PAEDIATRIC ANAESTHESIA

AIRWAY MANAGEMENT

Describe the anatomy of the neonatal airway, how this changes with growth and development and the implications for airway management

Compare and contrast the neonatal respiratory system with the adult: PAST QUESTION 36%

PERIOPERATIVE MEDICINE – PHYSIOLOGY

Describe the foetal circulation

Describe the circulatory and respiratory changes that occur at birth

Circulatory changes that occur after birth

Respiratory changes that occur with birth

Define the thermoneutral zone, describe temperature regulation in the neonate and the physiological responses to lowered and raised environmental temperature, the effects of anaesthesia on these responses and how this changes with growth and development

Thermoneutral zone

Physiological response to hypo- and hyper-thermia

Temperature regulation in the neonate, physiological responses to lowered and raised environmental temperature, the effects of anaesthesia on these responses and how this changes with growth and development

Describe the physiology of the cardiovascular, respiratory, renal and neurological systems in the neonate and the changes that occur with growth and development and the implications of this for anaesthetic care

Describe the composition of body fluids in the neonate and explain the changes that occur with growth and development

Describe glucose homeostasis in the neonate and explain the changes that occur with growth and development

Describe vital signs for children of different ages

GENERAL ANAESTHESIA AND SEDATION – CLINICAL AND APPLIED PHARMACOLOGY

Describe how the pharmacokinetics of drugs commonly used in anaesthesia in neonates and children differ from adults and the implications for anaesthesia

Describe the changes in the pharmacodynamics of volatile agents, analgesics, opioids and neuromuscular blocking agents in the neonate and the changes that occur with growth and development and the implications for anaesthesia

Describe the pharmacology of agents used for premedication in children, including midazolam, clonidine, and ketamine

Outline how the pharmacokinetics of morphine, bupivacaine and suxamethonium differ in the neonate compared to the adult. Briefly describe the clinical implications of these differences: PAST QUESTION 73%

Outline the pharmacological differences between neonates and adults with reference to sevoflurane, vecuronium, and morphine: PAST QUESTION 42%

REGIONAL ANAESTHESIA

Describe the difference in pharmacokinetics of local anaesthetic agents in neonates and children from adults and the implications for regional blockade

Describe the maximum safe doses of local anaesthetic agents in different age groups
AIRWAY MANAGEMENT
Describe the anatomy of the neonatal airway, how this changes with growth and development and the implications for airway management

**Compare and contrast the neonatal respiratory system with the adult:** PAST QUESTION 36%

<table>
<thead>
<tr>
<th>Differences between neonatal and adult resp system</th>
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<tbody>
<tr>
<td><strong>Anatomy</strong></td>
</tr>
<tr>
<td>Upper airways</td>
</tr>
<tr>
<td>Larynx</td>
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<tr>
<td>Lower airways</td>
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<td>Lungs</td>
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<tr>
<td>Lung volumes</td>
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<tr>
<td>Tidal volume VT</td>
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<tr>
<td>FRC</td>
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<tr>
<td>VD/VT</td>
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<tr>
<td>FVC</td>
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<tr>
<td>Ventilation/ gas exchange</td>
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<tr>
<td>Respiratory rate</td>
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<td>I:E ratio</td>
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<tr>
<td>Specific compliance</td>
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<tr>
<td>Oxygen consumption</td>
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<td>Physiological dead space</td>
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<tr>
<td>Control of ventilation</td>
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<tr>
<td>Hb</td>
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PERIOPERATIVE MEDICINE – PHYSIOLOGY
Describe the foetal circulation
- foetal circulation supplies foetal tissues with O2 + nutrients from the placenta; bypasses the foetal lungs
- foetal Hb (OHDC L shifted) ensures DO2 maintained despite low PaO2

**Foetal circulation** - Structure

- 2 umbilical arteries
  - arise from internal iliac a
  - return deoxygenated foetal blood to placenta
  - PaO2 18mmHg; SpO2 45%

- 1 umbilical vein
  - supplies oxygenated blood from placenta to foetus
  - PaO2 28mmHg; SpO2 70%
  - 60% of blood from umbi vein enters IVC; 40% enters liver

- 2 ducts
  - ductus venosus: shunts blood from umbi vein to IVC
  - ductus arteriosus: shunts blood from pulmonary trunk to descending aorta

- Foramen ovale
  - Shunts blood from RA to LA

- Immature myocardium
  - Does not obey Starlings Law
  - Does not adjust contractility for any given preload
  - SV is fixed; CO is HR dependent
  - Normal HR at term = 110-160

**Foetal circulation** - circulation:

- Oxygenated blood returns via umbi vein:
  - 40% flows to liver via portal vein ➞ hepatic vein ➞ IVC
  - 60% bypasses liver via ductus venosus ➞ directly to IVC

- Blood reaches the heart ➞ divided into 2 streams by interatrial septum:
  - 1. Oxygenated blood from IVC directed via Eustachian valve through foramen ovale ➞ LA ➞ LV ➞ ascending aorta ➞ O2 rich blood to head + upper body
  - 2. Blood returning from SVC (drains myocardium + upper body; ↓PaO2) ➞ directed into RV ➞ descending aorta by ductus arteriosus + ↑PVR
  - arrangement has several features:
    - Patency of ductus arteriosus maintained by low PaO2 + vasodilating effects of prostaglandin E2
    - NB: ~10% CO passes through lungs ➞ low O2 in lungs ➞ vasoconstriction ➞ ↑PVR
    - Blood with least O2 delivered to brain
    - Blood with least O2 delivered to umbil arteries for gas exchange
    - Both RV + LV eject to systemic circulations; similar size + wall thickness

**Mechanisms whereby O2 transfer is facilitated at placenta**

- placenta = large vol, low pressure, low resistance A-V shunt responsible for transfer of O2 and nutrients to meet demands of growing foetus
- 1. ↑blood supply to placenta: uterine flow ➞x20 during pregnancy; not autoregulated and is pressure dependent
- 2. ↑foetal blood supply to placenta: umbilical arteries supply foetal deoxygenated blood to placenta; foetal CO is 1L/min (25055% goes to placenta)
- 3. HbF: affinity for O2 than HbA; HbF = 2a2y; lower affinity for 2,3,DPG ➞ shifts HbF OHDC to L ➞ means that HbF has ↑affinity for O2 and assists it to load O2 in placenta; ↑saturation at given pO2 than adult Hb
- 4. Hb concentration: ↑concentration HbF ➞ O2 carrying capacity
- 5. Double Bohr effect: Bohr effect operative in both maternal and foetal circulations

**Physiological principles**

- Bohr effect: describes how changes in pCO2 and pH affect O2 transport
  - ↑pCO2 and ↓pH stabilises deoxy-Hb facilitating release of O2 ➞ R shift in OHDC
  - ↓pCO2 and ↑pH ➞ L shift OHDC
- Double Bohr effect: describes both effects happening on either side of placental gas exchange in mother + 1
  - ↑pCO2 in maternal inter villous sinuses assists O2 unloading ➞ ↓pCO2 on foetal side assists O2;
  - Foetal blood flows from umbilical artery to umbilical vein ➞ releases CO2 to mother and ↑O2
- Haldane effect
  - Describes how changes in O2 saturation of Hb affect CO2 transport.
  - DeoxyHb is able to bind H+ improving carriage of CO2 as HCO3 and carbamino compounds
- Double Haldane effect:
  - As maternal blood unloads O2, it is able to take up more CO2 for a given change in pCO2
  - As foetal blood takes up more O2 it releases more CO2 for a given change in pCO2

**Approximate values:**

<table>
<thead>
<tr>
<th></th>
<th>Umbilical vein</th>
<th>Umbilical artery</th>
<th>Maternal arterial</th>
</tr>
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<tbody>
<tr>
<td>PO2</td>
<td>30mmHg</td>
<td>15</td>
<td>~100mmHg</td>
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<td>pCO2</td>
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<td>30</td>
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<tr>
<td>pH</td>
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<td>7.3</td>
<td>7.4</td>
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<tr>
<td>%saturation Hb</td>
<td>30</td>
<td>70</td>
<td>100</td>
</tr>
</tbody>
</table>

Describe the circulatory and respiratory changes that occur at birth

**Circulatory changes that occur after birth**

*Describe the cardiovascular changes that occur in the foetus at birth: PAST QUESTION 35%*
Responses to neonatal O2 demand:
- O2 consumption in neonate = 6-7ml/kg/min = 2x adult per kg basis
- Neonatal alveolar ventilation = 120-140ml/kg/min (2x that of adult on per kg basis)
  - Achieved by ↑RR to 30-40min rather than ↑VT
  - This pattern of ventilation ↓WOB and hence O2 cost of ventilation

Respiratory changes that occur with birth
Discuss neonatal respiration including the first breath and response to increased oxygen demand: PAST QUESTION

- During birth, the neonate has to transition from obtaining O2 supply from maternal circulation via placenta (parallel circuit bypassing the lungs) to
  - obtaining its own O2 from gas exchange in lungs (blood flowing in series circuit)

First breath:
- trigger: Relative asphyxia → central + peripheral chemoreceptor stimulation + sensory bombardment → stimulates resp centre and lung ventilation
- lung compliance
  - 1st breath requires a very large –ve intrathoracic pressure (~-60cmH2O – due to poor compliance of lungs)
  - subsequent breaths are easier due to establishment of air-liquid interface + surfactant
- foetal lung fluid
  - before delivery: foetal lung contains 20ml/kg fluid
  - some fluid expelled during thoracic compression associated with vaginal delivery
  - rest absorbed due to pulmonary vascular resistance facouring fluid shift into pulmonary vasculature
  - fluid rapidly replaced by air after delivery + initiation of ventilation
  - ↑chest wall compliance
    - chest wall is very compliant → allows compression of chest to facilitate passage through birth canal
  - ↑in FRC
    - FRC rises rapidly after 1st breath
    - By 10mins the FRC is 17ml/kg, and by 30-60mins it is almost the same value as adults at 30ml/kg

Neonatal lungs:
- not viable before 24 weeks: inadequate surface area, inadequate surfactant, immature control
- Airway: jaw angle 140 degrees, high larynx (C3-4); long epiglottis; narrow cricoid; short trachea (4cm); large nasal airway
- Control:
  - High rate minimises WOB
  - ↑ response to ↑PCO2
  - unreliable response to hypoxia
  - Transient apnoea is normal
  - true apnoea: >15sec, ↓d PO2, ↓HR

Factors that can modify above changes
- ↑RAP → persistence of foramen ovale
- ↓PVR → persistence of ductus arteriosus
- PGs and hypoxia → inhibit closure of ductus arteriosus

The sequence of changes is:
1. Removal of low resistance placenta
   - clamping of umbilical cord → removal of low resistance placenta → ↑SVR, TLVEDP, flow → ↓RAP
2. Closure of ductus venosum: over 3-10 days
3. Inflation of the lungs
   - Relative asphyxia → central/peripheral chemoreceptor stimulation + sensory stimulation → resp centre + ↑lung vol + resistance of extra-alveolar vessels + ↑alveolar PO2 → ↓HPV
   - end result: ↓PVR + ↑pulmonary blood flow
4. Closure of PDA
   - ↑PaO2 + ↓circuiting + locally produced PGs (PGE1, PGE2) → constriction of ductus → flow
   - Permanent closure: 2-3weeks
   - COX inhibitors can prevent complete closure in CHD who rely on shunt from PDA for pulmonary blood flow
   - Hypoxia in neonatal anaesthesia can trigger re-opening of PDA
5. Closure of foramen ovale
   - ↓PVR, ↑pulmonary blood flow, ↑LAP → LAP>RAP → closure of foramen ovale
   - Permanent closure 4-6weeks

Factors that can modify above changes
- ↑RAP → persistence of foramen ovale
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- PGs and hypoxia → inhibit closure of ductus arteriosus
Define the thermoneutral zone, describe temperature regulation in the neonate and the physiological responses to lowered and raised environmental temperature, the effects of anaesthesia on these responses and how this changes with growth and development

**Thermoneutral zone**
- Temperature is measure of average kinetic energy of a substance per degree of freedom of its constituent molecules
- Body temperature is tightly controlled to maintain optimal conditions for enzyme activity; 35-41°C

**Thermoneutral zone**
- Range of environmental temperature in which the metabolic rate (and O2 consumption) is minimal and steady
- Heat production is balanced by heat loss
- Adults = 27-31°C; neonates 32-34°C
- Deviations from threshold tempera -> thermoregulatory responses -> ↑ heat production, ↓ heat production, or ↑ heat loss

**Interthreshold range**
- Range of core body temp where no autonomic thermoregulatory responses occur:
  - Approx 0.2°C at normal temp (37°C) in nonanaesthetised state
  - Influenced by circadian rhythms, food intake, thyroid function, drugs

**Temperature sensation + regulation**
- Sensors: central + peripheral
  - Central
  - Periphera
    - Cold Re: dermis; excited by cooling -> signals to hypothalamus via Adelta fibres; regular + periodic discharges at constant temp; ↑ discharge <25°C
    - Warm Re: bulb of Ruffini; deep to dermis; excited by warming; active from 30-40°C; max 44°C; signals via unmyelinated C fibres
  - Ascending thermal info -> travels along lateral spinothalamic tract in anterior spinal cord -> synapse at reticular system of medulla -> posterolateral + venteromedial nuclei of medulla
- Experimtial responses
  - CNS
  - Cardiovascular
  - Musculocutaneous: shivering
  - Metabolic: BMR; non shivering thermogenesis
Physiological response to hypo- and hyper-thermia

Hypothermia
- Hypothermia = core temp <35°C
- Sensory → regulator → effector: behavioural + physiological responses → ↑ heat production or ↓ heat loss
  - ↑ heat production: voluntary + involuntary muscle activity (shivering); non-shivering thermogenesis
  - ↓ heat loss: behavioural changes; piloerection; cutaneous vasoconstriction
- temp <34°C: confusion
- temp 30-32°C: loss of consciousness
- temp <28°C: arrhythmias (VF)
- frost bite: severe form of cold injury due to freezing of peripheral tissues; damage due to cell dehydration + mechanical effects of ice crystals

Hyperthermia
- Occurs when heat loss mechanisms fail
- Hyperthermia → sensor → regulator → ↓ heat production or ↑ heat loss
  - ↓ heat production: behavioural (4-activity, 4-feeding, appropriate clothing)
  - ↑ heat loss: sweating (evaporation); cutaneous vasodilation
- Extreme heat: thermoregulatory mechanism can fail → head stroke, heat exhaustion, heat collapse
- Temp >42: unconscious; cellular damage, coagulation of proteins; cerebral oedema; irreversible neuronal damage

Summary of effects:

<table>
<thead>
<tr>
<th></th>
<th>↑heat loss</th>
<th>↓heat loss/ ↑heat production</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNS</td>
<td>Remove clothing; 4activity</td>
<td>Huddle; add clothing</td>
</tr>
<tr>
<td>Cardiovasc</td>
<td>↑ peripheral vasodilation + ↑CO</td>
<td>Vasoconstriction</td>
</tr>
<tr>
<td>Musculocutaneous</td>
<td>Sweating</td>
<td>Piloerection; Shivering: ↑BMR</td>
</tr>
<tr>
<td>Metabolic</td>
<td>↑BMR</td>
<td>Non shivering thermogenesis: hormonal (thyroid, adrenaline); brown fat (uncoupled oxidative phosphorylation → ETC to produce heat rather than ATP. Vital in neonate)</td>
</tr>
</tbody>
</table>

Temperature regulation in the neonate, physiological responses to lowered and raised environmental temperature, the effects of anaesthesia on these responses and how this changes with growth and development

Temperature regulation in the neonate
- Thermoneutral zone = range of ambient temperature in which body temp can be maintained without ↑ heat production (metabolic rate) > resting level → within this ideal zone, the person is in thermal equilibrium with their environment
  - Adults: 25-30°C
  - Term neonates: 32-34°C
  - Pre-term infant: 35-36°C due to ↑ evaporative heat loss
  - Within thermoneutral zone, body temp is controlled by Δposition and Δskin blood flow
- Shivering poorly developed
- Non-shivering thermogenesis:
  - ↑ metabolism of brown fat
  - brown fat has ↑ mitochondrial content and SY input
  - SY stimulation via thermoRs release NAD → acts on β3 adrenoceptors → ↑effect of lipase
- Sweat glands
  - ↑ sweat gland density cf adult, however ↓ability to sweat
  - behavioural response ↓/ absent

Physiological responses to lowered and raised environmental temperature

Reasons neonates are more prone to heat stress:
- immature shivering response
- large surface area to volume ratio
- thin subcut tissue
- limited sweating capacity
- limited ability to control personal environment
- heat loss due to evaporation from wet skin

Response to cold
- behavioural changes
- skin vasoconstriction
- non-shivering thermogenesis (brown fat metabolism: can ↑ metabolic rate 2x > resting)
- ↑ muscular activity

Response to heat
- behavioural changes
- skin vasodilation
- sweating

Brown fat
- located: interscapular areas, perinephric fat, around intra-abdominal vessels
- highly vascular + abundant mitochondria + richly innervated by adrenergic fibres
- produces heat through uncoupled oxidative phosphorylation which uses ETC to produce heat rather than ATP
- Proposed mechanisms:
  - 1. Presence of large amounts of non-esterified FAs uncouple mitochondrial phosphorylation from respiration → energy directly lost as heat
  - 2. Recycling of TGs and FAs by lipolysis and re-esterification → ↑ ATP hydrolysis + heat production
Describe the physiology of the cardiovascular, respiratory, renal and neurological systems in the neonate and the changes that occur with growth and development and the implications of this for anaesthetic care.

### Definitions
- premature: <37 weeks
- neonate: birth to 28d
- infant: <=1 year
- toddler: 1-3 years
- child: 3-puberty
- adolescence: puberty to 18yrs

### Cardiovascular Function
- Cardiac muscle immature at birth
- Behave as fixed CO state
  - HR = important determinant of CO
  - SV relatively fixed
  - Myocardium less contractile: ventricles less compliant + less able to generate tension during contraction → limits SV → CO therefore rate dependent
- ↑VA + PSY tone → ↑prone to bradycardias
- neonatal heart ↑↑ sensitive to systemic or PVR → ↓CO
- ↓SVR → ↓SBP
- O2 transport
  - ↑metabolic requirement
  - ↑CO, ↑HR, ↑TRR
  - do not tolerate bradycardia or interruption in ventilation
  - HbF 70-80% total Hb → HbA

### Transitional Circulation
- foramen ovale closure by 6 weeks; patent FO in 30% adults
- PPHN
- PDA: 50% extreme prems; contracts few days; closure 2-4 weeks
- Congenital heart disease
- persistence of foetal circulation with hypoxia and acidosis

### Implications
- Do not tolerate fluid overload
- Hypoxia and laryngoscopy → profound bradycardia
- ↑sensitivity to –ve inotropic effects of anaesthetic agents cf older children → avoid deep anaesthesia, esp. ↑conc volatiles
- maintain normal HR → excessive tachycardia → inadequate ventricular filling in diastole
- bradycardia associated with ↓CO
- atropine may counteract ↓CO seen with volatiles and will protect against VA mediated reflexes

### Respiratory
- Sniffing position does not help BVM or visualisation of glottis → need to be in neutral position
- Easily obstructed
- Endobronchial intubation common
- Straight Magill blade used in neonates + infants
- Un-cuffed tubes to avoid oedema until age 8-10
- Small leak should be present
- Tube size = age/4 + 4

### Implications
- WOB up to 15% O2 consumption
- Low distending pressures of lung + prone to collapse → use CPAP/PEEP
- Gastric distension common after BVM
- Anaesthetic agents → laryngela dilators → upper airway obstruction.
- ETT have ↑resistance which ↑WOB: all neonates
### PAEDIATRIC ANAESTHESIA

**Other**
- Volumes same as adult by 1 week
- Surfactant produced from 24-26 weeks
- VA tone upper airway predisposes to bradycardia + laryngospasm
- Onset and emergence with volatiles due to alveolar vent

**Renal**
- 4RBF and 4GFR during <2 years due to Trenal vascular resistance
- tubular function matures over 1st few weeks of life
- fluid and electrolytes: ECF compartment is expanded; TBW 85% body weight in prem, 75% in term, cf 60% adult
- UO 1-2ml/kg/hr

**Neuro**
- well developed responses to painful stimuli
- neuronal fine tuning of pain pathways
- Cerebral vessels thin walled + fragile
- Cerebral autoregulation present + functional from birth

**Other:**
- newborn liver: 20% of hepatocytes in adults + grows until early adulthood
- liver = principle site of drug metabolism
  - phase I processes sig at birth
  - phase II (conjugation): well developed (sulfation) or limited (glururonidation)
  - In general: drug effects are prolonged
  - Maturation of enzymatic processes over 1st few weeks
- Plasma protein binding to toxicity
- hepatic stores of glycogen + immature gluconeogenic enzyme systems
- Implications
  - Drugs should be given in boluses + titrated rather than by infusions
  - Susceptible to hypoglycaemia should not be starved excessively + glucose should be added to fluids

**Haematology**
- 70-90% Hb = HbF
  - HbF combines more readily with O2; released less readily as there is less 2,3DPG
  - age 3 months: HbF to 5% and HbA predominates OHDH shifts to right as levels of HbA and 2,3DPG
- Hb and Hct at birth
  - vit K dependent clotting factors (II, VII, IX< X) and platelet function are deficient in 1st few months

**Temperature control**
- large surface area to weight ratio with minimal subcut fat
- thermoregulation limited to become cold easily
  - poorly developed shivering, sweating, vasoconstriction mechanisms
  - risk of heat loss; body surface area, thermal conductance, evaporative heat loss
  - brown fat
  - located around scapulae, mediastinum, kidneys, adrenals
  - non shivering thermogenesis
  - O2 requirement
- hypothermia: associated with hypoxia, wound healing, prolonged coagulation, platelet function, drug metabolism, cerebral depression, myocardial depression, acidosis, immunity
  - implications:
    - vulnerable to heat + evaporative losses
    - heat loss during anaesthesia mostly via radiation
    - optimal ambient temp to prevent heat loss: 34oC for premature infant, 32oC neonate, 28oC adolescent/ adult

Describe the composition of body fluids in the neonate and explain the changes that occur with growth and development

**Volumes same as adult by 1 week**
- post op apnoeas esp. if prem, anaemic, opiates
- Limited resp reserve; prone to fatigue

**Other**
- Surfactant produced from 24-26 weeks
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Describe glucose homeostasis in the neonate and explain the changes that occur with growth and development.

**Foetus**
- constant supply of glucose across placenta: diffusion according to uptake + Transplacental gradient
- energy from: glucose, amino acids, lactate, FFA, ketones
- Foetal blood glucose = 70% maternal
- insulin secretion by foetus:
  - does not cross placenta
  - secretion regulated by plasma [glucose] + [aminoacids]
  - β cells in 3rd trimester
- utilises amino acids from mother → gluconeogenesis
- foetal liver = 3x glycogen cf adult

**Neonate**
Glucose homeostasis after birth:
- Reference ranges:
  - Normal BSL range: 2.8-5.6mmol/L
  - Neonate: BSL >2mmol acceptable for 1st 24hrs then >2.5mmol/L
- glucose = main energy source for newborn
  - only glucose: kidneys, erythrocytes, heart
  - ketones + glucose: brain
  - foetal brain uses ↑glucose cf adult: 10-12% total body weight
- At birth
  - ↑glycogen: mins to hours → prevents hypoglycaemia
  - ↑Ad, NAD, GH → minor role
  - ↓insulin over days
- BSL post delivery depends on:
  - Substrate: glycogen store, fats, amino acids
  - Enzymes: functioning liver + metabolic pathways
  - Hormones: pancreas, hypothalamus, pituitary
- Hypoglycaemia
  - Physiological hypoglycaemia
    - 1st 4-6hrs post birth: physiological ↓glucose to ~2.5mmol/L
    - → lipolysis + ketosis
  - Pathological hypoglycaemia
    - ↑insulin
    - altered endocrine function
    - inadequate glycogen/ fat: SGA, IUGR
    - metabolic disorder
    - sepsis/ infection/ resp distress → ↑demand
- Clinical signs: cyanosis, seizure, apnoeic episodes, ↑RR, weak/ high pitched cry, floppiness, lethargy, poor feeding
- 1st few weeks: adaptation due to regular feeding + maturation of metabolic system (+GIT)

**Infants and older children**
- children: poorer tolerance to fasting state: hypo at 24hrs cf adult days
- poorer glucose production → ↑demand
  - ↑BMR + ↑weight of brain
  - poorer liver + metabolic systems
  - substrates e.g. amino acids from muscles
- early childhood characterised by predisposition to produce ketones
  - faster + ↑rapid ↑ketones
- Hypoglycaemia: BSL<2.2mmol/L
## Describe vital signs for children of different ages

<table>
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<tr>
<th>Age</th>
<th>RR</th>
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GENERAL ANAESTHESIA AND SEDATION – CLINICAL AND APPLIED PHARMACOLOGY

Describe how the pharmacokinetics of drugs commonly used in anaesthesia in neonates and children differ from adults and the implications for anaesthesia.

**Pharmacokinetics**

<table>
<thead>
<tr>
<th>Absorption</th>
<th>Distribution</th>
<th>Metabolism</th>
<th>Excretion</th>
</tr>
</thead>
<tbody>
<tr>
<td>PO</td>
<td>↑PH → ↓absorption acidic drugs, ↑absorption basic drugs</td>
<td>↑TBW + ↑ECF → ↑VD</td>
<td>Phase I reactions (ox, red, hydrolysis)</td>
</tr>
<tr>
<td></td>
<td>↑gastric emptying → variable absorption</td>
<td>water soluble drugs e.g. sux</td>
<td>↓activity p450</td>
</tr>
<tr>
<td>IM</td>
<td>↑bile: ↑absorption lipid soluble</td>
<td>↑fat, ↑muscle: ↑distribution to peripheral compartments</td>
<td>↑[plasma] e.g. thio</td>
</tr>
<tr>
<td>transdermal</td>
<td>↑muscle mass → variable absorp</td>
<td>↑CO to brain → ↑effects of induction agents</td>
<td></td>
</tr>
<tr>
<td>Rectal</td>
<td>thin skin + variable blood flow</td>
<td>poor BBB → ↑effects of water soluble drugs e.g. morphine</td>
<td></td>
</tr>
<tr>
<td>Lung</td>
<td>↑FRC cf adult (similar by end of 1st week)</td>
<td>↑uptake volatiles → faster onset and offset</td>
<td>Phase II reactions (conjugation)</td>
</tr>
<tr>
<td></td>
<td>↑FRC, ↑MV, ↑alveolar vent</td>
<td></td>
<td>- sulfonation mature at birth</td>
</tr>
<tr>
<td></td>
<td>↑uptake volatiles</td>
<td>↑free drug, ↑toxicity, ↑excretion e.g. LA, diaz, barbiturates, phenytoin</td>
<td>Hepatic blood flow</td>
</tr>
<tr>
<td></td>
<td>↑uptake volatiles</td>
<td>↑free drug, ↑toxicity, ↑excretion e.g.</td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Describe the changes in the pharmacodynamics of volatile agents, analgesics, opioids and neuromuscular blocking agents in the neonate and the changes that occur with growth and development and the implications for anaesthesia.

**Inhalational**

- ↓MAC in neonate → peaks 6-12months → ↑to adult value over few years. Mechanism unknown
- des good in neonate: rapid wake up; ↓post op apnoeas
- R to L shunt will ↓onset due to ↓blood exposure to volatile
- ↑emergence delirium → ↑with sevo/ des due to faster offset

**IV anaesthetic agents**

- Generally neonates have ↑sensitivity to induction drugs, ↑permeability of BBB and immaturity of resp centre (↑apnoea)
- Propofol
  - ↑induction dose (3-4mg/kg) cf adult (1-2mg/kg) and ↑maintenance dose due to rapid distribution and metabolism (↑CO)
  - not licensed for sedation in children due to propofol infusion syndrome
  - 60% pain on injection
  - SE: bradycardia
- Thiopentone
  - Neonate: ↓PB + ↓cortical maturity + ↓distribution due to ↓fat/ muscle mass → ↓dose
  - Infant: ↑dose due to ↑CO
- Ketamine
  - ↑dose due to ↑metabolism in child (neonate ↓metabolism → ↓dose)
  - less hallucinations and dreams in younger cf older children
  - SE: ↑PONV 30%, salivation, ↑ICP
- Benzos
  - ↑↑T ½ in neonates: ↓enzymes and blood flow
  - ↓T ½ in child
  - diaz: ↑↑ 1/2 : not good for short procedures
  - midaz = less fat soluble → slower onset

**Analgesics**

- morphine: ↑sensitivity due to ↓receptors, ↑resp depression, ↑penetration BBB
  - fent: similar PD in neonate / child / adult

**NMBDs**

- ↓maturity of NMJ → ↓dose
- sux: beware bradycardia
- pan: delayed excretion due to ↓renal function

**LAs**

- ↓block duration and require 4x weight scaled dose than adult due to:
  - differences in myelination, nodes of ranvier
  - issues with fast absorption (↑CO, thin skin), poor metabolism
- so neonates need more LA, but ↑risk of toxicity
Describe the pharmacology of agents used for premedication in children, including midazolam, clonidine, and ketamine

### Ketamine
- **Chem**
  - Phenylethylamine derivative
- **Uses**
  - Induction, sedation, Dissociative anaesthesia; analgesia
  - General anaesthesia; hypnosis
  - Neurosurgery
- **Pres**
  - CCS 10/50/100mg/ml racemic ketamine hydrochloride
- **Action**
  - Non-competitive NMDA R antagonist
  - Acts on BZD Rs in CNS
- **CNS**
  - Dissociative state
  - Sedation + analgesia
  - NCBF, TCBF, TICP, TICP
- **CVS**
  - TSNS tone → ↑circulating Ad + NAd → ↑HR, ↑BP, ↑CVP, ↑CO
  - Mild direct myocardial depressant
- **Resp**
  - Bronchodilation
  - Pulmonary compliance
  - Secretions
- **Toxicity/SE**
  - Emergence delirium, dreams, hallucinations; N/V; rash
- **Route/ dose**
  - IM: 5mg/kg
  - PO: 5mg/kg
  - IM: 0.05mg/kg
  - PO: Buccal: 0.5mg/kg
  - Nasal: 0.2mg/kg
- **pKa**
  - 7.5
  - 6.5
- **Onset**
  - IV: 30sec; IM: 3-5mins;
  - PO: 15-20min
- **Duration**
  - IV: 5-10mins; IM: 10-20mins
  - 3-7hrs
- **Notes**
  - Bioavailability: PO 40%; IM 80%
  - Bioavailability 100%
  - Very lipid soluble; penetrates BBB / 20% protein bound
  - 50% liver to inactive metabolites

### Midazolam
- **Chem**
  - Benzodiazepine derivative
- **Uses**
  - Oral, IV induction, sedation, Analgesia; anterograde amnesia
- **Pres**
  - CCS midazolam hydrochloride for injection
  - Tablets: 100-300microg/ CCS 150microg/ml clonidine hydrochloride
- **Action**
  - Induction, sedation, hypnotic, anti-seizure
  - Antihypertensive + analgesia + sedative + anxiolytic
- **CNS**
  - Hypnosis, sedation, anterograde amnesia
- **CVS**
  - TSNS tone → ↑circulating Ad + NAd → ↑HR, ↑BP, ↑CVP, ↑CO
  - Mild direct myocardial depressant
- **Resp**
  - Bronchodilation
  - Pulmonary compliance
- **Toxicity/SE**
  - Emergence delirium, dreams, hallucinations; N/V; rash
- **Route/ dose**
  - IM: 4µg/kg
  - PO: 4µg/kg
- **pKa**
  - 7.5
- **Onset**
  - IV: 3-5min; PO 15-20min
- **Duration**
  - IV: 30mins; IM: 1-2hrs
- **Notes**
  - Unpleasant taste
  - Prolonged use: upregulate α-adrenoceptors → rebound HTN
  - 4µg/kg IV/SY depressant

### Clonidine
- **Chem**
  - Aniline derivative
- **Uses**
  - Induction, sedation, analgesia; central nervous system (CNS), vascular tone
- **Pres**
  - Tablets: 100-300microg/ CCS 150microg/ml clonidine hydrochloride
- **Action**
  - α2 adrenoceptors:
  - - on target tissues: presynaptic on SY nerve fibres (peripheral); post synaptic within CNS/ SC (central); platelets
  - - GPCR Gi coupled adenylyl cyclase inhibition → ↓cAMP
  - α2 presynaptic adrenoceptor agonist → ↓NAd release from SY nerve terminals → ↓SY tone + ↑TA tone
- **CNS**
  - Sedation + analgesia: central α2 agonism → inactivation of locus ceruleus + activation of descending inhibitory pain pathways
- **CVS**
  - TSNS tone → ↑circulating Ad + NAd → ↑HR, ↑BP, ↑CVP, ↑CO
  - Mild direct myocardial depressant
- **Resp**
  - Bronchodilation
  - Pulmonary compliance
  - Secretions
- **Toxicity/SE**
  - Emergence delirium, dreams, hallucinations; N/V; rash
- **Route/ dose**
  - IM: 4µg/kg
  - PO: 4µg/kg
- **pKa**
  - 6.5
- **Onset**
  - IV: 3-5min; PO 15-20min
- **Duration**
  - IV: 10mins
- **Notes**
  - Drowsiness + dry mouth 50%
  - Sedation: general anesthesia; premedication; anxiolysis / analgesia / sedation / HTN
  - Antihypertensive + sedative + anticholinergic + sympatholytic effect
  - Induction, sedation, hypnotic, anti-seizure
  - Migraine/ menopausal flushing/ chronic pain/ opiate or etoh withdrawal

### Special points
- Little effect from renal impairment
- Short DoA due to high lipophilicity, high metabolic clearance, and rapid rate of elimination
Outline how the pharmacokinetics of morphine, bupivacaine and suxamethonium differ in the neonate compared to the adult. Briefly describe the clinical implications of these differences: PAST QUESTION 73%

Outline the pharmacological differences between neonates and adults with reference to sevoflurane, vecuronium, and morphine: PAST QUESTION 42%

---

**Background**
- **neonate** = first 28 days of life
- **morphine** = naturally occurring opiate analgesic
- **bupivacaine** = long actin amide LA
- **suxamethonium** = depolarising NMBD
- **sevoflurane** = volatile anaesthetic (fluorinated ether)
- **vecuronium** = NDNMBD (benzylisoquinolone)

**Pharmacokinetic differences: neonate vs. adult**
- **Absorption**
  - Poor compliance with PO intake + gastric emptying → unreliable PO/GI absorption
  - Unpredictable skin blood supply → less reliable transdermal, subcut, intramuscular absorption kinetics
  - RR → MV → absorption of volatiles
- **Distribution**
  - Proportionally ECF → Vd (esp. for hydrophilic drugs)
  - Plasma protein (albumin and α1 acid glycoprotein) → fraction unbound
  - Plasma pH → ionised fraction
  - Immature BBB → penetration of lipid soluble drugs
- **Metabolism**
  - Immature liver enzyme system → hepatic phase I and II metabolism
  - Plasma cholinesterase levels
- **Excretion**
  - Immature kidneys → GFR (10% of adult) → renal clearance of drugs
  - Tubular secretion mechanisms

**Pharmacokinetic differences of above drugs**

<table>
<thead>
<tr>
<th></th>
<th>Morphine</th>
<th>Bupivacaine</th>
<th>Sux</th>
<th>Sevo</th>
<th>Vec</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>4 PO absorption unreliable IM/SC</td>
<td>Unreliable cutaneous absorption → safe dose ≤3mg/kg</td>
<td>IV therefore absorption unaffected</td>
<td>↑MV → ↑absorption of volatiles → faster induction</td>
<td>Unchanged</td>
</tr>
<tr>
<td>B</td>
<td>[protein] → unbound fraction immature BBB → ↑CNS availability</td>
<td>↓1-acid glycoprotein → ↑free drug ↓pH (pK 8.1) → ↑ionised fraction → slower onset</td>
<td>↑Vd → ↓availability at NMJ → need ↑dose</td>
<td>↑cardiac index → slightly ↓rise of FA/FI ↓blood:gas solubility</td>
<td>↑TCI → faster onset ↑Vd → ↓availability at NMJ may need ↑dose</td>
</tr>
<tr>
<td>M</td>
<td>4 hepatic glucuronidation</td>
<td>↑DoA</td>
<td>↑hepatic metabolism</td>
<td>↑DoA</td>
<td>↑hepatic metabolism</td>
</tr>
<tr>
<td>E</td>
<td>4 renal function → ↓renal clearance</td>
<td>↑DoA</td>
<td>↓renal excretion</td>
<td>↑DoA</td>
<td>↓renal excretion</td>
</tr>
<tr>
<td></td>
<td>response depression and apnoea</td>
<td>More rapid induction ↑MAC</td>
<td>Net effect dose per kg similar to adult</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

NB re sux:
- Opposite forces at work
  - ↑ECF volume → ↑Vd → ↓activity
  - Countered by ↓pseudocholinesterase levels in neonate
  - End result clinically is little change in duration of action

**Pharmacodynamics**
- What the drug does to the body
  - Different sensitivities to drugs; permeability of BBB; sensitivity of resp centre
Describe the difference in pharmacokinetics of local anaesthetic agents in neonates and children from adults and the implications for regional blockade

**Absorption**
- Can be given IV, epidural, spinal, compartment block, peripheral nerve blocks, mucouous membranes, topical
- ↑CO neonates/children of adults = ↑uptake LA from high blood-flow regions → absorption of LA on mucous membranes in infants
- absorption from neuraxial space due to ↑CO → ↑initial plasma concentrations + ↓DoA

**Distribution**
- 4α-1 acid glycoprotein = ↓PB → ↑free fraction of LAs → ↑risk toxicity
  - neonates have 20-40% adult levels → reach normal levels at 12 months
  - ↓max dose of amides in neonates
  - ↑VD of LAs
    - due to ECF content
    - ↑peak plasma conc after bolus → ↑toxicity after single dose
    - ↑risk of drug accumulation with infusion → ↑plasma conc → ↑T ½ and ↓clearance
    - loose fascial attachments around nerves → spread + ↑length of block
    - red cell storage:
      - neonates: ↑Hct + large RBCs (physiological macrocytosis) → entrapping ↑LA in RBCs → ↑Cmax after single bolus dose but secondary release thereby ↑1/2 life
      - infants: physiological anaemia → ↓RBC storage of LA thereby ↓systemic toxicity of LA after single shot injection

**Metabolism**
- immaturity of hepatic enzyme systems until ~3 months (CYP3A4 for lignocaine + bupivacaine, and CYP1A2 for ropiv and levobupiv)
- potential for toxicity from accumulation of lignocaine metabolite MEGX in neonates
- infusion rate in infants should be ↓after 24hrs to prevent accumulation

**Elimination**
- T1/2 elimination depends on metabolism + distribution
- Longer elimination ½ life due to ↓metabolism + clearance
  - neonates: ↑Hct + large RBCs (physiological macrocytosis) → ↑toxicity after single dose
  - infants: physiological anaemia → ↓RBC storage of LA thereby ↓systemic toxicity of LA after single shot injection

**Implications for regional anaesthesia**
- caudal = lumbar epidural analgesia common
- continuous infusions
  - prolonged elimination = concern for continuous infusions
  - seizures associated with high bupivacaine infusion rates
  - Bupiv: max infusion dose of: children + adults: 0.4mg/kg/hr; neonates + infants: 0.2mg/kg/hr
  - Lignocaine max infusion dose of: 0.8mg/kg/hr neonates
- Max safe dose for single shot peripheral nerve blockade similar for adults
  - Bupiv: 3mg/kg
  - Lignocaine 3mg/kg without adrenaline; 7mg/kg with adrenaline
  - Ropivacaine 2mg/kg

<table>
<thead>
<tr>
<th>Protein binding</th>
<th>Lignocaine</th>
<th>Bupivacaine</th>
<th>Levobupivacaine</th>
<th>Ropivacaine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neonate</td>
<td>Adult</td>
<td>Neonate</td>
<td>Adult</td>
<td>Neonate</td>
</tr>
<tr>
<td>Protein binding %</td>
<td>25%</td>
<td>55-65%</td>
<td>50-70</td>
<td>95%</td>
</tr>
<tr>
<td>Vd L/kg</td>
<td>1-5L/kg</td>
<td>0.2-1L/kg</td>
<td>4L/kg</td>
<td>0.8-1.5L/kg</td>
</tr>
<tr>
<td>Clearance ml/kg/min</td>
<td>5-20</td>
<td>10-15</td>
<td>7</td>
<td>14</td>
</tr>
<tr>
<td>Elimination ½ life (hr)</td>
<td>3</td>
<td>1-2</td>
<td>6-22</td>
<td>1-3</td>
</tr>
</tbody>
</table>

Describe the maximum safe doses of local anaesthetic agents in different age groups

- continuous infusions
  - prolonged elimination = concern for continuous infusions
  - seizures associated with high bupivacaine infusion rates
  - Bupiv: max infusion dose of:
    - children + adults: 0.4mg/kg/hr
    - neonates + infants: 0.2mg/kg/hr
  - Lignocaine max infusion dose of:
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