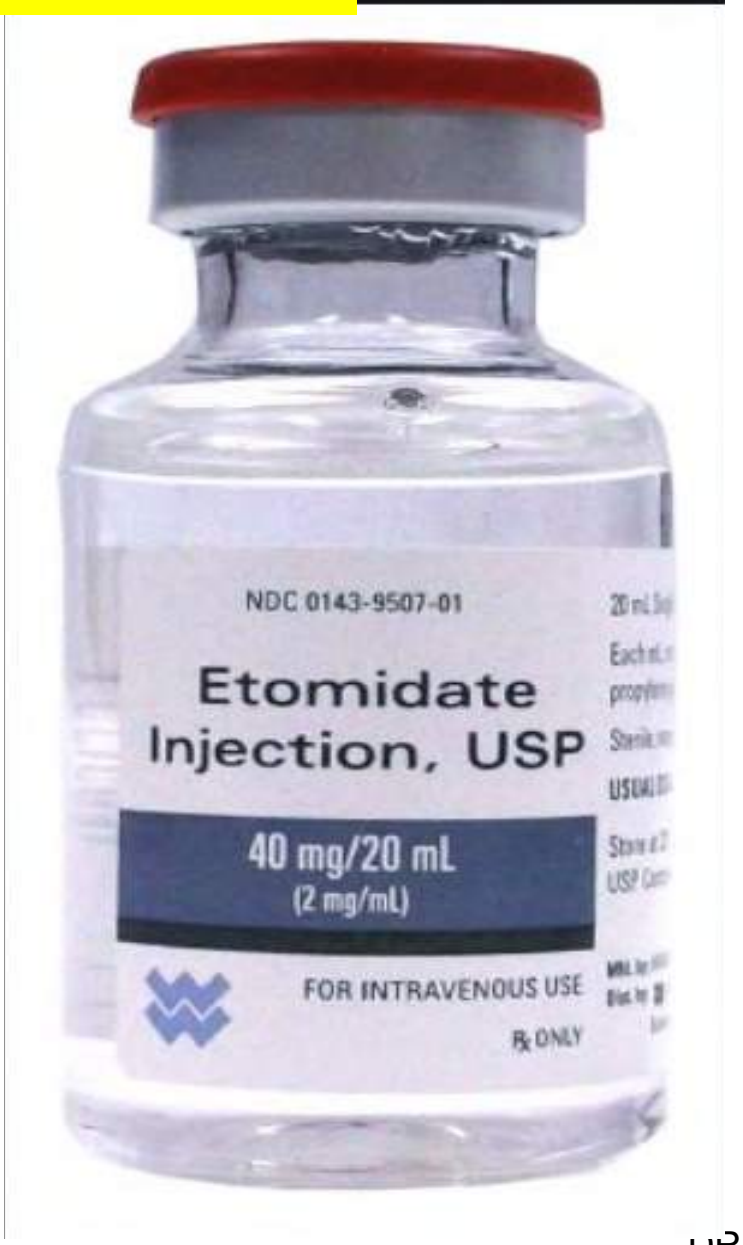
Etomidate



Nonbarbiturate

Rapid induction- 5-10 sec

Rapid recovery 5-10 min

Used – induction ,v short procedures
No analgesia
Not suitable for long procedures

safe for cardiac anaesthesia

X pregnancy

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- MOA: It enhances effect of inhibitory neurotransmitter, GABA at the $GABA_A$ receptors and thus promotes CNS depression
- Advantage: Useful for induction of anesthesia in patients susceptible to hypotension because of coronary artery disease
- Disadvantage: Known to inhibit adrenal steroid hormone synthesis eg aldosterone, testosterone, estrogen etc

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Myoclonic movement, rigidity

Thiopentone	Propofol	Etomidate
UltrashortactingBarb	Non-barbiturate	Non-barbiturate
Induction Rapid 15-20 sec	Rapid 15-45 sec	Rapid 5-10 sec
Recovery 15-20 min	3-15 min	5-10 min
Poor analgesic, weak muscle relaxn	Good analgesia	Poor analgesic
Induction, short procedures	Induction + maintenance	Induction, short period
Disorientation many hours	***Extremely Rapid recovery*** (mcq)	Rapid recovery
Treats Convulsions, Used for verbal communication	ICU: 2.4 mg/kg/hr – sed^{n}	Not long procedures

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Thiopentone	Propofol	Etomidate
Post –op N, V, cough ↓ BP, ↓ myocardium	Less Post-op N, V ↓ BP	Post – op N, V LessHypotension
Irritation (extravas^{n})	Irritation IV admn	Irritn, pain – inj.
Shivering, apnea laryngospasm Don't mix with Sch C/I:Acute Intermittnt. Porphyria	Bradycardia, excitement, involuntary movements	Myoclonic movement, rigidity ↓ cortisol, aldosterone C/I: Pregnancy
No ↓ cerebral bl. flow No ↑ ICT: Preferred Neurosurgery, head trauma, brain tumors	preferred OPD, ambulatory surgical procedures, spinal tumors	SAFE IN CVS CONDITIONS - CAD, SHOCK

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BZD

- Sedation , Short procedures, Sedation before GA
- Endoscopies, angiographies, cardiac catheterization, reduction of fractures, ECT
- BZDs are also used as pre anaesthetic medication

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- Midazolam potent > Diazepam, No local irritn,1-2.5 mg IV
- Lorazepam 2-4 mg, Diazepam 0.2-0.5 mg/kg
- Resp depression, anterograde amnesia for at least 2 hours

- **Conscious sedation (MCQ)**

BZDs

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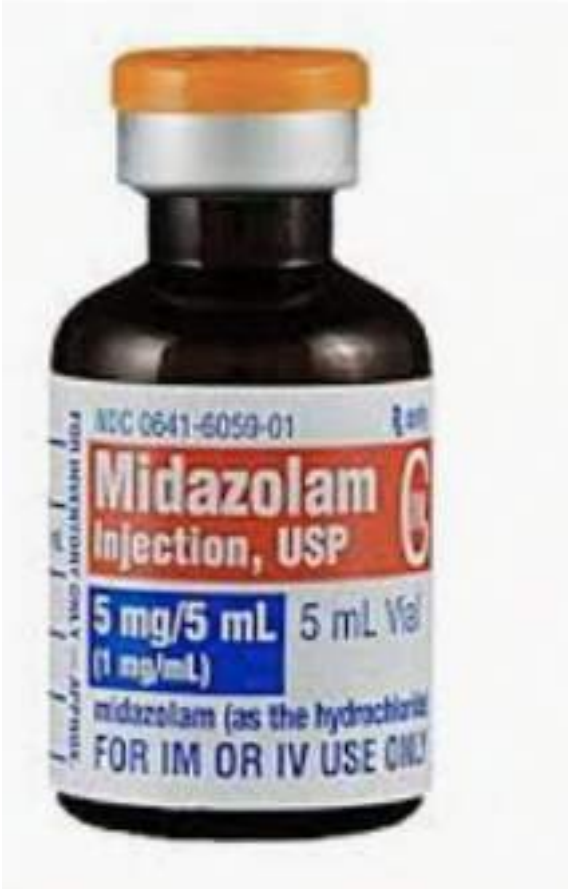

BZD

- **Conscious sedation:**
- **Medazolam –less resp ,cvs depression**
- **no pain at injection site**
- **Diagnostic, short procedures, dental procedures under LA (in place of GA) in**
- **– apprehensive**
- **- medically compromised**
- **- with altered level of consciousness**
- **-to decrease physical mental stress**

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IV anaesthesia –special types

- Dissociative anaesthesia

  ketamine

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- Neurolept analgesia

  Droperidol + fentanyl

ketamine

Dissociative anaesthesia

Amnesia
Analgesia
catatonia

ketamine

KETAMINE (phencyclidine derivative) –

0.5-1.5 mg/kg high lipid solubility- rapid distribution

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MOA-

Glutamate antagonist:

blocks NMDA receptors

Dissociative anesthesia - ketamine

Sense of dissociation from one's own body and from surroundings (viva question)

Light sleep or trance/ sedation

Amnesia

Analgesia

Catatonia (Immobility)

Patient conscious, can cooperate,

less CVS, RS risks, less GA risk

Suitable for asthma patients

Thus suitable for high risk cases for GA

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Therapeutic uses

Premedication with –atropine

diazepam(to avoid delirium)

Onset of action -3-5 min

Duration: 30-40 minutes

Can be used as sole agent for--

- ✓ **mainly in children and young adults -- --diagnostic procedures of short duration**
- ✓ **Short surgical procedures**
- ✓ **burn dressing,**
- ✓ **CT scan**

Raises HR B P CO –suitable for hypovolemia hypotension and shock cases

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Adverse effects

Increases BP,HR –

not used for patients with HT MI

Increases ICT—

not used for head injury patients

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Unpleasant dreams, emergence delirium (excitement, hallucinations) and nystagmus during recovery

↑ **psycho-motor activity (hallucinogen like – PCP like effect)**

↑ ***Pcp =phencyclidine piperidine***

contraindications

A known case of psychiatric disorder X

H/O CVA stroke x

MI x

HTN x

Head injury cases X

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Ketamine –incompatible with diazepam and thiopental

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- *Should never be mixed in same syringe or infusion*
- *It is a drug of abuse* –can be easily mixed in drinks
- *Date rape drug* ---amnesia and sedation

Neurolept-analgesia

Droperidol + fentanyl

Neuroleptic opioid analgesic

Iv administration Lasts 30-40 min

Produce quiescence Psychic indifference

With intense analgesia

Without loss of consciousness patient can cooperate

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Diagnostic and minor surgical procedures:

A/E-hypotension ,bradycardia,respiratory depression

Extrapyramidal symptoms

No more preferred

Adddition of 65% N2O +35% O2 =neurolept anaesthesia

Neurolept analgesia

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neuroleptic

Narcotic analgesic

Newer drugs

- Alpha 2 adrenergic agonist
- dexmedetomidine

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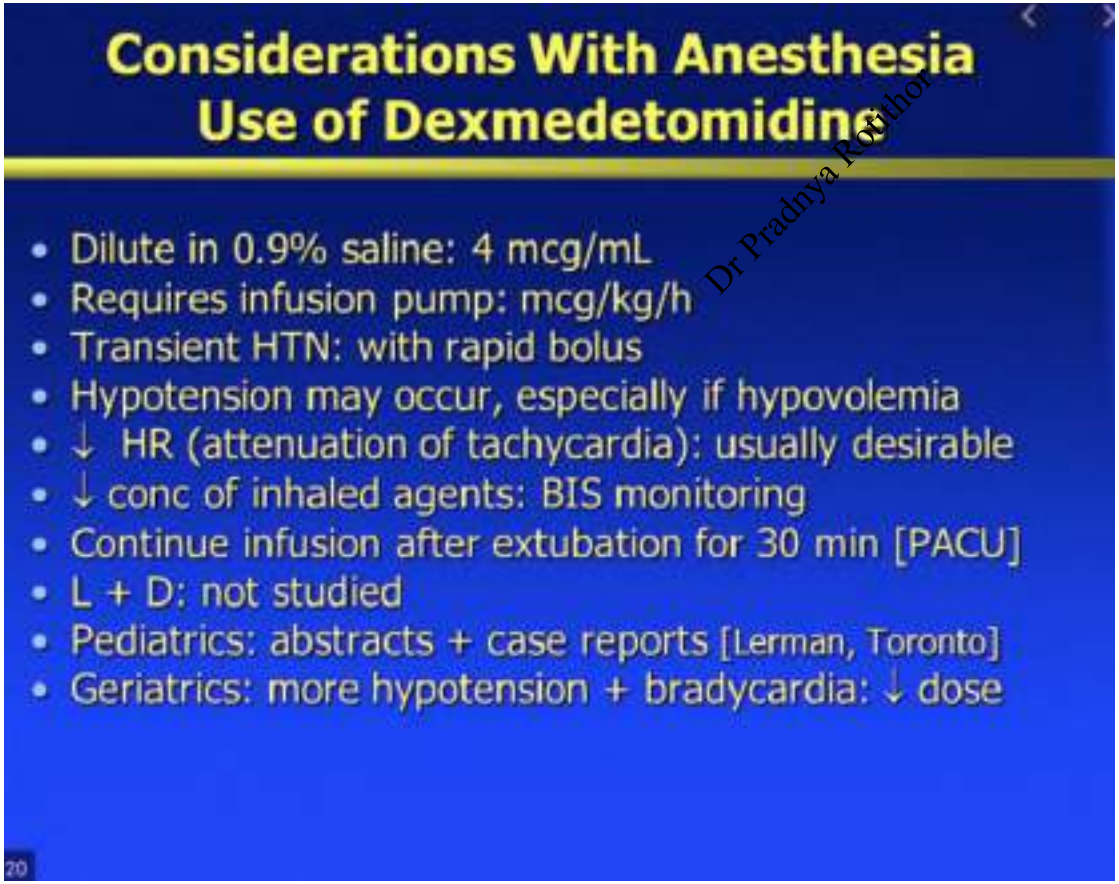
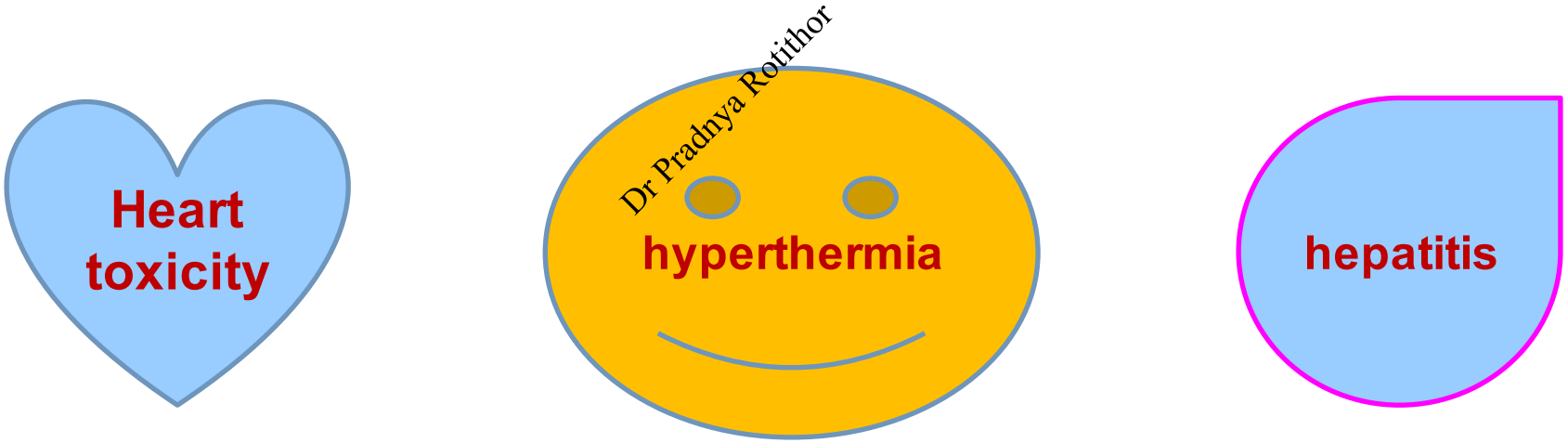
Newer drugs
Alpha 2 adrenergic agonist
dexmedetomidine



Only for info

Take home messages

3H -halothane toxicity



Understand these concepts

- MAC
- Blood Gas partition coeficient
- Diffusion hypoxia
- Second gas effect

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Study this classification !!

What are the Drugs used as GA ? (Classification)

- **Inhalation:**
  1. **Gas:** Nitrous Oxide
  2. **Volatile liquids:**
     - Ether
     - Halothane
     - Enflurane
     - Isoflurane
     - Desflurane
     - Sevoflurane

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- **Intravenous:**
  1. **Inducing agents:**
     - Thiopentone, Methohexitone sodium, propofol and etomidate
  1. **Benzodiazepines (slower acting):**
     - Diazepam, Lorazepam, Midazolam
  1. **Dissociative anaesthesia:**
     - Ketamine
  1. **Neurolept analgesia:**
     - Fentanyl

MUHS -SAQs

1)Write a note on dissociative anaesthesia

2)Classify general anaesthetic agents with examples

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Lots of MCQs/viva questions

Nitrous –most rapid less potent

Thiopental –ultra short acting barbiturate

Propofol –outpatient procedures

Ketamine-dissociative anaesthesia

Succinylcholine –endotracheal intubation

Pharmacotherapy of Parkinson's disorder

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Progressive degenerative disorder causing DA deficiency

- Extrapyramidal motor disorder
- Imbalance between inhibitory DA and excitatory Ach
- Disease of older people
- Mostly idiopathic
- Degeneration of neurons in SN PC and nigrostriatal tract that controls muscle tone and coordinates movements
- First described by James Parkinson in 1817
- Breakthrough treatment in 1967 –levodopa

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Neurodegenerative disorders

- Parkinsonism: ↓ DA - ↑ Ach
- Alzheimer : ↓ Ach
- Huntington Chorea: DA over activity

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Symptoms and signs

RAFT

Rigidity
Akinesia
Facial expressions
Tremors

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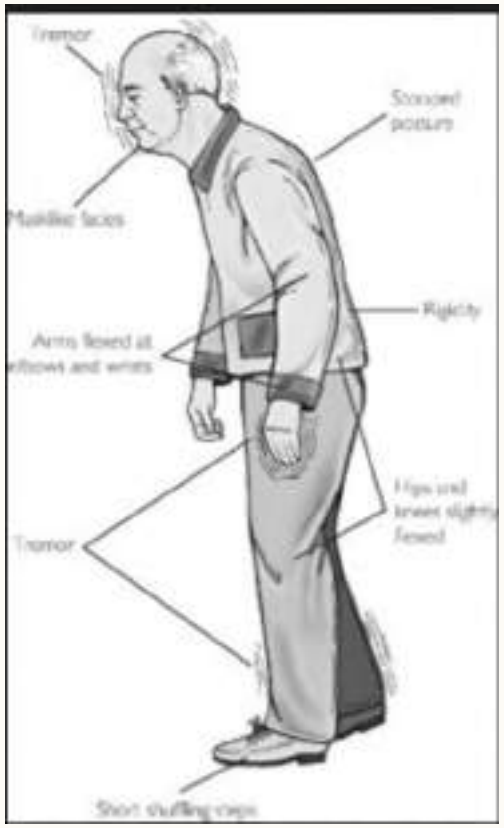
Droopy stooped posture
Instability shuffling gait
Seborrhoea sialorrhoea drooling
Incoordinated movements
Pill rolling movements



Pill rolling tremor

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Cogwheeling

Difficulty in doing day to day activities

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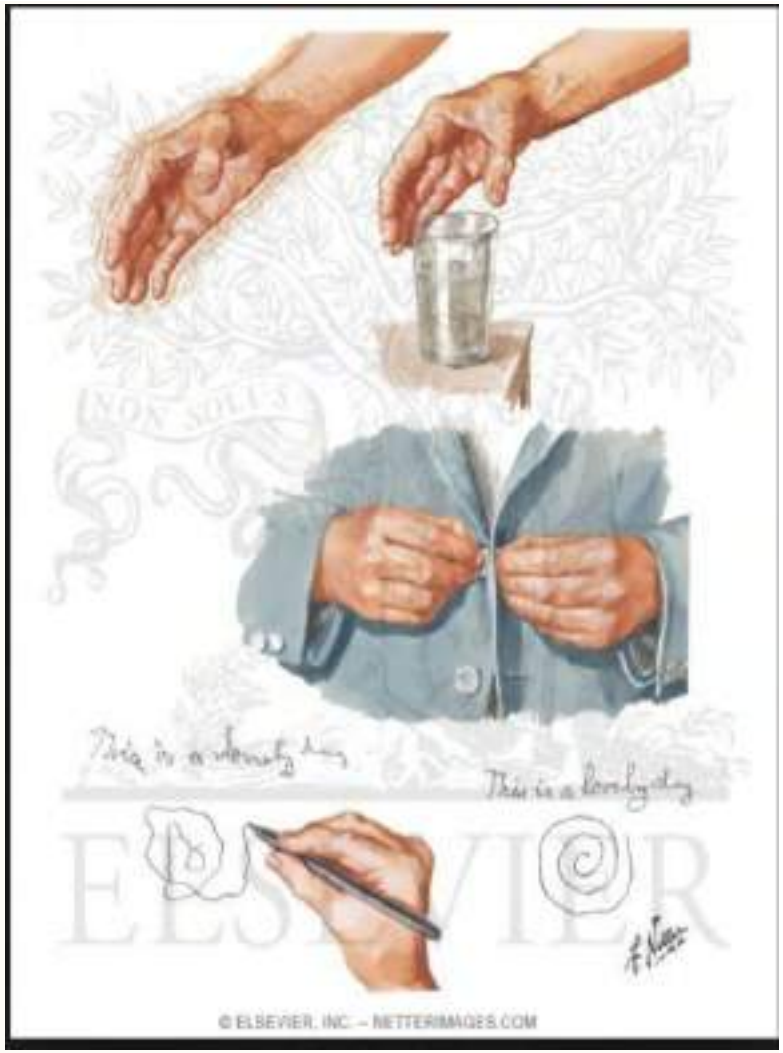
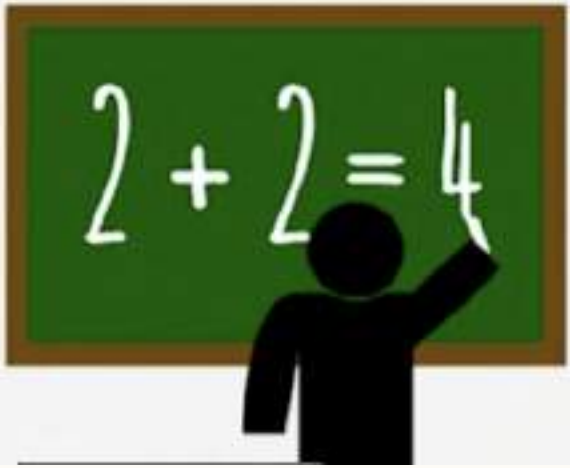


$R_{X=}$ DOPAMINE REPLACEMENT

Since Parkinson disease is primarily a disease of dopamine loss, it makes sense that treatment should have something to do with restoring dopamine



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HISTORICAL SIDE NOTE

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THERAPIES TARGETING DOPAMINE

Dopamine Replacing Drugs

Carbidopa/Levodopa
- Sinemet
- Sinemet CR
- Rytary
- Duopa (intestinal gel)

Dopamine Agonists
- Pramipexole (mirapex)
- Ropinirole (requip)
- Rotigotine (neupro patch)
- Apomorphine

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Dopamine Extending Drugs

MAO-B inhibitors
- Selegiline
- Rasagiline (azilect)

COMT inhibitors
- Entacapone (comtan)
- Tolcapone

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Principles of treatment

- How do we treat dopamine deficiency ?---

–Can't give DA directly ---BBB X

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- ***Make it available*** -----levodopa–**prodrug**
- ***Stimulate neurones to secrete more dopamine*** –bromergocryptine
- ***Reduce metabolism of DA***- COMT, MOA-B inhibitors
- ***Decrease relative excess of Ach*** –anticholinergics
- antihistamines

Classification --- SAQ

– Drugs affecting DA system

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– Drugs affecting cholinergic system

Drugs affecting DA system

- 1. Dopamine presursor:
- Levodopa
- 2. Peripheral DOPA decarboxylase inhibitors:
- Carbidopa, benserazide
- 3. Direct DA agonists
- Bromocriptine, pergolide, piribedil
- Ropinirole, pramipexole
-

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4. COMT inhibitors:
Tolcapone, entacapone

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- **5.** MAO-B inhibitors:
  - Selegiline
- **6.** Dopamine facilitator
  - Amantadine

B. Drugs affecting cholinergic system

–1. Central anticholinergics:

– Trihexyphenidyl (Benzhexol), procyclidine, biperiden, benztropine

–2. Antihistamines

– Promethazine, orphenadrine, diphenhydramine

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Give dopamine ? XXXX BBB

- Giving DA does not help as it does not cross BBB
- Levodopa is the prodrug. √ √ √ BBB
- LEVODOPA ----------→ DOPAMINE

(prodrug) dopa-decarboxylase

(l-Aromatic Amino Acid Decarboxylase)

(AAAD)

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MOA OF LEVODOPA

- **ORAL DOSE 100% -----95% DDC---DA –acts on peripheral tissues and CTZ**
- **Most of the drug toxicity is due to this action**
- ***ONLY*** **5% available to cross BBB**
- **1-2% enters brain and is taken up by surviving neurones**
- **Converted to DA – stored and utilized as neurotransmitter**

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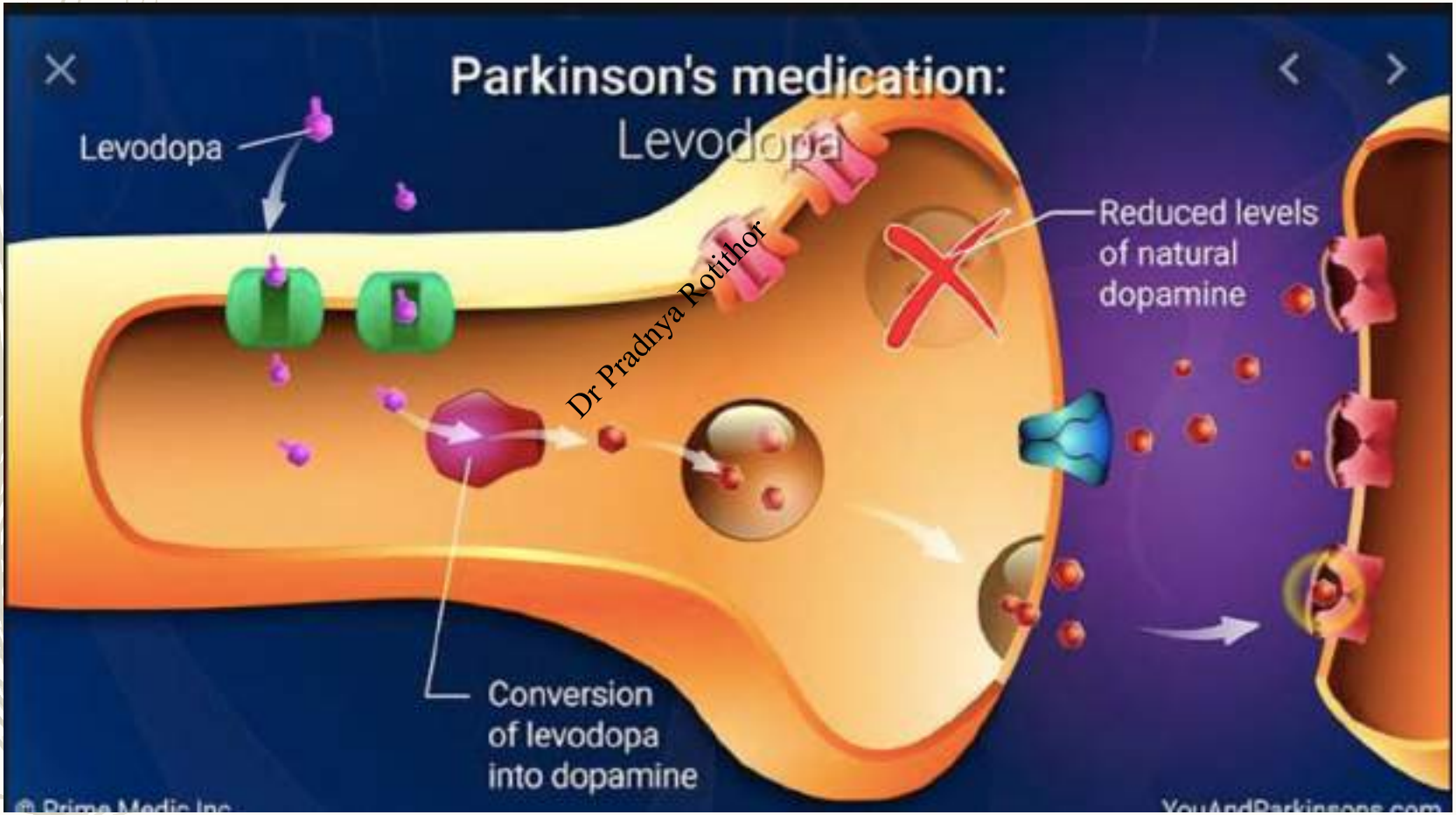
Parkinson's medication:
Levodopa
Levodopa
Reduced levels of natural dopamine
Conversion of levodopa into dopamine
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Levodopa – actions

- **CNS**: (D1,D2) Hypokinesia & rigidity respond better than tremors, then posture, gait, handwriting, speech, facial expression, and behavior (**general alerting response)**

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- **CVS: Peripheral dopamine → β receptors in heart →** Tachycardia, palpitation
- ***postural hypotension*** ***---Central action of DA***

- **CTZ: stimulation: Nausea,Vomiting**
- ***Action of peripheral DA as CTZ is outside of BBB***
- Endocrine: ↓ PL release

- 1)N V –almost all patients suffer
- Tolerance gradually develops
- 2) postural hypotension –1/3 rd patients suffer
- 3)cardiac arrhythmias and exacerbration of angina----Beta R action by peripheral DA
- 4) alteration in taste sensation

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ADR of L-dopa

At the initiation of therapy

Levodopa – long term A/E

1)Fluctuations in motor performance -> 2-5 years

"End of dose" deterioration - Wearing off (tolerance)

"on off" phenomenon/ "switches":

Progressive Degeneration → corpus striatum secretes DA on a moment to moment basis → rapid fluctuations (short t ½ - 1-2 hrs)

All or none response develops—patient is alternatively well and disabled

on – near-normal mobility off- unable to even rise from a chair

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2)Behavioral changes –anxiety ,depression confusion ---cause –excess DA in limbic system

3)Abnormal movements of face tongue limbs –all patients suffer—may become as disabling as original disorder –no tolerance develops to this ADR

dose limiting ADR

Fluctuations in motor performance

– To minimize the fluctuations –

– COMT inhibitors (tolcapone, entacapone)

– Long acting DA agonists

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Contraindications- LEVODOPA

- Psychoses
- Narrow angle glaucoma
- Arrhythmias
- Melanoma (l dopa is precursor of skin melanin)

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Levodopa - Interactions

- **D2 blockers**: : **They reverse effects of levodopa as they cross BBB**
  - **Neuroleptics/antipsychotics** **phenothiazines**
  metoclopramide
- ***Domperidone blocks levodopa induced nausea and vomiting but does not block anti parkinson action as it does not cross BBB but acts on CTZ which is outside BBB***
- Antihypertensive drugs enhance postural hypotension of L dopa
- **Proteins in meals compete for absorption**
- **→ Give half an hr before meals**

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Pyridoxine interaction

- Enhances peripheral decarboxylation of LEVODOPA
- Hence
- Less is available to cross BBB
- Thus
- Pyridoxine abolishes therapeutic effect of Ldopa

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- Levodopa (l-dopa) given alone -
- (almost 95% metabolized in the periphery) (gut liver metabolism)
- Before reaching brain, metabolised by peripheral dopa-decarboxylase-DDC

Hence carbidopa is added..VIVA

- **Peripheral dopa-decarboxylase inhibitors**:
  CARBIDOPA, benserazide
- Concentrate levodopa in the brain

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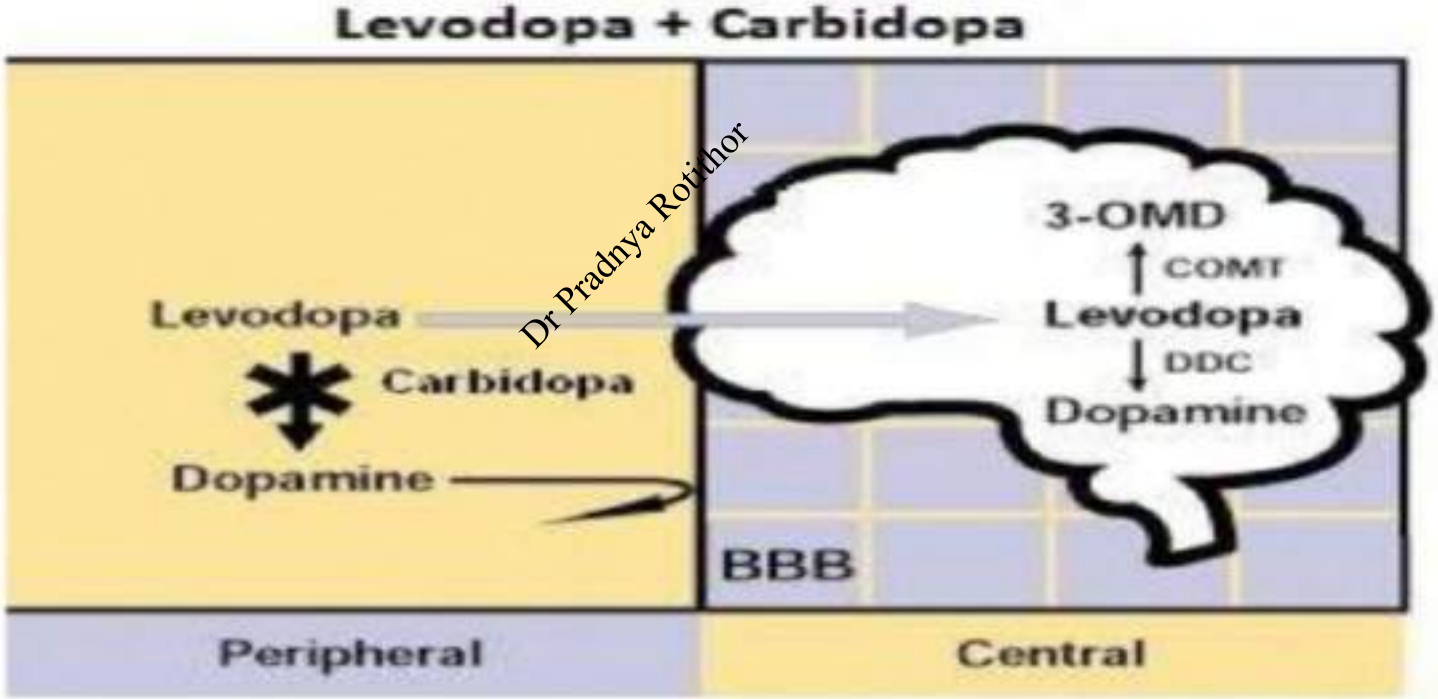
- **LEVODOPA ---//--------→ DOPAMINE**

  dopa-decarboxylase

Remember—

Carbidopa/benserazide DO NOT CROSS BBB

Mechanism of Action:



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Combination - synergism

L-dopa	Carbidopa
100 mg	10 mg
250 mg	25 mg
100 mg	25 mg

100 l dopa + 25 mg benserazide

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L-dopa (0.4-0.8 g/d) + Carbi (75-100) or benserazide (100-200) in 3-4 divided doses

2-3 tablets 3-4 times a day 1 hr before meals

To start with 25:100, later 10:100

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L-dopa-carbidopa = Co-care l-dopa

ADVANTAGES SAQ

- ***Extracerebral DDC inhibitors do not penetrate BBB and do not inhibit conversion of levodopa into DA in the brain***
- ***They prevent peripheral conversion of Ldopa to DA***
- **LEVODOPA ---XXX--------→ DOPAMINE**
- **dopa-decarboxylase inhibitor(carbidopa)**

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Advantages--

- Dose req. of L-dopa ↓ to about ¼ ↑ bioavailability, ↑ t ½
- ↓ N, V (↓ peripheral DA), ↓ cardiac complications hence therapeutic dose can reached quickly
- ↓ on-off (Vs L-dopa alone)as cerebral DA levels are more sustained
- Tolerance delayed, Better compliance with higher degree of improvement
- Pyridoxine reversal of Ldopa effect minimized
- Some patients who do not respond to levodopa alone may also respond to combination

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PROBLEMS NOT RESOLVED
or may even get accentuated

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Postural hypotension **MCQ**

Involuntary movements And

Behavioral abnormalities—may even increase and appear earlier

Bromergocryptine ergot derivative

- Potent D2 agonist Partial D1 agonist
- Long acting
- Lowers dyskinesia better than levodopa
- No oxidative neuronal degeneration like levodopa
- High dose if used alone and has Intolerable side effects
- Now replaced by newer potent selective D2 agonist ropinirole/pramiprexole
- Brom 1.25/2.5 mg tablet

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MAO-B inhibitors - Selegiline, Rasagiline

Selective Irreversible

DA neurons →Inhibit DA breakdown

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-early stage – monotherapy

-late stage – adjuvant to l-dopa-carbidopa →

↓ l-dopa requirement

↓ Involuntary movements (dyskinesias)

-5 mg breakfast, 5 mg lunch

-Higher doses / with TCA, SSRI → amine excess→ Cheese reaction / Serotonin syndrome

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COMT inhibitors **tolcapone,entacapone**

- **Entacapone:** only peripheral:
- less hepatotoxic→ **PREFERRED:** 200 mg tid/qid
- Tolcapone: Brain and periphery, –
- more potent, long duration, but hepatotoxic
- **less preferred** 100 mg tds

- **Other adverse effects: common to both:**
- **Dyskinesia, sleep disturbances**
- **Nausea, Diarrhea**
- **Postural hypotension**

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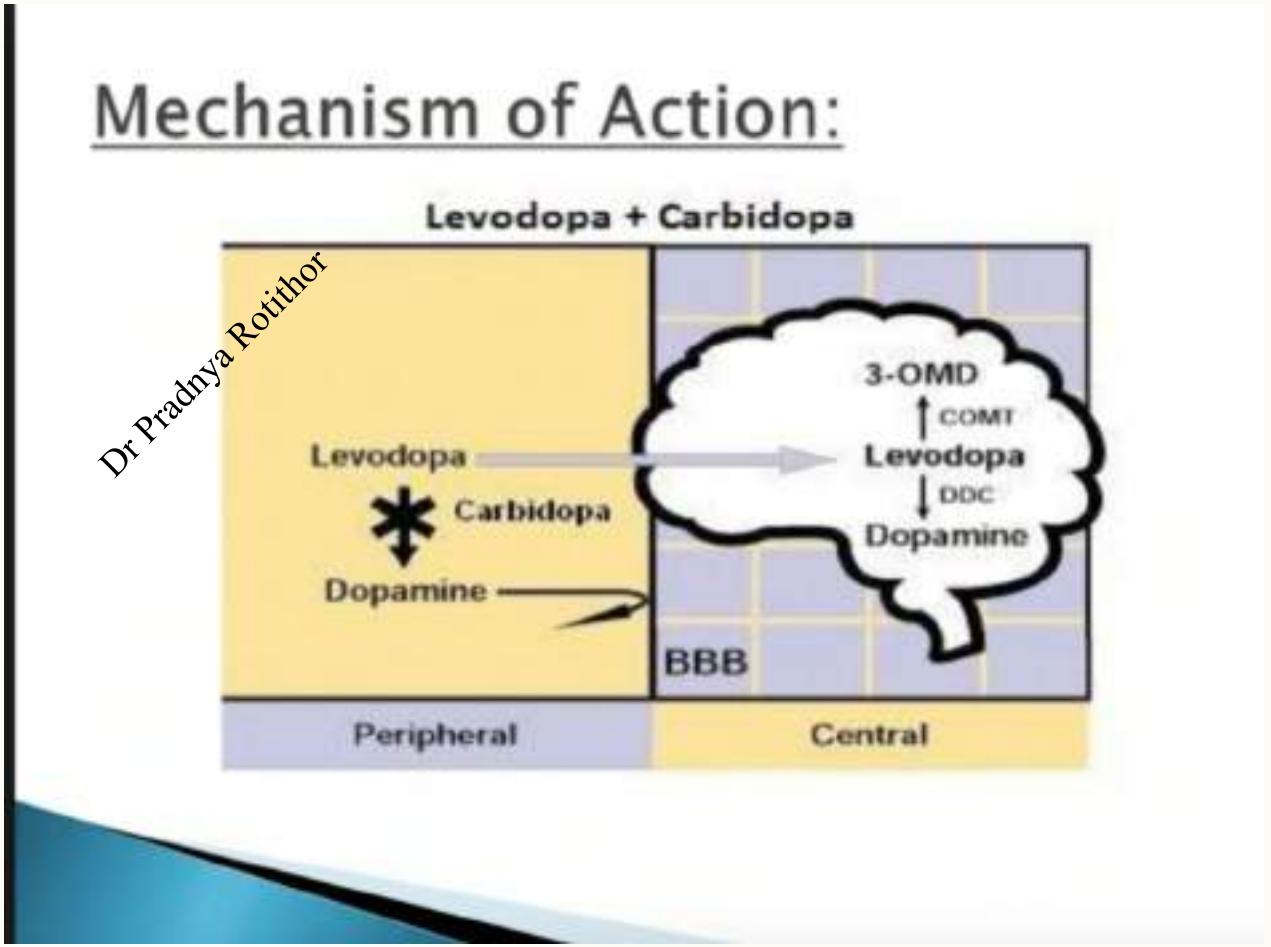
Mechanism of Action:



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DA facilitator – Amantadine (Antiviral)

- 1. ↑ presynaptic DA release
- 2. ↓ DA reuptake
- 3. Weak antimuscarinic
- 4. blocks glutamate NMDA receptor –reduces dyskinesia

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- Uses
- 1. Early stage -- alone
- 2. If no response to l-dopa
- 3. with l-dopa as adjunct
- 4. Drug-induced Parkinson

PHARMEDIA

Amantadine =antiviral drug

DA facilitator

Dose -100mg BID

ADR

Ankle oedema

Nausea
insomnia
Dizziness
Confusion
hallucinations

Vasoconstriction due to
Local catecholamine release

Antimuscarinic effects

Livedo reticularis
Discoloured skin
Due to passive congestion

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Rescue therapy

- **Apomorphine Subcutaneous**
- D4 agonistic effects
- When “On-off” not controlled by
  -DA agonists or –COMT inhibitors

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B. Drugs affecting cholinergic system

- Antimuscarinics (anticholinergics)
- ATROPINE substitutes

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- **1. Central anticholinergics:**
- Trihexyphenidyl (Benzhexol), procyclidine, biperiden, benztropine
- **2. Antihistamines:**
- Promethazine, orphenadrine, diphenhydramine

- Corpus striatum-Restore DA-Ach balance

- -Early stage --Late-stage as adjunct

- -***Drug of choice: Drug-induced Parkinson (neuroleptics/antipsychotics induced Parkinson)***

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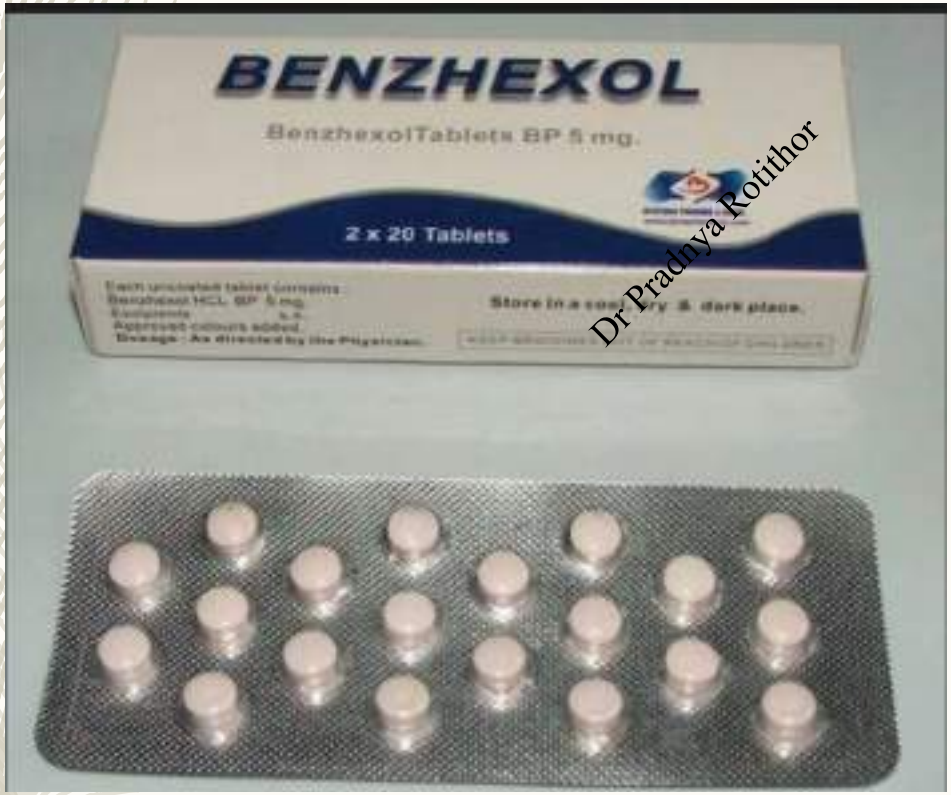
- **Tremors, Rigidity, Sialorrhea respond better (than bradykinesia)**

- Easily available ,Less expensive, less Adverse Effects

- A/E: ATROPINE LIKE, confusion, delirium, hallucinations, precipitate glaucoma



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Drugs inducing Parkinson

- **Antipsychotics/Neuroleptics:**
  - Butyrophenones: haloperidol, droperidol
  - Phenothiazines: chlorpromazine
  - Atypical antipsychotics: much less
- **Antiemetics:** D2 blockers: metoclopramide, domperidone
- **Central alpha2 agonists:** Alpha methyl dopa, clonidine
- **Catecholamine depleter**: reserpine
- **Adrenergic neurone blocker**: guanethidine

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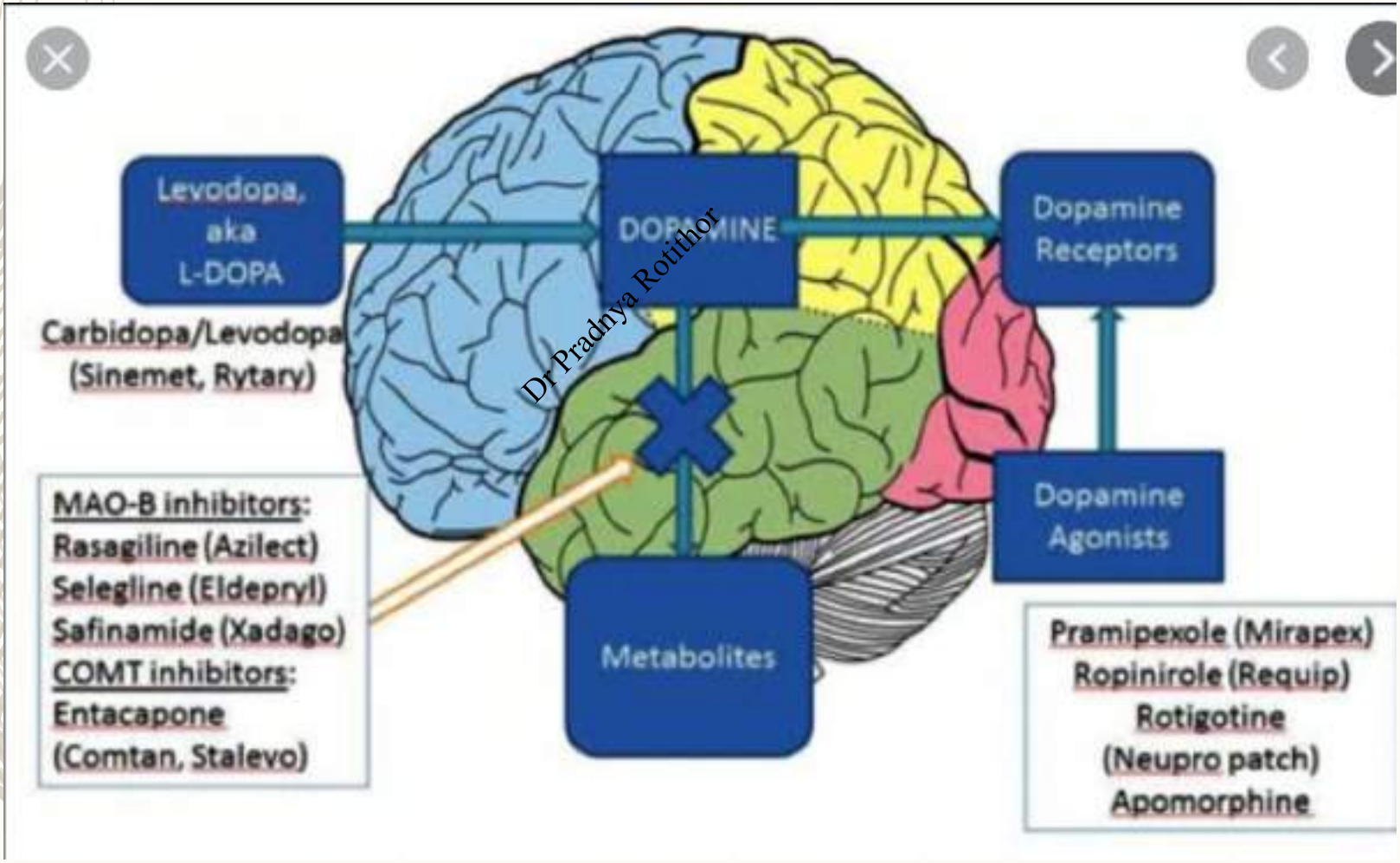

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Parkinson's Hand Tremor
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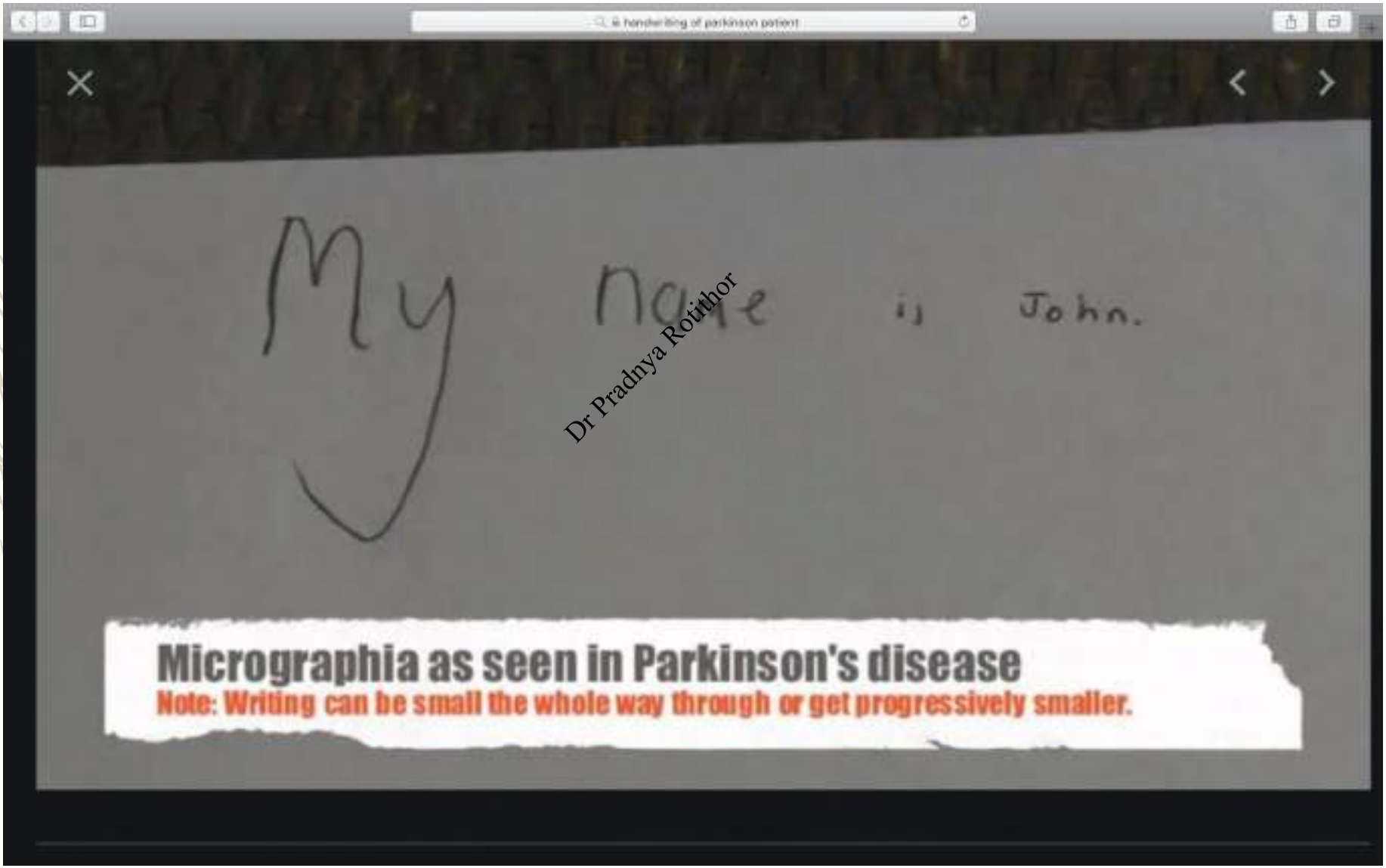

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Thank you