Local Anaesthetics

HISTORY

• first local anaesthetic to be discovered was ***cocaine***, an alkaloid from the leaves of the plant ***Erythroxylon coca***, found in the highlands of Peru
• pure alkaloid first isolated by Neimann
• von Anrep, 1880, was the first to describe the sensory anaesthetic action of subcutaneous injection and recommended its use as such, however this was not acted upon
• in 1884, S. Freud used the CNS actions to wean a colleague from opioid addiction
• Koller, at about the same time as Freud, introduced its topical use into ophthalmology
• Hall, in 1884 introduced its use into dentistry and in the following year Halsted demonstrated its efficacy in blocking conduction in nerve trunks
• Corning, also in 1885, produced spinal anaesthesia in dogs however it was several years before this was used in surgery

• the search for chemical substitutes for cocaine began in 1892, with the work of Einhorn & colleagues $\rightarrow$ ***procaine*** in 1905

• Löfgren synthesised ***lignocaine*** in 1943 and since then, with the exception of chloroprocaine, all new local anaesthetics introduced into clinical practice have been amino-amides

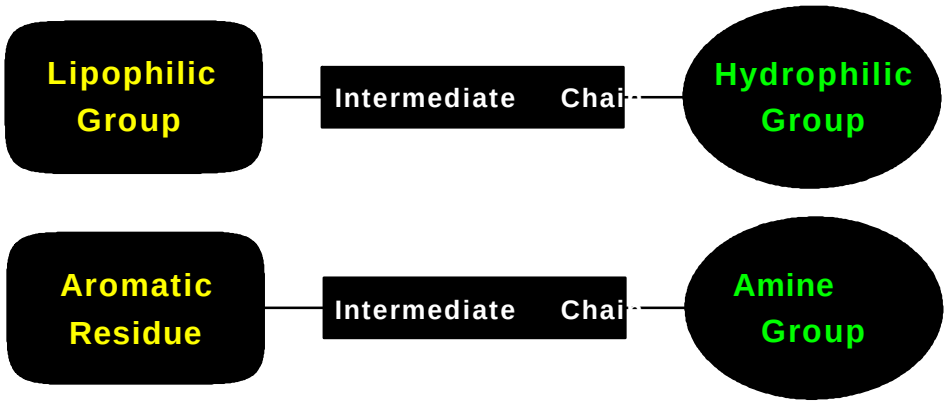
GENERAL PROPERTIES

• the following are considered to be the desirable properties for a local anaesthetic,

a. nonirritating to the tissues
b. should not cause any permanent damage to nerves
c. should exhibit no systemic toxicity
d. effective topically and by infiltration
e. rapid onset of action
f. duration of action should be sufficient to allow contemplated surgical procedures, however not so long as to require an extended period of recovery

Chemistry and Structure-Activity Relationships

• all typical local anaesthetics contain hydrophilic and hydrophobic domains that are separated by intermediate alkyl chains
• this was first described by ***Löfgren***, as follows,



• the hydrophilic group is usually a ***tertiary amine***, though, it may be a secondary amine
• the hydrophobic region is usually an ***aromatic residue***
• the ***intermediate bond*** is either of the ***ester*** or ***amide*** type and the nature of this bond determines many of the properties of the agent
• the ***ester*** linkage is readily hydrolysed during metabolism, eg., procaine can be divided into three main portions,

a. the aromatic acid - para-aminobenzoic acid
b. the alcohol - ethanol
c. the tertiary amide - diethyl amine

• changes to any part of the molecule lead to alterations in activity & toxicity
• increases in the length of the intermediate alcohol group, up to a ***critical length***, result in greater anaesthetic potency
• beyond this critical length, increased toxicity results
• compounds with an ethyl ester, such as procaine, exhibit the least toxicity
• the length of the two terminal groups on the tertiary amino-N group are similarly important
• the addition of a butyl group to mepivacaine results in bupivacaine, which differs by,

a. increased lipid solubility & protein binding
b. greater potency
c. a longer duration o

Mechanism of Action

• local anaesthetics prevent both the generation & conduction of nerve APs
• their main site of action is the nerve cell membrane
• there being little evidence for an action in the axoplasm at pharmacological concentrations
• they effectively block the large transient increase in voltage gated gNa^+
• as anaesthetic action progresses the threshold for excitability is increased and the safety factor for conduction is decreases
• when these two effects are sufficiently well developed, conduction in the nerve is blocked
• raising the external $[Ca^{++}]$ may either intensify or reduce the level of blockade
• the former occurs by altering the kinetics of the Na^+ channel and the later by altering the surface membrane potential, thereby reducing the inactivation of the Na^+ channels
• local anaesthetics also reduce the resting membrane permeability to K^+
• however, this occurs only at high concentrations and no consistent alteration of resting membrane potential is observed
• one exception is that lignocaine increases K^+ conductance in cardiac Purkinje fibres
• studies on giant squid axons show that quaternary local anaesthetics are effective only when they are applied to the inside of the nerve membrane and are voltage dependent
• therefore, the binding site is probably located within the Na^+-channel, close to the internal opening
• the mammalian Na^+-channel consists of 4 glycosylated proteins, each possessing 6 homologous transmembrane segments, with an aggregate molecular size > 300,000 daltons
• studies with radioactively labelled neurotoxins, eg. tetrodotoxin, and antibodies show that the distribution of channels is not uniform in the nerve cell membrane
• channel density being greatest at the nodes of Ranvier, where they may comprise up to 15% of the membrane surface
• other theories involve the action of local anaesthetics in the lipid membrane etc., similar to the theories for the inhalational agents
• however the major action is specific receptor binding in the sodium channel,

a. Shanes (1958)
   - local anaesthetic potency proportional to effectiveness in increasing surface pressure in monomolecular layer; increased pressure closing Na^+ channels

b. Metcalf & Burgen (1968)
   - local anaesthetics cause increased disorder in lipid membrane resulting in changes in permeability; supported by pressure reversal of blockade

NB: however, the major mechanism of action is binding to a ***specific receptor*** site within the Na^+ channels, resulting in physical blockade

Differential Sensitivity of Nerve Fibres

Classification of Nerve Fibres				
Type	Myelination	Diameter	V_c(m/sec)	Function
Aα	Heavy	12-20 µm	70-120	Motor & proprioception
Aβ	Moderate	5-12 µm	30-70	Touch & pressure
Aγ	Moderately	3-6 µm	15-30	Motor to muscle spindles
Aδ	Lightly	2-5 µm	12-30	Pain, temp., & touch
B	Lightly	1-3 µm	3-15	Preganglionic autonomic
C	None	0.4-1.2 µm	0.5-2	Pain & reflex responses
	None	0.3-1.3 µm	0.7-2.3	Postganglionic sympathetic

NB: $V_c \sim 6xD$ m/s for myelinated A fibres

- as a general rule, small fibres are more susceptible to the effects of the local anaesthetics than large diameter fibres
- the smallest mammalian fibres are unmyelinated and are, usually, more readily blocked than myelinated fibres
- however, the spectrum of sensitivity of the unmyelinated fibres overlaps the range for the myelinated fibres and some Aδ fibres are blocked before, and at a lower [LA], than are most C fibres
- therefore, both ***fibre size*** and ***fibre type*** are determinants of sensitivity to local anaesthetics (Nathan & Sears, 1961)
- this is logical as the ***mode of transmission*** along different classes of fibres is different (saltatory vs. continuous)
- sensitivity does ***not*** depend on sensory vs. motor
- muscle efferents and proprioceptive afferents are blocked equally as these are a similar diameter (Aα/Aβ)
- gamma-efferents are smaller and are blocked earlier, leading to the preferential early loss of reflex activity
- work from computer simulations agrees with the findings of Chiu & Richie 1894, that differential blockade is ***not*** the result of minimal concentrations required to block axons of different diameters
- rather this results from differences in the ***critical lengths*** of axons which must be exposed to the anaesthetic, smaller axons having shorter critical lengths
- early in the course of nerve blockade, local anaesthetic diffuses inward across the neurolemmal sheath, then along intrafasicular routes and small discrete lengths of the most accessible fibres are exposed
- small fibres, with their short critical lengths are the first blocked and the same process occurs during recovery from blockade

NB: fortunately, ***pain fibres*** being small diameter, C & Aδ, are usually blocked early

Physicochemical Properties & Anaesthetic Action

- three main factors determine the action of the local anaesthetics,
    a. lipid solubility
        - the highly lipid soluble agents are the most potent and have a longer duration of action
    b. protein binding
        - the higher the protein binding the longer the duration of action
    c. acid dissociation constant

▪ ***Effects Of pH***

- local anaesthetics in the form of the unprotonated amine tend to be only slightly water soluble
- therefore they are marketed in the form of their water soluble salts (HCl)
- local anaesthetics are ***weak bases*** and the solutions are quite acidic
- this increases the stability of the local anaesthetic and also any added vasoconstrictor
- however, it is the unprotonated form which diffuses into the nerve trunks and is responsible for the anaesthetic action
- the typical local anaesthetic $\boldsymbol{pK_A's \sim 8\text{-}9}$, so that only 5 to 20% will be in the unprotonated form
- addition of ***alkali*** to local anaesthetic solutions increases their activity *in vitro*
- however, this is not observed *in vivo*, probably as the pH of any injected solution is rapidly brought to physiological pH
- once the local anaesthetic has diffused into the nerve trunk, the protonated form of the drug is responsible for the majority of the anaesthetic action, binding to the Na^+-channel
- this led to the use of ***carbonated*** solutions of local anaesthetics
- CO_2 readily diffusing into the nerve, raising the $[H^+]$ by dissociation and increasing the proportion of the protonated species
- it is now apparent that both forms of the drug have anaesthetic action
- whether there is a single receptor for these two entities is unsettled
- therefore, local anaesthetics with a pK_A closer to physiological pH will have a more rapid onset of action

Physicochemical Properties of Some Local Anaesthetics					
Agent	MW	pK_A(25°C)	τ (tau)[1]	Protein Binding	Relative Potency
Procaine	236	8.9	0.02		1
Chloroprocaine	271	8.7	0.14		1
Tetracaine	264	8.5	4.1		8
Prilocaine	220	7.9	0.9		2
Mepivacaine	246	7.6	0.8	75%	2
Lignocaine	234	7.9	2.9	60-75%	2
Etidocaine	276	7.7	141	94-97%	6
Bupivacaine	288	8.1	28	90-97%	8

[1] the heptane:buffer partition coefficient

- ***Frequency & Use Dependence***

• the degree of block produced at a given concentration of anaesthetic is markedly dependent upon the recent frequency of nerve stimulation
• a resting nerve is far less sensitive to the effects of the local anaesthetics, the degree of block being directly proportional to the preceding frequency of stimulation
• this is due to the requirement for the inner gates of the sodium channel to be open for the local anaesthetics to gain access to the binding site
• local anaesthetics exert this property to different degrees depending upon their lipid solubility, pK_A and molecular size

PHARMACOKINETICS

• this is important due to ***systemic toxicity*** following regional techniques and can be divided into ***absorption kinetics*** and ***systemic disposition kinetics***

Absorption Kinetics

• most studies follow serum [LA] after regional techniques but this is the algebraic sum of absorption, distribution, metabolism & excretion
• by studying the last three after IV bolus administration, the effects of these can be removed and absorption from regional depots studied
• the major determinants of systemic absorption are,

a. the physicochemical properties of the local anaesthetic
b. dosage
c. route of injection
d. absence, or addition of a vasoconstrictor
e. vasoactive properties of the local anaesthetic itself
f. pathophysiological factors

• systemic absorption following epidural anaesthesia is ***biphasic***
• the more lipid soluble agents showing a lower net absorption, probably due to greater retention in fat & tissues in the epidural space (also lower solubility in blood)
• therefore, the effects of additional adrenaline are less for the longer acting, lipid soluble agents

■ ***Prolongation Of Action By Vasoconstrictors***

• the duration of action of a local anaesthetic is proportional to the time the agent is in contact with the nerve axon
• consequently, factors which keep the local anaesthetic at the nerve, prolong the duration of anaesthesia
• cocaine constricts blood vessels by potentiating the action of NA, thus, delays its own absorption
• Braun in 1903 demonstrated that the addition of adrenaline to local anaesthetics greatly intensified and prolonged their duration of action
• solutions of local anaesthetics usually contain either adrenaline (1:200,000), noradrenaline (1:100,000), or one of the synthetic vasoconstrictors
• this action of the vasoconstrictors serves two functions,

a. delays absorption from the active site
b. decreases the peak serum concentration

• the later effect allows metabolism to keep pace with absorption and therefore reduces the incidence of toxic effects

• occasionally systemic absorption of the vasoconstrictor may lead to side effects and concurrent administration of α/β-blocker is required
• sympathomimetic amines may also be associated with

a. delayed tissue healing
b. tissue oedema, or
c. local necrosis

• these occur due to the combined effect of increased tissue metabolism and decreased blood flow

■ ***Site Of Injection***

• the site of injection is a major determinant of systemic absorption via the following factors

a. blood flow
b. tissue binding, and
c. the blood:tissue partition coefficient

• absorption from various areas, in order of decreasing rate,

a. intercostal block
b. caudal block
c. epidural block
d. brachial plexus block
e. sciatic-femoral block
f. subcutaneous infiltration

• for any given site, the rate of absorption will be increased as the ***concentration*** is increased, with subsequent higher serum concentrations

Systemic Distribution Kinetics

• following systemic absorption, local anaesthetics must undergo distribution to the interstitial and cellular fluids, followed by elimination, which is mainly via metabolism and to a small extent renal excretion
• the major determinants of distribution are,

a. the physicochemical properties of the local anaesthetic
   i. lipid solubility
   ii. protein binding
   iii. pK_A
b. regional blood flow
c. acid-base balance

• the longer acting amide-linked local anaesthetics exhibit higher protein binding
• they also bind to RBC's and the blood:plasma binding ratio is inversely proportional to plasma binding
• the principal plasma binding protein is a_1***-acid glycoprotein***
• the reduced binding of lignocaine in the neonate is due, in part, to lower levels of this protein
• clearance of the amide-linked agents depends on ***metabolism***, as renal excretion accounts for only 1-5% of the administered dose
• lignocaine is a high extraction ratio drug, having a high "first pass metabolism" and poor ***bioavailability £ 35%***
• hepatic clearance is therefore dependent upon ***liver blood flow***
• in diseases where liver blood flow is reduced, such as CCF or hypovolaemia, the clearance of lignocaine is reduced and serum concentrations will be higher
• also, in cardiac failure, the V_d for lignocaine is increased, reducing the clearance further
• age also affects the disposition of lignocaine
• clearance is equal, however the elderly have a higher V_d and terminal elimination half-life

METABOLISM OF LOCAL ANAESTHETICS

• the toxic effects of these compounds are frequently determined by their relative rates of absorption and metabolism
• the rate of metabolism varies considerably between agents and individuals
• tissue binding has a similar effect, removing the agent from the circulation and reducing potential toxicity
• eg. in regional IV anaesthesia, ~ ½ of the administered dose is still bound to the peripheral tissues 30 min after removal of the tourniquet

Ester-linked Local Anaesthetics

• most of the esters, are rapidly hydrolysed by ***plasma butyrylcholinesterase*** and ***liver esterases***
• as spinal fluid contains little, or no esterase, intrathecal administration produces a prolonged effect which persists until the agent is absorbed into the blood stream
• the relative rates of hydrolysis in serum are,

Agent	Hydrolysis (plasma)	Potency	Toxicity
chloroprocaine	4.7 μmol/ml/hr	1	≤ 1
procaine	1.1 μmol/ml/hr	1	1
tetracaine	0.3 μmol/ml/hr	8	7

• procaine is hydrolysed to para-aminobenzoic acid & diethylaminoethanol
• the in vitro half-life is 39-43 secs and is prolonged in liver and renal disease
• chloroprocaine is hydrolysed to 2-chloro-para-aminobenzoic acid (CABA) & diethylaminoethanol
• the in vitro half-life is ~ 20 secs but is prolonged in neonates and atypical butyrylcholinesterase homozygotes
• plasma butyrylcholinesterase activity is only ~ 50% in the newborn and doesn't reach adult values until about 1 year

Amide-linked Local Anaesthetics

- the amide local anaesthetics are generally degraded in the hepatic endoplasmic reticulum
- the initial reaction being ***N-dealkylation***, with subsequent hydrolysis

- an exception is ***prilocaine***, where the initial step is hydrolytic forming ***o-toluidine***
- this is further metabolised to 4- & 6-hydroxytoluidine
- the later is believed to be responsible for the ***methaemoglobinaemia*** which follows high doses

- lignocaine undergoes N-dealkylation to ***monoethylglycine-xylide*** (MEGX)
- this in turn is either N-dealkylated to glycine-xylide (GX), or hydrolysed to 2,6-xylidine
- 2,6-xylidine in further metabolised to 4-hydroxy-2,6-xylidine, which appears in the urine
- MEGX & GX are found in significant concentrations in the blood of patients receiving lignocaine
- both of these agents have pharmacological activity and their respective half lives are,

1. MEGX $t_{\beta½}$ ~ 120 mins
2. GX $t_{\beta½}$ ~ 10 hrs

- mepivacaine is N-demethylated to 2,6-pipecoloxylidine (PPX)
- conjugates of the 3 & 4-hydroxy derivatives are found in the urine

- metabolism of bupivacaine is less well studied, but PPX is formed
- thus the use of amide local anaesthetics in patients with severe hepatic disease should be avoided
- the amide-linked local anaesthetics are extensively protein bound ~ 55-95%, particularly to α_1-acid glycoprotein which is significantly affected by a number of clinical conditions,

a. increased concentration - cancer, trauma, AMI, uraemia, smoking
b. decreased concentration - OCP, neonate, pregnancy

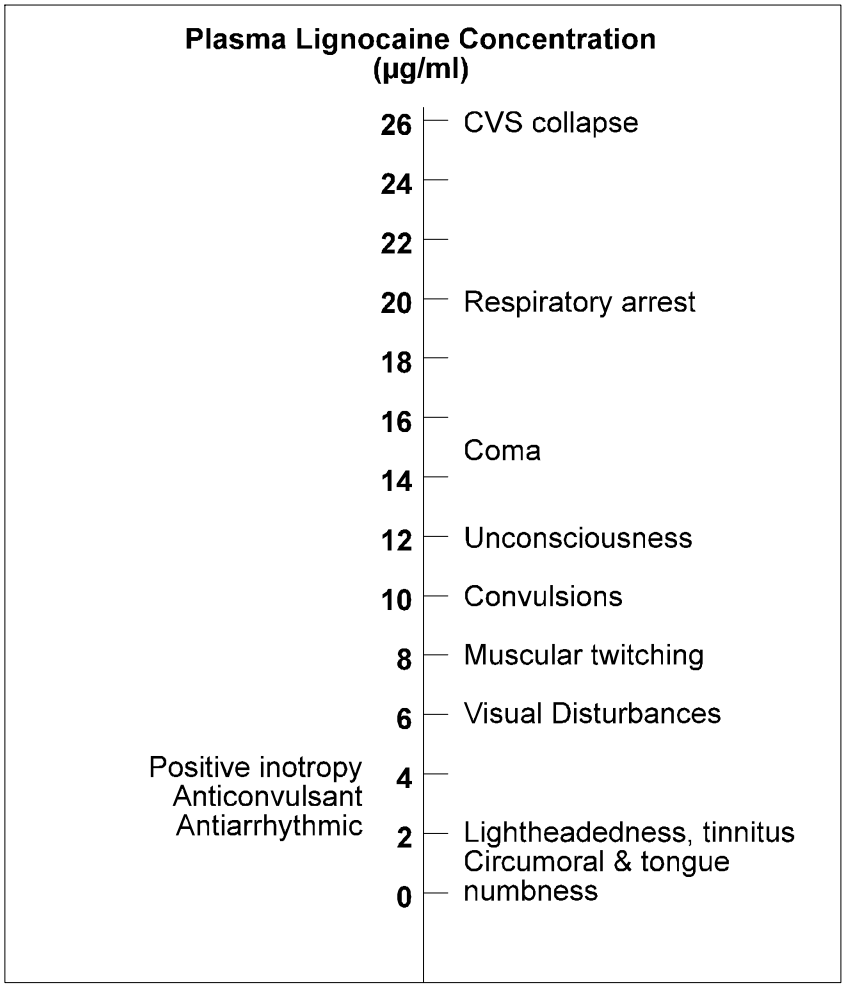
- uptake by the lung may also play an important role in the distribution of the amide-linked local anaesthetics

LOCAL ANAESTHETIC TOXICITY

• in addition to blocking transmission in nerve axons, local anaesthetics affect all tissues where conduction of impulses occurs
• therefore, there are significant actions in,

1. the CNS
2. autonomic ganglia
3. the NMJ
4. all forms of muscle fibre, especially cardiac

NB: the significance of such adverse actions is directly proportional to the $[LA]_{pl}$ achieved and the relative potency of the agent



• the toxic effects of the local anaesthetics can be divided into,

1. systemic toxicity
   i. CNS
   ii. CVS - direct myocardial effects
   - peripheral vascular effects
2. local tissue toxicity
3. allergic reactions
4. miscellaneous effects
   i. membrane stabilisation - NMJ
   - autonomic ganglia
   - anti-ACh
   ii. methaemoglobinaemia

• toxicity is frequently assessed by two parameters,

1. the ***relative toxicity ratio*** = LD_{min} / LD_{min}(procaine)
2. the ***anaesthetic index*** = $\frac{\text{relative anaesthetic potency}}{\text{relative toxicity ratio}}$

• an anaesthetic index of > 1.0 means the anaesthetic potency is greater than the relative toxicity

Systemic Toxicity

Central Nervous System

• earliest signs of toxicity are circumoral & tongue numbness, tinnitus, nystagmus, and dizziness
• following absorption, all nitrogenous local anaesthetics may cause ***CNS excitation***

→ restlessness, tremor, & eventually tonic-clonic convulsions

• unfortunately, EEG recordings give little indication of impending convulsive activity
• CNS stimulation is then followed by depression
• death is usually due to subsequent ***respiratory depression***
• CNS depression may occur without an excitatory phase, particularly if other depressant drugs have been administered prior to the local anaesthetic
• both stimulation and depression of the CNS are thought to be due to ***neuronal depression***
• depression of the polysynaptic inhibitory pathways in the ARAS being responsible for the excitatory effects
• this is consistent with the observed suppressive effects of the local anaesthetics on seizure activity in epileptics
• artificial support of respiration is essential in the later stages of intoxication
• the barbiturates are effective in suppressing the convulsive activity of the local anaesthetics, but only in near anaesthetic doses, therefore, diazepam is the drug of choice

■ ***Central Nervous System***

• factors which influence the occurrence of CNS toxicity include,

1. relative potency
   - the relative ***toxicities*** approximate the relative anaesthetic ***potencies***
2. rate of injection
   - and the rate at which a particular blood concentration is achieved
   - volunteers being able to tolerate higher absolute levels of a given agent when infused at slower rates
3. P_{aCO2} → ***inversely*** related to the convulsive threshold
4. pH → ↓ pH → ↓ convulsive threshold

• ***respiratory acidosis***, with an increase in P_{aCO2} and decrease in pH, is consistently associated with a ***decrease*** in the convulsive threshold
• ***metabolic alkalosis***, with an increase in P_{aCO2} and pH exerts less of an effect, suggesting that pH is the principal determinant
• an elevation of P_{aCO2} will increase cerebral blood flow and delivery of the agent to the brain
• a decrease in ICF pH will increase conversion to the protonated form
• hypercarbia, acidosis, or both will decrease plasma protein binding and increase the free drug fraction
• acidaemia will however increase protonation and decrease the rate of diffusion into the cell

■ ***Cardiovascular System***

• the local anaesthetics can exert an effect both directly on the myocardium and on peripheral vascular smooth muscle
• the primary site of action of the local anaesthetics, once absorbed, is the ***myocardium***
• effects here include decreased,

a. conduction
b. contractility - dose dependent
c. excitability

• most studies have been done with ***lignocaine***, which produces,

a. no change in the resting V_m
b. ↓ $\delta V/\delta t_{max}$ → ↓ conduction velocity
c. ↓ APD & ERP
d. the ***ratio*** of ERP:APD is ***increased*** in Purkinje fibres and ventricular myocardium

• CVS effects are usually only seen at high doses, when CNS effects are already evident
• they are not usually seen with regional techniques
• rarely, inadvertent intravascular administration may result in sudden death, presumably due to VF
• this is more likely with solutions containing ***adrenaline***
• lignocaine produces little or no change in the ECG at therapeutic concentrations
• however, at increasingly toxic levels, prolonged conduction → - ***PR and QRS intervals***
• very high levels may supress SA node activity → sinus bradycardia or sinus arrest
• similar depression of the AV node occurs → progressive AV block ± AV dissociation
• local anaesthetics have little or no effect on slow Ca^{++} channels
• there are some reports of blockade of Ca^{++} flux in myocardial sarcolemma at high concentrations

• most studies of cardiac toxicity involve ***bupivacaine***, as the agent precipitates VF in animal species and man
• bupivacaine markedly depresses dV/dt_{max}
• also the rate of recovery from steady state block is much slower
• this slower rate of recovery results in an incomplete restoration of $\delta V/\delta t_{max}$ between action potentials at rates ≥ 100 bpm
• this decrease in the rate of depolarisation leads to a partial conduction block at fast rates and predisposes to ***unidirectional block*** and reentrant type tachyarrhythmias

• the precise mechanism by which the local anaesthetics depress ***contractility*** is unknown
• lignocaine and bupivacaine both produce dose dependent reductions in $\delta P/\delta t_{max}$ and increases in LVEDP
• they also produce a direct pulmonary vasoconstrictive effect
• the ***cardiotoxicity*** of the more potent agents, such as bupivacaine, appears to differ from that of lignocaine, in that,

a. the ratio of the dose required for irreversible cardiovascular collapse, and the dose required for CNS toxicity, the ***CC/CNS ratio***, is lower for bupivacaine and etidocaine than for lignocaine
b. ventricular arrhythmias and fatal VF, may occur after rapid IV administration of large doses of bupivacaine, but not lignocaine
c. the pregnant animal or patient is more sensitive to the cardiotoxic effects of bupivacaine than the nonpregnant
d. resuscitation is far more difficult after bupivacaine induced cardiovascular collapse
e. ***acidosis & hypoxia*** markedly potentiate the cardiotoxicity of bupivacaine (***not*** via tissue uptake/binding)

• studies with sheep indicate that the lower CC/CNS ratio for etidocaine and bupivacaine may be due to greater ***tissue uptake*** of these agents
• VF was seen in ~ 50% of unanaesthetised dogs administered a supraconvulsant dose of bupivacaine
• no such arrhythmias were seen with lignocaine, etidocaine, or mepivacaine treated dogs
• thus, it is unlikely that the ***piperidine ring*** structure of bupivacaine is responsible for its toxicity

NB: the theory that lipid solubility & protein binding are important is ***not*** supported as etidocaine is both more lipid soluble and has greater tissue binding

• studies on isolated muscle revealed that ***procaine*** has a similar effect upon the myocardium to ***quinidine***,

a. increasing the effective refractory period ↑ ERP
b. raising the threshold for stimulation ↑ V_t
c. prolonging conduction time ↓ v_c

• the rapid hydrolysis of procaine renders it inappropriate for antiarrhythmic therapy
• subsequent studies led to the synthesis of ***procainamide***

• most local anaesthetics cause a ***biphasic*** peripheral arteriolar response, with initial vasoconstriction followed by vasodilatation
• as the dose of local anaesthetic is increased, the action is changed from one of stimulation and vasoconstriction to inhibition and vasodilatation
• ***cocaine*** is the only local anaesthetic which produces ***vasoconstriction*** at most doses
• the initial effect is vasodilatation, however, this is followed by a prolonged period of vasoconstriction regardless of the dose
• cocaine has been shown to inhibit noradrenaline uptake by tissue binding sites
• this property has ***not*** been demonstrated with any other local anaesthetic

■ ***In Summary***

1. at relatively nontoxic levels either no change or a slight increase in BP may be noted
2. concentrations of local anaesthetic that produce CNS toxicity will result in marked increase in HR, BP, and CO, directly related to the duration of the convulsive activity
3. further increases in blood concentrations will result in cardiovascular depression
4. if an excessive amount of local anaesthetic is administered then a profound state of cardiovascular depression may ensue, related to the negative inotropic and vasodilatory action of the local anaesthetics

Local Tissue Toxicity

• most local anaesthetics in clinical use rarely produce localised nerve damage
• there were a number of reports of prolonged motor and sensory deficits with the use of ***chloroprocaine***
• this is believed to be related to the antioxidant ***sodium bisulphite***
• the use of pure solutions has not been associated with any reported toxicity
• commercial solutions of chloroprocaine contained,

a. chloroprocaine - 3%
b. sodium bisulphite - 0.2%
c. hydrogen ions - titrated to a pH ~ 3.0

• in a buffered solution at pH = 7.0, only reversible block is seen
• thus, it is the combination of ***sodium bisulphite*** and the ***low pH*** of the commercial solution which results in toxicity
• the tolerance of peripheral nerves to this toxicity appears to be much higher than that for spinal nerves (NB: myelination)

• skeletal muscle appears to be more sensitive to the irritant properties of the local anaesthetics than other tissues
• in general the more potent, longer acting agents such as bupivacaine and etidocaine result in greater muscle irritation

Allergic Reactions

• only rarely are individuals hypersensitive to the local anaesthetics, manifest as urticarial skin reactions, asthma, or fatal anaphylaxis
• more commonly, side effects of systemic toxicity are mistaken as being allergic in nature

• these reactions appear to be more common with the ***amino-ester*** linked local anaesthetics, which are derivatives of ***para-aminobenzoic acid***, which is a known allergen
• thus, allergy frequently extends to similar chemical compounds, eg. individuals allergic to procaine are frequently allergic to tetracaine

• although agents of the amide-linked class are essentially free of this side effect, as they are not derivatives of para-aminobenzoic acid, they may contain preservatives which are not,

1. multidose containers may contain the preservative ***methylparaben***, which has a chemical structure similar to PABA
2. the anti-oxidant ***metabisulphite***, which is present in adrenaline containing solutions

• cross sensitivity may occur with a number of foodstuffs, many of which contain preservatives such as metabisulphite and hydroxybenzoate
• some antihistamines are occasionally used as local anaesthetics for individuals who have become hypersensitive to all of the conventional agents

- ***Miscellaneous Effects***

1. Neuromuscular Junction & Sympathetic Ganglia
   - the effects of procaine and physostigmine are competitive while those of procaine and dTC are additive
   - it appears that local anaesthetics do not interfere with synaptic transmission by simple competition
   - instead a ***LA / receptor / ACh complex*** is formed which has negligible conductance
   - further, local anaesthetics decrease muscle twitch & tetanic response to maximal motor nerve volleys and injection of ACh
   - this is possibly due to decreased ACh release from the prejunctional terminal, as the muscle remains responsive to direct electrical stimulation
2. Methaemoglobinaemia
   - the initial step in metabolism is hydrolytic forming ***o-toluidine***, which is further metabolised to 4 & 6-hydroxytoluidine $\rightarrow$ ***MetHb***
   - ***prilocaine*** ^{3} ***600 mg*** doses are required for the development of significant MetHb
   - little significance for the majority of patients with normal oxygen carrying capacity
   - however, this effect has limited the use of prilocaine, despite the fact that it is the least CNS toxic of the amide local anaesthetics
   - methaemoglobinaemia is spontaneously reversible, or may be treated with ***methylene blue*** ~ 1 mg/kg
3. Other Actions
   - local anaesthetics depress the contraction of ***smooth muscle*** in the GIT, bronchi and blood vessels
   - when used for epidural, or spinal anaesthesia, they result in sympathetic paralysis and may lead to increased tone of the GIT musculature

Factors Affecting Systemic Local Anaesthetic Toxicity

• the degree of toxicity is clearly related to,

1. the ***absolute blood level***
2. the ***rate of change*** of blood level
3. pre-existing CVS / CNS disease

NB: the blood levels which are achieved after appropriate regional anaesthetic techniques ***rarely*** result in systemic toxicity

• however, toxicity may ensue after inadvertent intra-arterial injection, or the administration of an excessive dose
• following rapid intravascular injection, toxicity is primarily related to ***anaesthetic potency***

• following extravascular injection, the pharmacokinetic profile of the drug also plays a part
• thus, absorption is related to,

1. the site of injection
2. the choice of drug
3. the dose
4. the presence of vasoconstrictors

• the rate of absorption parallels tissue blood flow, being the greatest from the intercostal muscles
• the relationship between absolute dose and blood levels appears essentially ***linear*** over the clinical concentration range
• differences in the rate of metabolism and the volume of distribution, allow the use of greater concentrations and dosages of some agents
• eg., the epidural administration of 300 mg of etidocaine (20 ml of 1.5%) produces similar blood levels to 150 mg of bupivacaine (20 ml of 0.75%)
• the effect of the addition of adrenaline depends upon,

a. the response of the vasculature at the site
b. the drug itself

• among the ***amino-amides***, prilocaine has the shortest distribution and elimination half lives
• the distribution half-lives of the other amides are similar
• the elimination half-lives of lignocaine, mepivacaine and etidocaine are similar, whereas that of bupivacaine is the longest
• thus, the potential for systemic toxicity is lowest for prilocaine and greatest for bupivacaine
• the half-lives of the amides will be prolonged in patients with cardiac or liver disease, thus potentiating their toxicity

• among the ***amino-esters***, chloroprocaine has the fastest rate of plasma hydrolysis, followed in order by procaine and tetracaine
• thus, the potential for systemic toxicity is lowest for chloroprocaine and greatest for tetracaine

Contraindications

a. allergy / hypersensitivity to local anaesthetics

b. allergy / hypersensitivity to solution additives

c. ***adrenaline*** is contraindicated for,
   i. conditions where tachycardia is detrimental (thyrotoxicosis, CCF, IHD)
   ii. anaesthesia around end-arteries
   iii. intravenous regional anaesthesia

d. epidural/spinal anaesthesia in the presence of significant
   i. hypotension / hypovolaemia
   ii. coagulopathy

e. the presence of local tissue sepsis

f. patient refusal

- ***Precautions***

a. resuscitation equipment and drugs should be available

b. reliable IV access should be established prior to blockade

c. injection should follow ***aspiration*** to ensure extravascular administration

d. the ***lowest effective dose*** should be used

e. care should be taken when administering to patients with,
   i. pre-existing neurological & cardiac disorders
   ii. cardiac glycoside toxicity
   iii. hepatic or renal impairment
   iv. a predisposition to malignant hyperpyrexia *now disproven
   v. porphyria *depends upon patient/type

f. foetal bradycardia may follow excessive maternal administration with subsequent hypoxia & acidosis

g. inadvertent IV or subarachnoid administration around the head and neck may be associated with systemic toxicity similar to that seen with larger doses (retrobulbar, stellate ganglion, interscalene)

h. retrobulbar blocks have been associated with respiratory arrest

ESTER LOCAL ANAESTHETICS

Cocaine

• is an alkaloid from the leaves of ***Erythroxylon coca*** and is an ester of benzoic acid
• it stimulates the CNS and in low doses produces euphoria and "well being"
• higher doses cause convulsions, coma, medullary depression & death
• cocaine stimulates the vomiting centre
• blocks the uptake of catecholamines into peripheral nerve terminals, and therefore enhances SNS activity and administered catecholamines
• SNS augmentation probably produces the vasoconstriction and mydriasis
• small doses may produce a bradycardia, due to central vagal stimulation
• larger doses result in tachycardia, increased TPR and hypertension
• larger doses may produce direct myocardial depression, VF & death

• cocaine blocks conduction when applied directly to nerve tissue & may therefore be used in surface anaesthesia
• cocaine was used in the past for ophthalmological procedures, however has now been abandoned due to sloughing of the corneal epithelium & increased intraocular pressure
• the only use today is as a topical local anaesthetic in ENT (5%)
• cocaine itself constricts blood vessels and the use of adrenaline is contraindicated as it sensitises the myocardium

Procaine (NOVOCAINE)

• synthesised by Einhorn in 1905
• procaine has a short duration of action and a high pK_A, therefore it spreads poorly through tissues due to the high protonation
• as for other ester local anaesthetics it is rapidly hydrolysed in the body by butyrylcholinesterase
• this produces para-aminobenzoic acid, which inhibits the action of the sulphonamides
• procaine may prolong the action of ***succinylcholine***, since it competes for the same enzyme
• similarly, the anticholinesterase agents increase the toxicity of normal doses of procaine by inhibiting its degradation
• degradation is also reduced in patients with atypical butyrylcholinesterase
• procaine has vasodilator properties and is readily absorbed following parenteral administration
• therefore, it does not remain at the site of injection unless combined with a vasoconstrictor agent and is ineffective for surface anaesthesia
• procaine forms insoluble salts in conjugation with a number of other drugs, prolonging their duration of action
• this is unrelated to its local anaesthetic actions
• it has been used in the treatment of patients with malignant hyperpyrexia, forming poorly soluble salts of administered drugs
• possible allergy to procaine must be considered when hypersensitivity to these agents occurs
• the amount of procaine given with large IM doses of procaine-penicillin G may result in CNS toxicity

Chloroprocaine

- is a halogenated derivative of procaine and has similar pharmacological properties
- the rapid plasma hydrolysis results in a short duration of action and low toxicity (potency = 1.0)
- onset of action is ~ 6-12 mins and the duration ~ 60 mins, depending upon the administered dose
- maximal recommended doses are 1000 & 800 mg, with and without adrenaline
- it is ineffective for topical anaesthesia but suitable for infiltration, or peripheral nerve block in a 1.0% solution
- the low toxicity, short duration, rapid metabolism and low foetal:maternal blood partitioning make it a suitable choice in obstetrics
- suspected neural toxicity with epidural/spinal administration actually related to the addition of sodium bisulphite to the adrenaline containing solutions
- this was enhanced by the low pH of the solution and the limited buffering in the subarachnoid space

Tetracaine

- this is also an ester of PABA but is a potent, long acting agent which is hydrolysed at a much slower rate
- its actions are similar to those in this group
- suitable for spinal anaesthesia, hypo & hyperbaric, in a 1.0% solution when the dose ranges from 5.0 to 20 mg
- onset of action is ~ 10 mins and the duration of action 60 to 90 mins
- maximum recommended dose is ~ 100 mg for a 70 kg male

NB: this is a useful agent when the amide agents are contraindicated

AMIDE LOCAL ANAESTHETICS

Lignocaine (XYLOCAINE)

- introduced in 1948, produces a faster acting, longer lasting, more intense and more extensive degree of anaesthesia than procaine
- suitable for surface, infiltration, nerve block, caudal, epidural, and spinal anaesthesia
- the solution is extremely stable and may be sterilised by autoclaving a maximum of 2 times

Chemical Properties			
pK_A			7.85
pH	1.0% 1.5% 2.0%	plain aqueous solutions	• 5.0-7.0
pH	1.0% 1.5% 2.0%	with adrenaline	• 3.0-4.5
potency			2
plasma half-life, $t_{½\beta}$		adult neonate	• 1.8 hours • 2 hours

- ***Contraindications***

a. allergy/hypersensitivity to amide local anaesthetics

b. allergy/hypersensitivity to solution additives

c. adrenaline is contraindicated for,
   i. conditions where tachycardia is detrimental (thyrotoxicosis, CCF, IHD)
   ii. anaesthesia around end-arteries
   iii. intravenous regional anaesthesia

d. epidural/spinal anaesthesia in the presence of significant hypotension/hypovolaemia

e. epidural/spinal anaesthesia in the presence of a significant coagulopathy

f. in the presence of local tissue sepsis

Lignocaine Recommended Dosages (70 kg adult)			
Procedure	Concentration	Volume	
		Plain	Adrenaline
Infiltration	0.5% 1.0% 2.0%	40 20 10	100 50 25
Intravenous Regional	0.5%	40	C/I
Nerve Plexus Blocks			
Brachial Plexus	0.5% 1.0% 2.0%	40 20 10	100 50 25
Intercostal (per segment)	1.0%	C/I	3-5
Paravertebral (per segment)	1.0%	3-5	3-5
Pudendal	1.0%	10	10-20
Paracervical	1.0%	10	C/I
Sympathetic Nerve Blocks			
Stellate ganglion	1.0%	5	5-10
Lumbar chain	1.0%	10	5-20
Epidural[1]			
Thoracic	1.0% 2.0%	10-20 5-10	15-30 5-15
Lumbar • analgesia • anaesthesia	 1.0% 1.5% 2.0%	 10-20 5-15 5-10	 15-30 15-30 10-25
Caudal • analgesia • anaesthesia	 1.0% 1.5%	 10-20 5-15	 15-30 15-30

[1] dose = 2-3 ml / segment required T_4-S_5 ~ 36 ml !!
clinically, less than this is frequently satisfactory, therefore fractionate dose

• the ***maximum*** recommended doses in the adult are,

a. plain ~ 3 mg/kg

b. with adrenaline ~ 7 mg/kg

NB: following epidural anaesthesia with 400 mg / 70 kg adult,
blood concentrations reach 2.0-4.0 µg/ml, toxicity beginning at ~ 5 µg/ml

• unlike procaine, lignocaine is an ***aminoethylamide*** and is therefore the agent of choice for those subjects allergic to the ester-linked local anaesthetics
• lignocaine is relatively quickly absorbed from the GIT and after parenteral administration
• effective without a vasoconstrictor, though, in the presence of adrenaline the rate of absorption and the toxicity are significantly reduced
• metabolised in the liver by the mixed function oxidases, by dealkylation to,

a. monoethylglycinexylide (MEGX)

b. glycinexylide (GX) ~ 75% → urine as ***4-hydroxy-2,6-dimethylaniline***

• toxic doses of lignocaine lead to death by ventricular fibrillation, or cardiac arrest
• in contrast, procaine tends to depress respiration more than the circulation

Drug Interactions	
Drug Class	Effects
Antiarrhythmic agents	potentiation of cardiac effects
β-blocking agents • propranolol • metoprolol	decreased lignocaine metabolism
Cimetidine	decreased lignocaine metabolism
Anticonvulsant agents • phenytoin • phenobarbitone • carbamazepine	increased lignocaine metabolism
Adrenaline Containing Solutions	
CNS active drugs • tricyclics • phenothiazines	sustained hypertension/hypotension
Ergot derivatives	sustained severe hypertension
Ganglion blockers	sustained severe hypertension
Inhalational anaesthetics	cardiac arrhythmias
Cardiac glycosides	cardiac arrhythmias

Bupivacaine (MARCAINE)

Chemical Properties			
pK_A			• 8.1
pH	0.25% 0.375 % 0.5%	plain aqueous solutions	• • 4.5-6.0
pH	0.25% 0.375 % 0.5%	with adrenaline	• 3.5-5.5
potency			• 8
protein binding			• 95%
lipid solubility			• > lignocaine
plasma half-life, $t_{½\beta}$	adult neonate		• 3.5 ± 2 hrs • 8.1 - 14 hrs

• is an amide-linked local anaesthetic structurally related to lignocaine and mepivacaine (a butyl group is substituted for the amino N-methyl group)
• bupivacaine is particularly suited to,

a. postoperative analgesia
b. therapeutic pain blocks
c. obstetric analgesia/anaesthesia
d. surgical anaesthesia for long duration procedures

• produces prolonged anaesthesia with a slower onset of action
• the presence of adrenaline 1:200,000 decreases the rate of systemic absorption and the peak plasma levels, however, the ***duration*** of anaesthesia is relatively unaltered
• its mean duration of action is longer than tetracaine, though, the toxicity of the two is similar
• postoperative analgesia can be maintained for ~ 7-14 hours with intercostal blockade, or ~ 3-4 hours with epidural blockade
• peak plasma levels following caudal or epidural administration are reached within 30-45 minutes, followed by decline over 3-6 hours
• although more toxic, a lower ***foetal/maternal ratio*** has been observed cf. other agents
• thus, bupivacaine is the recommended for obstetric analgesia/anaesthesia, with the exception of paracervical block
• although bupivacaine is metabolised in the liver, dose reduction is probably not warranted, however, caution should be used with repeated doses
• similarly, renal disease is unlikely to affect bupivacaine clearance in the short term (~ 24 hrs), however, toxicity may result with prolonged or repeated administration

- ***Contraindications***

a. allergy/hypersensitivity to amide local anaesthetics

b. allergy/hypersensitivity to solution additives

c. obstetrical paracervical block

d. intravenous regional anaesthesia (Bier's block)

e. ***adrenaline*** is contraindicated for,

   i. conditions where tachycardia is detrimental (thyrotoxicosis, CCF, IHD)

   ii. anaesthesia around end-arteries

   iii. intravenous regional anaesthesia

f. epidural/spinal anaesthesia in the presence of significant hypotension/hypovolaemia

g. epidural/spinal anaesthesia in the presence of a significant coagulopathy

h. in the presence of local tissue sepsis

Drug Interactions	
Drug Class	**Effects**
Antiarrhythmic agents	potentiation of cardiac effects
Adrenaline Containing Solutions	
CNS active drugs • tricyclics • phenothiazines	sustained hypertension/hypotension
Ergot derivatives	sustained severe hypertension
Ganglion blockers	sustained severe hypertension
Inhalational anaesthetics	cardiac arrhythmias
Cardiac glycosides	cardiac arrhythmias

Bupivacaine Recommended Dosages (70 kg adult)		
Procedure	Concentration	Volume (ml)
Infiltration	0.25% 0.5%	5-60 5-30
Intravenous Regional	***Contraindicated***	
Nerve Plexus Blocks		
Minor nerve blocks	0.25% 0.5%	5-30 5-20
Brachial plexus	0.25% 0.5%	20-40 20-30
Hip joint blocks • sciatic • femoral • obturator • lateral cutaneous	 0.5% 0.5% 0.5% 0.25%	 20-30 10-20 10-20 5-10
Coeliac plexus	0.25%	40-50
Diagnostic & Therapeutic Blocks	0.25-0.5%	2-30
Epidural	dose = 2-3 ml / segment required	
Thoracic	0.25% 0.5%	5-15 3-8
Lumbar • analgesia • anaesthesia	 0.25% 0.5%	 10-30 10-20
Caudal • analgesia • anaesthesia	 0.25% 0.5%	 15-40 15-25

- the ***maximum*** recommended doses in the adult are,

  a. plain ~ 2 mg/kg

  b. with adrenaline ~ 2 mg/kg

  NB: this equates to ~ 25 ml of 0.5% in a 70 kg adult

Cinchocaine (NUPERCAINE)

- cinchocaine is a potent local anaesthetic of the amide type, chemically related to lignocaine
- it is ~ 15 times as potent and toxic as procaine
- usage is virtually restricted to ***subarachnoid anaesthesia***
- anaesthesia usually occurs within 2-3 minutes but may take as long as 10 minutes
- the average duration of action is 2-3 hours for abdominal surgery but may be longer following "saddle blockade"
- exhibits high lipid solubility and protein binding, accounting for its prolonged duration of action
- the elimination half life is the longest of all of the amide agents
- metabolism does occur, however, cinchocaine is predominantly excreted ***unchanged*** in the urine
- the contraindications and precautions are essentially the same as those for lignocaine
- its use in pregnancy has not been evaluated and should only be used during delivery if the expected benefits outweigh the potential risks
- in view of the very low total doses employed, toxicity is extremely rare
- systemic toxicity is similar to that seen with lignocaine
- the heavy solution, cinchocaine 0.5% 3 ml ampoules, is usually used for abdominal surgery
- the doses of ***heavy cinchocaine*** required for anaesthesia to the level,

a. T_{10} dermatome ~ 5-8 mg = 1.0-1.6 ml

b. T_4 dermatome ~ 10-15 mg = 2.0-3.0 ml

- cinchocaine may also be prepared as a ***hypobaric*** solution
- in the same concentration, 15 mg per 3 ml, in sterile water the specific gravity is ~ 1.0006

Prilocaine (CITANEST)

- equipotent to lignocaine with a longer duration of action and lower toxicity
- rapid plasma hydrolysis makes it the agent of choice for regional IV blockade
- causes ***methaemoglobinaemia*** in high doses but this is rarely clinically significant
- used in all types of anaesthesia in similar concentrations to lignocaine

Mepivacaine

- used for infiltration, nerve block, caudal & epidural anaesthesia but is ineffective topically
- similar potency and onset to lignocaine but slightly longer duration of action
- used in similar concentrations to lignocaine
- ***not recommended*** for obstetric use due to high foetal:maternal ratio

Etidocaine

- is a long acting derivative of lignocaine, with much higher lipid solubility and protein binding
- it is ~ 2-3 times more potent than lignocaine but less toxic than bupivacaine
- effective in infiltration, nerve block, epidural & caudal anaesthesia
- results in a high degree of ***motor blockade*** when administered into the epidural space

CLINICAL USES OF LOCAL ANAESTHETICS

• the clinical uses of local anaesthetics may be divided into,

a. surface anaesthesia

b. infiltration anaesthesia

c. nerve block anaesthesia - peripheral
- plexus

d. intravenous regional anaesthesia

e. spinal/subarachnoid anaesthesia

f. spinal/epidural anaesthesia

g. other uses - antiarrhythmic
- reduction in ICP
- blunting of cardiovascular responses to intubation/extubation

Surface Anaesthesia

• anaesthesia of the mucous membranes of the mouth, nose, pharynx, oesophagus, tracheobronchial tree & genitourinary tract can be produced by direct application of aqueous solutions of the local anaesthetics
• tetracaine, lignocaine and cocaine are the most frequently used
• other local anaesthetics are unsuitable, penetrating mucous membranes poorly
• cocaine has the unique advantage of also producing vasoconstriction
• the shrinkage of mucous membranes decreases operative bleeding and improves visualisation of the operative field
• similar effects can be achieved with the other agents by the addition of ***phenylephrine*** 0.05%
• this should not be added to cocaine
• adrenaline is unsuitable for this use as it penetrates mucous membranes poorly
• maximal safe doses for a 70 kg man are,

a. lignocaine ~ 750 mg

b. tetracaine & cocaine ~ 50 mg

• peak action occurs after 2-5 mins with lignocaine & cocaine, and after 3-8 mins with tetracaine
• anaesthesia lasting for 30-45 and 45-60 minutes respectively
• anaesthesia is entirely superficial and does not extent beyond the ***submucosa***
• local anaesthetics are rapidly absorbed via this route → potential systemic toxicity
• absorption is particularly rapid through the tracheobronchial tree
• plasma concentration-time curves being similar to those after IV injection

• ***EMLA*** or ***eutectic mixture of local anaesthetics*** is a 5% mixture of lignocaine (25 mg/g) & prilocaine base (25 mg/g)
• a eutectic mixture being one in which the melting point is less than either of the constituent solids
• there has been one case report of methaemoglobinaemia from cutaneous absorption in a neonate

Infiltration Anaesthesia

• the ***duration*** of action can be ~ doubled by the addition of adrenaline (1:200,000 or 5 µg/ml)
• by decreasing the rate of systemic absorption and reducing the peak systemic concentration, the risk of ***toxicity*** is proportionately reduced
• thus, maximal amounts of local anaesthetic can be increased by ~ 1/3
• however, adrenaline containing solutions are ***contraindicated*** for,

a. conditions where ***tachycardia*** is detrimental
   i. thyrotoxicosis
   ii. arrhythmic disorders
   iii. CCF, IHD
b. anaesthesia around ***end-arteries*** → fingers, toes, ears, nose & penis
c. ***intravenous*** regional anaesthesia

• the main advantage of this technique is the lack of disruption to normal bodily functions
• the chief disadvantage being that relatively large amount of the drug must be administered for anything above a minor surgical procedure

Field Block Anaesthesia

• produced by the subcutaneous injection of local anaesthetic in such a manner as to interrupt nerve transmission proximal to the site to be anaesthetised
• this is particularly useful at the volar surface of the forearm, the anterior abdominal wall, scalp and the lower extremity
• doses & concentrations are the same as for infiltration anaesthesia

Nerve Block Anaesthesia

• injection of local anaesthetic into, or about, individual peripheral nerves & plexuses produces anaesthesia in a greater area for a given amount of drug than any of the above techniques
• blockade of mixed peripheral nerves also affects motor segments, denervation usually starting several cm from the site of blockade
• the onset of sensory blockade depends upon the pK_A of the anaesthetic and, thus, the amount in the unprotonated form,

a. lignocaine ~ 3 mins to onset
   ~ 35% being in the basic form at physiological pH
b. bupivacaine ~ 15 mins to onset
   ~ 5-10% being in the basic form

• ***diffusion*** is more important where plexuses are being blocked
• the latency of lignocaine at the ulna nerve is ~ 3 mins, c.f. the brachial plexus, where the latency is ~ 15 mins
• the latency for bupivacaine at the brachial plexus ~ 20 mins
• the duration of nerve block is especially determined by the lipid solubility and protein binding of the local anaesthetic
• in general local anaesthetics can be divided into three categories,

Category	Duration	Agents
Short Duration	20-45 min	procaine, chloroprocaine
Intermediate	60-120 min	lignocaine, prilocaine, mepivacaine
Long Duration	400-450 min	bupivacaine, tetracaine, etidocaine

• these categories directly parallel the respective ***anaesthetic potencies***
• the duration can be increased by increasing the amount of drug injected
• however, this increases the risk of toxicity ***more*** than it lengthens duration
• increasing the volume of anaesthetic also increases the likelihood of affecting neighbouring structures
• in an attempt to provide rapid onset, long duration and acceptable drug doses, combinations of lignocaine & bupivacaine are sometimes used
• this is complicated by the affects of individual pK_A's and the pH of the solutions

NB: the addition of ***adrenaline*** is a safer means of increasing the duration

• differential fibre blockade in a mixed peripheral nerve depends upon,

a. concentration of local anaesthetic
b. fibre size
c. internodal distance
d. frequency & pattern of nerve transmission
e. anatomical factors

• the vascular supply is usually centrally located and when local anaesthetic is injected about a nerve, it diffuses from the outer surface to the core along its concentration gradient
• thus, the outer fibres are the first to be blocked and these are usually distributed to the more proximal structures than are those of the core
• if the volume & concentration are sufficient then eventually all fibres will be blocked
• if insufficient, then only the outer fibres will be affected
• further, vascular uptake of the local anaesthetic occurs from the centre, so the termination of blockade begins with the central fibres
• as with other regional anaesthesia techniques, the addition of adrenaline (1:200,000) will significantly increase the duration of blockade

Intravenous Regional Anaesthesia

• accomplished by the IV injection of local anaesthetic into a previously exsanguinated limb, with maintenance of exsanguination by pneumatic tourniquet above arterial pressure
• solutions used include,

a. lignocaine ~ 2-3 mg/kg → 40 ml 0.5% / 70 kg adult*

b. prilocaine ≤ 5 mg/kg 0.5-1.0%

• despite the risk of ***methaemoglobinaemia***, the later is preferred due to the lower systemic toxicity
• *cuff failure may result in potentially toxic plasma levels
• the onset of blockade is usually within 2-3 mins
• at the end of surgery ~ 15-30% of the injected lignocaine is released in to the circulation
• peak serum concentrations are seen in 4-5 mins and are less than those observed with brachial plexus, or lumbar epidural blockade
• the technique is more effective for the upper than the lower extremity
• though, use of an ankle tourniquet is successful for foot procedures

NB: * bupivacaine is ***not*** approved for IV use

- ***Contraindications***

1. patient refusal
2. allergy to local anaesthesic
3. infection at the site of injection
4. contraindication to placement of a limb torniquet
   i. A-V dialysis shunt
   ii. severe Raynaud's disease
   iii. sickle cell anaemia
5. procedure of uncertain or prolonged duration
6. patient unable to cooperate during surgery

- ***Technical Difficulties***

1. thin patients - risk of neuropraxias
2. obesity
3. hypertension
4. severe atherosclerosis
5. poor venous access

CENTRONEURAXIS BLOCKADE

• spinal or epidural blocks produce,

a. sympathetic blockade

b. sensory analgesia

c. motor blockade

• depending upon the dose, concentration and volume of local anaesthetic
• despite these similarities, there are significant physiological & pharmacological differences
• ***spinal anaesthesia*** requires a small mass of local anaesthetic, virtually devoid of systemic effects, and produces a profound and reliable degree of sensory blockade
• ***epidural anaesthesia***, in contrast, uses a large mass of local anaesthetic, associated with pharmacologically active plasma concentrations, and produces a less reliable and sometimes patchy sensory blockade
• it is unclear which was being produced by Corning in 1885, who injected cocaine between the spinous processes in dogs
• Bier (1898) was more definitive, producing post-spinal headache in himself
• early advances were in spinal anaesthesia for three reasons,

a. prior to the synthesis of procaine in 1904, cocaine was the only agent available, producing systemic side effects with large administered doses

b. the end point for spinal administration was easier, not requiring sophisticated glass syringes/needles

c. spinal administration also produced muscle relaxation, dedicated relaxants not yet being available

• centroneuraxis blockade is indicated whenever the surgical procedure can be accomplished with a level of blockade which in not associated with adverse cardiorespiratory sequelae
• the level of sensory analgesia required is of prime importance, anaesthesia to the T_{10} dermatome producing considerably less physiological impact than that to the T_4 dermatome

■ ***Epidural vs. Spinal***

• factors in favour of epidural vs. spinal technique include,

a. unpredictable procedure length

b. requirement for prolonged postoperative analgesia

c. high risk of post-dural puncture headache
- age < 40 years
- pregnancy

d. "brittle" cardiovascular system requiring gradual onset of sympathectomy

SPINAL ANAESTHESIA

• produced by the injection of local anaesthetic into the lumbar subarachnoid space below the level of the termination of the cord ~ L_2
• spread of the agent within the subarachnoid space, and the subsequent level of anaesthesia, is governed by the injection of solutions that are heavier, or lighter than CSF, the patient then being placed in the head-up, or head-down position
• addition of ~ 10% glucose to a solution of local anaesthetic produces a heavier than CSF, hyperbaric spinal anaesthesia
• the height that is achieved is determined by the volume of solution that is injected and the degree of tilt of the patient
• hypobaric spinal anaesthesia is achieved by the addition of sterile distilled water to the local anaesthetic
• the [LA] in the CSF rapidly declines after administration as the drug is bound in the tissue and absorbed by the vasculature
• further, within ~ 15 mins a hyperbaric solution becomes isobaric
• at this point, changes in the position of the patient no longer affect distribution of the local anaesthetic within the subarachnoid space, the level of anaesthesia becoming "***fixed***"
• local anaesthetics act on the outer tracts of the spinal cord, but their major site of action is on nerve fibres
• because the [LA] decreases over distance from the site of injection and because different nerve fibres have different sensitivities → ***zones of differential anaesthesia*** develop
• since preganglionic sympathetic fibres are blocked by lower concentrations of local anaesthetic than either somatic sensory or motor nerves, the level of sympathetic denervation during hyperbaric anaesthesia extends ~ 2 levels cephalad of the level of sensory anaesthesia
• similarly, motor nerves being less sensitive than sensory nerve, motor blockade is ~ 2 levels caudal of sensory blockade
• blood concentrations are relatively low during spinal anaesthesia and the altered physiological responses are primarily the result of ***sympathetic blockade***

Anatomy

• the spinal cord is continuous cephalad with the ***brain stem***, via the foramen magnum, and caudally with the ***conus medullaris***
• the distal termination varies with age due to differential growth of the vertebral bodies and CNS,

i. infant → **L_3**
ii. adult → **L_1** - lower border

• the cord is surrounded sequentially by three membranes,

a. pia mater - highly vascular, investing the brain and spinal cord
b. arachnoid mater - delicate, non-vascular, attached to the dura
c. dura mater - longitudinally arranged, fibro-elastic membrane
- extends from the foramen magnum to the ***filum terminale*** (**S_2**)

• the ***filum terminale*** is an extension of the pia mater, beginning at the ***conus medullaris*** and terminating in conjunction with the periostium of the coccyx
• between the pia and arachnoid lies the ***subarachnoid space***, which contains,

a. the CSF
b. blood vessels supplying the spinal cord
c. the trabecular network supporting the cord
d. the lateral dentate ligaments, extensions of the pia
e. the spinal nerves - 31 pairs

• although the cord finishes at ~ L_1, the subarachnoid space continues to S_2
• there is a potential space between the outer two membranes, the ***subdural space***
• this is not intentionally used but may explain the occasional unpredictable behaviour of an epidural anaesthetic, when there is no evidence for subarachnoid placement
• surrounding the dura is the ***epidural space***, which extends from the ***foramen magnum*** to the ***sacral hiatus***, and contains,

a. nerve roots - from the cord to inter-vertebral foramina
b. the venous plexus of Batson
c. lymphatics
d. fat & areolar tissue

• posteriorly this is bounded by the ***ligamentum flavum***, or "yellow ligament", which also extends from the foramen magnum to the sacral hiatus
• this is really two ligaments, the right and left ligamenta flava, which are joined in the midline
• immediately posterior to these are the ***vertebral laminae***, ***spinous processes*** and ***interspinous space***
• extending from the external occipital protuberance to the coccyx, these are covered by the ***supraspinous ligament***, which joins the vertebral spines

• Blomberg (1986), with the use of an epiduroscope in cadaver specimens, consistently identified the presence of a ***dorsomedian connective tissue band*** in the midline of the epidural space
• anatomic dissection and CT scans have also identified epidural septa
• the sacrum is formed from the fusion of the five sacral vertebrae
• the ***sacral hiatus*** represents the failure of fusion of the laminae of S_5 and usually part of S_4
• this usually results in a "V-shaped" bony defect, covered by the posterior ***sacrococcygeal ligament***
• it may be located by palpating the ***sacral cornu***, the remnants of the S_5 articular processes
• there is a large degree of anatomical variation at this site
• 1/20 patients the defect may be absent, or noncommunicating, precluding the caudal approach
• the sacral canal contains the terminal portion of the ***dural sac***, which usually terminates at the level of S_2, or the PSIS's
• the termination is lower in children, increasing the risk of subarachnoid puncture
• the canal also contains the valveless internal vertebral venous plexus

Cerebrospinal Fluid

Composition of CSF	
Volume	• 120-150 ml (25-35 ml in spinal space)
Pressure (lumbar)	• 6-15 cmH_2O
Specific gravity	• 1.006 (1.003-1.009)
pH	• 7.32 (7.27-7.37)
P_{CO2}	• 48 mmHg
HCO_3^-	• 23-25 mmol/l
Sodium	• 133-145 mmol/l (< plasma)
Potassium	• ~ 2.9 mmol/l
Calcium	• 1-1.5 mmol/l
Inorganic Phosphorus	• 0.5-1 mmol/l
Magnesium	• 1.0-1.25 mmol/l
Protein	• 20-38 mg/dl (plasma ~ 6 **g**/dl)
Glucose	• ~ 3.5 mmol/l

• of the 25-35 ml in the spinal cord, most is in the region of the cauda equina, distal to the cord
• pH is less than plasma, the HCO_3^- about the same but the ***P_{CO2} higher***
• during steady state conditions, the cisternal and lumbar CSF have similar values
• however, during rapidly changing conditions, the lumbar CSF is slow to respond
• the CSF Na^+ varies but is slightly less than plasma
• Ca^{++} is less than, and Mg^{++} > plasma, and these change little is disease
• Cl^- is also slightly greater than plasma, however tends to decrease in the presence of elevated protein levels, which occur in numerous disease states

• normal formation ~ 500 ml/day (0.35 ml/min) and is ***inversely*** proportional to plasma osmolality,

$$\delta Osm\ 1\% \rightarrow \delta CSF\ formation \sim 6.7\%$$

• formation may also be inhibited by acetazolamide (≤ 50%), or large doses of frusemide
• steroids have an inconsistent effect and absorption is passive

• blood supply to the cord is from the paired posterior arteries from the posterior inferior cerebellar arteries, and the single midline anterior spinal artery
• vertical communication is poor, and the cord is effectively divided into ~ 3 large segments, supplied by the radicular spinal arteries
• the ***radicularis magna*** enters (78% left) between T_8-L_3 and may be damaged during dural or epidural puncture → predominantly motor deficit
• the artery of Adamkiewicz takes off high in ~ 15%, with the supply to the lumbar enlargement then being derived from the iliac contributions
• damage to these during pelvic surgery may produce lesions in the region of the conus medullaris
• supply appears most tenuous at **~ T_4**, representing a "watershed" between supply regions

Duration & Dosage

• factors which have been ***documented*** to be related to the height of block during spinal anaesthetic include,

a. patient characteristics,
   i. age
   ii. height
   iii. ***position*** during injection
   iv. anatomical configuration of the spinal column
   v. intra-abdominal pressure - pregnancy
      - ascites, intra-abdominal masses
   vi. CSF volume ? specific gravity of CSF, Cousins says not

b. technique / site of injection
   i. needle direction - long axis cephelad vs. 90°
   ii. ***site of injection***

c. solution characteristics
   i. solution ***baricity*** - cf. CSF
   ii. ***dose*** - mass of drug

• factors ***probably unrelated*** to the height of block include,

a. added vasoconstrictor
b. solution concentration
c. coughing, straining, bearing down
d. barbotage
e. CSF composition & circulation - Cousins/Bromage
f. injection rate - except possibly with hypobaric solutions
g. needle bevel - except Whitacare needle
h. gender
i. weight - unlike epidural dose requirements

• the ***duration*** of anaesthesia is dependent upon the absorption of the agent from the SA space, ie.,

a. the area over which the drug is exposed
b. its lipid solubility
c. spinal cord blood flow
d. ? the presence of vasoconstrictors

Local Anaesthetics Commonly Used for Spinal Anaesthesia			
Drug	Concentration	Additive	Baricity
Lignocaine	5% heavy	7.5% dextrose	hyperbaric
Bupivacaine	0.5% heavy 0.5% plain	8.5% dextrose -	hyperbaric iso/hypobaric
Cinchocaine	0.5% heavy 0.5% plain	6.0% dextrose sterile H_2O	hyperbaric hypobaric

NB: ***bupivacaine***, which is highly lipid soluble → ~ 2-3 hrs
lignocaine, which is less lipid soluble → ~ 1 hr

• Moore *et al*. (1987) found that the addition of ***adrenaline*** 0.2 mg prolonged the duration of anaesthesia at the operative site
• this is in contrast to previous studies, which showed no difference in two segment regression
• early studies showed there was no consistent relationship between the amount of vasoconstrictor added and the extent to which anaesthesia was prolonged, possibly because of,

1. failure to control the other determinants of duration of spinal anaesthesia,
   - patient age
   - amount of drug injected
   - area of distribution
2. failure to use a consistent, reproducible means of assessment of anaesthetic duration

• subsequent controlled trials have shown that vasoconstrictors ***do alter*** the duration of spinal anaesthesia, but that this depends upon the agent used
• addition to lignocaine or bupivacaine ***does not*** produce a meaningful prolongation of anaesthesia, as measured by two-segment regression
• whereas, ***tetracaine*** duration is increased > 2x with the addition of adrenaline or phenylehprine
• however, when assessed by anaesthesia at the operative site (lower segments), the duration was prolonged
• this failure of vasoconstrictors to affect the upper levels of anaesthesia (2-segment regression) may be due to failure to diffuse cephelad in sufficient concentrations
• original concerns that the addition of potent vasoconstrictors may result in reductions of spinal cord blood flow and ischaemia have ***not*** been supported
• in dogs, plain subarachnoid lignocaine increases spinal cord blood flow, whereas no increase is seen with adrenaline containing solutions
• the same effects are seen with bupivacaine
• the action of added vasoconstrictor appears to result from,

a. antagonism of lignocaine/bupivacaine induced vasodilatation
b. a_2***-adrenergic*** agonist antinociception

• the presence of α_2-adrenergic agonists probably improves the ***quality*** of block
• ***clonidine*** prolongs both the duration of motor and sensory blockade, however, affects the later to a far greater degree

Average Doses for Spinal Anaesthesia[1]		
Drug	T_{10}	T_4
Lignocaine	• 50-60 mg • 1.0-1.2 ml	• 75-100 mg • 1.5-2.0 ml
Bupivacaine	• 10-12.5 mg • 2.0-2.5 ml	• 15-20 mg • 3.0-4.0 ml
Cinchocaine	• 5.0-8.0 mg • 1.0-1.6 ml	• 10-15 mg • 2.0-3.0 ml

[1] 70 kg male, average height

■ ***Solution Baricity***

• the ***density*** of any solution is the weight in grams of 1.0 ml of the solution at standard temperature & pressure (20°C / 760 mmHg)
• ***specific gravity*** is the ratio of the density of a solution compared to that of water
• ***baricity*** is the ratio of the density of one solution as compared to another
• if the later solution is water, then baricity is the same as specific gravity
• the average specific gravity of CSF ~ 1.0069

Solution		Specific Gravity (20°C)	Baricity
CSF		1.0069	
Lignocaine	Heavy	1.03-1.036	hyperbaric
Bupivacaine	Heavy Plain	1.026	hyperbaric iso/hypobaric
Cinchocaine	Heavy Hypob.	1.0233 ± 0.0002 1.0006	hyperbaric hypobaric

■ ***Hypobaric Solutions***

• tetracaine & dibucaine are the 2 most commonly used agents in the USA
• hypobaric solutions of lignocaine or procaine approach their ***minimum effective concentrations***, and when diluted with CSF are too weak to provide a useful duration of anaesthesia
• ***cinchocaine 0.5%*** may be mixed with sterile H_2O and will provide 90-120 minutes
• useful for perineal or rectal procedures in the jack-knife position, or for unilateral procedures on a lower limb (eg. #NOF)
• not recommended for intra-abdominal procedures, as use of the head-up position to attain the thoracic segments may produce an unacceptably high level of blockade

- ***Isobaric Solutions***

• bupivacaine 0.5% in water is slightly hypobaric, but functionally isobaric
• injection in the sitting position, and maintenance for 2-3 minutes, results in anaesthesia 1-2 segments higher
• isobaric lignocaine may be prepared but suffers a similar fate to the hypobaric solution
• the major clinical advantage is that following injection, patient position has little effect upon distribution
• predominantly used for anaesthesia to T_{10} as higher blockade requires injection of large doses
• however, this does result in a longer duration of anaesthesia at the lower segments and may be useful for longer procedures (John Roberts, personal opinion)

- ***Hyperbaric Solutions***

• easiest, safest and most widely used solutions
• produced by the addition of ***glucose 5-8%***, greater concentrations having little effect upon spread
• distribution is governed by patient position for up to ***20-30 minutes***
• Shesky *et al.* in a controlled study of 72 patients showed that the total drug ***dose*** is more important in determining the level of anaesthesia than either the volume or concentration
• Bridenbaugh (Cousins), "there is no evidence that concentration of the injectate *per se* has any influence on clinical spinal anaesthesia"
• once the selected dose is injected into the CSF it assumes a new concentration dependent upon factors which influence distribution within the CSF
• ?? why then hypobaric lignocaine too weak - surely just inject greater volume

Agent Uptake

• uptake into neuronal tissues within the CSF is governed by,

1. solution ***concentration*** within the CSF
2. ***surface area*** of nerve tissue to which this is exposed
3. lipid content of the nervous tissue & ***lipid solubility*** of the agent
4. ***blood flow*** to the nervous tissue

• the point of highest concentration does not necessarily correspond with the point of needle insertion, but on the movement of the solution once injected
• concentration decreases in a logarithmic manner from this point, and tissue uptake is proportional to concentration
• the surface area of rootlets & roots as they traverse the SA space is high, with corresponding uptake of local anaesthetic
• the spinal cord also takes-up agent by 2 processes,

1. diffusion through the pia directly into the cord
   - this is slow and only affects the most superficial portions
2. CSF extension into the ***Virchow-Robin space***, which accommodate blood vessels penetrating the pia mater
   - this gives access to the deeper structure of the cord

• if accessibility were the only factor, then nerve roots would have the highest concentration of agent, however, due to the role of ***lipid content***, the concentration of local anaesthetic is greatest in the ***spinal cord***
• Cohen (Anesth. 1968) found not only higher concentrations within the cord, but a correlation between the degree of myelination and the drug concentration

> ***NB:*** however, the principal contribution to ***clinical anaesthesia*** is still the concentration of agent within the ***spinal nerves*** and the ***dorsal root ganglia***

• this, combined with the differing sensitivities of nerve fibres to blockade, results in differential levels of anaesthesia
• traditionally, this has been thought to produce sympathetic blockade ~ 2 segments above the sensory level
• however, Bengtsson *et al.* (Acta.Anes.Scand.1985) showed that the intensity and extent of sympathectomy during spinal anaesthesia were far ***less than*** the extent and intensity of sensory anaesthesia
• also, the duration of sympathetic blockade was less than either motor or sensory
• they concluded that preganglionic β-fibres, or sympathetic spinal pathways, are more resistant to blockade than A-fibres during spinal anaesthesia
• motor fibres are also more resistant, resulting in a differential level of blockade ~ 2 segments
• differential sensory blockade produces insensibility to pinprick ~ 2 segments above the level of anaesthesia (insensibility to touch)
• the approximate order of blockade of the following modalities is (MCQ),

ANS → temperature → pain → light touch → motor → proprioception

Elimination

• ***does not*** involve the metabolism of local anaesthetics within the subarachnoid space
• elimination is entirely by ***vascular absorption***, both into the spinal and the epidural vessels
• blood flow is far greater in the epidural space, thus although diffusion across the dura is required, this represents an important route of elimination
• movement across the dura is dependent neither upon lipid solubility, nor upon pK_A or degree of ionisation (??? Cousins/Bridenbaugh)
• differences in the rate of absorption, as a function of the absorptive area exposed, have yet to be proven pharmacokinetically
• ***lipid solubility*** would be expected to delay absorption, due to increased tissue binding
• however, studies of the time to peak plasma levels have shown no difference between bupivacaine and lignocaine
• similarly, the addition of vasoactive agents should influence uptake by altering SCBF, however neither adrenaline nor phenylephrine decrease SCBF in dogs
• also, the time to peak plasma levels of both agents is unaltered by the addition of vasoconstrictors
• decreased SCBF has been proposed as a reason for the prolongation of blockade with increasing age, however this has not been verified by plasma concentration/time studies

Systemic Effects of Spinal Anaesthesia

- ***Cardiovascular Consequences of Spinal Anaesthesia***

NB: the most important consequence of spinal anaesthesia is alteration of cardiovascular function

• the CVS effects of spinal anaesthesia ***are not*** due to the presence of LA in the ventricular CSF and depression of the vasomotor centres
• similarly, plasma levels are well below those required to produce direct effects on the myocardium or the peripheral vascular smooth muscle

• as the degree of CVS change is proportional to the degree of sympathectomy, the degree of change would be expected to correlate with the height of blockade
• unfortunately this relationship is neither predictable nor precise
• the most cephalad sympathetic preganglionic fibres arise from the spinal cord at the level of T_1
• therefore, complete sympathetic blockade ***may*** be achieved with sensory anaesthesia to ~ $\mathbf{T_3}$
• sensory anaesthesia above this level does not increase the deficit in physiological function
• each preganglionic fibre ascends & descends in the paravertebral sympathetic chain and synapses with up to 18 postganglionic fibres
• these are distributed peripherally in a ***non-segmental*** manner

NB: therefore, even low levels of ***sensory anaesthesia*** may be associated with significant ***sympathetic blockade***

• the most distal sympathetic fibres arise at the level of L_2
• spinal solutions usually being injected between L_3 & L_4 almost always involve the lowermost segments

• arteries & arterioles dilate, peripheral resistance and mean BP fall
• the reduction in BP is not proportional to the degree of sympathetic block, as reflex vasoconstriction occurs in areas where innervation is still intact, predominantly the upper limbs
• this reflex vasoconstriction ***does not*** involve the cerebral circulation
• as arterioles maintain some degree of ***autonomous tone***, even with total SNS blockade the fall in TPR is only ~ 15-18%
• thus, severe arterial hypotension is ***not*** due to arteriolar denervation

• the loss of SNS tone to ***veins & venules*** is equivalent to that lost by the arterial tree, however,

1. these retain minimal autonomous tone
2. larger venous blood pool, ~ 75% of blood volume

NB: the predominant effect is ***venodilatation*** → decreased venous return & CO

• the safety of spinal anaesthesia therefore depends upon the maintenance of an adequate venous return to the heart
• this may be accomplished by the elevation of extremities above the level of the RA
• during spinal anaesthesia with total sympathetic denervation, ***cardiac output*** remains unchanged in normovolaemic patients, providing the legs are positioned above the heart
• because of the critical role of venous return in the safe management of spinal anaesthesia, ***hypovolaemia*** from any cause is a relative contraindication
• in the absence of parasympatholytic premedication, high spinal anaesthesia is associated with a ***bradycardia*** which is the result of two factors,

a. preganglionic blockade of cardioaccelerator fibres (T_{1-4})
b. decreased RA volume / pressure
   i. Bainbridge reflex (generally discredited)
   ii. intrinsic chronotropic stretch receptors in the RA & adjacent great veins

NB: ***severe hypotension*** (> 20%) can only be ascribed to a decrease in CO secondary to a decrease in venous return

• ***coronary blood flow*** decreases in proportion to the decrease in mean arterial pressure with spinal anaesthesia to T_4, (Sivarajan *et al.* 1975)

a. mean arterial pressure, 119 → 67 mmHg
b. coronary blood flow, 153 → 74 ml/100g/min
c. myocardial O_2 extraction, 75 → 72 %

• however, myocardial MRO_2 also falls due to,

1. decreased preload- decreased LVEDV & work
2. decreased afterload - decreased LVSWI
3. bradycardia - decreased work

NB: the net result is a slight ***overperfusion*** of the myocardium, though, it is unknown if this relationship holds for subjects with IHD

• ***cerebral blood flow*** is maintained by autoregulation and only decreases if the MAP falls below 55-60 mmHg in normotensive patients
• this figure is higher in hypertensive patients, and hypotension should be treated earlier in these subjects
• CBF falling by ~ 20% with a reduction in MAP ~ 50% (Kleinerman 1958)

• except for ~ 10% decrease in hepatic blood flow, other vascular beds maintain regional perfusion
• renal autoregulation is well maintained

NB: this contrasts the ~ 70% decrease in hepatic blood flow , and the ~ 50% decrease in RBF under deep volatile anaesthesia (halothane ET ~ 1.5%)

• the exact level of what BP decrease is acceptable is speculative
• treatment of ***hypotension*** during subarachnoid should be commenced if the BP falls ³ **33%** from the normal resting level in otherwise healthy patients
• this may also be tolerable in patients with coronary artery disease, based upon levels of induced hypotension used in coronary care units
• in patients with ***essential hypertension*** changes in MAP ³ **25%** should probably be treated

• physiological means of restoring venous return include,

1. head-down tilt, which should not exceed 20° due to the adverse effects of raising jugular venous pressure, and
2. raising the legs > raising the shoulders & head

• vasopressors are of some value but α-adrenergic agonists with a predominant arteriolar effect should be avoided as the increase in afterload may increase MRO_2 > coronary blood flow
• agents which predominantly increase the HR should also be avoided, as should positive inotropes, as these are less effective in the treatment of a low venous return
• the most effective agents are those which have their predominant effect upon the venous circuit
• while no such specific agent exists, ***adrenaline*** has desirable effects, increasing venous tone with only modest increases in contractility & arterial tone
• ***ephedrine*** has a similar spectrum of activity to adrenaline but is less potent and has a longer duration of action

• increasing the circulating blood volume with IV fluids may also be used
• this practice restores cardiac output to the extent that venous return is restored, but at the expense of ***haemodilution*** and a decrease in O_2 carrying capacity
• no studies to date have assessed the increase in myocardial MRO_2 following the administration of large quantities of crystalloids, versus the increase in preload, CO and coronary blood flow
• administration of large volumes of crystalloid to normovolaemic elderly patients does result in,

1. a higher incidence of postoperative urinary retention
2. increased catheter insertion
3. increased UTI's

• other risks include CCF ± pulmonary oedema in patients with marginal LV function

Respiratory Complications

• arterial blood gas tensions are ***unaffected*** during high spinal anaesthesia, normal P_{aO2} & P_{aCO2}
• TV, IRV, and maximal negative P_{IP} are similarly unaffected
• the phrenic nerves remain unaffected even in mid-cervical levels of sensory anaesthesia, due to the differential levels of blockade mentioned above
• the diaphragm compensates for intercostal paralysis, especially as relaxation of the abdominal muscles decreases the resistance to descent of the diaphragm
• diaphragmatic movement may be impaired in,

i. obese patients
ii. patients with ascites
iii. pregnant women at term

• maximal forced ***expiration*** is greatly reduced and the patient is unable to effectively ***cough***
• this results from paralysis of the ***abdominal muscles***, rather than from effects on the phrenic nerve or diaphragm
• therefore, spinal anaesthesia may need to be avoided in patients with increased tracheobronchial secretions

• ***respiratory arrest*** can occur, usually as a result of ischaemic paralysis of the medullary respiratory centres due to profound ***hypotension***
• only a small number of such, if any, cases are due to paralysis of the phrenic nerves
• further, such cases are ***not*** due to ascent of local anaesthetic in the CSF with direct depression of the medullary chemoreceptor neurones

NB: concentrations of LA in cisternal CSF, with high spinal anaesthesia, are insufficient to cause pharmacological effects, levels are even lower in ventricular CSF

• the fundamental importance of cerebral perfusion is emphasised by the fact that ***respiratory depression*** nearly always precedes cardiac arrest
• furthermore, prompt restoration of CO immediately restores respiration, making nerve paralysis, peripheral or central, exceedingly unlikely
• therefore, ***spontaneous respiration*** during spinal anaesthesia is preferable, as,

1. assessment of ventilation gives an indication of medullary blood flow
2. IPPV and the increase in intrathoracic pressure may further decrease preload

• the incidence, magnitude and type of postoperative respiratory ***complications*** are the same after spinal anaesthesia and GA for the same procedure, when other factors are held constant
• other factors influencing postoperative complications include,

i. age, sex
ii. obesity, history of smoking
iii. site of the operation
iv. use of opioids for postoperative pain relief

• regional, including spinal anaesthesia, offers ***no advantage*** for the avoidance of respiratory complications after surgery
• no special advantage has been reported in the respiratory cripple, though, for perineal or urological procedures the use of a saddle block may confer some advantage (no data)

Gastrointestinal Function

• preganglionic sympathetic inhibitory fibres to the gut arise from $\mathbf{T_5}$-$\mathbf{L_1}$
• mid-thoracic anaesthesia is therefore associated with a contracted gut, due to the unopposed parasympathetic activity, providing excellent operating conditions
• nausea & vomiting may occur in ≤ 20% and is primarily due to ***gastric hyperperistalsis***
• ***atropine*** is effective in management of nausea associated with high spinal anaesthesia (T_5)

• hepatic blood flow is decreased with spinal anaesthesia, paralleling the reduction in MAP
• hepatic O_2 extraction is increased but hepatic function is largely unaffected
• postoperative hepatic dysfunction is similar following both spinal and GA, in both normal patients and those with hepatic disease
• as for patients with respiratory disease, regional techniques offer ***no proven*** advantages for patients with hepatic disease
• data from sheep show less reduction in hepatic blood flow, hepatic venous P_{O2}, and intrinsic drug clearance, cf. GA with halothane

Renal Function

• despite predictable decreases in renal blood flow, these are of little physiological importance
• lower concentrations of local anaesthetic are required for paralysis of bladder function
• studies vary as to whether they indicate a higher incidence of bladder catheterisation after centroneuraxis blockade
• clearly, the administration of large volumes of crystalloid/colloid in the elderly should be avoided

Neurological Complications

• residual neurological deficits are exceedingly rare with current techniques
• the acute onset of neurological problems may be due to,

1. injection of a local anaesthetic with ***histotoxic*** properties
2. injection of an ***excessive concentration*** of an anaesthetic which is not normally histotoxic
3. ***additives*** to the anaesthetic solution
4. ***traumatic*** damage during lumbar puncture

• local anaesthetics essentially devoid of histotoxic properties include,

i. lignocaine*
ii. tetracaine
iii. procaine

• Rigler *et al.* (A&A 1991) and Lambert *et al.* (A&A 1991) have described 4 cases of cauda equina syndrome following continuous spinal anaesthesia with ***hyperbaric lignocaine*** via ***microcatheters***
• these followed the use of large ***masses*** of drug, with the potential for pooling at the caudal end of the dural sac

• when complications result from the use of these agents, they are usually due to the method of injection, resulting in exposure to excessive concentrations
• complications are virtually never due to "allergic" responses to the agent
• traumatic damage characteristically involves a single nerve root
• the needle being directed laterally where the nerve root emerges through the dura, the nerve being tethered at this point is susceptible to damage
• such traumatic damage is rare in the cauda equina
• delayed onset neurological problems are usually the result of ***chronic arachnoiditis***
• this may occur due to the deposition of irritant materials during lumbar puncture
• spinal anaesthesia is usually contraindicated in patients with pre-existing spinal cord disease, though, there is no experimental evidence to support this recommendation
• probably wise as any deterioration may be ascribed to the anaesthetic

Summary

• with low spinal anaesthesia the potential for physiological trespass is far less than with a GA; the same does not apply for high spinal blockade
• with modern techniques both are safe, however, for mid or upper abdominal surgery equally satisfactory and safer operating conditions are provided by GA

Technique

- relies upon the 4 "P's",
    a. preparation
    b. position
    c. projection
    d. puncture

Preparation

i.	routine history, examination & investigations	
ii.	premedication	
iii.	IV access	+ volume preloading
iv.	baseline observations	
v.	needle selection	- "pencil-point" vs. cutting edge - size, ease of insertion vs. incidence of headache
vi.	solution selection	- duration of anaesthesia - speed of onset - extent of spread required
vii.	technique	- single shot - continuous catheter
viii.	aseptic technique	

Position

i. sitting
ii. lateral decubitus
iii. prone

Projection & Puncture

i.	introducer needle	
ii.	midline	
iii.	paramedian	
iv.	Taylor approach	- paramedian at L_5-S_1
v.	continuous catheter technique	

- ***Indications***

1. surgical procedures ***amenable*** to spinal anaesthesia
   - predominantly procedures below the umbilicus
   - upper abdominal anaesthesia to T_4 "as invasive" as general anaesthesia
2. ***circumscribed procedures***, where physiological trespass is minimal
   - rectal & perianal procedures
   - TURP
3. where an ***awake patient*** is advantageous
   i. procedure related - TURP → CCF, hypoosmolar syndrome
   - day case surgery
   ii. patient related - severe cerebrovascular disease
4. procedures where there is ***proven benefit***
   i. hip or knee joint replacement surgery - PE, blood loss, hospital stay
   ii. previous history of DVT / PE ? proven
5. ***obstetric*** anaesthesia
   i. awake mother
   ii. absence of neonatal drug effects
6. preferrable to ***avoid GA***
   i. full stomach
   ii. potential, or known difficult intubation
7. ***patient request***

- ***Contraindications - Absolute***

1. patient refusal
2. documented allergy to local anaesthetics
3. coagulation deficiency
4. severe / uncorrected hypovolaemia
5. skin/soft tissue infection at the intended injection site
6. meningeal infection
7. raised intracranial pressure
8. inability to remain still during the procedure

- ***Contraindications - Relative***

1. surgical procedure of indeterminate length
2. major surgical procedures above the umbilicus
3. hypovolaemia
4. surgical procedures with a high risk of major blood loss
5. afterload/preload dependent heart disease
   - valvular heart disease
   - HOCM
   - congenital heart disease
6. systemic sepsis
7. "minor" coagulation deficiency
   - mini-dose heparin
   - aspirin
   - chronic renal failure
   - PE with low platelets (> 100,000)
8. pre-existing neurological disease
9. chronic severe backache, deformities of the spinal column
10. inexperienced operator

Complications

1. physiological consequences of blockade
   i. cardiovascular
   ii. respiratory
   iii. other
2. failure of blockade
3. backache
4. post-dural puncture headache
5. neurological sequelae
   i. neurolytic - ***all*** agents are neurotoxic in high concentrations
      - 4 cases of cauda equina described with continuous SA technique
   ii. direct trauma - nerve roots
      - cord
   iii. compressive - intraspinal/epidural haematoma
   iv. infective - meningeal
      - epidural
   v. inflammatory - drugs, additives, wrong drug
   vi. multifactorial - anterior spinal artery & cauda equina syndromes
   vii. by association - exacerbation of pre-existing disease, etc.
6. allergy to local anaesthetics - rare & no cross sensitivity

Backache

- Lund found in a literature review ~ 2-25% incidence
- probable cause is flattening of the normal lumbar lordosis, 2° to relaxation of the paravertebral muscles and prolonged duration procedures
- Brown & Ellman found the incidence to be similar following both spinal and GA

Post-Dural Puncture Headache

- common complication of lumbar puncture → incidence is ≤ 1% with 25G needles
- occurs at least several hours post-puncture, usually on the first or second day
- bed rest ***does not*** prevent, merely postpones the onset of headache
- in obstetric patients, the incidence is greatly reduced with 26G versus 25G
- there is no effective gain by gauges smaller than 26G
- needles ≤ 22G should not be used
- in more severe cases diplopia and cranial nerve palsies have occurred, ? due to traction

Factors With an Increased Incidence of Headache			
Age	***younger***	>>	older patients
Gender	***female***	>	male
Pregnancy	***pregnant***	>>	nonpregnant
Needle size	***larger***	>>	smaller (≥ 25G)
Needle bevel	***transverse***	>	longitudinal
Needle type	***bevelled***	>	pencil point
No. of punctures	***multiple***	>	single
Procedure	***diagnostic***	>	anaesthesia

Factors Without an Increased Incidence of Headache
• Continuous spinal/catheter techniques
• Timing of ambulation

- ***Treatment***

1. ***conservative management***
   - i. bed rest - will ***not*** prevent PDPH and is no longer recommended
     - may increase the incidence of ***nausea***
     - delays the diagnosis of PDPH
     - it does have a role ***after*** the diagnosis of PDPH is made
   - ii. adequate fluid hydration
   - iii. simple analgesics
   - iv. abdominal binders & posture changes to increase venous return are poorly tolerated and generally ineffective
2. ***caffeine*** - may decrease the incidence and severity of PDPH
   - mechanism is in reducing vasodilatation, cf. migraine
3. ***autologous blood patch*** - severe headache or failed conservative management

- ***Epidural Blood Patch***

• first described by Gormley (1960) and has a success rate > 90-95%
• failure and performance of a second procedure has a similar success rate, ~ 95%
• volumes injected have ranged from 10 to 20 ml
• radionuclide studies with labelled red blood cells show that injection of 15 ml covers a mean distance of 9 segments
• the distribution is, however, asymmetrical, with ***cephelad*** spread being greater than caudad
• therefore, if the same segment cannot be used, the adjacent caudad space would be preferable

1. aseptic conditions
2. ~ 25 ml of blood is removed by venipuncture and placed immediately into the epidural space, preferably at the level of the puncture
3. ?? ~ 10 ml of the blood is sent for culture
4. the patient remains supine for 30-60 minutes

• if, due to multiple punctures, the site of the leak is uncertain, then the ***lowermost*** space should be used, due to the tendency to cephelad spread
• complications include,

1. backache ~ 35% but is usually mild and limited to ~ 48 hours
2. neckache ~ 1%
3. transient elevation of ***temperature*** (~ 5%) for 24-48 hours

NB: ***no cases*** of infection, arachnoiditis, or cauda equina syndrome have been reported

• epidural anaesthesia performed at a later date may be associated with a higher incidence of incomplete block or missed segments, though, there are no controlled studies to support this
• the use of prophylactic blood patch is controversial
• older studies showed that prophylactic or early ABP (< 24 hours) did not decrease the incidence

Neurological Sequelae

• Lund performed the major series of spinal complications, 582,190 cases, between 1948-1958

→ "no incidence of permanent motor paralysis (was) reported"

• cases have been reported, however, a cause-effect relationship has not been established
• spinal anaesthesia has been incriminated by "speculative aetiology by association"
• injuries may be categorised anatomically,

i. peripheral nerve
ii. cauda equina
iii. spinal cord / tract lesions
iv. intracranial

NB: determination of aetiology should be ***therapy oriented***, not fault motivated

• to this extent early neurological consultation should be sought

Comparison of Spinal & Epidural Techniques

• studies comparing the upper levels of sensory anaesthesia and sympathetic block have not been done as carefully with spinal anaesthesia
• however, most clinician have the impression that the onset of sympathectomy following spinal is much faster than that following epidural
• for this reason, cases where rapid onset of sympathectomy may be detrimental are probably better served by an ***incremental*** epidural technique
• the use of a catheter technique allows extension of the duration of surgery and continuation for postoperative pain relief
• epidural anaesthesia requires the administration of significantly larger quantities of agent, with the potential for,

1. systemic toxicity 2° inadvertent intravascular administration
2. systemic CVS effects due to therapeutic plasma levels
3. with inadvertent subarachnoid administration,
   i. risk of total spinal anaesthesia
   ii. risk of reactions to additive agents

• the potential benefit of avoidance of PDP headache is less obvious with the use of "pencil-point" and small gauge spinal needles, as the incidence approaches the accidental dural puncture rate with epidural needles, following which the incidence of headache is considerable (~ 70%)

EPIDURAL ANAESTHESIA

• adaptation of Tuohy's spinal needle for use with epidural blockade occurred in 1949
• early use was mainly by the caudal route
• lumbar epidural anaesthesia by continuous catheter became most popular in the 1950's for obstetric use
• during the 1960's LEA became the most widely used form of obstetric pain relief in Australia, NZ, Canada and the USA
• in the UK it was principally used for operative procedures and postoperative pain relief

NB: refer to anatomy notes for applied anatomy of epidural anaesthesia

Physiological Effects of Epidural Blockade

• excepting for sacral blockade by caudal anaesthesia, epidural blockade almost invariable results in some degree of sympathetic blockade
• the level of sympathectomy with epidural anaesthesia may be less than the sensory block, and less complete in terms of "quality"
• the most frequent uses of LEA can be divided into T_{10} and T_4 levels, only rarely will blockade to T_1 be required for thoracic surgery
• most, but not all of the accompanying effects are attributable to axonal blockade
• a significant difference between spinal & epidural techniques is that with the later, sufficient amounts of local anaesthetic are injected to produce high serum concentrations,

a. lignocaine 400 mg → 3-4 µg/ml
b. bupivacaine 150 mg → 1.0 µg/ml
c. lignocaine + adrenaline 400 mg → 2.5-3.0 µg/ml

NB: serum concentrations are more a function of ***total dose***, than either the ***volume*** or the ***concentration*** of solution injected

Systemic Effects of Absorbed Agents		
Receptor	β-agonism α-agonism	adrenaline adrenaline or phenylephrine
Smooth muscle	blood vessels heart other organs	adrenaline or local anaesthetic adrenaline or LA adrenaline or LA
Cardiac muscle		adrenaline or LA
Neural tissue	CNS CVS conduction	LA LA
Miscellaneous	NMJ	LA

Direct / Indirect Neural Blocking Effects		
Spinal nerves	*roots and trunks by axonal blockade	
sympathetic	efferent blockade	• peripheral vasoconstrictor T_1-L_2 • "adrenal" T_6-L_1 • "central" cardiac T_1-T_4
sensory	afferent blockade	• sensory blockade • blockade of visceral pain fibres • efferent neurohumoral response
motor	efferent blockade	• motor paralysis • reflex relaxation without paralysis
Spinal cord		
axons	• superficial sensory tracts - L, B, E • deep motor tracts blocked - etidocaine only i. dorsal horn modulation of pain transmission ii. possible "antalgesic" effect	
cell bodies	• selective blockade by opioids	
Parasympathetic activity 2° changes to sympathectomy		
£ ***T_5 sympathectomy***	• ↓ venous return ***may*** → ↑↑ vagal tone	
£ ***T_1 sympathectomy***	• → unopposed vagal tone	

Cardiovascular Effects of Epidural Blockade

• in contrast to spinal anaesthesia, the level of,

a. SNS blockade ~ the sensory level, or below

b. motor blockade ~ 4-5 spinal segments lower

NB: although the decreased level of SNS block should provide for greater CVS stability than with spinal anaesthesia, there are no ***controlled data*** to support this

• vascular absorption of LA may result in significant CVS changes following EA but not spinal anaesthesia

• there is a more gradual onset of sympathetic blockade following EA cf. spinal, which may provide a mechanism for initial responses which are less severe

• EA with ***bupivacaine*** (cf, L, C, E) also has a slower onset of sympathectomy and less tendency for the rapid development of hypotension

• animal data shows ***autoregulation*** at the level of the precapillary sphincters takes £ **30** ***mins*** following complete ablation of neural activity

Blockade Below T4

• results in peripheral sympathectomy in the lower limbs and pelvis
• if all splanchnic fibres (T_6-L_1) are blocked, then pooling of blood in the gut and abdominal viscera may also occur
• venular dilatation, cf. spinal anaesthesia, is the principal cause of the decreased venous return, and may be associated with an increase in ***vagal tone***
• in healthy, unpremedicated subjects, an 8 fold increase in lower limb skin blood flow is possible, with pooling of ≤ 1000 ml in the venous circuit
• Arndt *et al*. assessed splanchnic flow in healthy young volunteers,

a. 20 ml 2% plain lignocaine by LEA
b. sympathectomy to the lower thoracic segments
c. in 6 of 8 subjects splanchnic blood flow ***decreased*** by labelled rbc's
d. blood flow to the thorax and upper limbs showed a compensatory decreased

NB: ? possible that the 2 subjects with increase flow may have blocked all the splanchnic sympathetic fibres from T_6-L_1

• healthy subjects in the supine position compensate for the decrease in MAP with a reflex increase in sympathetic tone above the level of the block, mediated via the baroreceptors, by,

1. those segments which remain unblocked **T_1-T_5**
2. circulating catecholamines from the ***adrenal medulla***, due to any unblocked fibres from **T_6-L_1**

• major arterioles respond principally to ***neural stimuli***
• whereas the small arterioles and venules respond predominantly to circulating ***catecholamines***
• also, the ability of precapillary sphincters to achieve autoregulation within a short time of cessation of neural activity provides another means of compensation
• evidence that circulating catecholamines are important comes from the small decreases in HR & CO (~ -16%) which accompany blockade from C_5-T_4 with splanchnic sympathetics intact
• although quite large compensatory changes may be observed in unpremedicated patients, these tend not to be seen in premedicated patients
• the practice of preblock "rehydration" is capable of maintaining MAP close to preblock levels, providing the level of blockade is below T_4 and IVC obstruction is avoided
• blockade to T_5 is potentially more hazardous than that to T_{10} because,

1. a larger number of afferent fibres are blocked
2. blockade is "close" to the cardiac sympathetic outflow and any "overshoot" may produce changes equivalent to T_1 block
3. the afferent supply to the adrenal medulla is blocked

• the role of splanchnic blood flow is less clear
• coeliac plexus blockade may produce significant pooling & "splanchnicectomy faint", as the region receives ~ 25% of the CO

▪ ***Blockade Above T4 Total Sympathetic Blockade (T1-L4)***

• previously thought that control of chronotropy & inotropy resided in the vasomotor centres of the medulla
• changes of cardiac sympathetic activity ~ 20% can be achieved reflexly at the ***spinal cord*** level
• this can be overridden by vagal tone
• therefore, block from T_1-L_4 results in the additional blockade of,

1. segmental cardiac reflexes
2. vasomotor control of cardiac sympathetic outflow
3. sympathetic outflow to the head, neck and upper limbs

• studies by Bonica and McClean *et al*. have assessed blockade ***above*** $\mathbf{T_1}$ →

a. MAP and TPR - reduced by ~ 20%
b. CO - Bonica found little change or slight increase
- McClean found 15-20% decrease
c. CVP - markedly ***elevated*** (Bonica)
d. HR * maintained at ~ normal rate
? decrease in parasympathetic activity in proportion

NB: the elevation of CVP may represent failure of myocardial compensatory mechanisms in the face of diminished sympathetic and catecholamine drive

▪ ***Absorbed Local Anaesthetics***

• blood concentrations following CEA (3-5 µg/ml) are similar to those seen in treatment of arrhythmias, and are associated with excellent CVS stability, even in patients with severe myocardial disease
• studies in healthy patients show minimal CVS changes with concentrations ≤ 8 µg/ml
• studies of etidocaine and bupivacaine also show minimal CVS changes at expected blood levels
• however, rapid IV injection of either lignocaine or bupivacaine may cause brief reductions in contractility
• larger doses of bupivacaine may be associated with long-lasting myocardial depression and conduction disturbance, culminating in arrest
• arrhythmias are frequently preceded by ***bradycardia***, and this may be difficult to differentiate from high blockade and vagal dominance

• the systemic effects of absorbed ***adrenaline*** (~ 80-130 µg/ml) are predominantly b-***mimmetic***,

a. a moderate increase in HR
b. increased CO
c. decrease in TPR
d. decrease in MAP

• Bonica *et al.* investigated this by epidural administration of adrenaline only and observed similar effects, except that the changes were of a lesser magnitude and shorter lived

NB: Bromage has postulated that adrenaline containing solutions result in more profound ***sympathetic block***, as for the increase seen in motor blockade

• from a number of studies it appears that both,

i. systemic absorption of adrenaline, and

ii. enhanced sympathetic blockade

contribute to the changes seen with adrenaline containing solutions

■ ***Epidural Blockade & General Anaesthesia***

• Germann *et al.* (AIC 1979) assessed the effects of combined GA & EA,

a. in patients receiving GA first, EA resulted in ~ 22% decrease in MAP, and this was the only significant change

b. in the EA first group, MAP decreased ~ 20% from control, plus, induction of GA resulted in a decrease ~ 35% below the control value

c. HR (~ 60 bpm) and CO were not significantly altered
   - a "normal" HR may be considered inappropriately low in the light of a decrease in MAP and TPR

d. subsequent administration of ***atropine*** (0.6 mg) returned MAP to control values in both groups, with a HR ~ 110 bpm

e. head-down tilt resulted in a slight increase in SV, but no other significant haemodynamic change

f. RAP was not significantly altered at any stage during the study

g. arterial blood gases were unchanged, except for a decrease in P_{aO2} when EA was added to established GA

NB: these data showed no statistically significant difference in CVS changes with respect to the order of performance of a combined technique

• however, there are technical advantages to establishing EA in an awake patient
• this, plus several other studies support the combination of GA plus EA to the T_5 level in healthy patients
• all recommend the incremental administration of ***atropine*** to maintain a HR ≥ 90 bpm
• only the study of Germann showed a decrease in P_{aO2} with EA performed after GA, however an increase in FiO_2 is desirable whenever EA in combined with GA or IV sedation

Hypovolaemia & Epidural Blockade

• Bonica studied CVS changes in healthy volunteers, either normovolaemic or following withdrawal of ~ 13% of blood volume, with blockade to T_5 with and without adrenaline,

1. changes in normovolaemic patients were mild
2. in the presence of hypovolaemia, major reductions occurred in HR, MAP & CO
3. 5/7 of the plain lignocaine group required "vigorous" resuscitation, including the administration of adrenaline
4. CVS changes were less marked with the use of adrenaline containing solutions

NB: cardiac sympathetics were ***not*** blocked in these patients,
sudden, profound ***bradycardia*** 2° to reflex vagal overactivity following a marked decrease in venous return occurs only in awake humans, and is abolished by GA

• the greater effects seen with plain solutions may be due to,

a. (+) chronotropic effects of absorbed adrenaline protecting against vagal dominance
b. higher peak plasma lignocaine levels with plain solutions

Epidural Blockade & Venous Return

• obstruction to venous return should be avoided during EA whatever the cause
• epidural vein pressure will rise, owing to channelling of blood through the vertebral plexus and the azygous vein
• this may result in cephelad spread of local anaesthetic and decreases spinal cord perfusion,

1. the ***supine hypotensive syndrome*** of pregnancy
   - during contractions brachial artery pressures may be near normal 2° to the *Poseiro effect*, of combined aortic and caval compression
2. ascites
3. marked obesity
4. intra-abdominal masses - above the liver
   - below the liver
5. intestinal obstruction

- ***Reduction of Surgical Blood Loss***

• Keith studied EA versus GA for total hip replacement, avoiding arterial ***hypotension***, and found,

a. operative losses ~ 50% less with EA

b. no difference in postoperative losses

c. other studies have reported decreases of 30-40% with EA

NB: supports that EA reduces blood loss via mechanisms other than reduced MAP

i. absence of IPPV increases in venous pressure
ii. absence of sympathetic induced increases in venous pressure
iii. avoidance of reactive hyperaemia
iv. haemodilution

Function of the Hollow Viscera

- ***The Bladder***

• temporary atonia occurs 2° to blockade of $\mathbf{S_2}$-$\mathbf{S_4}$
• usually short-lived and causes no, or minimal increases in post-EA bladder dysfunction
• with continuous catheter techniques an indwelling catheter is required
• segmental thoracic EA usually spares the sacral segments
• relief of abdominal pain (T_5-L_1) may decrease reflex sympathetic tone (T_{12}-L_1) which increases bladder neck tone and predisposes to acute retention

- ***The GIT***

• denervation of the splanchnic sympathetic supply ($\mathbf{T_6}$-$\mathbf{L_1}$) results in a small contracted gut due to parasympathetic dominance
• studies of postoperative intestinal electrical activity show that intraoperative ± postoperative epidural blockade may be useful in preventing and/or treating ***adynamic ileus***
• this should not distract from other causes of adynamic ileus, ie. obstruction & peritonitis
• similarly, gastric emptying as measured by paracetamol absorption, is closer to control values after EA cf. the use of opioids for postoperative pain control
• there is ***no evidence*** to support the concerns regarding the viability of anastomoses performed on the contracted gut
• GA, reversal of muscular paralysis and opioids produce incoordinate intestinal peristalsis with high intraluminal pressures, and are more likely to result in breakdown of the suture line

- ***Thermoregulation, Shivering & MH***

• cutaneous vasodilatation may predispose to ***hypothermia*** if large areas are left uncovered
• the causes of shivering with EA may include,

1. a decrease in core temperature 2° to vasodilatation
2. systemic effects of local anaesthetics on the hypothalamic regulatory centres
3. differential inhibition of spinal cord afferent thermoregulatory fibres
   • loss of warm sensation before cold
4. a direct effect of cold solutions on thermosensitive areas within the spinal cord
   • such structures have been demonstrated in animals but not humans

NB: the best evidence supports (4),
injection of cold (20°C) solutions results in shivering in a large % of patients,
shivering is terminated in > 50% of these by injection of warm (41°C) solution

• injection of ***epidural pethidine*** (~ 50 mg) has been reported to abolish shivering in a high percentage of patients during EA for labour

• the use of local anaesthetics in ***malignant hyperthermia*** is safe
• femoral / lateral cutaneous nerve block is frequently used for muscle biopsy

Neuroendocrine Effects of Epidural Anaesthesia

• this area is difficult because,

1. measurement of "stress" responses is difficult
2. the clinical significance of their alteration is uncertain

• a sensory level to T_5 may or may not be associated with sympathetic blockade to this level, with continued sympathetic input to the adrenal medulla
• epidural anaesthesia ***does not*** block,

1. the visceral afferents from the upper abdominal viscera,
2. the release of hypothalamic hormones (ADH,..), or
3. the release of humoral trophic hormones (ACTH,..)

   which in turn may result in humoral release from target organs (eg. cortisol,..)

• whether the failure of EA to block vagal afferents is of clinical significance, or if it negates the favourable effects upon the adrenal medulla, are unknown
• a rough marker of benefit is the reduced ***hospital stay*** of patients having continuous EA for postoperative pain relief in upper abdominal operations
• also, there is a decreased incidence of ***DVT*** following hip replacement and prostatectomy

NB: however, a controlled study of upper abdominal surgery showed no difference between GA and EA, except for superior pain control in the CEA group

Adrenal Medulla

• studies with sensitive assays show that only high doses of volatile agents or opioids are sufficient to block the surgically induced increases in plasma catecholamines
• catecholamine levels are high in the postoperative period if opioids are used for pain relief
• that levels are decreased with CEA is supported by,

1. block of surgically induced catecholamine release in phaeochromcytoma
2. reduced catecholamine levels and myocardial MRO_2 after cardiac surgery
3. incidence of ST segment changes and arrhythmias in patients with severe IHD undergoing major upper abdominal surgery are ***reduced*** by the addition of EA to GA
4. prevents the reductions in uterine blood flow seen with catecholamine release during labour
5. maintenance of normal blood sugar responsiveness & glucose tolerance during surgery in patients with EA

Adrenal Cortex

• adrenal ***cortisol*** output may be increased 10x by surgical trauma
• epidural and spinal anaesthesia may ***delay*** the normal increase in cortisol secretion
• however, even in lower abdominal surgery, EA provides only a temporary effect, even if postoperative analgesia is via CEA
• Gordon *et al.* showed that with continuous block, ie. complete deafferentation continued into the postoperative period, the plasma cortisol levels did not rise
• upper abdominal and thoracic surgery show ***little difference*** between EA and GA, even with meticulous attention to maintenance of blockade
• this later effect is presumably 2° to vagal afferent input

Glucose Tolerance

• the blockade of reflex stimuli to the adrenal medulla and liver prevents the usual rise in BSL seen with surgery, providing the entire splanchnic outflow is blocked
• this may be achieved even in thoracic surgery and is extended into the postoperative period providing blockade is maintained
• the "inappropriately low" secretion of insulin during the hyperglycaemia under GA represents blockade of insulin release
• the abolition of hyperglycaemia under EA ***is not*** due to increase secretion of insulin
• this more likely results from the abolition of sympathetically mediated hepatic gluconeogenesis

1. suitable for management of "brittle" diabetics
   - unintentional hypotension, if combined with hypoglycaemia may have deleterious effects upon the CNS
   - insulin should not be given unless glucose is also administered
2. if insulin is administered for elevated BSL, then the decrease may be far greater than in the absence of EA

- ***Other Hormonal Effects***

1. reduced cAMP and adrenaline response to surgery
2. reduced renin, angiotensin, and aldosterone secretion
3. suppression of increases with surgery of,
   i. prolactin
   ii. GH
   iii. ACTH
4. suppression of the increases in plasma cortisol in labour
5. inhibition of intraoperative,
   i. lipolysis
   ii. increases in lactate & 3-(OH)-butyrate
      - ie. catecholamine induced anaerobic metabolism
6. reduction in perioperative negative nitrogen balance
   - urinary nitrogen losses are considerably reduced by postoperative CEA following lower abdominal surgery
7. thyroid hormone secretion ***is not affected*** by EA

Effects on Respiration

• aspect of epidural blockade which may influence pulmonary function include,

1. loss of sensory afferent input to the respiratory centres
2. motor efferent blockade to the intercostal and abdominal muscles (rarely phrenic)
3. sympathectomy induced changes in CO and pulmonary blood flow
4. vagal dominance in the presence of complete sympathetic blockade
5. effects of systemically absorbed adrenaline and local anaesthetics,
   i. respiratory centres in the medulla
   ii. chemoreceptors in the medulla and carotid bodies
   iii. myoneural junction
   iv. metabolism of succinylcholine in plasma

• the greater differential zone of motor blockade means that there is less effect on pulmonary ventilation for an equivalent level of sensory blockade, cf. spinal anaesthesia
• this may be offset in abdominal procedures, where a higher level of sensory anaesthesia must be achieved to provide adequate muscle relaxation
• the risk of phrenic palsy (C_{3-5}) is exceedingly low, as even with a sensory level to T_1, motor blockade only reaches T_{4-5}
• the principal exception is unintentional epidural/subarachnoid administration during interscalene brachial plexus blockade
• the most common cause of the rare instances of respiratory arrest is hypoperfusion of the brainstem
• patients with a sensory level extending to the chin may have normal respiration and be fully conscious, providing CVS homeostasis is maintained
• a sensory level of T_3 and a motor level of T_8 may be expected to result in essentially no change in VC and FRC, hence the patients ability to cough
• in patients with severe pain, adequate relief may actually improve respiratory exchange, P_{aO2}, FRC and VC

Extent of Motor Blockade

• factors determining the extent of motor blockade include,

1. local anaesthetic agent — - bupivacaine has the least, etidocaine the most
   - ***ropivacaine*** also has minimal motor blockade
2. dose of agent
3. repeated doses — - motor and sensory block "quality" increases
4. addition of adrenaline

Neural Effects of Epidural Anaesthesia

▪ *Mechanism of Action*

• injection of local anaesthetic into the epidural space acts by two means,

a. local anaesthetic diffuses across the dura into the ***subarachnoid space***, acting as for spinal anaesthesia,
   i. blockade of unmyelinated rootlets
   ii. peripheral long tracts & cell bodies

b. local anaesthetic diffuses into the ***paravertebral space*** through the intervertebral foramina, effectively producing multiple nerve root blockade

NB: the former is the more important site of action, except with caudal anaesthesia, when blockade of nerve roots is predominant

▪ *Other Effects*

• some local also reaches the brain by way of the dural cuffs and CSF, and by vascular absorption
• levels are generally below the minimum concentration for axonal blockade
• Bromage & Melzack have reported that patient often experience "phantom" limb pain during EA, presumably due to loss of afferent input from the body surface, joints and other structures
• at present there is ***no*** evidence of permanent changes in EMG recordings at appropriate concentrations used for epidural blockade
• intra-arterial injection of lignocaine produces a reduction in the evoked EMG, consistent with an effect on the motor nerve terminal
• therefore, high doses of lignocaine may have additive effects with the nondepolarising and depolarising muscle relaxants

Issues in Pregnancy *see Obstetric Notes*

1. supine hypotensive syndrome
2. placental drug transfer & early neonatal depression
3. ablation of maternal pain responses
   - maternal alkalosis
   - incoordinate uterine action
   - circulating catecholamines
4. interaction with maternally administered drugs *Mg^{++}
5. use of adrenaline in solutions
6. adequacy of the test dose
7. intercurrent diseases
   - preeclampsia
   - placenta praevia, abruption
8. prolongation of labour & instrumental delivery

PHARMACOLOGY OF EPIDURAL BLOCKADE

Absorption

• EA often involves the administration of maximal clinical doses of local anaesthetics
• as injection is remote from the site of action ***diffusion*** across membranes is important
• however, as the site of action is within the CSF, water solubility is of equal importance
• therefore, agents with their $\boldsymbol{pK_A}$ **~** ***pH*** of plasma tend to be most effective
• epidural fat acts as a "reservoir" for the fat soluble agents, ie. bupivacaine
• with repeat injections, epidural fat concentrations steadily rise, however blood concentrations remain stable
• this contrasts lignocaine, where repeat injections results in progressive accumulation in plasma
• the epidural venous plexus provides a rapid means of absorption into plasma
• direct injection into a vein may result in,

1. direct access to the brain via the basivertebral venous system
2. high peak drug concentrations in the myocardium

• the addition of ***adrenaline*** may greatly reduce systemic absorption, thereby enhancing the neural blockade and reducing the likelihood of systemic toxicity
• the time profile of absorption indicates peak levels at **~ 10-20** ***minutes***, therefore observation is required for up to 30 minutes
• ***acidic solutions***, containing antioxidants to stabilise adrenaline release local anaesthetic base less readily, therefore penetrate lipid barriers more slowly
• ***carbonated solutions*** release base readily and have greater penetrating ability
• ***hyaluronidase*** does ***not*** improve the onset time of epidural blockade and decreases the efficacy of motor and sensory blockade
• ***potassium*** additives reduce the sensory onset time, however are unacceptable for epidural administration due to depolarising phenomena & distressing muscle spasms

Disposition

▪ *Distribution*

• depends initially upon the "initial dilution volume" (V_{dI}), which reflects dilution of the dose in blood and the "buffering" effect of uptake by, and transit time through the lung
• bupivacaine & etidocaine have much higher values for V_{dI} than lignocaine or mepivacaine
• subsequent distribution of "unbound" drug depends upon the steady state distribution volume, $\mathbf{V_{dss}}$, which for bupivacaine is ~ 4x that for lignocaine (1028 vs 253 l)

- ***Metabolism & Excretion***

• metabolism of the ester agents, prilocaine & 2-chloroprocaine, by plasma cholinesterase produces short plasma half-lives and high therapeutic indexes
• metabolism of the amide agents by the liver is much slower, with ***hepatic extraction ratios*** of,

i. etidocaine ~ 0.74
ii. **lignocaine ~ 0.63**
iii. mepivacaine ~ 0.52
iv. **bupivacaine ~ 0.39**

NB: decreased hepatic blood flow following EA induced hypotension will further slow clearance, the effect being greatest for the low ER agents, ie. bupivacaine (???)

• ***clearance*** is the sum of distribution, metabolism and renal excretion, being,

i. etidocaine ~ 1.1 l/min
ii. **lignocaine ~ 0.95** l/min
iii. mepivacaine ~ 0.78 l/min
iv. **bupivacaine ~ 0.58** l/min

• however the values for V_{dl} are similar for all of these agents, thus the expected toxicity from lignocaine would be expected to be of a similar magnitude but shorter in duration
• clearance of ***mepivacaine*** is halved in neonates, whereas that of lignocaine is ~ the same as for adults, plus the foetal:maternal ratio is greater
• in aged patients the V_{dSS} for lignocaine is increased and the clearance decreased
• metabolism of lignocaine produces at least 1 active metabolite MEGX, which has a longer half-life and additive CNS toxicity
• GX has a much longer half-life, hence the potential for accumulation and may produce CNS toxicity

Drug		Onset		Duration	
				Plain	+ Adrenaline
2-chloroprocaine	3%	10-15	mins	45-60	60-90
lignocaine	2%	15	mins	80-120	120-180
bupivacaine	0.5%	20	mins	160-230	180-240

- ***Factors Altering Absorption & Disposition***

1. patient age & weight - ***no*** correlation with plasma levels
   * dose requirements reduced at extremes of age
2. acidosis
   - tissue acidosis would be expected to increase uptake in that tissue
   - with systemic acidosis the converse is true
   - however, by whatever means, toxicity is enhanced by hypoxia, hypercarbia & acidosis
3. hypothermia - may result in tissue acidosis
   - reduced hepatic biotransformation
4. heart disease - clearance of the amides is reduced by low CO states
5. hepatic disease - reduced intrinsic clearance
   * longer acting agents preferable, larger V_{dSS} acts as a buffer
6. renal disease - presence of acidosis & reduced plasma protein binding
   - again, longer acting agents preferable
7. lung disease - lung acts as an important "buffer"
   - presence of a large pulmonary shunt may increase toxicity

- ***Factors Associated with Administration of Epidural Blockade***

1. dosage
2. concentration - over the usual range causes no difference
   - high concentrations increase plasma levels ***disproportionately***
3. adrenaline - lower peak plasma levels
   - most pronounced with lignocaine
   - no advantage at concentrations > 1:200,000
4. speed of injection
   - slightly higher plasma levels with injection over 15 secs vs. 60 secs
   - detection of impending toxicity easier at slower rates
   - rapid injection may result in pain, or significant increases in CSF pressure
5. tachyphylaxis
   - increasing dose requirements for a given level of blockade increases the likelihood of toxicity
   - more likely to occur with short acting agents, which are also associated with less accumulation in epidural fat and higher plasma levels
   - therefore, for continuous techniques use long-acting agents

Site of Action

1. spinal nerves and paravertebral spaces
2. dorsal root ganglia, immediately adjacent to the "dural cuff" region
3. anterior and posterior nerve roots, within their dural root "sleeves" / "cuffs"
4. spinal nerve rootlets
5. peripheral tracts of the spinal cord
6. the brain

• ^{14}C-labelled lignocaine autoradiographic tissue assays performed on dogs suggest that the most important effect is rapid diffusion of agent into the CSF at the ***dural cuff region***
• peak concentrations of agent are seen in the CSF within 10-20 minutes, in concentrations sufficient to block nerve roots & rootlets
• the same work also showed the critical concentration for blockade exceeded at 30 minutes in the peripheral tracts of the cord and in the nerves in the paravertebral spaces
• sufficient concentrations are ***not*** achieved in the dorsal root ganglia, the central parts of the spinal cord, or in the brain
• factors supporting the peripheral cord effects include,

1. Urban showed that the ***regression*** of blockade follows a circumferential pattern, cf. the segmental pattern of onset, consistent with a persistent action on the cord after the initial effects on the spinal roots
2. Bromage has shown reflex changes in the lower limbs, consistent with an upper motor neuron disorder, during thoracic epidural sparing the lumbar segments

• differences in vascularity of the ventral and dorsal nerve roots ***have not*** been found to be a significant factor in uptake of anaesthetic, therefore is not an explanation of "differential" blockade with weaker solutions
• rather this differential blockade relates to the critical length of axons required for conduction blockade, supporting an action on the ***nerve roots***
• once in the CSF, penetration into the cord is governed by the concentration and the lipid solubility of the agent
• this is supported by data from epidural opioids, which have their predominant action in lamina II of the dorsal horn (substantia gelantinosa)

• the most likely mechanism for the rapid diffusion into the CSF is the anatomy of the dural cuff
• ***arachnoid granulations*** are plentiful along both the dorsal and ventral roots, and agents may only have to diffuse across a layer of arachnoid epithelial cells

Longitudinal Spread

• radiocontrast studies show greater cranial than caudal spread
• greater spread per unit volume is seen in older people, along with less "escape" into the paravertebral spaces

Factors Affecting Epidural Blockade

1. site of injection / nerve root size
2. age, height, and ? weight of the patient
3. posture
4. speed of injection
5. volume, concentration and dose of anaesthetic
6. choice of local anaesthetic
7. addition of adrenaline
8. carbonation
9. frequency and number of injections
10. needle or catheter injection

▪ *Injection Site / Nerve Root Size*

• blockade is most intense and most rapid at the site of injection
• subsequent spread depends upon whether injection is lumbar or thoracic,

1. lumbar epidural
   - cranial > caudal spread
   - delay in block of the $\mathbf{L_5}$-$\mathbf{S_1}$ segments
2. thoracic epidural
   - cranial = caudal spread
   - delay in block of the lower cervical & upper thoracic segments
   - controlled dosage in the thoracic region allows sparing of the lumbar segments, with retention of bladder control and sympathetic outflow to the lower limbs

▪ *Weight, Age & Height*

• there is ***no correlation*** between the dose and ***weight*** in adults
• Bromage found a correlation with age in > 2000 patients between the ages of 4 and 102 years
• there is an increased dose requirement between the ages of 4-18 years, gradually decreasing from 19-100 years
• increases in longitudinal spread (and duration) of analgesia with increasing age have been attributed to reduced lateral leakage of solution
• this is supported by,

1. studies of epidural pressure, which is higher following injection in older patients
2. epidurograms, showing more extensive spread in the elderly
3. external activity from ^{131}I-radiolabelled lignocaine

• other studies have shown that this may be an oversimplification

• Bromage found a weak correlation between height and dose-requirement
• the resulting average dose in adults 20-40 years for lignocaine 2% ~ 1.0-1.6 ml/segment,

a. doses should be reduced ~ 50% in the aged, or with severe arteriosclerosis
b. reductions ~ 30% in pregnancy

Posture

• *sitting* versus *lateral* position results in no clinically significant difference in cephelad spread
• in obese patients, a lower level of blockade is achieved in the sitting position
• the lateral position favours spread to the dependent side in pregnant & nonpregnant patients, however the differences are small
• in surgical patients, Seow *et al.* found the onset & duration of sensory & motor block was greater on the dependent side
• these differences were great enough to recommend dependent position for unilateral procedures

Speed of Injection

• increasing the speed of injection has ***no effect*** on bulk flow of solutions in the epidural space
• spread of analgesia is only minimally affected
• however, this may cause increases in CSF pressure and decreases in spinal cord perfusion pressure
• headache is more commonly reported with rapid injection
• all texts recommend ***slow***, ***incremental*** injection

Volume, Concentration & Dose of Agent

• studies by Bromage showed that the ***dose*** of drug (concentration x volume) determined the level of anaesthesia, between the concentrations of lignocaine 2%-5% and tetracaine 0.2%-0.5%
• the dose requirement for lignocaine decreased from ~ 30 mg/segment to ~ 20 mg/segment when the concentration was decreased from 2% to 1%
• with respect to motor blockade, dose is less important with dilute solutions
• motor blockade is minimal irrespective of volume with ≤ 1% lignocaine, unless repeated injections are given
• the intensity of sensory and motor blockade increases with each successive injection
• this phenomenon is important for dilute solutions of bupivacaine used in labour
• increasing ***dosage*** results in a linear increase in the ***degree & duration*** of sensory block
• increasing the ***concentration*** reduces the ***time of onset*** and increases ***motor blockade***

▪ ***Choice of Local Anaesthetic***

a.	surgical anaesthesia	- lignocaine 2% (+A) - bupivacaine 0.5%	
b.	postoperative pain	- bupivacaine 0.25%-0.5%	
c.	obstetric analgesia	- bupivacaine 0.125%-0.375% ± fentanyl - lignocaine 1.0%-1.5% for "missed segments"	
d.	operative delivery	- lignocaine 2% (+A)	
e.	diagnostic & therapeutic	- lignocaine 0.5% - lignocaine 1.0% - lignocaine 2% (+A) - bupivacaine 0.25%	sympathetic sensory motor prolonged sensory

• ***differential blockade***, or "sensory-motor dissociation" refers to the capabilities of the different agents to produce blockade of either fibre type
• different rates of development of motor or sensory block appear to be important
• also different penetration into the spinal cord appears to play a part (especially etidocaine)
• as the ***lipid solubility*** increases within the amino-ester agents, the rate of development of motor (A-fibre) blockade increases
• at equipotent concentrations & doses, A-fibres were ***more sensitive*** than pain (C-fibres)
• however, the ***rate of onset*** for motor blockade varies widely with lipid solubility, so that agents with low lipid solubility, such as prilocaine, result in slow onset of motor blockade
• in contrast, amethocaine (highly lipophilic) blocks A-fibres before C-fibres
• another factor in the rate of onset is ***frequency dependent blockade***

• due to these differences some have advocated the use of ***mixtures*** of agents to provide rapid onset and prolonged duration of epidural block
• to date, no study has demonstrated a clear advantage of any mixture over a sole agent
• Seow *et al.* in a double-blind randomised trial of various concentrations of lignocaine with bupivacaine, found,

1. no significant differences in the onset of blockade with any solution
2. faster onset to complete motor block with a 50:50 mixture
3. little advantage for any mixture if a catheter technique was being used
4. only for a single-shot technique did the 50:50 mixture have some merit, in more profound motor block and marginally prolonged duration cf. lignocaine alone, however, these gains were relatively small

• theoretically, reduction of the total dose of bupivacaine may reduce the potential for cardiotoxicity, however there are no firm data to support this approach

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NB: more important is the use of the appropriate single agent, in the appropriate dose, established by ***slow incremental injection***

▪ ***Addition of Adrenaline***

• generally agreed that this reduces vascular absorption to a variable extent and enhances the efficacy of epidural blockade
• however, enhancement is much less with the longer-acting agents such as bupivacaine
• addition of adrenaline 1:200,000 will enhance the intensity of motor blockade, quality of sensory blockade and duration of blockade, at least for lignocaine & prilocaine
• the combination of adrenaline & preservatives in premixed solutions may lower tissue pH to < 7 for up to 90 minutes
• theoretically this may reduce the release of local anaesthetic base, however, no delay in the onset of blockade is observed clinically
• another effect is via dorsal horn a-***receptors***, clonidine being as effective as adrenaline in prolonging the duration of subarachnoid tetracaine
• as clonidine is ***not*** a vasoconstrictor, it would appear that at least a part of the action of adrenaline is via dorsal horn modulation sensory input

■ ***Carbon Dioxide Salts***

• *in vitro* data show an ~ 10x increase in uptake of lignocaine into neuronal tissue with the CO_2 base
• double-blind clinical studies have shown an improvement in the "quality" of blockade, but no alteration of ***duration*** or ***onset***
• peak plasma concentrations are also slightly higher with CO_2 containing solutions

■ ***Number & Frequency of Injections***

• augmentation or diminution of blockade after repeated epidural injection depends upon,

1. the local anaesthetic used
2. the number of injections
3. the timing between injections

• a single "repeat" dose of ~ 20% of the original blocking dose given at ~ 20 minutes is said to consolidate the block, within the level of block already established
• this may "fill-in" missed segments, but the block is unlikely to be extended
• a "refill" dose given > 10 minutes outside the regression of analgesia (interanalgesic interval) may result in tachyphylaxis
• tachyphylaxis increases with the length of the ***interanalgesic interval*** up to 60 minutes, after which it remains constant at ~ 30-40% reduction in effect
• this is most clearly demonstrated with "continuous" techniques, using the short acting agents
• because the interanalgesic interval is so important, tachyphylaxis is far less common with the longer-acting agents such as bupivacaine
• Bromage found that tachyphylaxis increased with the number of injections given, further supporting the use of long-acting agents
• further, these agents have less tendency to accumulate in blood, whereas the short-acting agents result in cumulative blood levels

- ***Catheter / Needle Injection***

• with epidural catheter techniques there is undoubtedly a higher incidence of,

1. outright failure ~ 10% versus 1.2% (Cousins & Mazze)
   - inability to thread (5%)
   - blood in catheter (2.5%)
   - through an intervertebral foramen (1.3%)
2. complications

• the overall "irretrievable" failure rate with the use of catheters should be ~ 1%
• catheters inserted in the thoracic region tend to travel straight up without deviation, thus the failure rate is much lower

Problems with Epidural Blockade

1. level **too low**, or **inadequate block** of lower segments, **"missed" segments**
   - administer ~ 1/2 the original dose 30 minutes after injection
   - administer repeat dose with the unblocked segment dependent
   - use an adrenaline containing solution for top-up
2. **level too high, but inadequate sacral analgesia**
   - supplement blockade with a single-shot caudal
3. **"visceral" pain** during abdominal surgery
   - peritoneal manipulation may require blockade to $T_{5\text{-}6}$
4. **inability to thread the catheter**
   - false loss-of resistance prior to the ligamentum flavum
   - position of needle to cephelad in the interlaminar space
   - needle "straddling" the anterior aspect of the ligamentum flavum
   - needle "tenting" the dura mater
5. **dural puncture**
   - convert to a spinal technique
   - reinsertion at another (cephelad) interspace
   - sequential injection via the catheter only, and an adequate test-dose is essential
6. **subdural insertion of the catheter**
   - occurs frequently in myelography & spinal anaesthesia, incidence ~ 1%
   - spread is patchy, asymmetrical & may be extensive
7. **subarachnoid migration of the catheter**
8. **intravascular migration of the catheter**
   - aspirate prior to each top-up injection
   - inject incrementally at each top-up, observing the patient

9. **intravascular insertion of the catheter**
   - greater hazard in pregnancy, or in the presence of vena cava obstruction, and with insertion away from the midline
   - injection of a small amount of saline & withdrawal of the catheter 1-2 cm usually allows retrieval
   - best R_X is prevention,

   i. use a test dose through the needle, preferably with adrenaline

   ii. use blunt ended catheters without stylets

   iii. insert the catheter for only 3-4 cm

10. **tachyphylaxis**
    - use long-acting agents for continuous procedures
    - top-up ***before*** analgesia wears-off, or use a continuous infusion

Low-Dose Heparin

• international multicentre study for DVT reported,

1. only 2 patients (n=2045) on heparin had fatal PTE (0.09%)
2. incidence of DVT ~ 7.7% in this group by ^{131}I-fibrinogen scanning
3. 16 controls (n=2076) had fatal PTE (0.7%)
4. incidence of DVT ~ 24%
5. the incidence of deaths from haemorrhage was the same in both groups

• however, the major criticism of this study was no stratification into ***surgery type*** and increased risks with some procedures,

a. hip replacement

b. prostatectomy

c. thoracotomy

• also, they failed to address the wide variations in plasma heparin activity from low-dose therapy
• more objective studies have assessed different risk groups and stratified the risk-benefit equation for heparin
• similarly, if heparin is of only minimal or low benefit, and epidural insertion preferable, then the former may be forgone
• in groups where heparin is detrimental, such as prostatectomy & joint surgery, then epidural insertion may offer a more effective means of reduction in the incidence of DVT
• there is no data to confirm that patients taking antiplatelet agents are subject to a greater risk of injury secondary to epidural haematoma

Catheter Management

1. check insertion site daily & withdraw at the first signs of infection
2. avoid neural damage by withdrawal at the first signs of pain or paraesthesiae with insertion or reinjection
3. do not reuse multidose vials $\rightarrow$ preservative free, single-use solutions
4. do not aspirate solutions through rubber bungs
5. careful attachment of the syringe to the filter port, replacing either if directly contaminated
6. micropore filters reduce catheter contamination (in 1 study only) and reduce injection of particulate matter
7. Bromage advocates replacement of the catheter every 72 hours, due to the tendency to blockage by fibrosis around the catheter
   - however, if functioning OK may be left for up to 1 week
8. long-term catheters should be inserted subcutaneously under operative sterile conditions
9. intermediate duration catheters may be offered some protection by subcutaneous tunnelling (no supporting data)
10. catheters should be removed gently & checked for completeness
    - if resistance is encountered then flexion of the spine may help
    - large lengths of catheter should not be inserted due to the small risk of knotting

Indications

- ***General***

1. obstetric anaesthesia *see below
2. epidural anaesthesia alone
   → indications for spinal anaesthesia, plus
   i. where the ***duration*** of the procedure is extended / unpredictable
   ii. where ***extension of pain relief*** into the postoperative period is desirable
   iii. where the abrupt ***onset*** of sympathectomy is undesirable / contraindicated
   iv. young patients where the risk of ***PDP headache*** is high
3. combined epidural & general anaesthesia
   → indications for epidural anaesthesia, plus
   i. major and upper abdominal / thoracic procedures
   ii. prolonged procedures
   iii. procedures requiring "uncomfortable" positioning
   iv. patient request - ie. epidural but asleep

- ***Obstetric***

1. ***maternal*** *minimise stress response
   i. pain relief
   ii. pre-ecplamsia
   iii. cardiorespiratory disease
   iv. other diseases requiring minimal stress
      - diabetes
      - cerebrovascular disease
2. ***foetal*** *high chance of ***instrumental delivery***
   i. multiple foetuses
   ii. large foetus
   iii. malpresentation
   iv. premature foetus
   v. deformed/dead foetus
3. ***uterine*** - normalisation of abnormal physiology
   i. uterine hypertonicity / incoordinate action
   ii. cervical dystocia
   iii. placental insufficiency
   iv. ?? trial of scar

Complications

1. ***allergy*** to local anaesthetics or solution additives
2. ***systemic*** toxicity * CVS & CNS
   - i. absolute overdose
   - ii. accidental intravascular injection
3. ***local*** toxicity
   - i. nerves - ***all*** agents are neurotoxic in high concentrations
     * 4 cases of cauda equina described with continuous SA technique
   - ii. injection of the "wrong" drug, or a contaminated drug
4. ***needle*** related problems
   - i. venous puncture
   - ii. backache
   - iii. dural puncture - total spinal blockade
     - post-dural puncture headache
   - iv. subdural placement
5. ***catheter*** related problems
   - i. venous puncture
   - ii. inability to inject *fibrosis is marked at 2-3 days
   - iii. accidental displacement
   - iv. subdural / subarachnoid migration
   - v. cutaneous / meningeal infection
6. ***neurological*** sequelae
   - i. direct trauma - nerve roots
     - cord
   - ii. compressive - haematoma
     - abscess
   - iii. infective - meningitis
     - epidural
   - iv. inflammatory - drugs, additives, wrong drug
     - adhesive arachnoiditis
   - v. multifactorial - anterior spinal artery
     - cauda equina syndromes
   - vi. broken catheter - not a problem in the absence of infection
   - vii. "by association" - exacerbation of pre-existing disease, etc.
7. ***physiological*** sequelae
   - i. cardiovascular - hypotension, tachycardia or bradycardia
     - reduction in preload & afterload
   - ii. respiratory - abdominal paralysis & decreased cough, PEFR
   - iii. other - bladder dysfunction

- ***Post-Dural Puncture Headache***

• incidence is ~ 70-80% with inadvertent puncture with a 16-18G needle
• Cousins states that routine prophylaxis is advisable,

a. supine posture
b. IV & oral hydration + caffeine containing beverages
c. systemic analgesics
d. leave the catheter in situ & infuse 1500 ml of saline over 24 hours

• other authors would argue with the benefit of these manoeuvres
• epidural blood patch should be performed at > 24 hours

- ***Backache***

• supposedly greater with larger epidural needles, cf. spinal needles but ?? no supporting data
• in obstetric patients the incidence of backache is the same with or without epidural

- ***Bladder Dysfunction***

• occurs with blockade of the segments S_{2-5}
• block of these segments is often not required for postoperative pain relief
• careful management may avoid catheterisation postoperatively & during labour

- ***Major Neurological Sequelae***

• with the exception of the 2-chloroprocaine associated ***adhesive arachnoiditis***, epidural anaesthesia ***has not*** been associated with neurologic injury more frequently than other anaesthetic techniques, regional or general
• Usubaiga (1975) in a world-wide retrospective review of 780,000 cases, involving all age groups, including surgical and obstetric patients, found an incidence of **1:11,000**
• Kane (1981) reviewed the literature and found a range of incidence from 1:5000 to no complications
• Scott & Hibbard (1990) found 1 case in 505,000 obstetric epidurals
• however, in none of these cases was the neurological deficit ***proven*** to be related to insertion of an epidural, nor were other factors excluded

NB: Bromage reports over 40,000 epidural blocks with ***no incidence*** of neurological complication

■ ***Major Neurological Sequelae***

• possible ***contributing factors*** in patients receiving epidural anaesthesia

1. ***direct trauma*** to nerve roots or spinal cord
2. ***compression*** of nerve roots or spinal cord
   - i. epidural haematoma
   - ii. epidural abscess
   - iii. cephalopelvic disproportion - spinal cord feeder vessels
3. ***neurotoxicity***
   - i. low pH & added antioxidants - 2-chloroprocaine
   - ii. neurotoxic additives - ethanol, benzyl alcohol
     - chlorocresol
     - methyl paraben
   - iii. wrong drug
4. spinal cord ***ischaemia***
5. anterior spinal artery ***thrombosis or spasm***
   - i. trauma by needle
   - ii. spasm ? by adrenaline or other factors
   - iii. hypotension & pre-existing vascular disease
   - iv. hypotension & large injectate volumes

• factors ***unrelated to epidural insertion*** which may contribute,

1. <u>anatomical abnormalities</u>
   - high take-off of radicularis magna (15%) & ligation of feeding vessels (1:20,000)
2. <u>undiagnosed neurological disease</u>
   - i. von Recklinghausen's disease ~ 1:3,000
   - ii. AV malformations ~ 1:15,000
   - iii. vertebral angiomata ~ 1:4-6,000
   - iv. atherosclerotic "spinal stroke" ~ 1:20,000
   - v. prolapsed intervertebral disc ~ 1:6,000
   - vi. spinal metastases ~ 5% of all cancer patients
   - vii. primary spinal tumour ? unknown incidence
3. <u>damage to the neuraxis during surgery</u>
   - i. compression of the pelvic nerves
     - ***"maternal obstetric paralysis"*** ~ 1:2,500-6,400
   - ii. ligation / compression of spinal nerves during aortic surgery
   - iii. compression of peripheral nerves by retraction / packing during abdominal or pelvic surgery
   - iv. stretching of peripheral nerves by abnormal posturing

Epidural Haematoma

• needle or catheter trauma may cause bleeding but this usually stops
• haematoma & neurological symptoms are rare in the face of normal coagulation

> ***NB:*** > 100 cases of ***spontaneous*** epidural haematoma have been reported in the presence of ***anticoagulation***, unassociated with epidural blockade

• CEA has been extensively used for lower limb vascular surgery, with heparinisation during and after surgery
• the series of Rao & El-Etr and Odoom had > 4000 patients with ***no incidence*** of haematoma
• they inserted the catheter the night before surgery and postponed cases where there was any vascular breach
• they also allowed the block to wear-off intermittently to assess lower limb function
• with symptoms / signs anticoagulation should be ceased and CT performed immediately, as for good recovery decompression within ***12 hours*** from the onset of symptoms is required

Epidural Abscess

• in a series of 39 cases Baker *et al.* found 38 associated with ***endogenous infection***
• important ***diagnostic features*** were,

1. severe back pain
2. local back tenderness
3. fever, leukocytosis
4. abnormal myelogram or CT/MRI

• the occurrence in association with ***systemic infection*** supports its relative contraindication
• as for haematoma, early investigation and decompression are required if recovery is to be satisfactory
• *Staphylococcus aureus* is the most common pathogen, and therapy should cover this prior to sensitivities, ie. Penicillin & Flucloxacillin
• the majority of these have followed continuous caudal techniques prior to the emphasis on sterile procedure
• to date, no case has been reported in association with epidural steroids, however theoretical risks are present and meticulous technique is required

Anterior Spinal Artery Syndrome

• the most likely causes are,

1. direct trauma
2. reduced perfusion pressure / venous congestion

• the contribution of the small doses of adrenaline (1:200,000) is doubtful, except possibly in patients with severe atherosclerosis in association with hypotension
• studies of spinal cord blood flow show no significant changes with adrenaline containing solutions
• the syndrome does occur in association with ***pregnancy***, possibly due to,

1. vascular spasm in preeclampsia
2. hypercoagulability of blood
3. prolapsed discs due to the exaggerated lordosis

• this syndrome may occur with ***hypotension*** unassociated with epidural blockade
• angiomas of the vertebral bodies and spinal cord are relatively common and may compress the cord, especially if intraspinal pressure increases, as in labour
• CSF should be obtained to exclude infection, subarachnoid haemorrhage, demyelinating disease and carcinomatous meningitis
• CSF protein will invariably be high in spinal cord ischaemia

Arachnoiditis & Transverse Myelitis

• "seems likely that the reported cases of adhesive arachnoiditis after epidural blockade are due to chemical contamination", the classical example being 2-chloroprocaine
• however, the features of arachnoiditis may be produced by infection trauma or haemorrhage
• partial or complete lesions in the cauda equina result in loss of bladder function, incontinence of faeces, and sacral anaesthesia
• these have occurred rarely following epidural blockade but are more likely to occur following,

1. ligation of the nutrient iliac vessels supplying the distal cord
2. compression of the sacral nerve roots during pelvic surgery

• two recent reports (Schell *et al.* 1991 & Rigler *et al.* 1991) were in association with ***spinal catheters*** and hyperbaric bupivacaine

Differential Diagnosis

• local anaesthetics, in clinically used concentrations, ***do not*** cause neural damage or meningeal irritation; a properly placed epidural needle or catheter with no evidence of contact with nerve roots during insertion does not damage spinal nerves or the spinal cord unless gross infection or haematoma results
• "associated but unrelated" cases of spastic paraplegia may occur following childbirth in patients receiving epidural blockade
• there are 5 reported cases in the absence of epidural insertion supporting this assertion
• all 5 of these had features of anterior spinal artery involvement

Peripheral Nerve Lesions

• are the ***most common*** neurological sequelae, and require distinction from central lesions
• common sites are,

1. the lumbosacral trunk - L_{4-5}
   - compression on the ala of the sacrum during delivery
   - resultant footdrop and weakness, and anaesthesia
2. sacral nerves
   - during delivery or pelvic surgery
3. femoral nerve - L_{2-4}
   - during pelvic surgery
4. lateral femoral cutaneous nerve - L_{2-3}
   - commonly damaged in lithotomy
   - direct pressure or retraction close to the inguinal ligament
5. lateral popliteal nerve - L_4-S_2
   - pressure over the head of the fibula

NB: patients with preexisting neurological compromise, such as diabetic neuropathy, are at greater risk

Test Doses

• Moore & Batra 1981 described the use of a test dose containing 15 µg of adrenaline (3 ml of 1:200,000)
• monitoring of HR and BP should be maintained for 5 minutes, preferably with an ECG
• intravascular injection should be readily recognised by a rise in ***HR ~ 20 bpm***
• usually occurs within 40 seconds and lasts for < 1 minute, with the following exceptions,

1.	β-blocked patients	- no HR rise - show an earlier rise in systolic BP, easily missed
2.	pregnant patients	- increased false positive/negative rate - potential adverse effects on uterine tone
3.	advanced age	- reduced responsiveness to catecholamines
4.	general anaesthesia	- same

• most controversy surrounds the use of adrenaline in obstetrics
• intravascular injection may decrease uterine blood flow and jeopardise the foetus
• however, there is ***no data*** to support this premise
• patients on β-blockers will not display a HR rise, their rate may actually decrease with decreasing pressure

NB: there is ***no*** failsafe way of determining intravascular placement of the catheter, therefore,

1. prior to administration of the main dose, ***aspiration*** should be repeated
2. administration of the main dose should be done slowly and ***fractionated***
3. the patient should be ***observed closely*** for signs of CNS toxicity