Pharmacology VIVAs April 2013 – April 2009

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Please ignore highlighted colours. They were used while we made the
document together and would be a bit too time consuming to remove.
April 2013

(By Ku)

Question 1" Can you tell me about heparin?

• A mucopolysaccharide, anticoagulant; present endogenously in eg mast cell/liver, with variable weight., MW 5000-25000da. Weak organic acid.

How does it work?

• Potentiates formation of at3-2a complex. Inhibits 10, 2, at high dose also 12, 11, 9.

How is it's mechanism of action different to LMWH?

• LMWH inhibits 2a only. 10a

Why is it's MOA different? (Different molecular weights) How are they administered?

• IV vs SC (better bioavailability, longer duration)
• Due to different molecular weight. – I can’t find from internet an explanation.

Is their excretion different? Why?

• Heparin: heparinas (hepatic) → renal excrete.
• LMW: renal excretion unchanged.
• Due to different MW. LMWH already enzymatic degraded, is more readily filtered at glomeruli.

How do you monitor their effects?

• APTT for heparin, not reliable for LMWH. (eg. Keep APTT 1.5-2x normal, bolus 5000IU bd/tds, titrate by 1000IU/hr).
• APTT range 24-32 sec (or remember 25-30)

What are their adverse side effects? Mechanism of HIT 1 and 2.

• Low BP (vasodilate), osteoporosis, thrombocytopenia, drug displacement PPB albumin, eg. NSAID / midaz ie high albumin PPB.
  o 1: non immune, usu. little significance
  o 2: immune, 1-2/52, IgG-PF4-heparin → causes thrombosis, high mortality once plt count falls, from PE, stroke, limb ischaemia.
How can you reverse them? Can you reverse heparin with protamine?

- Protamine. Yes. Incomplete with LMWH as it’s lower MW, less negative charge, less neutralisation with prtamine = +ve charged/base. 1mg~100iu, give no more than 50mg every 10mins, guided by time of dose for heparin + ACT.

Why only partially? How could you improve coagulation in a trauma patient?

- FFP/
- tranexamic acid: inhibits conversion of plasminogen to plasmin.
- Aprotinin: inhibits plasmin, and preserves plt function.
- Factor VIIa etc

**Question 2**" Sheet of paper with made up analgesic agent with pharmacodynamic / pharmacokinetic things written down (basically like tramadol with different name) Went through each point and why this would be a useful/ disadvantageous point for an analgesic agent in recovery.

**Quirky bits like "would low oral bioA be a problem?"** - no, as long as you adjusted dose etc. But if in recovery, may have low PO absorption or NBM, so preferable to use IV.

Talked a bit about activating descending inhib. pain pathways with 5-HT and NA reuptake inhibition. Conversion between oral & IV morphine and this agent.

"Question 3" Tell me about inotropes Classified.

- Sympathomimetic (direct/indirect; endogenous/synthetic, non-catecholamine/catechol)
- PDEi
- Cardiac glycoside
- Ca2+
- Thyroxine
- Cortisol
- Glucagon
- Levosimendan

Did you mention digoxin (’yes in cardiac glucosides.’) ah yes, tell me how that brings about increased contractility. Does it do anything else?

- Inhibits myocardocte Na/K exchange→[Na] inc→ So inhibits Na/Ca exchange and [Ca2+] inc.
- Decreased chronotropy and dromotropy. mechanism of effect.. direct or indirect.

Can you give me some examples of phosphodiesterase inhibitors? Which subtype is milrinone specific for? Do you know any non-selective ones?

- Aminophylline, milrinone (PDE3 specific).
How do they cause increased inotropy? Didn't ask about side effects really.

- Inhibits metabolism of cAMP, hence through maintaining cAMP (PKA) \( \rightarrow \) inc Ca\(^{2+} \).

Have you heard of calcium sensitisers? ('Yes, I mentioned that and gave levosimendan as an example') Excellent, how does it work?

- **Stabilise Ca-TnC.**

**What are it's side effects?** (arythmias and hypotension) **Common**? Not really..

Why isn't it used more often?

- It’s an inodilator, inc contractility with no inc in CMRO2. May dec BP and other agents may be more appropriate. Eg. Dobutamine. (but admittedly, Levo cf dobutamine has better mortality, arrhythmia, ischaemia mx profile). Also it’s very expensive, so similar concept as to why we don’t use Xenon in everyday practice.

Question 1 **Can you tell me about Ketamine? What is its mechanism?** –

- Phencyclidine derivative, used as anaesthetic agent IV/IM, or analgesic.
- NMDA-R Ca channel antagonist, bind to phencyclidine binding site.
- NMDA-R: Ligand gates, voltage gated, ionotropic; Assc w AMPA-R + neurokinin-1 R
- Also: opioid-R / muscarinic R (secretion) modulation +/- dopamine R antagonist

What dose would you give for IV and IM and why the higher dos?

What kind of anesthesia does it produce? i said dissociative anesthesia and explained the symptoms.

*hallucinogenic experience: deprivation, dissociation, trance like state, theta predominance on EEG*

*eyes open, nystagmus, trance like state.*

They asked how can you determine the depth of anaesthesia for ketamine - i said i did not know

What is the cardiovascular affect of Ketamine?

What happens if you give a shocked hypotensive patient Ketamine - talked about Norad depletion and unmasking of its negative ionotropic effects leading to decreased BP

**Question 2 Can you classify Anti emetics?**
By MoA: (9)

- 5HT3 R blocker
- Antihistamine
  - eg. Cyclizine (Andrew: not licensed for use in Aus; but say it’s licensed in NZ. Another eg = promethazine = a phenothiazine).
  - phenothiazine: prochlorperazine
- Dopamine 2 R blocker
  - Butyrophenones: droperidol
  - Benzthiazepine: benzamides: metoclopramide
  - phenothiazine
- Anticholinergic eg. hyoscine
- Dexamethasone
- Propofol
- Cannabinoids
- Benzodiazepine
- NK-1 R blocker eg. aprepitant

Tell me about droperidol? - went through Physicochemical, Mech and uses and got cut off.

- 2.5mg/ml, clear colour solution, IV formulation, in glass ampoule.
- Potent antagonist D2R
- Use in PONV treatment +/- neuroleptic anaesthesia
  - Form of anaesthesia produced by combination of opioid eg. Fentanyl, butyrophenones eg droperidol, N2O.
  - Characterised by state of reduced motor activity/passivity (neurolepsis), profound analgesia, sedation, amnesis and CVS stability.

What dose do we use? - 0.625mg for PONV treatment.

What is the half life? i said i dont know, they said

- ~2 hrs; but DoA ~12 hrs.

if the half life is short and the duration of action is long, how does that work? - Spoke about receptor binding etc

- Time for plasma concentration to reduce by 50%. 5 t1/2 to complete elimination process.
- Plasma conc may reduce by tissue uptake
  - eg. Lung uptake in fentanyl
  - distribute in propofol
- but accumulation in tissue and subsequent redistribute back to plasma
- Another possibility = presence of active metabolites.
- Effect site trapping.
- Mechanism of drug eg. Aspirin irreversibly inhibits platelet; omeprazole irreversibly inhibits proton pump.
- Synergism with concurrent drug.
What are the side effects – Know difference between EPSyndrome, TD, NMS, EPSyntom

- Low BP (alpha blocker effect)
- Drowsiness
- PRL release (D2) gynaecomastia, galactorrhea.
- EPS and long QT - they moved on before i could mention others
  - Tardive (= late occurring) dyskinesia (Tardive dyskinesia is characterized by repetitive, involuntary, purposeless movements. Some examples of these types of involuntary movements include:
    - Grimacing
    - Tongue movements
    - Lip smacking
    - Lip puckering
    - Pursing of the lips
    - Excessive eye blinking
  - ?caused by dopamine hypersensitivity
- NMS is a life threatening disorder: altered mental status, rigidity, fever and autonomic instability in response to the use of antipsychotic or withdrawal of L-Dopa/Dopamine agonist in PD.
  - Usual onset <2 weeks, inc with rapid rise in dose, parenteral therapy, or an acute illness.
- Excessive rapid postsynaptic dopamine receptor blockade is thought to be responsible.
- Treatment:
  - Stop antipsych; supportive care
  - Extrapyramidal symptoms can be treated with antiparkinsonian medications ie dopamine
  - muscle relaxation eg Diazepam.
  - Dantrolene (a direct-acting skeletal muscle relaxant)
  - bromocriptine (a dopamine agonist) are also helpful.
- Extrapyramidal symptoms (EPS) are various movement disorders such as
  - acute dystonic reactions; pathological tone
  - parkinsonism (akinesia): can’t initiate movement
  - Tardive dyskinesia
  - Akathisia (can’t stop movement);
  - suffered as a result of taking dopamine antagonists, usually antipsychotic (neuroleptic) drugs
- Extrapyramidal syndrome (EPS) is due to the blockade of dopamine receptors in the basal ganglia, leading to Parkinson-like symptoms such as slow movement (bradykinesia), stiffness, and tremor.

What inc risk of QT?
  - PMHx suggestive of: arrhythmia: palpitation, syncope.
  - ECG showing long QT
  - QTc \((\text{Defined as QT interval} \div \sqrt{\text{RR interval}})\)
    - \(\geq 480\) ms - 3 points
    - 460-470 ms - 2 points
450 ms and male gender - 1 point

FHx of sudden death
Concurrent drugs inc QT

VA, ondansetron, antibiotic erythromycin, antifungal fluconazole, TCA, phenothiazines.

What’s mix of QT/Torsades?

ACLS
Mg2+

What’s no good for Torsades?

Amiodarone.

Tell me about the SHT channel? Tell me about ondansetron - What are its side effects

- Ionotropic channel: ligand gated ion channels, activate Na/K.
- SE = constipation, headache, dizzy, and rarely: long QT

**Question 3 Classify topical local anesthetics –**

- Amides: eg. Lignocaine spray, gel
- Esters: amethocaine (tetracaine).

Tell me about EMLA? I totally forgot that lignocaine was in it and i wasted a lot of time trying to remember it.

- Eutectic mixture of LA
- 2.5% prilocaine, 2.5% lignocaine. Emulsion with water/oil phase = white paste.
- Has lower melting point, so present in liquid rather than solid at room temp.

What does Eutectic mean? how does it affect the properties of the Topical agent. Talked about lower melting point.

- 2 or more compounds mixed to produce a substance behaves with a single set of physical characteristics.

What else is in the EMLA cream - it took a while but i said Emulsifying agent then were happy and moved on.

- H2O, Na2CO₃ (buffer) (AD)
- H2O swells stratum corneum → ↑ penetration

What are the side effects of EMLA - mentioned O toludine and the MethHb Mechanism (should have classified into local and systemic).

- Local: skin irritate, vasoconstrict (difficult for cannulation)
• systemic: neuro, CVS, MetHb O-toluidine from hepatic met. PAB allergenic.
• inc absorption if broken skin or on mucosa

What risk factors increase the toxicity –

• Anaemia, Pregnancy, G6PD def?
• Sulphonamides/phenytoin (reducing compound) inc risk of MetHb; others eg. Congenital MeHb, neonates.

How does G6PD affect increase.... Didnt get a chance to answer (didnt know anyway!)

**Question 4** Can you classify oxytocics?

• Oxytocin
• ergot alkaloids,
• PG-miso and PGF2alpha. **(carboprost)**
• KETAMINE (note examiners are really nice and try to help you pass! I know everyone says it but i actually experienced it)

Tell me about oxytocin – got through physiochem, kinetics.

• Physchem: octa or nonapeptide (v similar to ADH).
• Kinetics: Oxytocinase (hepatic/renal met) no oral bioavailable
• T1/2 1-5mins.

ADH effect, hypotension with reflex tachy ?bp overshoot

What are the CVS side effects - Got a bit confused here. eventually settled on Brady and hypotension.

• Vasodilation, reflex tachy, inc myo MRO2, dec BP ➔ cardiac ischaemia
• Uterine rupture
• Pulm oedema

What is the mechanisms of Hypotension - **direct vasculature relaxant**

If we gave a slow infusion instead of a bolus how would that improve the CVS side effects - i said it would lessen them, they asked How? - i had no idea

• Infusion inc plasma conc gradually, rather than abrupt inc as in bolus; compensatory mechanism able to more effectively reduce side effect.

**Question 1**

Can you tell me some of the uses of ketamine?

• Def
• Use: iv
• Sedation
• Analgesia: rescue,

How does it work? What exactly does it antagonise? Besides the NMDA receptor effects, does it act by any other mechanism? (Was looking for opioid receptor actions)

• Non competitive antagonist at NMDA-R (= Ca channel)

What sort of doses would you give somebody for induction with ketamine?

• IV 1-2mg/kg
• IM = 5 x IV = 5-10mg/kg.

Why is the IM dose higher than the IV dose?

• Conc gradient to drive diffusion from muscle → plasma.
• Metabolized.

How would the patient behave? What would they be doing?

• Gen slower onset than others: onset ~90sec
• Dissociative state: eyes open, theta waves. Thalamo-cortical-limbic dissociation. Patient appears to be dissociated from environment, not asleep.
• Other effects: CVS, Resp, CNS, GI, GU

You mentioned their eyes would be open, would they be doing anything characteristically?

• (Wanted REM/nystagmus)
• Inc muscle tone, maybe jerking movement.

So we’ve talked about all these uses of ketamine and it sounds like a pretty wonderful drug, why don’t we use it more often?

• SE limits its use
• PharmK slower onset than others

Other systemic effects:

• Direct SNS effect: inc HR, inc CO, MAP
• If active shocked, depleted endogenous

EEG:

• BIS: not reliable
• Clinical: movement; signs of SNS: lacrimation, diaphoresis, HTN, tachycardia.

**Question 2**
Can you tell me about some of the drugs we can use to treat intraoperative hypertension?

- SE of anesthetic agents propofol & volatile
- BB blockers
- Analgesics
- Alpha 2 agonists
- Nitrates
- SNP
- Hydralazine
- Ca channel antagonist

That list of drugs is quite specific, is there anything else we can do during the operation to drop the blood pressure?

Let’s talk about GTN. Nitrate reductase. How exactly does GTN cause a fall in blood pressure? Does it act primarily on the arterial or venous system?

- Indirect source of NO (met by hepatic nitrate reductase + tissue thiols aka sulphhydryl group ⇒ glycerol dinitrate (10% active) & nitrite. Nitrite ⇒ nitric oxide synthetase ⇒ NO ⇒ ↑guanylate cyclase ⇒ cGMP, inhibit Ca2+ influx and inc Ca2+ uptake to SR, vasodilate.
- The mechanism by which nitrates produce NO is widely disputed. Some believe that nitrates produce NO by reacting with sulfhydryl groups, while others believe that enzymes such as glutathione S-transferases, cytochrome P450 (CYP) causes activation.
- Venous > arterial
- NB: NO synthase (in endothelium), produces NO from L-arginine

Let’s talk about SNP – how is that different from GTN? Between the two, which one is more potent?

- Different in that it’s ‘direct’ donor of NO, to smooth muscle, inc cGMP…
- SNP more potent, (every molecule get 4 NO) as per Adam.
- Major effect = dec arteriole tone, preload.
- PharmK: both have short half-life
- Met: GTN: hepatic reductive hydrolysis
  - SNP: reacts w Hb⇒metHb; and release 5 CN-, which have 4 fates.
  - Cyana-metHb, thiocyanate, cyanocobalamin (b12), cyanate toxicity.
  - So tx by: NaNO3, Na thiosulphate, B12, dicobalt edentate chelate CN- (ie 4 things)

**Question 4**

Let’s talk about pharmacokinetics in a patient who has taken an overdose of an unknown orally ingested drug. What PK parameters can we alter in this patient?
• Absorption: dec absorption w charcoal, chelate drug, NG tube aspirate, prokinetic to dec GIT absorption eg. Charcoal.

  • Dis: eg. alkalinise patient with aspirin so more ionized, more PPB, less tissue uptake.
  • Met: eg. Paracetamol: methionine, NAC,
  • Eli: dialysis (no direct with high PPB, but mainly to excrete the acid load in aspirin), NaHCO3 to alkalise urine to inc excretion

A – activated charcoal, lavage, emesis How does activated charcoal work? How exactly does it bind drugs?

  • Reversible manner; Chelates to inactive compound
  • Binding is reversible so a cathartic such as sorbitol may be added as well.
  • It interrupts the enterohepatic and enteroenteric circulation of some drugs/toxins and their metabolites.

Let’s talk about D now (mentioned IV chelating agents) What IV chelating agents do you know?

  • Suggamadex = gamma-cyclodextrin
  • Digibind – digoxin
  • Intralipid
  • Dicobalt edentate chelates cyanide ions in cyanide poisoning.
  • Na Ca edentate chelates heavy metal lead in lead poisoning.

Besides that, have you heard of digibind? What about something used in the management of local anaesthetic toxicity? How about metabolism? (talked about replacing precursors in paracetamol toxicity)

  • Glutathionation ; Benzyl; if depleted → hepatic toxicity
  • Inc risk w concurrent hepatic disorder; ETOH; phenytoin,

Can you walk me through the pharmacology of paracetamol toxicity?

  • Pathogenesis: sulphation 20% + glucuronidation 60%. Some N-hydroxylation → NAPBQI rapid conjugation with glutathionine, excreted.
  • Centrilobar necrosis.

What about E? (Talked about alkalinising urine) What drug are you specifically referring to here? What is the mechanism of aspirin toxicity?

  • Alkalinizing urine in aspirin toxicity, so more ionized, more excreted.

Define pain.

  • Unpleasant sensory experience associated with actual or potential tissue damage

list types of analgesia and mechanism of action.
• Paracetamol
• NSAID
• Weak opioid
• Potent opioid
• Descending inhibitory pathway
• Membrane stabilizers
• NMDA
• LA

Mechanisms of action of tramadol. Is tramadol directly acting at all these receptors?

• Considered as prodrug, as the o-desmethy tramadol is ~200x more potent than tramadol at Mu-R block. (no prodrug at mu receptor).
  o 40 opioid, 40 noradrenergic, 20 (serotongergic)

what enzyme metabolises mu? Is this enzyme present in everyone (talked about genetic variability and enzyme inducers and inhibitors).

• CYP2D6: genetic polymorphism, 10% Caucasian lack this enzyme.
• Also enzyme inhibition

Name some enzyme inhibitors.

• Cimetidine
• Fluconazole
• metronidazole

2) Mechanism of action of NSAIDS. what is the difference between cox 1 and 2? Side effects of NSAIDS. types of nsaids (non selective, relative selectivity and selective cox 2). name a cox 2 inhibitor.

Gabapentin:

• Ca channel blocker
• ↑GABA synthesis & release
• NMDA antagonist
• No Na channel effect

3) what Factors speed up inhalation induction with sevo in a 5 year old child?

• Rapid SoO (reduced B:G PC,
• higher MV:FRC ratio),
• higher relative BF to VRG,
• although MAC higher in 5 year old.

why does a leak in gas circuit decrease speed of induction?

• (because of entrainment of atmospheric air diluting the volatile concentration)
• Lowered P gradient.

Why does increased cardiac output slow induction?

• SoO related to time to equilibrium of PA(Vapour); inc CO in removal of dissolved vapour and dec time to equilibrium.

how do you reduce cardiac output in a 5 year old child?

• Usu. it’s preferable to maintain CO rather than reduce. But to answer this question:
  • CO = SV * HR;
  • SV function of preload, contractility, afterload.
  • CO reduced by
    o Dec HR
    o Dec preload
    o Dec contractility
    o Inc afterload

Draw a wash in curve for desflurane. Superimpose a wash in curve for 70% nitrous oxide?

What is happening at the shoulder and at the top of the nitrous curve?

the shoulder is due to equilibrium being reached in V1 thus driving gradient for wash in is reduced from alveoli to blood i.e. venous - arterial difference is reduced. Slow increase from shoulder onwards is due to approaching equilibrium in V2 & V3

why is nitrous rise faster and higher than the desflurane curve? (use alot, 70%)

N2O faster as:

• Higher conc
• Concentrating effect
• F:B PC coefficient similar ~0.47
Monday pm

1) What is the fate of epidurally administered fentanyl, and morphine.

What percentage of the dose gets into the spinal cord for both. ???

In what layer is the blood brain barrier. – **arachnoid mater**

- Mechanical: tight junction; dec permeability to water/electrolytes of ependymal **endothelial** cells in cerebral cap
- Chemical: enzymatic degradation in the endothelial cells eg. MAO, dopa decarboxylase

What is an epidural and an intrathecal dose of fentanyl or morphine.

- **Epidural:**
  - Analgesia/neuraxial anaesthesia dose differ: **analgesia 40mcg; anaesthesia 100mcg.**
  - Morphine: usu. for analgesia only: **3–3.5mg**
- **Intrathecal:**
  - Fent 10-20mcg
  - Mor 50-150mcg.

Asked about side effects of epidural morphine, how would you treat the itch?

- SE are:
  - Systemic: usu low as dose used for epidural morphine is small. (ie constipation, urinary retention)
    - Itch.
    - But if histamine release: dec BP, itch.
  - Delayed: CNS: sedation, confusion. NV
  - Resp: depression.
  - CVS: dec HR, MAP.
  - Viral reactivation.
- Itch: tx with naloxone, ondansetron +/- antihistamine (but likely due to sedative effect).

When do you get respiratory depression and how would you check for it.

- May get delayed resp depression with cephalic movement of morphine.
- Possibility up to 24 hrs
- Check by assessing RR, LOC over 24 period.

2) How does dexamethasone exert its effect as an antiemetic.

- ?reduction of 5HT at neuronal and GIT levels.

At what point in a case would you give it.

- Ideally just after induction at start of surgery
• Avoids perineal discomfort
• Gives time for onset of effect (nuclear R, regulates gene transcription/protein production)

How much of dexamethasone is glucocorticoid/mineralocorticoid.

- No MR effect

same Q for hydrocortisone.

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Why do we use hydrocortisone for adrenal replacement.

- It’s analogue to cortisol = endogenously released glucocorticoid/mineralcorticoid.


- Refractory shock to catecholamines
- Electrolyte disturbance typically: low Na, high K.
- Hypoglycaemia
- Abdo pain

What dose of hydrocortisone would you give, does it depend on the procedure?

- 200mg stat then 100mg qid in addisonian crisis.
- Otherwise for prophylactic:
  - Those with 10mg prednisone /day indicated, as <10mg should have preserved HPA axis.
- Low risk surgery: 25mg
- Medium risk: 25mg + 100mg tds 1/7.
- High risk: 100mg tds for 3/7

Above from Oxford Handbook and PHW.

3) Draw an FA/FI curve for isoflurane, at what ratio does it stabilise.

- = in order of B:G PC, except for des/N2O, due to concentrating effect.
  - Iso around 0.5;
  - Sevo ~0.6
  - Des ~0.7
  - N2O 0.8-0.9
  - Halo ceiling around 0.6 in animal studies (AD); ~0.3-0.4

Why.

- Rapid rise = VA presented to alveoli
- Stabilize as the rate of removal by CO approaches rate of delivery by MV.
- There’s also effect on dec MV by VA
- CO usu preserved so rate of removal not changed. (dec SVR balanced by inc HR/SV by SNS tone) except in halothane.

What about halothane and sevoflurane.

Would it eventually reach 1, why not.

- It would not. Get close – but exponential function never reach 1
- Halothane has shown by animal study to reach 0.6 – potent resp depressant. (AD)

What speeds induction.

- Inc delivery: MV, Fi/flow, IPPV so resp dep is bypassed,
Dec removal: inc B:G PC, dec CO.
Inc delivery to effect site: higher relative BF to VRG (in baby)
Concentrating effect/2\textsuperscript{nd} gas effect with N\textsubscript{2}O.

If I decreased CO to 0 what would happen to the curve.

- If no CO, no delivery to effect site, so no induction and no resp depress.
- Just looking at FA/FI, curve would have a continuous raise.
- This situation is not possible, as having no CO is not compatible with normal physiology.

**September 2012**

*(By Hollingworth)*

**Draw wash in curve for 6% des, for 70% nitrous oxide and for 6% nitrous oxide?**

- **Causes for the differences in the curves.**
  - Blood:gas partition coefficient ie solubility
  - Concentration effect
- **What are the factors that affect speed of gas induction in an infant with sevoflurane?**
  - Pt factors:
    - Size of FRC
    - Ventilation
    - CO
    - A/V difference (defined by agent lipid solubility)
  - Anaesthetic Factors
    - Size of circuit
    - Concentration of volatile
    - FGF
- **What happens if premed was given to the infant?** –
  - ↓MAC required

N\textsubscript{2}O = 70%, N\textsubscript{2}O 6% would be between des & N\textsubscript{2}O
Define pain? unpleasant sensory or emotional experience associated with actual or possible tissue damage, or described in terms of such damage

- MoA of morphine? works at mu, kappa & delta receptors which are Gi GPCRs which cause opening K channels (mu & delta) & closing Ca channels (delta)
- It's sites of action? action in
  - CNS in
    - higher centres – thalamus – 2nd,3rd order neuron synapse
    - spinal cord –
      - ↓ periph redistribution of mu receptors, inhibition of C fibres > A delta
    - presynaptic membrane 1st order neurone in dorsal horn
- Morphine’s effect on descending pathway? potentiates descending inhibitory pathways via action at locus cereules, NRM & PAG
- What is gabapentin? gabapentinoid which is anticonvulsant which used also used in chronic neuropathic pain
- What is its MoA?
  - Ca channel blocker
  - also causes NMDA antagonist, ↑ synthesis of GABA, ↑ release of GABA

Given a picture of a graph of rocuronium and atracurium, I found it quite difficult to get my head around it. Y axis is reduction in contraction depth, x is log dose, each point has 95% CI drawn in and a line connecting the the dots. What do the points represent? Is it graded or quantal response?

- How do you define ED95?
  - 2 versions:
    - median effective dose to create desired effect in 95% of population
    - (but = wrong. correct = median dose required to achieve 95% twitch reduction in 50% of population)
- Where is ED95 on the graph?
- Factors that affect the onset of NMB?
  - Drug factors:
    - dose
    - potency of drug
    - location of injection
  - Pt factors:
    - required mm to be blocked: larynx>diaphragm>AbP
    - Acidosis
    - ↓ K, ↓ Ca, ↑ Mg
    - Vd ie dehydration
    - Special – neonates, elderly
- drug reactions:
  - Potentiators of NMD eg volatiles, Mg, Ca channel blockers, lignocaine

Tuesday

1. Define potency. = ability of drug to produce a defined effect. Commonly defined by EC50
Another type of potency besides ec50 (MAC).
Draw quantal dose response curve for sevoflurane (% response vs MAC).
MAC = chance of movement 50% thus @40yrs MAC = 1.8

Described effect of fentanyl 1mcg/kg (wanted precise decrease in MAC ??) then 5mcg/kg then 50mcg/kg.
- 3mcg ⇒ ↓ 50% MAC
- 50mcg – used alone to as surgical anaesthesia

2. Short acting muscle relaxant drugs – mivacurium and suxamethonium.
Which would you use.
Offset reversal.
Adverse effects of repeated doses of suxamethonium. accumulation of succinyl monocholine which has weak agony properties & is agonist at Muscarinic receptors ⇒ brady cardia
How to treat phase 2 block. anticholinesterase agents, time
How to reverse mivacurium. nil reversal – plasma cholinesterase, FFP in extreme circumstances

3. Tell me about phenylephrine. direct acting alpha 1 agonist. unknown metabolism
Effects on systolic and diastolic BP vs adrenaline (particularly effect on diastolic BP.)
- phenyl = direct α1 agonist. raise SVR, \( ∴ \) SBP & DBP & MAP. effectively same as Norad
- adrenaline = mixed α & β agonist. low donc: β effects predominate ie drop DBP with slight incr in SBP & MAP & CO
4. Tell me about Aspirin.
How do you measure the effect of aspirin on platelets.

- various invitro assays
- bleeding time –
  - standardized cut, below bp cuff of standard pressure, await time to stop bleeding
  - diff methods – normal is Ivy (3-10mins), duke 2-5mins
  - normal bleeding time prior to spinal
- TEG
  - measure of metabolic products of COX pathway

By how much does aspirin affect bleeding time. **around 50%**. can see paradoxical shortening of bleeding time with medium dose aspirin ie >600mg

Does this change with uraemia – bleeding time = best way to measure aspirin with co-uraemia

how much does bleeding time increase if you give a uraemic patient aspirin. is ↑ed by mechanism other than COX inhibiton

What is the half life of aspirin? **3hrs but saturatable metabolism** so highly variable

Duration of effect on platelets. 5-7 days. length of platelet life

Who would you not give aspirin to.

- children – Reyes (severe liver damage, encephalopathy)
- late pregnancy
- prior to high risk surgery eg eye/neurosurg
- severe renal/liver disease
- active PUD

What proportion of people exhibit this bronchoconstriction response. **10 – 20%**

How would you tell who was at higher risk. What is the mechanism.

- incompletely understood:
  - inhibition of prostaglandins responsible for bronchodilation
  - shunting into lipoxgenase pathway ⇒ leukotriines which exhibit histamine like effect
• why only 20% -
  o abnormal low PGE2 in lung
  o over expression of leukotriene receptors

another viva

Drugs used in ischemic heart disease
  o antiplatelets
  o B blockers
  o Vasodilators:
    ▪ Nitrates
    ▪ ACEIs
  o AntiHTNs
    ▪ diuretics
    ▪ CCBs
    ▪ K channel blockers with nitrate action

• Classification of Beta blockers
  o B1 selective: esmolol, metoprolol, atenolol
  o lipid soluble: esmolol, propanolol
  o intrinsic sympatomoetic activity: labetalol, carvediolol, bisoprolol
  o membrane stabilisers: labetalol, metoprolol,cairevidiol, propanolol

• Isomerism
  o drugs with same chemical formula but different structural or spatial arrangement
  o structural – diff structural arrangement
  o stereoisomers: diff spatial arrangement
  ▪ enantiomers – chiral centre with mirror image
  ▪ diastereoismoer – multiple chiral centres
  ▪ geometric isomer – double bond (usually carbon) or ring like structure.

• Bioavailability
  o = proportion of administered dose which reaches systemic circulation intact
  o usually a %
  o \( F = f_g \times f_h \)
    ▪ \( f_g = \) fraction absorbed – 1 = completely absorbed
    ▪ \( f_h = \) measure of amount of drug escaping 1st pass metab ie drug not extracted by liver. \( f_h = 1 – Eh \) (hepatic extraction ratio)

S/E of Propofol:
  o CVS: ↓HR, ↓SVR, ↓MAP, ↓contracility
  o Resp: ↓RR, ↓VT, ↓MW, apnoea
  o CNS: amnesia, sympatholitic, ↓CBF, ↓ICP, ↓IOP
  o M/skel – spont movemet (not seizure), hicups
  o Renal - ↓GFR
  o ↓uterine tone
  o other:
    ▪ pain on injection up to 25%
    ▪ propofol infusion syndrome - paeds
  o what is the apneic dose? 2.5mg/kg \( \Rightarrow \) apnoea in 25-30%

• how many % of people would be apneic if given 1mg/kg propofol? 
  5-10%
• Drugs used in anaphylactic shock
  o adrenaline
  o IVF
  o steroids
  o 2nd line - antihistamines
April 2012

By Hollingworth

1. You have a pt needing surgery who is at risk of PONV, what drugs do you use for prophylaxis intraop?
   • serotonin antagonists
   • anti histamine
   • dopamine antagonists
   • steroids
   • benzodiazipines
   • substance P
   • Anticholinergics

pharmacology of Droperidol – butryphenone. dopamine (D2) antagonist, alpha1 antagonist, antiH, anti 5HT3. 2.5ml in tan coloured vial. 0.625mg 2hr plasma half life, works for 12-24hrs. 90% PPB, liver metabolism, 80% renal, 20% faecal route. SEs limited by dystonic reactions, ??cardiac arrhythmias, 25% anxiety for ~24hrs post use

MOA of Cyclizine – Anti-histamine, but also anti-cholinergic (hence tachycardia). Specifically used in motion sickness as H & Ach targets VIII which inputs to CTZ.

where are the 5-HT receptors that you are targeting? Central (all pathways except VIII & NTS), & peripheral – GIT – ECL cells release 5HT3 acts locally on enteric nervous system

Any other drugs targeting 5-HT?

apart from CTZ, where else does antimuscarinic targeting- All pathways except CTZ & drugs/toxins .-. NTS, VIII, higher centres, visceral,

2. Why is Propofol a popular GA drug?
   Fast onset, offset
   predictable deleterious side effects which can be reversed ie sympatholytic
   Useful side effects: ↓upper airway tone – LMA, ETT, airways vasoD, amnesia, ↓cerebral metabolic rate, monitorable with BIS
   Predictable CSHT
   Is it really fast onset? Yes. How long does it take for pt to go to sleep? How long is one arm brain circulation time? <1minute
   Is the induction really smooth? Muscle movements are not associated with Eg epileptic activity ie ETOMIDATE
   Do you see excitation symptoms on induction? Yes – plane 2 of anesthesia seen with all induction drugs
   Can you use Thio for LMA? Difficult as has limited upper relaxation. would need very high doses
Apart from Thio not suppressing airway reflexes, what else does Thio have to contribute to bronchospasm? Histamine release, anaphylaxis.

Tell me why propofol have faster waking up vs Thio? ↑clearance rate, 1st order kinetics, less active metabolites – defined by CSHT

What’s CTSH?
Why Thio’s CTSH is long vs Propofol?
Anything else contributing to Thio’s long CTSH apart from slow elimination?-

What’s propofol’s CI in number? 30ml/kg/min

What pt would you not use propofol? known allergy, haemodynamically unstable (relative contraindication)

3. How many ways can you classify opioids?

- natural (opiate)(codeine, morphine), semi synthetic (heroin, oxycodone, apomorphine), synthetic
- full agonist, partial agonists, antagonists
- exogenous, endogenous

How is morphine metabolized? glucorinated in liver to M3G (75%), M6G (10%) & demethylation to nor-morphine

In what setting do you think M-3-G’s hyperalgesia can be significant? chronic pain. sensitizing role (occurs without activation of mu receptor)

If you give a pt 30mg iv morphine in total on post-op day 1, and the next day you decide to give the same analgesic dose but in oral, how much do you give and why? would 1:3 conversion. 90mg orally, long acting split, with break through

If the pt have severe renal impairment say GFR <30 what dose will you give? I said I’ll try to avoid morphine as I have much better choices in that setting. What drugs can be your choices? oxycodone, fentanyl – patch, tramadol with reduced dosing

What features of those alternative drugs do you think making them more favourable choices?

- fentanyl – dealkylation to norfentanyl which not affected by renal impairment as 10% parent drug excreted via kindey
- oxy – nor-oxycodone – oxymorphone bth weak potency. renally excreted but less active than M6G
- tramadol – opiate activity only 40% of activity. with dose reduction can still benefit from NA & 5HT3 reuptake inhibitor & ↑5HT3 release effects

If you only have morphine to give him, what dose will you give? No more than half. What else would you do? Increasing dosing interval.

4. Can you classify non depolarizing NMBD for me?

by drug group: benzylisoquinolinumos, aminosteroids
by duration of action: short acting, intermediate, long acting

Let’s focus on atracurium- what’s the difference btw atrac and cis-atrac? one of 10 diastereoisomers, 3-4x more potency, no histamine release, Hofman metabolism ony (70%).

How do you compare the potency? Generally with ED50. Anaesthetists & NMBDs tend to use ED95? = median dose which causes 95% depression of twitch in 50% of population of people. Quantal curve (should actually be Edso95) (commonly drawn graphs are EC95 graphs)
How do you get 95% twitch depression? ???

How does a nerve stimulator work? supramax stimulus 50-80mA, causing activation of voltage gated Na channels & propagation of an AP along nerve to NMJ

What’s the mechanism of post-tetanic potentiation? ↑Ach synthesis & release from presynaptic membrane due to ↑Ca in presynaptic membrane

Traditionally you obtain ED95 under GA using barbiturates, nowadays under GA using volatiles, do you get different ED95 values? Volatiles block multiple pathways of mm activation – centrally, presynaptic NMJ, post synaptic membrane stabilizer (decrease active time of nAChR. Barbituates do not have that effect

If I have a pt losing a lot of plasma protein, say nephrotic syndrome, which one’s elimination rate is affected more? Atrac. Is it clinically significant? No, it’s not. Look like all <20% protein bound to me??

What’s the receptor occupancy rate for a NMBD do you start to see twitch depression? >75%

Can you draw me a graph of the twitch height vs occupancy? Just make it up….

1. Tramadol. MoA. 40% opioid, 40% NA reuptake inhibitor, 20% serotonin.

Preparations. Phenylcyclidine derivative; clear solution for injection & various strength capsules

Doses. 3mg/kg IV. 100mg qds in adults

Effects of liver failure. Renal excretion and renal failure. Need dose reduction. bd dosing 300mg in liver failure, 200mg bd in renal. (90% excretion urine, 10% faeces)

Other patient factors altering duration of action. Interaction with fluoxetine. codeine metabolism CYP2D6 – (M1) O-desmethyl-tramadol.

3. Washout curves of sevoflurane and isoflurane. Why do we use Fa/Fao.
Fa/FAO: Depicts removal of drug from body in relation to current state of drug in alveoli

explanation of phases. 3 compartment model – central, rapid, slowly equilibrating
Why rapid initially then slow. Exponential curve. 1st order kinetics. level of elimination is dependant on current level of drug $\frac{dx}{dt}=kx$. or $y = e^{-kx}$

4. Drug interaction. Classify and describe. !!!!!!!!

- Pharmaceutical incompatibility –
  - pH incompatible – thio & midaz (precipitation); sux & thio (alkylaine hydrolysis of sux)
  - osmolarity – blood with mannitol ⇒ haemolysis
  - GTN binds to plastic

PK
- Absorption – PPI & salicylates; adrenaline & LAs
- Distribution – amiodarone displaces warfarin from PPBs
- Metabolism –
  - Enzyme inducers eg phenytoin; enzyme inhibitors eg cimetidine, omeprazole
  - Competition for metabolism:
    - plasma esterases – remi, atrac, etomidate
    - P-Che – sux, esters, mivacurium
- elimination – probenecid & cephalasporins compete for secretion at renal tubule

PD
- agonists & partial agonists
- synergistic effects – fentanyl & propofol – apnoea
- combined toxicity – **triple whammy**: ACEI, diuretics & NSAIDs ⇒ renal impairment
1. **What is bioavailability?** Proportion of administered drug which reaches the systemic circulation unchanged.

\[ F = F_g \times F_h \]

- \( F_g \) = amount absorbed from GI tract
- \( F_h \) = drug 100% absorbed

\[ F_h = (1 - E_h) \]

- \( F_h \) = measure of amount of drug escaping 1st pass metab

Define, drew graph. Now imagine this is a graph of IV versus IM adrenaline. How would it change? Now, you give the adrenaline down the ETT, how would it change? faster than IM, slower than IV?!

What other factors affect bioavailability?
- nature of membrane to cross
- blood flow
- solubility of drug
- ionization
- formulation

Tell me about 1st past metabolism? Tell me about hepatic extraction ratio? see above

What are examples of high and low extraction ratio drugs?

- high = propofol = high extraction ratio ie >0.7 ∴ perfusion dependant
- low = NSAIDs, warf, STP. = <0.3 ratio ∴ enzyme dependant

What else could affect drug metabolism in the liver. Phase 1 and 2 reactions etc etc
2. Tell me about nicotine!!!

potent parasympathetic alkaloid
nightshade family of plants
up to 3% of cigarette
small doses acts as stimulant ⇒ large dose harmful
short half life ~5mins in mouse, elim half life 2hours.
to effect site in 10-20seconds in brain
receptors at ganglia in SNS & PNS, CNS, and NMJ in somatic nervous system
nicotine has higher affinity for CNS receptors
metab by liver CYP (glucuronidation) ⇒ cotinine
metab inhibited by menthol. ∴ why menthol added to some cigs

action:
- CNS: ↑dopamine reward circuits ⇒ euphoria & relaxation (mediated by cholinergic-dopaminergic link via grehlin)
- ↓MAO activity ⇒ addictive properties
- SNS: activates ↑adrenal release of adrenaline

3. Shown a drug ..... They said 'This is lignocaine' without even given me a chance to say what it was. Can you tell em about the structure activity of this molecule?
LAs: (aromatic ring) Lipophilic – intermediate – hydrophilic (amine, linkage either ester or amide)

- **Lipophilic portion** (aromatic ring) - Inc lipid solubility, inc potency
  - But inc toxicity as tissue binding, DoA, vasoD properties
- **Hydrophyllic portion** – tertiary amine – defines affinity for receptor
- A weak base = Ionised/unionized portion ie pKa.
- Chirality – **lignocaine is achiral**
- Amphipathic molecule – allows movement through & to act within cell membranes
- **Ester** (-COO) v amide (-NHCO)
  - Metabolism quicker
  - Paraaminobenzoate metabolite
  - DoA/Cl

Diff parts .... Where would this molecule become ionised? How ionised is lignocaine? Basic, so ionsied, when pH is below its pKa. pKa = 7.9; ~25% unionized.

Point to it .... What structural changes occur with bupivacaine?

Changes to the tertiary amine (aromatic end = same)

Intermediate chain becomes 4 C chain ie buty.

Why is bupivacaine so much more toxic? (5)

- Because it’s an racemic mixture where the R-enantiomer is associated with higher AE.
- High lipid solubility
- High PB, so if penetrate to tissue also high TB and long DoA (toxicity)
- ↑VD (L1, B0.9, R0.5)
- More vasodilate (PLBR)
- Higher Na channel bind affinity.

T1/2 lig: 100, rop 120, bup 160 mins. But DoA: 1-2, to 4-6 hrs.

T1/2 Keo: ATR: alfentanil 1.1, thio 1.2 min, remi 1.3 min, prop 2.5min, fent 5.5min

What levels of lignocaine would you see when you get toxic effects .... What symptoms as levels increase? (3, 4, 5 / * 4, 5, 7)

2 mcg/ml = numbness of tongue
5 = slurred speech, impending seizure; vasoD & hypotension
10 = CVS toxicity

Lignocaine: CNS level toxicity: 5mcg/ml.

Ropi: CNS level: 4mcg/ml.
Bup (3 numbers): CNS plasma level 3mcg/ml, CVS 5mcg/ml. CNS:CVS ratio: 3 (vs 4 R, 7L)

**What is the CVS:CNS ratio?**

Ratio of dose → CVS / CNS toxicity. (Presuming CNS precedes CVS) L7:1, R4:1, B3:1

4. **Can you list for me the antiplatelet agents?** aspirin, dipyridamole, clopidogrel, GP2b,3a inhibitors, dextran

What is clopidogrel? a prodrug, inhibits ADP receptor by creating disulphide bridge ⇒ ↓activation, aggregation, ↓binding to Gp2b/3a

What do you mean its a prodrug? drug which needs metabolizing for it to be active (liver ⇒ carboxylic acid derivative). some people have over-acting metabolism ⇒ ↑chance of bleeding complications

Tell me about its pharmacokinetics? 50% urine, 50% faeces. high PPB 98%, plasma half life of around 1 hr. Onset of action is slow ∴ loading doses used

Where is it metabolised? CYT P450 2C19 .... Do you know anything that changes its efficacy .... (Spoke about aspirin, PPI's etc) ...

Tuesday am

1. **Opiods Opioids are commonly used in clinical practice, but have some important side effects. Could you tell us about some opioid side effects?**

   CNS – sedation, confusion, (seizures), euphoria, dysphoria, miosis
   Resp – blunting CO2 & O2 drive (↓RR, large VT), anti-tussive, bronchoconstriction (histamine)
   CVS – bradycardia, periph vaso dilation, sympatholysis, potentiation para NS
   Skin – itching (histamine), trigeminal nucleus pruritis
   GIT - ↓gastric emptying, ↑sphincter tone, constipation, urinary retention
   Muscloskel – muscle rigidity
   other – activation of herpes virus, ↑ADH release

how opioids produce nausea and vomiting –

- gastric distension - ↑emetic input to CTZ.
- activation of vestibular system
- direct stimulation of CTZ
- antagonism of inhibitory input from higher centres to CTZ
- via NTS – relay from visceral input directly to emetic centre
...is it a dose related response? No.

What other effects can high dose opioids have? I said muscle rigidity including truncal rigidity. How does this pose a problem clinically? I said difficulty in ventilation, may require use of muscle relaxants, etc. They were looking for something more but I didn't know exactly what they wanted and then they prompted: so how will this affect oxygen consumption? I said increase due to increase aerobic/anaerobic metabolism.

How does muscle rigidity affect the CVS system? No direct effect on cardiac muscle, but

- due to increased oxygen demand, can produce tachycardia, risk of ischaemia. They seemed happy.
- isometric mm $\Rightarrow$ ↑afterload $\Rightarrow$ ↑myocardial workload

2. Anti-cholinergics - categorise into

- tertiary amines (atropine, hyoscine, scopolamine); quaternary amines (glycopyrrolate, ipratropium)
- non selective (atropine/hyoscine/glycol); selective (M1 pirenzipine (GI antacid), M2 gallamine), ipratropium bromide (M3)

Have you ever used glycopyrrolate? What is glycopyrrolate? quaternary amine

Where might we use glycopyrrolate?

- as part of reversal to minimize cholinergic effects of neostigmine
- bradycardia – non life threatening
- anti-sialogue – pre med

How does glycopyrrolate differ from atropine? Doesn't cross BBB because of structure, therefore no risk of sedation, central anticholinergic syndrome.

What is this? Do you think that everyone will experience the central effects of atropine? No, elderly at risk. Do you think this might happen, say at even 1200mcg? Seemed like a loaded question, so I said no. Seemed happy.

Where else can we use atropine? Premed. Not sure. I think they were looking for organophosphorus poisoning.

What are some of the other routes by which we can give atropine? lipophilic $\Rightarrow$ oral, IM, INTRATRACHEAL. (OBA is highly unpredictable but quoted ~25%)

What effect does atropine have on cardiac output? Minimal effect. ↑HR, but with all other things being equal this has limited effect of ↑CO due to decreased filling.

3. Propofol PK Here is a graph of propofol plasma concentration over time given to an obese patient. Explain what is happening. Multicompartment model $\Rightarrow$
• V1 central, V2 rapidly equilibrating, V3 slowly equilibrating.
• these compartments include many physical areas & are theoretical
• vessel rich group, muscle, adipose, bone

Now how would this graph differ if the dose was calculated for lean body mass instead if total body weight in this obese patient? Propofol does not accumulate in obese patients despite its highly lipophilic nature.

• induction – dose on IBW
• maintenance dose on TBW with no compensation for ↑ adipose stores

→ graph – induction peak would be same, but then maintenance portion might ↓ as are undosing for TBW

How would you calculate the

• clearance: dose/AUC or = elimination rate/plasma concentration
• Vd: dose (mg)/desired plasma conc (mg/L)
• half life – term half life = 0.693 x VDs (L)/clearance (L/hr)
• rate constant for elimination from this graph. elimination rate (mg/hr)= clearance (L/hr) x plasma conc (mg/L)

4. Amiodarone AF is a common condition, can you tell us some of the pharmacological therapy used for rapid AF?

• βBlockers
• CCBs
• amiodarone
• digoxin
• Magnesium
• Electrolyte replacement

What is Amiodarone? Benzofuran derivative

How does it work? classed as K channel blocker but activity in all classes of antiarrhythmic

Draw for me a cardiac action potential from the SA node and indicate how amiodarone alters it. **Amiodarone has effects at all channels & all tissues!**
but also has effects on Na channel & Ca channel

Delayed Repolarization by Potassium-Channel Blockade

Class II

Ventricular Action Potential

- Class IA: e.g., quinidine
  - Moderate Na⁺-channel blockade
  - ↑ ERP
- Class IB: e.g., lidocaine
  - Weak Na⁺-channel blockade
  - ↓ ERP
- Class IC: e.g., flecainide
  - Strong Na⁺-channel blockade
  - → ERP

CCBs – slow rate of rise of depolarization on pacemaker cell. Also shorten plateau on myocardial AP. ↓ ERP
Effects phase 3 **RAD**: Refractory period, AV conduction prolongation, Duration of AP ↑ed

Here is some data regarding amiodarone (showed me a piece of paper with half life, Vd (70L/kg) and clearance figures). What is a loading dose? loading dose = VD x desired plasma concentration

Why do we use it? Prolonged half life means takes time to get to therapeutic level (biphasic 2-10 days up to 100days)

What problems are there with using a loading dose? I said possible toxicity esp if low therapeutic ratio. How can you calculate the loading dose for amiodarone? I think the half life and clearance figures were there as distractors. Didn't actually have to calculate it, just mention the principles.

Amiodarone can have some serious toxic side effects. If a patient took their year's worth of amiodarone in a month, and presented to hospital, how would you manage them?

CVS: bradycardia, α blocker (minimal direct –ve ionotropic effect on heart)

- ABC,
- supportive treatment of bradycardia:
  - pharmacological pacing – atropine, isoprenaline or dobutamine, adrenaline
  - may require external pacing/temp pacing wire
- hypotension (α blocking effects) – vasopressors
- ??intralipid

1. **Anticholinesterases** = quaternary or tertiary (physo) amines

- short acting – edrophonium
- intermediate acting – neo, pyrido, phystostigmine
- long acting - organophosphates

Classify and MOA – by binding to acetylcholinesterase and forming a complex. this complex prevents Ach being bound. Complex takes time to be hydrolysed by AchE

when can neostigmine be used to antagonise sux – phase II block

**compare and contrast neostigmine and phystostigmine** –

- physo = tertiary, neo = quanternary ammonium compounds
- neo is derivative of phystostigmine
- neo has greater stability & equal/greater potency than phystostigmine
- physo crosses bbb – ∴ CNS cholinergic side effects prevent it being used to reverse block at muscular nAchR
why does physo cross BBB ??? = tertiary amine

uses of physo –

• central antichol synd eg OD of drugs eg cyclizine
• glaucoma
• Rx delayed gastric emptying
• alzheimers

3. asked to identify picture of noradrenaline.

Structure Activity Relationships of catecholamines:

• presence of –OH at 3,4 position of benzene(aromatic) ring ⇒ catecholamines ie max α & β agonist activity
• for max sympathomimetic activity:
  o amine gp 2 carbons away from aromatic gp
  o hydroxyl group in chiral β position in R configuration
  o –OH gps in 3,4 position of aromatic ring – forms a catechol which is essential for receptor binding
• modify amine:
  o primary or secondary amine ⇒ direct action
  o tertiary amine ⇒ poor direct action
  o if amine has
    ▪ bulky substituents ⇒ ↑ed β activity
    ▪ non bulky ⇒ ↑α activity
how do you increase B2 selectivity. modify OH group to position 3, 5
⇒ OH group to 3 only ⇒ α specificity like phenyl

How would you formulate it if i want to administer the drug orally (lipid sol and resistant to MAO).

can you give possible reasons as to why a noradrenaline infusion given to a critically ill pt does not show clinical response?

- NA = predominant α activity ie vasopressor
- critically ill generally:
  - max SNS output
  - shocked ⇒ anaerobic metabolism ⇒ acidotic ⇒
    - ↓smooth muscle response to all catecholamines
  - -ve inotrope state
- ↑ing SVR to defend MAP ⇒ ↓CO which may compound shocked state

4. LAs. MOA. unionized ⇒ moves across axonal membrane, ionized within axoplasm ⇒ binds to inactive channels & prevents further activation

lipid sol and implications. lipid solubility directly related to potency. bupiv > ropiv > ligno

why is bupi > cardiotoxic:

- ↑VD (than ropiv) 0.8L/kg
- ↑tissue binding (PPB 95%; ropiv = 94%, ligno 25%)
- more Vasod (than ropiv)
- longer t1/2 elim – 160mins
- ↑lipid solubility
- ↑binding affinity for Na channels

intralipid – yet to be fully understood:

- chelates LA within lipid micelle ⇒ concentration gradient away from receptor binding (lipid sink)
- counteract LA inhibition of myocardial fatty acid oxidation ⇒ ↑energy production & reversal of cardiac depression

September 2011

(By Shanmuganathan)
1. DES Mac value
How does MAC change with age? Give figures. How old are the subjects on your standard curve. Draw dose response curve. Are there any other MAC? Superimpose MACaw and MACbar. Define MAC, MACaw & MACbar. Mark ED95 on the curve. What is the Mac at ED95? What is the MAC if patient are given 1mcg/kg and 100mcg/kg fentanyl. Draw desflurane wash in curve. At what time fa/Fi will reach 90%? 30mins

Des Mac 6%. Decreases by 6% every decade from 2yrs onwards
MAC is the minimum alv conc of an inhaled anaesthetic agent at std temp and atmos pressure required to eliminate movement to a painful stimulus in 50% of subjects
MACaw is the when 50% of the population will open their eye and respond to & obey verbal commands
MACBAR is the MAC required to ablate autonomic responses to 50% of the population
MAC-ED95 is a MAC of 1.3
Fentanyl will have a synergistic and complementary effect on the use of des. Adding 1mcg/kg of fentanyl will decrease MAC (MACBAR by 40% and proportionally a greater decreased in MACBAR then MACaw) 100mcg/kg fentanyl will produce anaesthesia on its own
3mcg/kg ⇒ ↓MAC by 50%
Washin Curve y = 1 – e^{-kx}

??Discuss curves as a group

2. Define colloids
Classify colloids. What is HES? What is commonly used. What is 6% mean? What is in the bag? Half life? What is albumin? How is it made? What is in the bag? Half life? How is it metabolized? What is the infection risk?

Colloids are fluids that contain macromolecules
Colloids: i) HES ii) Dextrans iii) Gelatins iv) Albumin v) blood
MW 130-400 kDa made form corn or potato starch.
6 or 10% HES/100mls of saline.
degree of molar substitution (glucose units on starch replaced by hydroxyethyl gps) 0.3-0.5
deviation from mean – diff protein weights in molecule
Osmolarity: 310 mOsmol/L, ph: 3.5-7.
half life up to 17days + (to months)

Albumin is fractionanted from pooled human plasma heated to 60C for 10hrs to inactivate viruses. suspended in saline
Human albumin: 40g/L, H2O, Na:140mmol/L, Cl: 128mmol/l, octanal: 6mmol/L, Trace aluminium. ?? Metabolised by the liver. Lower infection risk.

3. How are drugs handled by kidney? Which part of the kidney get involved? What factors influence this? Tell me about ionization, protein binding, MW, solubility. Give an example of drug that formulated in salt form to improve solubility. List drugs that cause kidney impairment. How do you avoid gentamicin toxicity. You do not
normally give gent for orthopedic surgery, what do you normally use? How does cephalosporin affect kidney?

Kidneys are important for elimination of unchanged drugs & their metabolites. Water soluble drugs are easily excreted. Process of i) Glomerular filtration, ii) active tubular secretion, iii) passive tubular reabsorption. Drug that enters the renal tubule lumen depends on the fraction bound to proteins and GFR. Reabsorption from tubules is due to lipid solubility. Rate of reabsorption is influenced by pH ie ionization & rate of renal tubular flow.

Ionization: drugs exist in unionized and ionized forms which is a function of pKa and the pH of the surrounding fluid. Unionized fraction is able to diffuse thru the lipid membrane with ease. Ionized drugs are poorly absorbed. Can lead to ion trapping.

Protein binding: Drugs can bind to albumin (acidic) or α₁AG (basic) and effects distribution of drugs as only the free fraction is active. Protein binding is inversely related to Vd. Drug protein complexes are maintained by weak bond (ionic, hydrogen and van der Waals) and can dissociate once plasma conc falls. Binding is non selective and drug with similar physiochemical properties can compete for spots.

MW: size dictates ability to cross lipid membranes. Small MW can diffuse across otherwise carrier transports are needed. 4nm – 8nm. <4nm pass with no issues, inbetween depends on charge of molecule (less for –ve charged mols)

Solubility: characterizes ease to diffuse across membranes.

Nephrotoxicity: Direct Tubular Effects –
  i) PCT (aminoglycosides, Amphothericin B, Radiocontrast),
  ii) DCT (NSAIDs, ACE-I, Cyclosporin)
  iii) Tubular obstruction (acyclovir, methotrexate)
Acute interstitial nephritis – B lactams, vancomycin, NSAIDs, Phentoyin
  iv) colloids – tubular swelling

READ UPTODATE
?? cephazolin effects on the kidney

4. Compare and contrast fentanyl and alfentanly. I m interested in physical chemical properties. Tell me why alfentanly has quicker onset? What would lipid solubility affect clinically if infusion is used. Define CSHT. Draw CSHT for both. How fentanyl redistributed after iv bolus? What is the role of lung? Which drug has the highest lipid solubility in phenylpiperidine opioid group? You mentioned fentanyl patch, why alfentanly does not have topical formulation?

Alfentanly is 1/10th the potency of fentanyl. Keo: 1.1min (6.4min), 90% unionized (<10%), Vd: 0.4L/kg (4L/kg), Lipid solubility: 125 (955).
Quicker onset is due to very large unionized fraction and a higher dose can be given as it is less potent increasing the conc gradient for diffusion into effect site. Lipid solubility will affect tissue accumulation during an infusion
CSHT is the time for the plasma con to fall by 50%. The context is the duration of the infusion.
Rapidly redistributes to inactive tissues, fat, muscle, with an associated decrease in plasma conc. Lung serves as a storage site with 75% undergoing 1st pass pulmonary uptake limiting the systemic dose.
Sufentinal
Alfentinal is not very lipid soluble and would struggle to diffuse across the skin.

Monday pm Pharm:

1. Local anaesthetic toxicity: What to do? Cardiac and CNS effects at differing levels? Why is Bupivacaine worse than lignocaine wrt CVS? Treatment - what is in intralipid? What antiarrhythmic to use?

Stop injection, ABC’s, supportive treatment and Intralipid
CC:CNS ratio of the dosage required to produce cardiovascular collapse to the dose required to produce CNS toxicity (seizure). Bupivacaine is worse as it has a higher tissue binding and slower dissociation from the receptor = longer duration of toxicity. Intralipid 20% - fat emulsion used to reverse LA toxicity acting as a sink to draw LA away from site of action.
Adam says controversial with regards to antiarrythmic. Amiodarone ?Bretylium

2. Vecuronium: Draw log concentration versus %, what is ED95 of Vec? Why is the shape of the graph steep? What happens when you add Neostigmine? What is the antagonist to NDNMB?

ED90 is 0.057 (so ED95 will be slightly higher)
Spare receptor theory. Once all spare receptors are blocked the dose needed to go from 75% to 95% is small = steep slope.
Neostigmine produces a right shift in the dose response curve.
Ach is the antagonist to NDNMB

3. Inotropes: Classify inotropes. What is the main MOA of inotropes? What are the mechanisms of action of digoxin? Digoxin therapeutic index and levels of toxicity? Treatment of toxicity? Other inotropes discussed: Noradrenalin, PDE-inhibitors (named 4 - discussed mostly aminophylline), calcium.

Class 1: Increase cAMP levels – Adrenoreceptor agonist (adren, norad, dopa, dobuta)
PDE-III (milrinone & amionphylline) Glucagon
Class 2: Effect ion pumps/sarcolemma – Cardiac glycoside (digoxin)
Class 3: Modulation of intracellular Ca – (Calcium gluconate & chloride, Levosemedin [Ca sensitizer])
Class 4: Metabolic/endocrine – T3 or glucagon

Digoxin reversibly inhibits Na/K-ATPase by binding to the extracellular alpha subunit. This indirectly increases intracellular Ca by decreasing the gradient for Na-Ca exchange. Additional Ca is stored in the SR. Produces a Treppe effect
0.5-2.5ng/ml is therapeutic, >3ng/ml is toxic.

Treatment of i) predisposing causes (HypoK, HypoMg, ↑Ca, hypoxmia), ii) treat cardiac dysrhythmias (ligno 1-2mg/kg, pheny 0.5-1.5mg/kg), iii) temp pacing if heart block develops, iv) Digibind (bovine Fab fragments) of which the complex is eliminated by the kidney. 1 vial binds 500mcg.

My viva:


Fentanyl is a synthetic phenylpiperidine derivative
Between 100-150ng/g of tissue, dose not specified (Stoelting figure 3-17) - Refer to Adams graph

![Graph](image)

Elderly have a smaller central Vd, so maybe higher peak conc
Apnoeic threshold = 1.5-3ng/ml

2. Insulin: What is insulin?

Insulin is a polypeptide consisting of 2 chains linked by a disulphide bridge. Formed as a preproinsulin.

Can you compare the time to peak effect and duration of action of neutral insulin given intravenously v subcut.

IV: rapid duration 15 mins onset, 1-2hr duration.

Subcut: onset 1hr, peak 2-3hrs duration 6-8hrs

Why the difference? How is it metabolised?
When given subcut insulin is in hexamers and needs to dissociated to monomers for absorption from subcut tissue. Metabolised in the liver and kidney by proteolytic enzymes. 50% metabolized in the 1st pass.

What effects the metabolism?

Renal dysfunction effects insulin > then hepatic dysfunction

What are the effects of insulin? - see PHSL viva question 2011B

What is glucagon. How does it work? See PHSL viva 2011B

Does glucagon always work in an anaesthetic setting? (This was a bit confusing; I started talking about glucagon receptors in cardiac muscle, then moved on to the requirement for glycogen to be present for glucagon to be effective, which I think is what they wanted.)

3. Sevoflurane/ Fa/Fi: What is sevoflurane? How does it differ from other volatiles (wanted information on the carbon structure, and also the type of halogen substitutions). Draw the Fa/Fi curve for sevo. What affects Fa/Fi? How about in neonates? What is the second gas effect? Is N2O really a highly soluble gas? Compared to sevo? What about washout curves? What is the effect of cardiac output on washout?
Sevo is a polyfluorinated isopropyl methyl ether. achiral!

Machine to alv – i) Inhaled partial pressure (conc effect & 2\textsuperscript{nd} gas effect), ii) Alv ventilation, iii) Anaesthetic breathing circuit including FRC
Alv to blood – i) B:G coefficient, ii) cardiac output, iii) alv-vD
Blood to Brain – i) B:B coefficient ii) CBF iii) Arterial to venous partial pressure diff

2\textsuperscript{nd} gas effect is the ability of high volume uptake of one gas to accelerate the rate of increase of P\textsubscript{A} of a companion gas.
N\textsubscript{2}O B:G coefficient 0.46. but compared O\textsubscript{2} and CO\textsubscript{2} is 40 & 20 times more soluble.
N\textsubscript{2}O is a perfusion limited gas so slowing CO will slow washout.

4. Isomers: What is an isomer. Define and classify them, with examples. Why are some drugs presented as racemic mixtures, and some as enantiopure preparations? What is a chiral centre? I was shown a diagram of L-DOPA. Where is the chiral centre? What is R-DOPA? Discuss the structure-function relationships of this molecule. What are the effects of orally ingested L-DOPA? What other drugs are used to treat parkinson's disease?
Isomers is the existence of 2 or more compounds that have the same atomic composition but different structural arrangement.

**Structural**: Enflurane + Isoflurane

**Stereoisomers**: Geometric (mivacurium) or Optical ➔ Enantiomer (1 chiral centre ie ketamine [racemic mixture]) or Diastereomers (>1 chiral center ie atracurium)

Enantiopure preparations have only one form of the enantiomer which has all the desirable pharmacological effects.

Racemic mixtures are optically inactive so there is no rotation of polarized light. What does that mean in practice?

**Chiral centre is a C or quaternary N surrounded by 4 diff chemical groups.**

Bonds are arranged so that there are 2 possible forms which are mirror images but cannot be superimposed.

R-Dopa is similar but has the opposite chirality. Is biologically inactive. Rotates polarized light clockwise.

Administered with Carbidopa (peripheral carboxylase inhibitor - stops conversion to dopamine in the systemic circulation), Entacapone (COMT-I – slows the elimination of carbidopa or L-dopa), synthetic dopamine agonist ie Bromocriptine & pergolide, Selegilene is a irreversible MAO-B which blocks the catabolic pathway for dopamine in the CNS, Anticholinergic to correct the balance between dopamine and Ach.

**Monday am Room 1**

1. **NSAIDs.** What are they? Uses? Went through side effects by system. Why do they cause bronchoconstriction? Which patients are at risk?

Pain, anti-inflamm, anti pyretic, Rheumatoid, Gout

**GIT** – Decreased mucosal blood flow + secretion of mucus & HCO₃ = ulceration

**Haem** – decreased plt aggregation = increased risk of bleeding

Renal – medullary ischaemia

CVS – Imbalance between TXA and PGI₂ favoring clotting & thrombotic events

Asthma – Shunting of arachidonic acid towards lipoxygenase pathway = bronchoconstriction

2. **IV fluids.** Name crystalloids, what's in normal saline? Why 154mmol/L of Na+ isn't this much higher than physiological? What problems can result from too much N/saline? what's in Hartmann's? What happens to lactate. What are colloids? Name them. Does gelofusine or HES last longer? Why? What's the MW of HES? of Gelofusine?

N/S – H₂O, Na:154, Cl:150 pH:5, Osmolality: 285 measured, 308 calculated. Yes it is physiologically higher because it was initially assume that salt in the blood was 0.9%.

Hyperchloremic metabolic acidosis

CSL – H₂O, Na:129, Cl:109, HCO₃:29 K:5, Ca:2, pH:4-7, osmolality 275. Lactate is a gluconeogenic substrate ⇒ also exogenous lactate ⇒ net ↓H conc on metab.

Colloids are fluids with macromolecules. Gelofusine has a T₁/₂ 2.5hrs, HES has a long T₁/₂. Due to MW, Gelo MW:35kDa, HES MW:450kDa.
3. Antiemetics. Classes and examples. Tell me about droperidol. What else is it used for? What side effects? Tell me about metoclopramide. What side effects? If you’re called to recovery and your patient is vomiting would you give dexamethasone? How does dexamethasone work?


Droperidol – butyrophenone, D₂ antagonist & α₁ adrenolytic effects. Used for prophylaxis against PONV, Neuroleptic anaesthesia, Premed. S/E include neuroleptic malignant syndrome, CVS (HoTN with reflex tachy, ↑ QTc, ventricular arrhythmia) Endo (hyperPRL ➔ galactorrhoea, gynaecomastia) GIT (N+V, diarrhea) No to dex
Dex is a steroid. Exact mechanism unknown but up regulates a variety of cell process/cascades via intracellular receptors, leading to nuclear transcription which contribute to the antiemetic effect.

4. Vasopressors. Similarities and differences between ephedrine, metaraminol and phenlephrine. He drew a line on the paper and asked for the 3 drugs to be placed along spectrum of indirect <--> direct action. Could you give these drugs orally? Why? Something about tachyphylaxis. Do you know any problems with use of these 3 agents in pregnant women? If there is hypotension unresponsive to repeated doses of these vasopressors would you give vasopressin? Would it work? Why?

Ephedrine – Indirect acting synthetic non catecholamine. Actions on α (limited α) & β-R causing release of endogenous Norad. Can be taken orally as its not metabolized by MAO in the GIT. Good control of BP in pregnant women without decrease in uterine flow but associated with increased incidence of fetal acidosis compared to phenyl. CVS effects are similar to adrenaline but less intense and 10× longer. Produces tachyphylaxis.

Metaraminol – Direct & indirect acting synthetic non catecholamine. Stimulates α mainly but β-R’s well. Undergoes uptake into postganglionic symp nerve ending where it releases norad and acts as false neurotransmitter. Not broken down by COMT or MAO, CVS – intense peripheral vasoconstriction with less increase in contractility. Maintains good maternal BP without significant fetal acidosis.

Phenylephrine – Direct acting synthetic non catecholamine stimulating α₁-R directly. Minimal effects on β-R’s. Mimics the actions of norad but is less potent & last longer. Causes a reflex bradycardia. CVS - ↑BP ➔ CO due to reflex bradyC and ↑ afterload. Good for maternal BP control. Less fetal acidosis.

Yes to vasopressin works via a different receptor V1-R to cause vasoconstriction.

**PHARMACOLOGY**
Examiner 1

Can you classify IV induction agents? Tell me about Ketamine? I started saying it's a phencyclidine, NMDA antagonist, clear colourless solution... & I got stopped quite quickly and asked can you tell me what's in an ampoule of Ketamine? What does racemic mean? What is an enantiomer? Why is being racemic important for ketamine? Which enatiomer of ketamine has which effects? What is the mechanism of action of ketamine? Can you describe the NMDA receptor? Why would ketamine be beneficial to use in a trauma patient who has sustained large blood loss? Would it always increase the BP and HR? Why not? List other drugs that act at NMDA receptors.

Classification:

• Barbiturate (thio, methohexitone) &
• non barbiturate –
  o fast acting (Prop, Etomidate)
  o slow acting (ketamine, midaz, fentanyl)

Ampoule: Ketamine HCL 100mg/ml, pH:3.5-5, benzothonium chloride
Phencyclidine derivative, NMDA antagonist.

Racemic mixture has optical isomers in equal amounts so polarized light is not rotated.

• S+ (increased affinity for the NMDA –R, intense analgesia, rapid metabolism, lower incidence of emergence phenomena)
• R- (bronchodilation)

NMDA-R is a member of the glutamate family. Ligand gated channel that allows Ca, Na & K to flow. Blocked by extracellular Mg in a voltage gated dependent fashion. Ketamine has a stimulating effect on the SNS ➔ MAP, CVP, HR. Not all ways as the critically ill have depleted endogenous catecholamine stores and SNS compensatory mechanisms.

Other drugs include methadone, N₂O, dextromethorphan, pethadine

Examiner 2

List for me different situations when you would use rocuronium? What are the side effects of rocuronium? How do these compare with the side effects of suxamethonium? In what situations would rocuronium be preferable to suxamethonium for a rapid sequence induction? When would you not use rocuronium for a rapid sequence? How can we clinically speed the onset of rocuronium? What do you mean by ED95? What is the ED95 for rocuronium? For Sux? In what multiples of this are our usual doses given? Why does giving multiples of ED95 speed the onset of a muscle relaxant? If we gave cis-atracurium in multiples of its ED95 would it also speed the onset for this drug? What else will speed the onset of a muscle relaxant?

Facilitate surgical relaxation, for intubation, for controlled ventilation.
Roc S/E – allergic reaction/anaphylaxis, pain on injection.
Sux S/E – hyperK, myalgias, arrhythmias, raised IOP, raised intra gastric pressure, myoglobinuria, MH, Sux apnoea.
Roc for RSI – Children under 12yrs where muscular dystrophies haven’t presented, Anaphylaxis, MH, Sux apnoea
Sux for RSI – Known difficult airway requiring quick control of airway, allergy

Speed clinically assessed by monitoring twitch count.

ED95 is the dose of drug needed to decrease the strength of a single twitch by 95%.

Roc ED 95 - 0.3mg/kg.
Sux ED95 - 0.25mg/kg

2× for roc. 4× for sux. Because it produces a larger conc gradient to facilitate rapid diffusion into the NMJ

Cis-atrac is given in multiples of its ED95. Intubating dose 0.15mg/kg, ED95: 0.05mg/kg

Potentiates speed of onset:

• Pt factors (increased CO, increasing age, myasthenia, HypoK, burns, ↑age),
• Drugs (Volatile, LA’s, aminoglycosides, Ca^{2+} channel blockers)

How can we manipulate gastric acidity? Give examples of drugs that reduce gastric volume and pH? How do antacids work? What is the benefit to using a non-particulate preparation? Can you write the chemical equation for the reaction between sodium citrate and gastric acid? I said I wasn't sure of the formula for citrate, and she said ok then use sodium bicarbonate instead... so I wrote that and figured out it would form H2CO3

What are the problems with the formation of H2CO3 in large amounts, for example if a patient takes regular doses of an antacid? I said it would dissociate to form CO2 which in large amounts would cause high gastric pressures And what will the patient do? I said they might reflux or burp, then the bell rang :)

\[
\text{NaHCO}_3 = \text{bicarb} \\
\text{Na}_3\text{C}_3\text{H}_5\text{O}_7 + 3\text{HCl} \leftrightarrow \text{H}_3\text{C}_3\text{H}_5\text{O}_7 + 3\text{NaCl} \\
\]

ONE How do you choose a volatile. They wanted the answer as broad as possible – physical, PK, PD, interactions, cost, neurosurgery, interaction with CO2 absorber.

TWO • Non-opioid options for post-operative pain • Further detail on NSAIDS. Is the lack of antiplatelet activity of selective COX2 inhibitors an advantage or disadvantage in acute post-op period. • Why don’t we use aspirin for analgesia

NSAIDs inhibit the action of COX which converts arachadonic acid to PGH_{1} to other precursors. Lack of plt activity is an advantage for the acute post op period as it will allow haemostasis to occur. Aspirin is a irreversible COX inhibitor on plts so plt are dysfunctional for their life span thus preventing clot formation especially post surgery.
THREE • Local anaesthetics • Structure and function relationships • Metabolism • Differential block • Maximum dosage of drugs

Lipophilic (unsaturated aromatic ring), hydrophilic (tertiary amine) portion separated by an amide or ester linkage. Lipophilic portion essential for the LA activity. Increasing the hydrocarbon chain or increasing the C-atoms on the tertiary amine or aromatic ring ➔ diff potency, solubility, metabolism, duration of action.

LA gain access to the Na channel in the activated open states. Block is dependent on frequency (frequency dependent blockade) and diameter of nerve & myelination. \( C_m \) of motor fibers is 2× that of sensory fibers. LA needs to exposed to a minimal length of myelinated fibers to stop conduction ie 3 node of ranviers. Preganglionic symp B fibre < C fibers < A fibers

Amide undergo metabolism by microsomal enzymes with in the liver. Initial step is conversion to

- aminocarboxylic acid and cyclic aniline
- followed by hydroxylation, N-dealkylation.

Process is complex and slow thus systemic toxicity is more likely.

Ester undergo hydrolysis by cholinesterase enzymes in the plasma + liver (lesser extent). Metabolites are inactive. No cholinesterase enzymes in the CSF so LA needs to be absorbed systemically before broken down.

FOUR • Showed a picture of adrenaline, asked me “what drug is this” • Describe structure-function relationships of sympathomimetics • Asked how salbutamol looks. (Told them I have no idea). • How can catecholamines be classified. (I got a bit thrown because they asked specifically for catecholamines, not sympathomimetics). • Volume of distribution of noradrenaline. (That was just plain weird).

\[
\text{Epinephrine} \quad \begin{array}{c}
\text{OH} \\
\text{OH} \\
\text{OH} \\
\text{CH}_2\text{NHCH}_3
\end{array} \quad \text{Norepinephrine} \quad \begin{array}{c}
\text{OH} \\
\text{OH} \\
\text{CH}_2\text{NH}_2
\end{array}
\]

SAR of sympathomimetics – all derived from phenylalanine ⇒ tyrosine ⇒ DOPA ⇒ dopamine ⇒ NA ⇒ adrenaline.

- Presence of OH group on carbon 3 & 4 on the benzene ring = catecholamine.
- Dopamine = 3,4-dihydroxyphenylethylamine. (DOPA decarboxylase)
- Hydroxylation of \( \beta \) chain of dopamine = Norad. (dopamine \( \beta \) hydroxylase)
- Methylation of the terminal amine of Norad = adrenaline. (PNMT)
- Addition of isopropyl instead of methyl group = isoproterenol (synthetic catecholamine).
Synthetic non catecholamines don’t have the OH groups on 3 & 4 carbons.

- OH on 3 & 4 position = max α & β activity.
- OH on 3 carbon = α activity > β.
- OH on 3 & 5 carbon = β2 selectivity.

Natural catecholamine: adrenaline, norad, dopamine
Synthetic catecholamine: isoprenaline, dobutamine
Synthetic noncatecholamine: Indirect (ephrine, metaraminol) Direct (phenylephrine)

Norad Vd: 0.1-0.4l/kg

"Pharmac" 1. What drug would you give to treat hypotension, bradycardia post SAB ephedrine or phenylephrine, can you draw basic structure of these agents, catecholamine skeleton, modification at each position how does it affect the activity /metabolism basically SAR, didn’t do too well in this part. Tell me about metaraminol. Straight forward pharmac question

See above

Metaraminol is an indirect synthetic noncatecholamine with actions mainly on α1-R’s. clear colorless solution in a prefilled syringe of 0.5mg/ml. Given as a bolus or infusion titrated to response.
PK – limited data available
PD –
- CVS (↑ SBP & DBP due to ↑ SVR. Reflex bradyC),
- Resp (slight ↑ in TV & ↓ in RR),
- CNS (CBF ↓)
- GU (↓ uterine blood flow and renal blood flow. may cause uterine contraction via α-R)
- Metabolic (indirect inhibits insulin release glycogolysis, and lipolysis.)

2. Differences between fentanyl, remif and alfent. Onset and off set, why is there a difference. Basically diff in Vd, pka, ionisation Define CSHT draw graph of the three opioids.
3. What are anticholinesterases? *I divided into 3 groups and the mech of axn uses, differences between neostigmine and edrophonium, adverse effects. Anticholinergics: glycopyrolate and atropine. Adv effects, compare with onset with neostigmine.*

**Classify by site of attachment**
- Anionic site: edrophonium
- Esteratic site: organophosphates
- Both: Neo, pryido, physostigmine

**Edrophonium**
- Quaternary ammonium, compound, reversible inhibitor of acetylcholinesterase. Part of the effect is prejunctional. Peaks effect 0.8-2mins, duration of 10mins. Dose of 0.5mg/kg for reversal
- Used for diagnosis of myasthenia gravis, not for reversal of NMDBs
- PD – CVS (↓ HR, increases conduction time, and decreases effective refractory period. Resp (↑ bronchial secretions, bronchoconstriction) GIT (increase ssalivation, lower oesophageal + gastric tone & gastric motility) GU (increases ureteric peristalsis)
- PK – Vd:0.9-1.4l/kg, Cl:7-12ml/min/kg T₁/₂:110mins. 15× less potent then neostigmine.

**Neostigmine**
- Quaternary amine, ester of alkyl carbamic acid. Reversible inhibitor. Dose of 50mcg/kg. peak effect 7-11min with duration 40-60mins
- PD – similar to edrophonium
- PK – Vd:0.4-1L/kg, Cl:6-11ml/kg/min, T₁/₂:15-18mins

4. What are the new updates in CPR? *I talked about the AHA 2010 update. Role of adrenaline and atropine just went straight into the axns of each defibrillator biphasic and monophasic difference and advantage. I didn’t know much about this just guessed about smaller current and less adv effects, any other drugs you would like to use mentioned anti arrhythmic which they didn’t seem to be too excited about, prob they wanted vasopressin. They did go into a bit about amiodarone though.*

Continued emphasis on high quality CPR.
- Look listen and feel has been removed.
- C-A-B instead of A-B-C
- Compression at least 100/min instead of roughly 100/min
- Depth of compression at least 5cm.
My viva:

• What is rocuronium?

Monoquaternary aminosteroid nondepolarising muscle relaxant. Presented as a clear colourless solution of rocuronium bromide

• When do you use it?

Facilitating intubation, adequate surgical relaxation, allowing controlled ventilation

• Why would you choose roc over other agents?

Low potency allowing quick intubation, low side effect profile, can be reversed quickly with sugammadex.

• Discussed inverse relationship between potency and onset

Low potency drugs allow a bigger dose to be given. Therefore higher concentration gradient achieved allowing rapid diffusion into effect site and thus = quicker onset

She asked about the affinity of drug for the receptor

• Draw dose response curve and show more potent drug

• What advantage does roc have over atracurium?

No histamine release, low potency, can be reversed quickly with sugammadex

• Ways to pharmacologically reduce gastric acid

i) Antacids ii) Antihistamines iii) Antimuscarinic iv) PPI v) somatostatin analogues

• Tell me about particulate antacids

Drugs that neutralise or remove acid from the gastric contents. React with HCL to form neutral, less acidic, poorly soluble salts. Neutralisation of gastric acid promotes gastric motility. Via action on gastrin.

• Draw the equation

?? Mg(OH)₂ + 2HCL \rightarrow MgCl₂ + 2H₂O

• Disadvantages of long term use of eg Mylanta

Mylanta has 4 diff antacids (NaHCO₃, MgOH, CaCO₃, AlOH). NaOH – HTNsive pt may not tolerate the increased Na load.
MgOH – osmotic diarrhoea, neuromuscular, cardiovascular impairment in pt with renal dysfunction
CaCO₃ – Metabolic alkalosis, HyperCa in renal dysfunction, HypoPO₄, release of CO₂ in the stomach

Iron absorption

i) Absorbed by the enterocytes in the duodenum and upper jejunum. Ferric converted to ferrous in the stomach. Ferrous is much more soluble. Ferric precipitates at a pH >3. Some aa can bind with ferric iron to form soluble chelates which are absorbed across the duodenum. Ferrous iron is transported across the apical membrane by DMT1

ii) dietary Hb and myoglobin is degraded and release haem. Haem is soluble in alkaline duodenal content and readily absorbed as an intact metallo-porphyrin involving a haem receptor. Haem is broken down in the enterocyte by haem oxidase releasing Fe²⁺.

Once in the cytoplasm ferric binds to apoferritin to form ferritin. Ferrous is converted to ferric by a ferrioxidase on the basolateral membrane. This binds to transferrin. Each transferrin has 2 binding site. Transferrin is 1/3 saturated under normal conditions.

Iron balance is amount absorbed/day = amount lost/day. Males: 0.6-1mg/day, females: 2.1mg/day. No phsl control mechanism for excretion therefore body content is solely by regulation.

Normal body stores are 3500-3700mg in a male. Females have lower levels due to lower weight, lower Hb and increased losses.

Immune

Protein digestion

Metabolic alkalosis

• Inducing 5yr old with sevo – what factors speed onset?

Input - i) Inhaled PI, ii) alv vent, iii) characteristics of the breathing circuit, iv) FRC,

Uptake - i) Solubility of anaesthetic vapor in body tissues, ii) CO, iii) Alv to venous diff

• Why does FGF make a difference?

The volume of the anaesthetic breathing circuit act as a buffer to slow acheivement of \( P_a \). High gas flow rates negate this buffer effect.

• Size of circuit? Paed vs normal

Mapelson E (Ayres T piece) – Valveless, low resistance with small dead space. Open ended 500mls reservoir bag (jackson rees modifications) type F

• Wash-in curve 70%N₂O, then 9% desflurane – what is blood-gas partition coefficient?

Why are curves different? Where would N₂O curve be if it was given at 9%?
By Ku, Shanmuganathan, Hollingworth

**B:G coefficient** – The rate of increase of Pa to Pl is inversely related to the solubility of the anaesthetic in the blood.

If I give someone an intubating dose of Rocuronium, how do I know that they are paralysed? (needed to eventually say muscle stimulator)

- **How do peripheral nerve stimulators work?**

Consists of a i) oscillator ii) display iii) constant current (allows for automatic compensation for changes in tissue impedance) iv) controls.

Oscillator is the basis of the nerve stimulator and provides a pulse at a required frequency and width.

To propagate a nerve impulse a certain threshold stimulus must be applied to the nerve. Cathode (-ve electrode) current departs altering the resting membrane potential and producing an area of depolarization which spreads along the nerve.

- **What is a supra-maximal stimulus?**

A stimulus who’s strength is significantly above the required threshold to activate the nerve or muscle in contact with the electrode.

- **If we gave a single twitch, what will the response be?**

(lots more questions probably coming but I had wasted a lot of time on the definition of supra-maximal stimulus

What drugs are used to treat pulmonary hypertension?

i) nitric oxide ⇒ direct ↑cGMP
ii) prostacyclin ⇒ stim cAMP ⇒ vasoD
iii) sildenafil – PDE V inhibitor ⇒ ↑cGMP ⇒ ↑smooth mm vasoD (PDEV localized to lungs & penis)
iv) CCBs
(warfarin – Rx 2nd complications)

- **Do you know what Milrinone is?**

Bypyridine derivative PDE3-I. 50µcg/kg followed by an infusion of 0.5µcg/kg/min. T1/2: 2.7hrs, eliminated 80% unchanged from the kidney. Wide therapeutic ratio therefore risk of overdose is low.

- **How does it work?**

Primary role is as ionodilator ⇒ ↑CO. used in cardiogenic shock

PDE degrade CGMP & cAMP thus inhibition of PDE3 ⇒ ↑cAMP & cGMP ⇒ produce pulmonary vasodialtion.
PDE$_5$ is specific for cGMP. Sildenafil is a PDE$_5$-I

- What are the peripheral effects of milrinone?

- How does this occur? (wanted info about 2nd messenger systems)

- Name another 2nd messenger system
cAMP, Ca$^{2+}$, Phosphoinositides (IP$_3$ & DAG)

(I said phospholipase C, they were happy with that)

- Are there any anaesthetic induction drugs that you would avoid in pulmonary HT?
  - ketamine
  - Nitrous oxide

Draw a FA/FI curve for Desflurane

- What is happening here at the shoulder?

$F_A$ is approaching $F_I$ as the uptake by tissues esp the VRG has equilibrated. After 3 time constants 75% of the returning venous blood has the partial pressure of the alv. The continual rise represents uptake of the volatile by VPG

- Why does sevoflurane have differences at the start and right at the end (The examiners drew a curve just below mine, with a gap near the begining and end)

higher blood gas soulbility

- What is a partition coefficient?

is the ratio of concentrations of a compound in 2 phases at equilibrium.

- If a patient is at equilibrium with 5% des, and the blood:gas partition coefficient is 0.42, and the gas concentration is 1 ng/mL, what is the blood concentration? (I was flipping out at this point and my recollection of the question and figures may need some straightening)

0.42ng/ml

- If the brain:gas coefficient is 0.53, what is the brain concentration?

like the above im guessing 0.53ng/ml

Tell me about clopidogrel (I didn't get far before they cut me off)

- What is its mechanism of action?
Blocks ADP receptors on the plt surface, preventing GPIIb/IIIa binding thus inhibiting plt activation, aggregation and degranulation. Irreversibly modify the ADP receptor therefore last the life span of the plt.

• What makes it a pro-drug?

Requires CYP2C19 for its activation in the liver.

• What can reduce its effectiveness, starting from the point of administration?

CYP2C19 poor metabolizer at high risk for treatment failure. CYP2C19 is an impt drug metabolizer for barbiturates, PPI, antidepressents.

• What is it's duration of action?

For the life of the plt.
T_{1/2} : 0.5-1hr

What is MAC?

MAC is the minimum alv conc of an inhaled anaesthetic agent (at std temp and pressure) required to eliminate movement in response to a painful stimuli in 50% of pts. MAC gives a common measure of potency. MAC 1.3: prevents movement in 95% of the pop
MAC awake: 0.3
MACBAR: 50% of the pop will not have an autonomic response

• draw a curve of dose response curve for MAC

y axis = % moving to stimulus
x axis = MAC 0 – 2 (log or graded) or ET AA with appropriate no,

• can you find MAC for an individual?

No – quantal graph. le yes/no response

• what is the effect of body temp and atm pressure on MAC?

a high altitude (low pressure;
• pp = conc x ATM
• ∴ need to ↑conc if ↓ATM to achieve same pp
• ∴ at high altitude need to dial higher conc
• machine calibrated for sea level mean will read MAC >1 when pp in alveoli (&brain is thus 1 MAC)

b ↑temp ⇒ ↑MAC
Placental drug transfer

- what are the factors
- talk about ionization/ion trapping/Fick's law

How do you treat anaphylaxis?

- adrenaline, steroid (antiH only as 2nd line – prevent 2nd phase response)
- what receptors do each drugs act on?
- what other effect does antihistamine have

Transdermal, buccal mucous membrane and inhaled

- nicotinic receptors, what types are there? neuronal, ganglionic, neuromuscular

Autonomic ganglia & NMJ, CNS. Designated N₁ & N₂ respectively. Belong to a family of ligand gated channels.

- effect of nicotine on naive patient vs chronic smokers: concept of tolerance

Tolerance is the progressively decreasing response to repeated dosing of drug or the need to increase dose to achieve the same effect. Infers a decrease in potency, not efficacy.

Mechanism: i) Altered receptor number due to down regulation or decrease transcription ii) altered receptor response to activation, iii) Altered pharmacokinetics

April 2009

(By Ku)

PK's and PD's of local anaesthetic injected intrathecally - Didn't seem interested in PK's though, despite the question

- MoA: frequency dependent Na⁺ channel blockade,
- PD: Na⁺ channel blockade, disrupt AP transmission,
  - Tactile
  - Pain
  - ANS (but mainly SNS, as ?????PSNS not transmitted via SC).
• +/- motor blockade; proprioception

By system:

• CVS: brady, low BP
• Resp: dec FRC, dec intercostals tone
• Endo: dec adrenal activity
• Temp: no sweat, shiver, NST, vasomotor constriction
• Muscle: flaccid paralysis

• Where does it go? Effect site? Mechanism of action of LA’s?
  o Moa:
    o Diffuse through axonal sheath into axoplasm, ionised, binds to open inactivated state of Na and prevents it from leaving the open inactive state, so further activation of channel prevented.
• What we see clinically –
  o ie, blockade of autonomic nerves, sensory/pain fibres, motor block
• Duration of action factors?
  o Lipid solubility,
  o Tissue protein binding affinity (related to lipid solubility)
  o Rate of systemic absorption (related to site of injection, vasoD, adrenaline…etc)
  o metabolism
• What effect does pKa have?
  o pKa and pH determines degree of ionicity; more unionised, more lipid soluble and faster speed of onset.
• Metabolism
  o Eg amides longer than ester;
  o Hepatic failure, slower met, longer DoA.

Therapeutic Index

• Definition
  o = the ratio of the median effective dose (ED50) and the median lethal dose (LD50)
  o TI = LD50 / ED50
  o Derived from quantal dose-response curves.
  o indicates relative risk of toxicity with overdose →↑ therapeutic index → ↑ safety margin from toxicity
  o low therapeutic index requires shorter dosing intervals (to limit peak toxicity) and more frequent plasma level monitoring
  o eg. Digoxin, phenytoin.
• Why is it not clinically important?
  o Interindividual variability
  o idiosyncratic reactions such as MH
  o age, intermittent illness or other drugs may lower or raise the therapeutic index
    ▪ epilepsy → ↓ convulsive dose of lignocaine
    ▪ midazolam → ↑ convulsive dose of lignocaine
  o LD50 derived from animal data, so not really applicable to human.
  o TI may be misleading if the log dose-response curves have different slopes for effectiveness and toxicity, and there may be significant overlap of ED and LD log-dose response curves → margin of safety therefore more useful.
Other indices of adverse effects

- Margin of safety:
  - percentage by which the ED99 needs to be increased to cause toxic effects in 1% of the population
- CNS:CVS ratio
- Shown graph of Gentamicin plasma monitoring nomogram - why do we measure it at these time points?
  - (I said that peak may not be as important, also initially due to redistribution rather than clearance - seemed to accept that as what he wanted)

Gentamicin dosing:

1. Trough samples are taken immediately before a dose and peak sample taken 10 min after iv, and 1 hour after im injection.
2. Aim peak concentrations are 4-10µg/ml, trough concentration <1-2µg/ml.
3. Approach using normograms

Side effects/Toxicity/Drug interactions

1. Nephrotoxicity
2. Ototoxicity
3. Others: eg headaches, nausea, vomiting, rashes and abnormal LFT’s
4. Drug interactions eg NDMR, inhibits plasma cholinesterase

Beta-blockers

- Classification –
  - gave cardioselective, non-selective
    - Met, ate, esm vs. propan, carvedilol
  - Intrinsic sympathomimetic activity
  - Membrane-stabilising activity
  - Combined alpha-beta activity - He still wanted more!!
  
  +
  - Lipid vs water soluble.
    - Eg. Metoprolol, propanolol, esmolol vs atenolol, sotalol
  - Partial agonist eg. carvedilol
- Wanted to talk about lipid soluble vs water soluble, different agents, how does it affect PK’s, duration of action, el 1/2 t
  - Absorption:
    - Hydrophilic usu. poor absorption vs lipophilic
  - 1st pass met:
    - Hydro minimal 1st pass met; unlike lipo = significant 1st pass met.
  - Vd, PPB
    - Lipo: large Vd, low PPB, sign hepatic met;
    - Hydro: small Vd, high PPB, minimal hepatic met, renal elim.
- Lipo: generally longer t1/2 than hydro? → No
- CNS penetration: lipo > hydro. So cause CNS dep, fatigue.

- Is labetalol 1:1 alpha:beta blocking? How is it different?
  - No; alpha:beta = 1:3 (oral), 1:7 IV
  - So cause peripheral vasodilate with alpha blockade, without reflex tachycardia as beta blockade.

**COX**

- What is it?
  - Cyclo-oxygenase;
  - Arachidonic acid → endoperoxidases → PG, PGI2, TXA2.

- What are the different types?
  - COX1- responsible for production of PGs eg RBF, haemostasis, gastric mucosa.
  - COX2 – inducible form, in response to tissue damage, facilitates inflammatory response.

- What is constitutive? – relating to an enzyme or enzyme system that is continuously produced in an organism, regardless of the needs of cells

- What does COX do?
- Why COX2 inhibitors?
  - Aimed at inhibiting specifically the COX2, and leaving COX1 still functional

- Are they better?
  - Talked about slightly lower incidence of GI issues, but increased thrombosis - similar renal failure; maybe better with asthma, etc

- Who wouldn’t I give NSAIDs to?
  - Renal impairment, ACEI/other drug interactions eg. Warfarin, lithium. 3rd trimester pregnant women, aspirin to children, allergic, bleeding concern, GI bleed, asthmatic sensitive,

- How does aspirin work?
  - Irreversible inhibition of COX.

- Low dose vs high dose - what is the difference?
  - Low dose: selective inhibition of platelet COX, preserve vessel wall COX; reduce TXA2 induced vasoconstrict/platelet aggregate;
    - Vessel wall PG spared; and diluted
  - High dose targets analgesic effect.
    - Inhibit both.

Other people got - CVS effects of propofol - easy

suxamethonium - easy

CVS effects of volatiles - easy

Diagnostic tests - 2x2 table, sensitivity/specificity, screening tests, etc – look up wiki
### Patients with **bowel cancer** (as confirmed on endoscopy)

<table>
<thead>
<tr>
<th>Condition Positive</th>
<th>Condition Negative</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Test Outcome</strong></td>
<td><strong>Positive</strong></td>
</tr>
<tr>
<td>Fecal Occult Blood</td>
<td>True Positive (TP) = 20</td>
</tr>
<tr>
<td>Screen Test Outcome</td>
<td>False Positive (FP) = 180</td>
</tr>
<tr>
<td>Test Outcome</td>
<td>Positive predictive value</td>
</tr>
<tr>
<td>Negative</td>
<td>= TP / (TP + FP)</td>
</tr>
<tr>
<td></td>
<td>= 20 / (20 + 180)</td>
</tr>
<tr>
<td></td>
<td>= 10%</td>
</tr>
<tr>
<td>Sensitivity</td>
<td></td>
</tr>
<tr>
<td>= TP / (TP + FN)</td>
<td></td>
</tr>
<tr>
<td>= 20 / (20 + 10)</td>
<td></td>
</tr>
<tr>
<td>≈ 67%</td>
<td></td>
</tr>
</tbody>
</table>

| Test Outcome       | Negative predictive value |
|--------------------| = TN / (FN + TN)          |
| Negative           | = 1820 / (10 + 1820)     |
|                    | = 99.5%                 |

| Test Outcome       | Specificity |
|--------------------|            |
| Positive predictive value |
| = TN / (FP + TN)   |
| = 1820 / (180 + 1820) |
| = 91%              |

### Screening test WHO criteria: (made up)

- Condition should be important
- Treatment available
- Facilities available for diagnosis/treatment
- Latent stage so screening allows for treatment
- Test should be available and acceptable to population
- Disease pathophysiology understood
- Policy on whom to screen/treat
- Benefit should outweigh cost
analgesics to treat post-operative pain, what is good about alfentanil? - easy

April 2009

(By Ku)

1. Antihypertensive agents used to drop blood pressure intraoperatively

- adrenoceptor blockade
  - beta, alpha, combined
- Vasodilators:
  - GTN
  - SNP
  - Hydralazine
- Anaesthetics:
  - VA
  - IV Ana
  - LA
- Sympatholytic:
  - Opioids
- Calcium channel blockers
- ACEi

Esmolol; Durations of action – why?

- Esmolol t1/2 10min
- RBC esterase, high Cl: 300ml/kg/min

Hydralazine - Cardiovascular effects, Mechanism of action

- ↑cGMP
- CVS: reduce arteriole tone > vein. (So usu. no postural BP drop). Reflex tachycardia
- Ses incl aplastic anaemia, SLE, fluid retention
- OBA 25-50%
- rapid acetylators t1/2 ↓ from 2-3hr to 45 mins

Pregnancy Class C drugs – what does that mean?

- A = safe: adequate no. studies showed no risk to fetus in pregnancy
  - Aussie: no AE seen.
- B = animal studies showed no risk to fetus, but no adequate human studies.
  - Aussie:
    - B1: small no. of data only. No risk shown. Animal studies no risk.
    - B2: small no. only. No risk shown. Small no risk in animal studies.
    - B3: small no. only. No risk shown. Larger no risk in animal studies.
- C = unknown in human, despite risk in animal studies.
  - Australian: owing to effects, suspect to cause AE, but not malformation. May be reversible AE.
- D = unsafe.
  - Australian: suspect to cause irreversible, malformation AE.
- X = high risk of permanent damage, shouldn’t be used.

2. N2O 70% with Sevoflurane – what effect does the N2O have
• MAC sparing
• Inc speed of induction
• May cause hypoxia if anti-hypoxic device fails

• Factors affecting uptake of sevoflurane
  - Fairly low B:G PC, so not affected much by CO.
  - PA sevo mainly affected by:
    - In: MV, Fi sevo, 2nd gas effect by N2O

• Respiratory effects of sevoflurane
  - Dec MV, with dec TV > inc RR.
  - Dec tone → obstruction, aspiration.
  - Dec drive.
  - Apnoea @ ~1.5-2MAC.
  - Dec FRC (relaxes diaphragm, intercostals).
  - Uncouples HPV, so may see inc V/Q ratio mismatch.
  - bronchodilates

• Changes in alveolar ventilation
  - N2O is relatively MV sparing.

  • mechanism
    - Sevo – Meyer-Overton Mechanism
      - Potency relate to oil:gas PC.
      - doesn’t explain ketamine.
      - So ?dissolved in neuronal lipid bilayer.
    - Mullins Critical volume hypothesis further states MoA by
      - Protein channels distorted so ion flux altered across membrane, once critical conc of VA is reached.
      - Supported by ‘pressure reversal’: inc pressure result in reversal of anaesthesia.
      - But doesn’t explain why enf/iso have different MAC.
        - Also Iso S isomer more potent than R isomer.
    - Specific target proteins proposed to exist:
      - For:
        - Explains stereoslectivity.
        - Dose-response curve steep = typical of receptor-ligand mechanism.
        - Binding sites identified on Glycine R and GABAaR.
      - So in summary: appears to potentitie GABAaR/Glycine R inhibitory effect with molecular MoA involving disrupting neuronal lipid membrane integrity.
  - N2O – NMDA-R block +/- GABAa-R

3. What type of drug is Suxamethonium

  • DMR
    - Mechanism of action
      - DMR
    - Why does it last longer than the natural agonist
      - Dicholine ester of succinic acid, more resistant to AChE metabolism.
    - Phase II Block
      - Definition: fade, reversed by Neo, T1:T4 <70%, PT facilitation.
      - Draw a dose-response curve for sux (paper given with axes of response against dose – NOT log dose – I added Log!.
        - Why do we log it – EC50
          - Transforms into a sigmoid shape (from a rectangular hyperbola (see p. 93 green book).
o To enable broader range of dose on same curve: dose vs response curves between different medications, or between ED50 and LD50, can be assessed
  a The slope of the curve allows assessment of dose-response between threshold and maximal response (i.e., when response first seen). ED50 depends on the slope as well as where threshold response starts.
  a The threshold dose can be easily identified (where curve starts to rise)
• What is EC50
  a Effective concentration to produce 50% of that drug’s maximal effect.
    (Katzung 29)
  a Allows for comparison of potency.
• What affects EC50
  o Potency (hence also affinity)
  o Steepness of log dose-response curve.

NB: quantal = ‘all or none’ and refers to effect seen in population statistics.

4. Pharmacokinetics of drugs in Hepatic Failure and Cardiac Failure

• Liver failure Pharm K:
  o A
    • Dec 2nd dec bile, eg Vit DEKA and inc effect of warfarin
    • High 1st pass met drugs: inc BA PO as dec met,
      • eg morphine, midaz, labetalol
    • high ER drugs: inc BA 2nd inc porto-systemic shunt.
  o D
    • inc Vd hydrophilic drugs: eg NDMR
    • dec PPB eg NSAID, warfarin
  o M
    • Dec pseudocholinesterase
    • Mainly phase 1 affected (exam report) with phase 2 if advanced dx
    • Mainly affecting drugs of low HER eg BDZ
    • High HER drugs affected by dec HBF.
    • Miller: but w dec PPB, inc free drug, inc liver met/uptake, so balance effect of dec met activity.
  o E
    • Dec renal Cl in hepatorenal syndrome
    • Dec Cl if biliary obstruction

Pharm D effect:

• Inc sensitivity to anticoagulants
• Inc effect to CNS drugs and risk of encephalopathy: opioids/BDZ/GA
• Fluid overload, esp w NSAID
• Down regulation of beta-R, so likely ↓ dose required for effect.
• Inc vagal tone, so dec HR, inc AWR

• Dose adjustments for Propofol
  o No need, as high extra-hepatic metabolism, so no effect on t1/2 of propofol.
  o Lipophilic, so no obvious effect from inc TBW.

Cardiac failure:

Pharm VIVAs 09-13 - 61
• Inc body water
• Renal failure
• Hepatic congestion
• What else?
• A: reduced as oedematous gastric mucosa inc diffusion distance; but likely dec 1st pass met as congested liver gets less portal blood flow with inc resistance?
• D: inc TBW; dec protein concentration, dec protein synthesis
• M: dec metabolism, dec HBF
• E: dec renal clearance, dec RBF.