Other Drugs

- Antiemetics
- Antiepileptics
- Antidepressants
- Diuretics

KSS School of Anaesthesia Basic Science Course
South Coast Training Group
Dr S M Walton
Consultant Anaesthesia and Intensive Care
Eastbourne
Antiemetics
Describe the physiology of vomiting?

- Vomiting centre coordinates vomiting

- Considered as collection of effector neurones situated in medulla.

- Collection projects to vagus and phrenic nerves and spinal motor neurones supplying abdominal muscles
What inputs does the vomiting centre receive?

1. Chemoreceptor trigger zone (CTZ)
   - Lies in area postrema on floor of fourth ventricle
   - Functionally outside blood brain barrier

2. Vestibular apparatus
   - Inputs via vestibular and cerebellar nuclei excite centre

3. Peripheral pain pathways
4. Intestinal chemoreceptors and baroceptors
5. Cerebral cortex
Neurotransmitters/ receptors

- **Dopamine/ Dopamine receptors (D2)**
  - Dopamine produced by astrocytes synapsing with CTZ

- **Serotonin/ (5-HT) receptors - especially 5HT3**
  - Receptors found in gut, CTZ and area postrema

- **Acetycholine/ muscarinic receptors**
  - Vestibular pathways

- **Substance P/ Neurokinin 1 receptors**
  - Midbrain
Emetic drugs → Dopamine → 5-HT3 → CTZ → Vomiting Centre

Labyrinth → Ach → Vestibular Nuclei → Ach → Vomiting Centre

Peripheral Pain Pathway
Chemoreceptor Baroceptor Gut
Cerebral Cortex

Limbic System
Can you classify antiemetics?

- **Action on Receptor**
- **Site of action**

- **CTZ**
  - Antidopaminergics
  - Antihistamines
  - 5HT antagonists

- **Vomiting Centre**
  - Hyoscine
  - Antihistamines

- **Gut**
  - Drugs reduce sensitivity
    - Metoclopramide, antacids
  - 5HT3 antagonists
  - Increase gastric emptying
    - Metoclopramide, domperidone
A closer look at dopamine antagonists

• Can be divided into:
  – Phenothiazines (neuroleptics)
  – Butyrophenones (droperidol, haloperidol)
  – Domperidone
  – Benzamides - metoclopramid

Anti-D2 Effects

Mesolimbic pathway - antipsychotic
CTZ pathway - antiemetic

Nigrostriatal pathway
Extrapyramidal effects

Tuberoinfundibular pathway
• Reduce growth hormone secretion
• Increase release of prolactin - dopamine inhibits release
• Temp regulation - Neuroleptic malignant syndrome
The Phenothiazines

Propylamines

- Chlorpromazine

Piperidines

- Thioridazine

Piperazine

- Prochlorperazine

Dirty Drugs - Antagonism on:

- D2, Histaminergic (H1)
- Muscarinic, Serotinergic (5HT3)
- Noradrenergic (α1 and α2),

Effects:

- Sedation
- Extrapyramidal - dyskinesia
- Hyperprolactinaemia
- Neuroleptic malignant syndrome
- Vasodilatation and hypotension
- Anticholinergic
- Cholestatic jaundice
- Haemolysis, leucopenia
Prochlorperazine
“Stemetil”

- Of the phenothiazines:
  - Most effective in PONV
  - Most extrapyrimidal side effects
    - Children and young adults
  - Least sedation
  - Least anticholinergic
The Butyrophenones
Haloperidol/ Droperidol

- Dirty Drugs: D2, muscarinic etc…
- Therefore similar effects to phenothiazines
  - More sedation than phenothiazines

- Haloperidol limited antiemesis
- Droperidol - prolonged QT - torsades
  - Dose related
Metoclopramide

• Benzamide
• Antiemetic action:
  » via D2 in CTZ
  » High dose block 5HT3
• Prokinetic effect via:
  » Peripheral D2
  » Selective stimulation gastric muscarinic receptors
• Side effects:
  • CNS
    » extrapyramidal at higher doses
    » Dyskinesia and occulogyric crisis
    » Commoner in females, young and elderly, renal failure
    » Neuroleptic malignant syndrome
  • Increase lower oesophageal sphincter tone
  • Hypotension
  • Hyperprolactinaemia - used to stimulate lactation
Cyclizine

• Used as:
  • antiemetic
  • Control symptoms of Meniers disease

• Mechanism of action:
  • H1 antagonism at CTZ, Vomiting centre
  • Anticholinergic action

• Side effects:
  • Increase lower oesophageal sphincter tone
  • Anticholinergic - tachycardia

  – Prepared with lactic acid at pH of 3.2
  • May cause pain on injection
  • Precipitation
The 5HT3 Antagonists

Ondansetron

- **Use**
  - Ineffective in motion sickness

- **Mechanism of action**
  - Activation of 5HT3 receptors peripherally and centrally induces vomiting
  - Chemo and radiotherapy cause release of serotonin from enterochromaffin cells

- **Side effects:**
  - Headache, flushing, constipation and bradycardia following rapid injection

- No evidence of superiority over other classes
Hyoscine and The Anticholinergics

- Antagonize muscarinic receptors little activity on nicotinic
- Naturally occurring tertiary amines
  - Hyoscine and atropine
  - Cross blood brain barrier
- Quaternary amines
  - Glycopyrrolate
  - Does not cross blood brain barrier
<table>
<thead>
<tr>
<th>Effect</th>
<th>Hyoscine</th>
<th>Atropine</th>
<th>Glycopyrrolate</th>
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<tbody>
<tr>
<td>Antiemetic</td>
<td>++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Sedation</td>
<td>+++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Anti-sialogue</td>
<td>+++</td>
<td>+</td>
<td>++</td>
</tr>
<tr>
<td>Mydriasis</td>
<td>+++</td>
<td>+</td>
<td>0</td>
</tr>
<tr>
<td>Bronchodilation</td>
<td>+</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Heart rate</td>
<td>+</td>
<td>+++</td>
<td>++</td>
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</tbody>
</table>
Hyoscine

- Anti-spasmodic, antiemetic, anti-sialogue
- IM with opioid for sedative, activity
- Transdermally for motion sickness
- Central anticholinergic syndrome
  - Excitement, ataxia, hallucinations, behavioral abnormalities and drowsiness
Discuss any other types of antiemesis

- **Steroids**
  - Mechanism of action unknown
  - Traditionally used in chemotherapy induced vomiting

- **Benzodiazepines**
  - Mechanism unknown ? Action at VC
  - Lorazepam used in chemotherapy

- **Canabinoids**
  - Nabilone acts on VC

- **Aprepitant**

- **Accupuncture**
  - Several studies have demonstrated effectiveness
  - Point
    - P6
    - Between tendons flexor carpi radialis and palmaris longus
    - 4 cm proximal to distal wrist skin crease
Antiepileptics
How do anti-epileptic drug works?

• Epileptic events are the result of repetitive neuronal discharges

• Stop propagating and recycling currents by following mechanisms:
  1. Stabilizing Na channels - prevent further AP generation
  2. Increase inhibitory transmitter levels
  3. Modulating GABA receptor function
  4. *Inhibit excitatory neurotransmitters and their receptors*
    » NMDA likely target in future
Sodium Channel Stabilisers

- Phenytoin
- Carbemazepine
- Sodium Valproate
Phenytoin

• **Action:**
  – stabilize Na channels (Class 1B anti-arrhythmic)
  also
  – Reduce Ca\(^{2+}\) entry into neurones blocking excitatory transmitter release

• **Side effects:**
  – **Idiosyncratic:**
    • Acne, coarsening of facial features, hirsuitism, gum hyperplasia, megaloblastic anaemia, aplastic anaemia, skin rash, hyperplasia
  – **Dose related:**
    • Ataxia, nystagmus, paraesthesia, vertigo, slurred speech
  – **Intravenous**
    • Hypotension and arrhythmia (heart block)
  – **Teratogenicity**
    • Craniofacial/ limb/ growth and cardiac abnormalities
    • Mental retardation
Phenytoin cont

• Drug interactions:
  – Induces hepatic mixed function oxidases
    • Increase metabolism of drugs warfarin
  – Metabolism of it can be induced/ inhibited by drugs

• Kinetics
  – Saturable hepatic hydroxylation resulting in zero order kinetics
  – 9% of population slow hydroxylators
Carbemazepine

• Action:
  – Same as phenytoin

• Side effects:
  – CNS
    • headache, diplopia, ataxia, vomiting, drowsiness
  – Metabolic
    • antidiuretic - water retention - HYPONATRAEMIA
  – Teratogenicity
    • facial abnormalities, IUGR, mental retardation
  – Misc
    • hepatitis, rashes, agranulocytosis

• Drug Interactions:
  – Induces hepatic enzyme- vecuronium/ phenytoin
  – Metabolism inhibited - Erythromycin
Sodium Valproate

- **Action:**
  - Stabilizing Na channels
  - **Stimulates central GABA inhibitory pathways**

- **Side effects:**
  - Abdominal:
    - nausea and gastric irritation, pancreatitis, hepatotoxicity
  - Haematological:
    - Thrombocytopenia
  - Teratogenicity
    - Neural tube defects
  - Transient hair loss
Other Agents

- **Barbiturates:**
  - Enhance GABA function/ Sedation limit use
  - Phenobarbitone induces hepatic enzymes (interactions warfarin, OCP, other anticonvulsants)

- **BDZ**
  - Enhance GABA function

- **Vigabatrin**
  - Inhibits GABA transaminases (irreversibly)
  - Side effects: sedation, fatigue, headache, agitation, depression

- **Lamotrigine**
  - Stabilize Na channels
  - Stevens-Johnson syndrome in 0.1%

- **Gabapentin:**
  - Mode uncertain (may bind to Ca channels in brain)
  - Membrane stabilizer
  - Excreted unchanged/ no interactions
Antidepressants
How do antidepressants work?

- **Increase levels of Serotonin, Noradrenaline**

- **Tricyclics** *block uptake*1
  - Amitriptyline, nortriptyline, imipramine, dothiepin

- **SSRIs** *Serotonin Specific Reuptake Inhibitor*
  - Fluoxetine, paroxetine, citalopram, sertraline

- **SNRIs** *Serotonin Noradrenaline Reuptake Inhibitor*
  - Duloxetine, venlafaxine

- **NaSSAs** *Noradrenergic and Specific Serotonergic Antidepressants*
  - Mianserin, Mertazapine

- **NRIs** *Noradrenaline Reuptake Inhibitors*
- **MAOIs**
Tricyclics

• Based on tricyclic ring structure

• Uses:
  – Antidepressants, Nocturnal enuresis, Chronic pain

• Action:
  – Block uptake 1
  – Dirty drugs - block:
    • Muscarinic receptor, Histamine receptors, α adrenoceptors

• Side effects at treatment doses:
  – Sedation
  – Seizures in epileptic patients
  – Anticholinergic - dry mouth, constipation, urinary retention, blurred vision
  – Postural hypotension (esp in elderly)
How do you treat tricyclic overdose?

- Effects of overdose:
  - CVS
    - Tachycardia
    - Prolongation of QT
    - Widening of QRS
    - Ventricular arrhythmias
    - Hypotension/PEA
  - CNS
    - Seizures
    - Depression/coma
    - Mydriasis
  - Anticholinergic effects

- Treatment:
  - Activated charcoal
  - Bicarb
    - Alkalization treat arrhythmias/ prolonged QT
    - Increase protein binding
    - Correct acidosis if present
  - Anti-arrhythmics:
    - Lignocaine and phenytoin
    - Avoid inotropes
  - Benzodiazepines/phenytoin
    - Treat seizures
  - Fluids to treat hypotension
  - Forced diuresis
  - Hypertonic saline
The SSRIs

• Prozac etc
• Selective Serotonin Reuptake Inhibitors
• Inhibit reuptake of 5HT
• Similar antidepressant effect to tricyclics
• Lower side effect profile
  – Less sedative, less cardiotoxic in overdose, less anticholinergic effects

• Side effects:
  – Gastrointestinal side effects - nausea and constipation
  – Headache, insomnia, reduced libido, mania
  – Restlessness and agitation - suicide < 25
What is Serotonin Syndrome?

- Iatrogenic increase in serotonin centrally
- Can be potentially fatal
- Requires combination of drugs to reach potential fatal toxicity
  - different mechanisms of action in elevating CNS serotonin

- Symptoms:
  - Clinical features similar to neuroleptic malignant syndrome - But with lack of muscle rigidity

- Treatment:
  - Supportive/ Stop treatments
<table>
<thead>
<tr>
<th>Class</th>
<th>Drugs</th>
</tr>
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<tbody>
<tr>
<td>antidepressants</td>
<td><strong>MAOIs</strong>, TCAs, SSRIs, mirtazapine, venlafaxine, St John's Wort</td>
</tr>
<tr>
<td>opioids</td>
<td>tramadol, pethidine, oxycodone, morphine...</td>
</tr>
<tr>
<td>CNS stimulants</td>
<td>phentermine, diethylpropion, amphetamines, sibutramine, methylenedioxymethamphetamine (MDMA or ecstasy), lysergic acid diethylamide (LSD), cocaine, heroin</td>
</tr>
<tr>
<td>5-HT1 agonists</td>
<td>triptans</td>
</tr>
<tr>
<td>illicit drugs</td>
<td>methylenedioxymethamphetamine (MDMA or ecstasy), lysergic acid diethylamide (LSD), cocaine, heroin</td>
</tr>
<tr>
<td>others</td>
<td>selegiline, tryptophan, buspirone, lithium, linezolid, dextromethorphan (DXM), 5-HTP, chlorpheniramine</td>
</tr>
</tbody>
</table>
MAOIs

- Monoamine oxidase in presynaptic membrane
- Responsible for deamination of amine neurotransmitters
- Types A and B
  - MAO-A
    - deaminates 5HT and catecholamines
  - MAO-B
    - deaminates tyramine and phenylethamine
MAOI

• 1st generation MAOI inhibit irreversibly and non-selectively
• 2nd generation MAOI inhibit reversibly and only MAO-A (RIMAs)
• 1st generation:
  – Phenelzine, isocarboxazid, tranylcypromine
• 2nd generation:
  – Moclobemide
• Rasagiline - antiparkinsonian
Side effects of MAOI

- **Hypertensive crisis**
  - Following tyramine rich foods
  - Cheese, pickled herring, chicken liver, bovril and chocolate
  - Indirectly acting sympathomimetics (ephedrine)

- **Interaction with Pethidine**
  - Cerebral irritability, hyperpyrexia and cardiovascular instability
  - Fentanyl also reported
How should you manage general anaesthesia in patients taking MAOI?

• Emergency surgery:
  – Avoid pethidine
  – Avoid indirectly acting sympathomimetic amines (ephedrine)
  – Use direct acting agents (cautiously as may precipitate exaggerated hypertension)
    • Metabolized by COMT therefore less exaggerated response

• Elective Surgery:
  – Withdraw for 14 - 21 days
  – May suffer relapse of depression
Diuretics
Can you classify the diuretics?

- Thiazides
- Loop diuretics
- Potassium sparing
- Aldosterone antagonists
- Osmotic
- Carbonic anhydrase inhibitors
According to site of action
The Thiazides

- Chemically related to sulphonamides
- Act on early segment of distal tube
- Inhibit Na and Cl reabsorption therefore increase water excretion
- Na in distal tube exchanged with K and H
- Reduce carbonic anhydrase activity resulting in increased bicarb excretion
- Bendroflumethiazide, chlorothiazide, metolazone
Thiazide - Effects

- Antihypertensive - ↓plasma volume and SVR
- Hypokalaemia, hypochloraeamic alkalosis, hyponatraemia, hypomagnesaemia
- Gout - thiazide and uric acid secreted by same mechanism
  - Inhibit uric acid excretion
- Metabolic - ↓insulin, ↓glycogenesis, ↑glycogenolysis.
  - Raise glucose in diabetics
- ↑cholesterol and triglycerides
- Blood dyscrasias
- NSAIDS antagonise
How do Loop Diuretics work?

- Carboxylic acid derivatives
- Furosemide and bumetanide
- Inhibit Na and Cl reabsorption in thick ascending limb + early part of distal tubule
- Impairs counter current multiplier system
- Reduces hypertonicity of medulla
- Loop of Henle large capacity so effects are marked (high ceiling diuretics)
Loop - Effects

- Arteriolar vasodilatation, reduce preload/afterload/pulmonary blood flow (before diuresis)
- Increase renal blood flow
- Hyponatraemia, hypokalaemia, hypomagnesaemia and hypochloraemic alkalosis
- Deafness rapid large bolus (with aminoglycosides and renal failure)
- ↑ lithium concentrations when co-administered
Potassium Sparing

- Amiloride

- Combined frequently in combination with loop diuretics to prevent hypokalaemia

- At distal convoluted tubule blocks Na/ K exchange creating diuresis and decreasing K excretion

- Use with ACE (reduce aldosterone secretion) can cause hyperkalaemia
Aldosterone Antagonists

- Spirinolactone oral, Potassium canremoate IV
- Use:
  - Heart failure, hypertension, ascites, nephrotic syndrome, primary hyperaldosteronism (Conn’s syndrome)
- Competitive aldosterone antagonist
- Aldosterone reabsorbs Na at distal tubule and excretes K
- Diuresis limited as only 2% of Na renal absorption under aldosterone control

- Effects
  - Hyperkalaemia, hyponatraemia
  - Gynaecomastia in men and menstrual irregularity due to anti-androgen effects
  - Contraindicated in Addison’s disease
Osmotic

- Mannitol is polyhydric alcohol
- Used to reduce ICP
- Used to preserve peri-operative renal function:
  - Jaundiced patients
  - Major vascular surgery
- Osmolarity > 320 mosm/kg contraindicated due to increased risk of renal failure
- Freely filtered at glomerulus and not reabsorbed
- Exerts osmotic effect
- Unable to pass intact BBB therefore draws extra-cellular brain water into plasma
- Head injury not intact
- Initially circulating volume increased may precipitate heart failure.
Carbonic Anhydrase Inhibitors

- Acetazolamide
- Weak diuretic
- Used primarily to treat mountain sickness.
- Inhibits aqueous humour production and used in glaucoma
- Inhibits carbonic anhydrase in proximal tubule
- H excretion inhibited and HCO₃ not absorbed
- Produces alkaline urine
- Na and water excretion slightly increased and increase K secretion.
- Results in metabolic acidosis
- Used to counteract respiratory alkalosis associated with mountain sickness