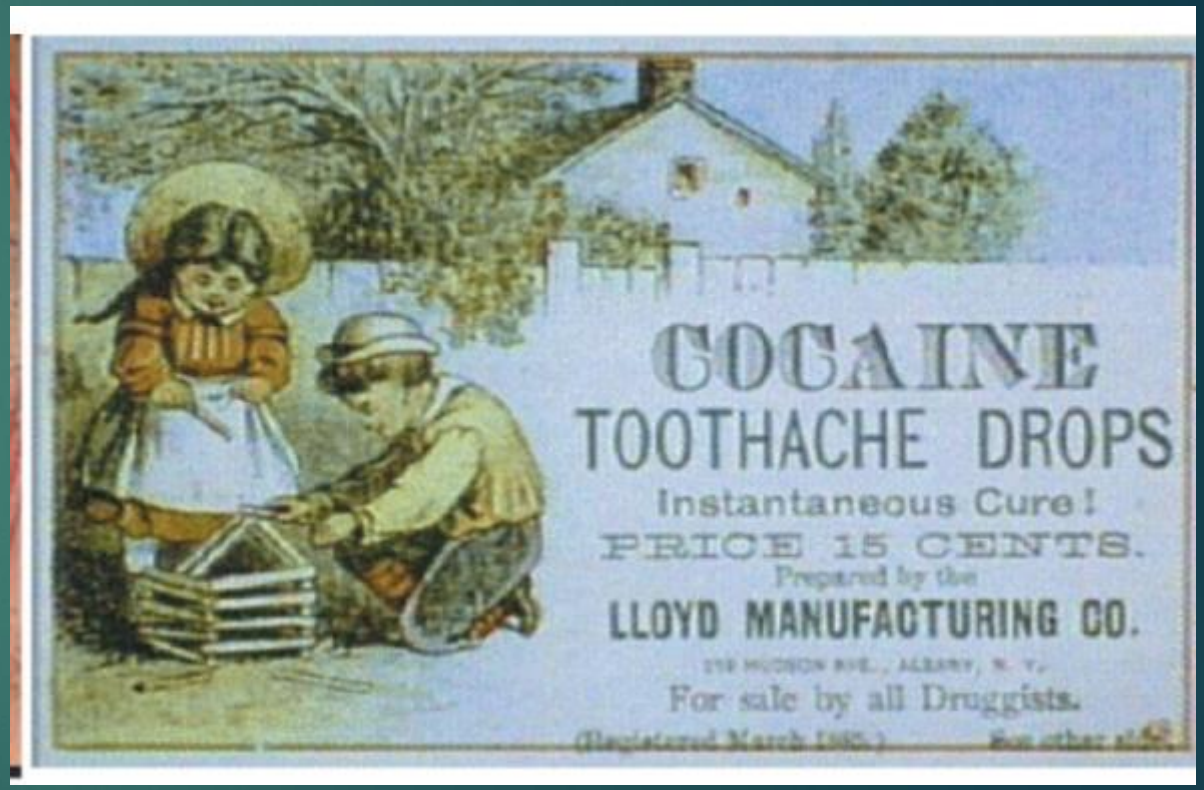
Local Anaesthetic Pharmacology: Basic Clinical Guide and Good Life Advice (For Surgical Registrars)



WARWICK CLARK
ANAESTHETIST

POWH/RHW/NBH

MARCH 2021

Pharmacology + Anaesthetic talk = Boredom and Useless… Why this ?

More normal topics to discuss this week might include…

- Sport
- COVID - 19
- Climate change
- Racial politics in America…

Turns out pharmacology and chemistry is useful …

Minneapolis Police Officer Thomas Lane points his gun at George Floyd in a body camera video.

Talk today useful : day and night…

Pharmacology and therapeutics

This will be a consideration of major therapeutic areas and major drug groups. The approach is to use basic pharmacological principles of pharmacodynamics and pharmacokinetics, and present much of the information as a mini pharmacopoeia.

The pharmacodmamics includes the mechanism of action of a drug, particularly where it may be important in understanding its use and/or its side-effects, whereas the pharmacokinetics include factors such as bioavailability (particularly to emphasise difference in routes of administration), plasma protein finding, clearance (metabolism if relevant) etc. The "take-home" message is to demonstrate the reason for dosage and dosing schedules, the effect of disease states on drugs, the effect of the drug on the patient, and potential clinically relevant drug interactions.

Drugs will be covered within disease topics, not as isolated entities.

Topics to be addressed:

Gastrointestinal tract

- antiulcer therapy (for example, H2 antagonists)
- antidiarrhoel, antiemetics, laxatives.

Central Nervous System

- opiates including palliative care
- minor and major tranquillisers
- anticonvulsants
- anaesthetics
- muscle relaxants
- local anaesthetics
- alcohol, tobacco
- chronic withdrawal and addiction.

Scenario 1

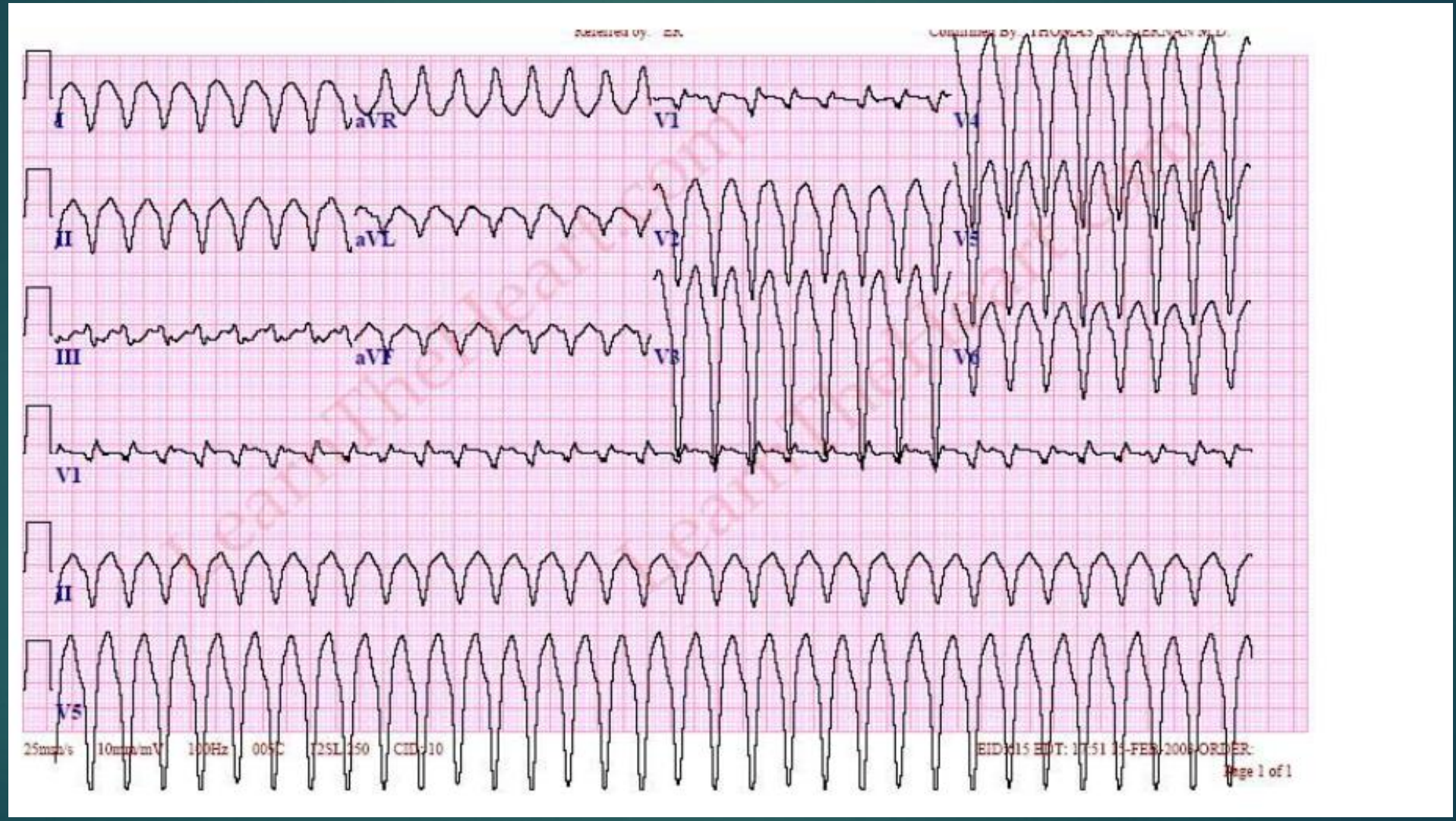
- You live in the Eastern Suburbs in flash pad…
- Your land lord puts up the rent… its going to be a struggle to pay… (but you love your view)
- Do you:
- A. Break the lease, move to Marrickville, become a hipster and save on rent? You only need 2nd hand clothes, some records and a bowl of pho to live on…
- B. Sell out? Become a materialist and narcissistic Eastern Suburbs tragic.?

On the way home you see a poster of the Kardashians… an idea forms…

1st Clinical Scenario

- Junior surgical registrar is struggling to get onto the training scheme and takes on some additional work in an unaccredited assisting year… at Dr Dubiovski's Bondi Junction Cosmetic Clinic.
- Sedation only BAM as no proper anaesthetic machine.
- 1st patient is 40 year old women with oxycontin 80mg bd for CBP.
- Ongoing wriggling due to opioid resistance despite anaesthetist "sedation"
- High volume LA infiltration
- How much LA can be given?
- You suddenly note some seizure like activity

You look up at the ECG

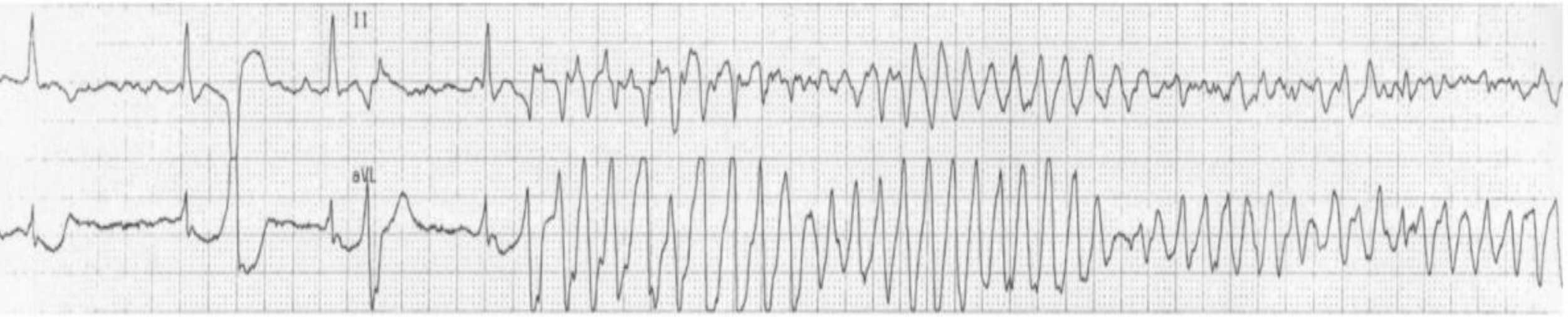


Things deteriorate…

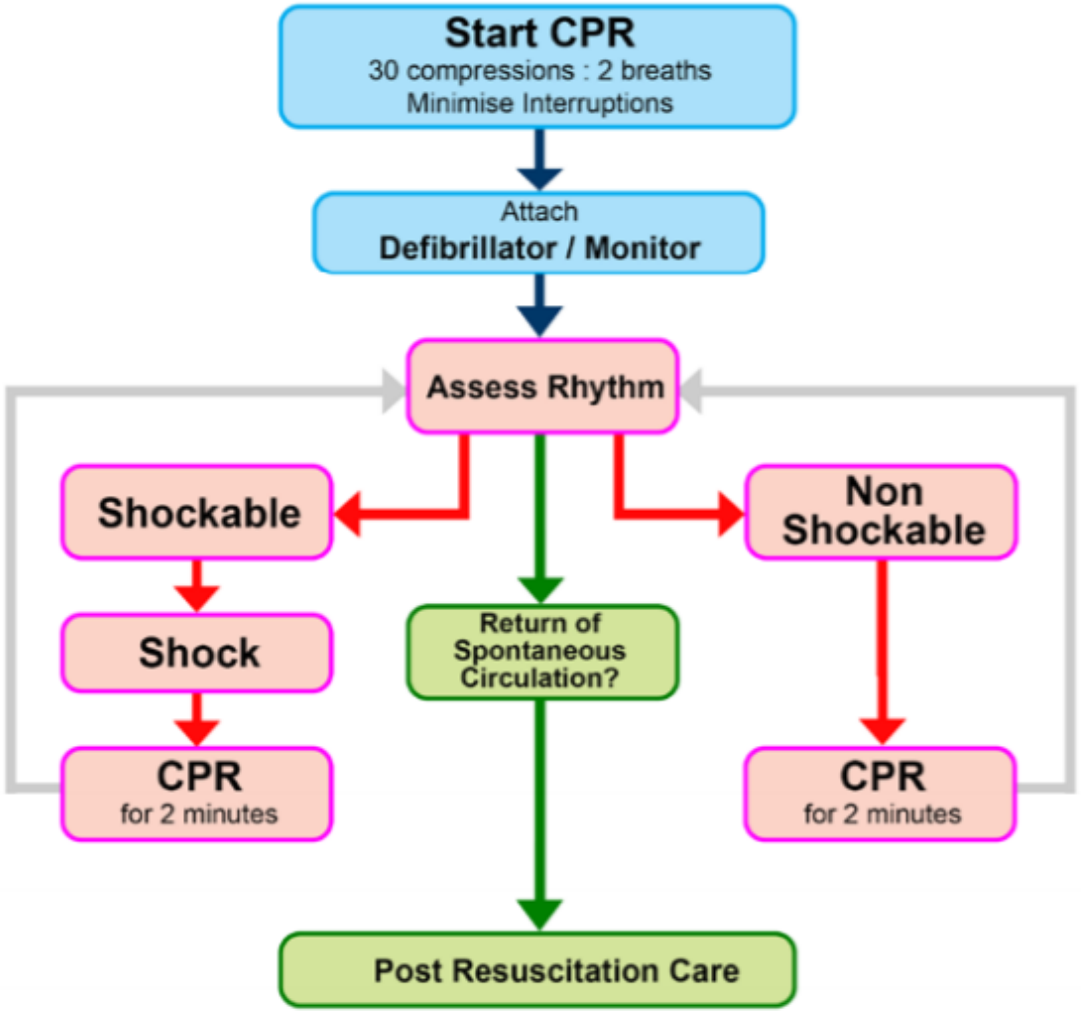
The trace changes…

What is it?

Now what?



Advanced Life Support for Adults



During CPR

Airway adjuncts (LMA / ETT)
Oxygen
Waveform capnography
IV / IO access
Plan actions before interrupting compressions
(e.g. charge manual defibrillator)

Drugs

Shockable

* Adrenaline 1 mg after 2nd shock (then every 2nd loop)
* Amiodarone 300mg after 3 shocks

Non Shockable

* Adrenaline 1 mg immediately (then every 2nd loop)

Consider and Correct

Hypoxia
Hypovolaemia
Hyper / hypokalaemia / metabolic disorders
Hypothermia / hyperthermia
Tension pneumothorax
Tamponade
Toxins
Thrombosis (pulmonary / coronary)

Post Resuscitation Care

Re-evaluate ABCDE
12 lead ECG
Treat precipitating causes
Aim for: SpO2 94-98%, normocapnia and normoglycaemia
Targeted temperature management

AUSTRALIAN RESUSCITATION COUNCIL
NEW ZEALAND Resuscitation Council WHAKAHAUORA AOTEAROA

Clinical Scenario 1 continued?

- Seizure like activity ends
- 30 seconds later Vt → frequent ectopics/bigeminy → torsade → VF arrest
- Note slightly prolonged QTc though a little disguised

AAGBI Safety Guideline

Management of Severe Local Anaesthetic Toxicity

1 Recognition

Signs of severe toxicity:

- Sudden alteration in mental status, severe agitation or loss of consciousness, with or without tonic-clonic convulsions
- Cardiovascular collapse: sinus bradycardia, conduction blocks, asystole and ventricular tachyarrhythmias may all occur
- Local anaesthetic (LA) toxicity may occur some time after an initial injection

2 Immediate management

- Stop injecting the LA
- Call for help
- Maintain the airway and, if necessary, secure it with a tracheal tube
- Give 100% oxygen and ensure adequate lung ventilation (hyperventilation may help by increasing plasma pH in the presence of metabolic acidosis)
- Confirm or establish intravenous access
- Control seizures: give a benzodiazepine, thiopental or propofol in small incremental doses
- Assess cardiovascular status throughout
- Consider drawing blood for analysis, but do not delay definitive treatment to do this

3 Treatment

IN CIRCULATORY ARREST

- Start cardiopulmonary resuscitation (CPR) using standard protocols
- Manage arrhythmias using the same protocols, recognising that arrhythmias may be very refractory to treatment
- Consider the use of cardiopulmonary bypass if available

GIVE INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Continue CPR throughout treatment with lipid emulsion
- Recovery from LA-induced cardiac arrest may take >1 h
- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

WITHOUT CIRCULATORY ARREST

Use conventional therapies to treat:

- hypotension,
- bradycardia,
- tachyarrhythmia

CONSIDER INTRAVENOUS LIPID EMULSION
(following the regimen overleaf)

- Propofol is not a suitable substitute for lipid emulsion
- Lidocaine should not be used as an anti-arrhythmic therapy

4 Follow-up

- Arrange safe transfer to a clinical area with appropriate equipment and suitable staff until sustained recovery is achieved
- Exclude pancreatitis by regular clinical review, including daily amylase or lipase assays for two days
- Report cases as follows:
  - in the United Kingdom to the National Patient Safety Agency (via **www.npsa.nhs.uk**)
  - in the Republic of Ireland to the Irish Medicines Board (via **www.imb.ie**)

If Lipid has been given, please also report its use to the international registry at **www.lipidregistry.org**. Details may also be posted at **www.lipidrescue.org**

Your nearest bag of Lipid Emulsion is kept .....

IMMEDIATELY

Give an initial intravenous bolus injection of 20% lipid emulsion **1.5 ml.kg^{-1}** over 1 min

AND

Start an intravenous infusion of 20% lipid emulsion at **15 ml.kg^{-1}.h^{-1}**

AFTER 5 MIN

Give **a maximum of two** repeat boluses (same dose) if:

- cardiovascular stability has not been restored **or**
- an adequate circulation deteriorates

Leave **5 min** between boluses

A maximum of **three** boluses can be given (including the initial bolus)

AND

Continue infusion at same rate, but:

Double the rate to **30 ml.kg^{-1}.h^{-1}** at any time after 5 min, if:

- cardiovascular stability has not been restored or
- an adequate circulation deteriorates

Continue infusion until stable and adequate circulation restored or maximum dose of lipid emulsion given

Do not exceed a maximum cumulative dose of 12 ml.kg^{-1}

An approximate dose regimen for a 70-kg patient would be as follows:

IMMEDIATELY

Give an initial intravenous bolus injection of 20% lipid emulsion 100 ml over 1 min

AND

Start an intravenous infusion of 20% lipid emulsion at 1000 ml.h^{-1}

AFTER 5 MIN

Give a **maximum of two** repeat boluses of 100 ml

AND

Continue infusion at same rate but **double** rate to 2000 ml.h^{-1} if indicated at any time

Do not exceed a maximum cumulative dose of 840 ml

This AAGBI Safety Guideline was produced by a Working Party that comprised:
Grant Cave, Will Harrop-Griffiths (Chair), Martyn Harvey, Tim Meek, John Picard, Tim Short and Guy Weinberg.

This Safety Guideline is endorsed by the Australian and New Zealand College of Anaesthetists (ANZCA).

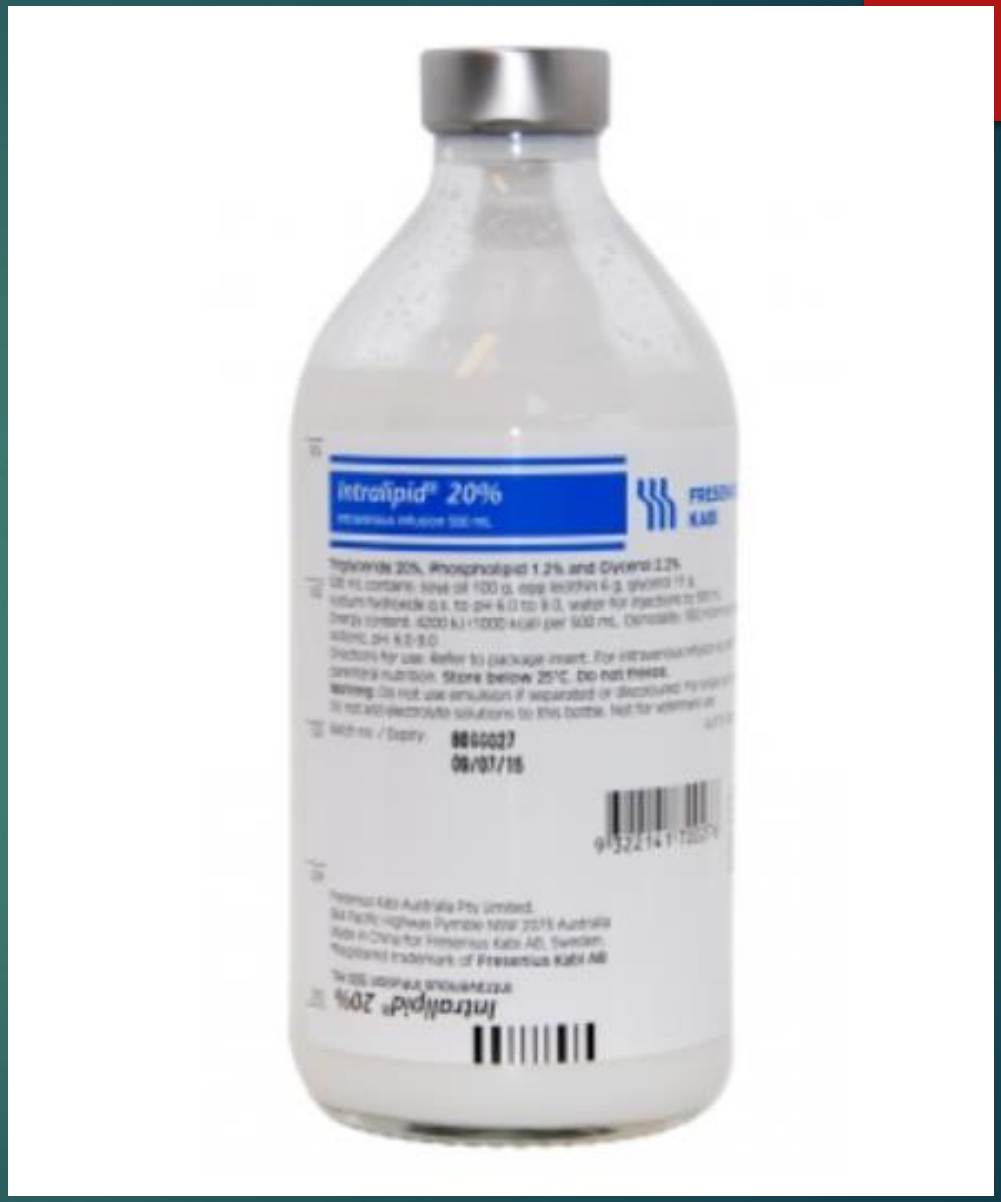
AAGBI Safety Guideline

Management of Severe Local Anaesthetic Toxicity

ACCOMPANYING NOTES

1 Recognition	Local anaesthetic intoxication can present in many different ways, making it very difficult to recognise. After injection of a bolus of local anaesthetic, toxicity may develop at any time in the following hour. Techniques involving infusion of local anaesthetic through a catheter allow intoxication to develop at any time.
2 Immediate management	Some hospital laboratories have encountered difficulty analysing blood drawn during lipid emulsion therapy. If clinical circumstances allow, it may be prudent to draw blood for later analysis before lipid emulsion therapy begins.
3 Treatment	1000 ml of 20% lipid emulsion should be immediately available to all patients receiving potentially cardiotoxic doses of local anaesthetic. 20% lipid emulsion is readily available from most hospital pharmacies, which may also be able to help departments with timely replacement of bags nearing expiry. Intralipid® 20% emulsion has been used in the majority of reported uses of lipid emulsion as an antidote. Alternative preparations have also been used in successful resuscitations. Although some propofol preparations are provided in Intralipid®, e.g. Diprivan®, these are not a suitable alternative due to the significant cardiovascular depression caused by the propofol. This does not preclude the use of small, incremental doses of propofol to treat convulsions. In extremely obese patients, doses of lipid emulsions should ideally be based on an estimate of lean body weight. The interaction between lipid emulsion treatment and other cardioactive drugs used in resuscitation is unclear. Some evidence suggests high doses of vasopressors are harmful in resuscitation in local anaesthetic intoxication. Conversely, some evidence suggests lipid emulsion therapy may be harmful in asphyxial cardiac arrest.
4 Follow-up	The immediate management of severe intoxication by LA is extremely demanding. In the aftermath, completion of forms on websites may seem unattractive. However, every case can help prevent another and improve treatment of the condition. Thus, reports to relevant registries are extremely important. Pancreatitis has occasionally been associated with acute lipidaemia, and therefore should be excluded.
5 Education	Educational material and up-to-date lists of relevant publications are available at **www.lipidrescue.org** This guideline will be updated regularly; the latest version can be found on **www.aagbi.org**

- Intralipid 20%
- 500ml bottle



SMH 2015 (July 28) – It's a "local" issue

One of the three cases involving a different clinic was treated at St Vincent's Hospital.

A spokesman for St Vincent's Hospital confirmed it had recently admitted a cosmetic surgery patient to the hospital's intensive care unit "due to local anaesthesia toxicity".

"Owing to patient confidentiality, we are not in a position to go into any more detail," he said.

Professor Walton and Dr Hore said consumers need to be aware of the risks associated with cosmetic surgery, which is largely unregulated in NSW, and should ask if the clinics they attend record and independently investigate adverse events.

Local Anaesthetic History

Coca plant

- Cocaine was first local anaesthetic discovered
- Derived from coca plant leaves in Peru.
- Consumed as a tea or leaves were chewed with lime juice resulting in energy and appetite suppression for hundreds of years in the traditional communities of South America

Medical/Surgical History - Cocaine

- Carl Koller – topical anaesthesia of the eye 1884
- Carl Schleich - 1892 – infiltration anaesthesia
- First larger operation was by August Bier 1899 – before orotracheal intubation (1901)
- He based in on his supervisor Quinke who developed the investigation lumbar puncture
- First operation a 34 year old labourer with tuberculous ulcer over ankle joint.
- Cocaine 15mg intrathecal given to good effect

Bier quotes

- "In America they have professional anaesthesiologists. Even in Germany this institution is often praised. I can't think of anything more boring…"
- 5 cases for lower limb procedure on various "backward" "servant girls", "bakers" and " brewery salemen" he then experimented on himself with his assistant Dr Hildebrandt. 5 – 15mg of cocaine used seemingly without animal or dose finding studies.

August Bier

- " I introduced the lumbar puncture needle after the usual Schleich infiltration anaesthesia. H. experienced this as pressure not pain.
- At 7.38pm I injected 0.5 cc of 1 percent solution of cocaine (0.005 g). This resulted in H experiencing a feeling of warmth in both legs…
- After 7 minutes: Needle pricks in the thigh were perceived as pressure.
- After 8 minutes : A small incision in the skin of the thigh as felt as pressure…
- After 10 minutes : A long needle was pushed down to the femur without evoking the least pain…
- After 13 minutes: A burning cigar was applied to the legs, and was felt as heat but not pain.

Centennial of spinal anaesthesia. Anesthesiology 1998;89:500-506

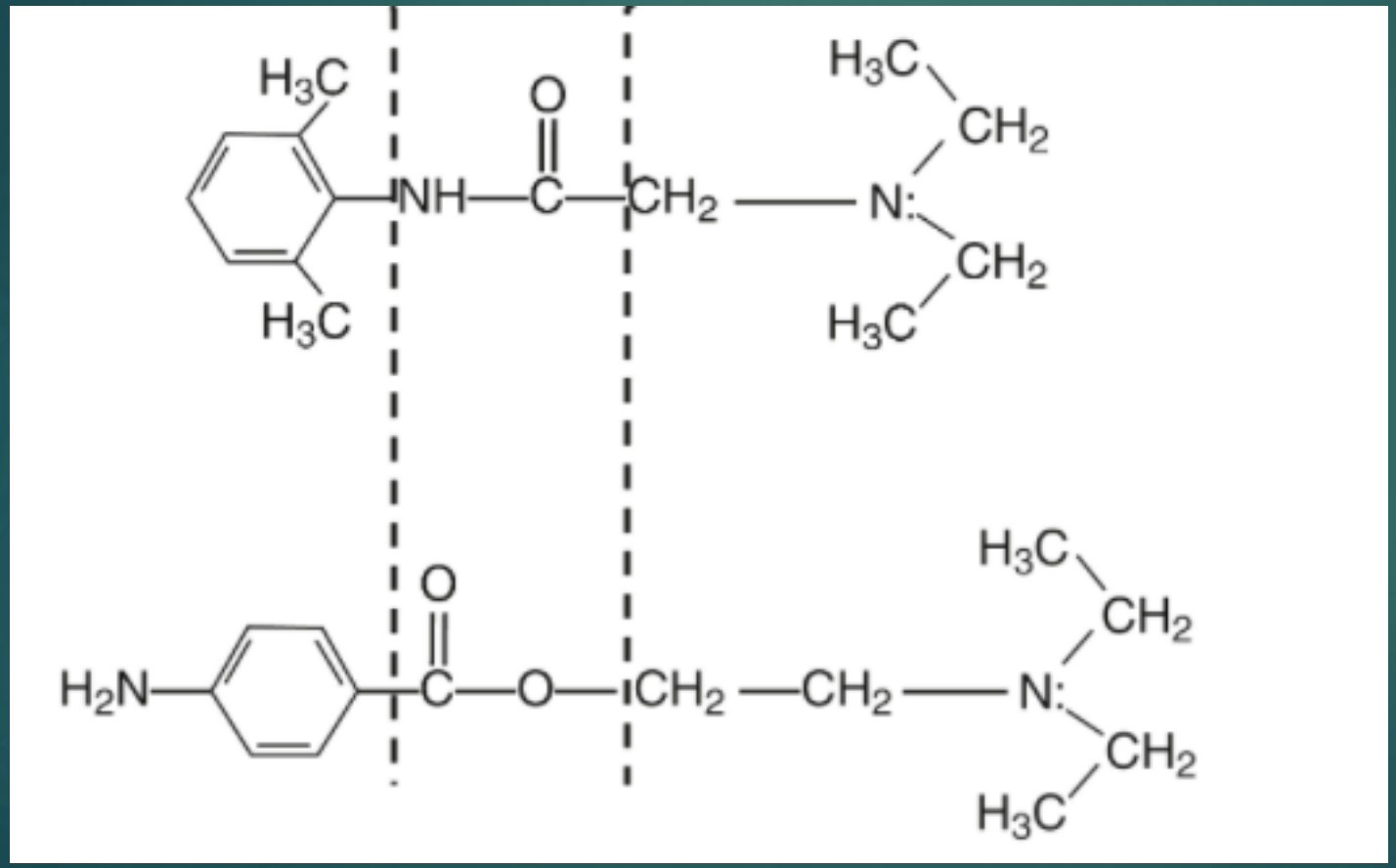
August Bier spinal cont

- After 20 minutes: Avulsion of the pubic hairs was felt simply as elevation of the fold of skin, but avulsion of chest hairs above the nipples were felt as very painful.
- After 23 minutes a strong blow to the shin with an iron hammer did not provoke pain.
- After 25 minutes: Strong pressure and traction on the testicles was not painful.
- After 45 minutes pain sensibility began to recover…

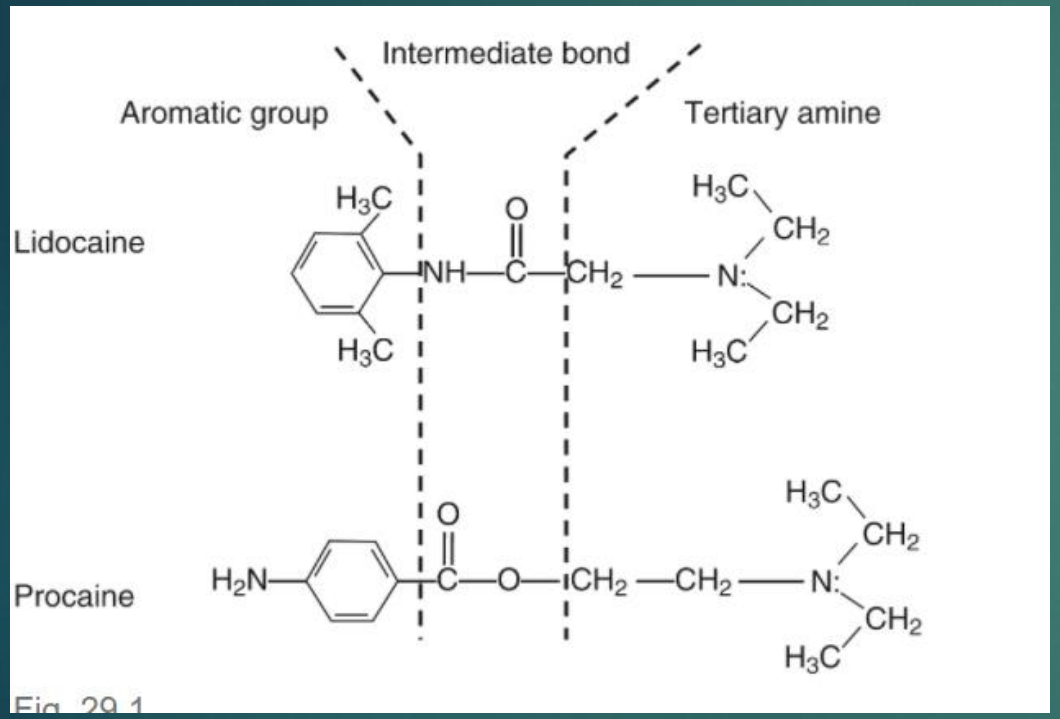
August Bier

- After performing these experiments on our own bodies we proceeded without feeling symptoms to dine and drink wine and smoke cigars. I went to bed at 11 pm, slept the whole night, awoke the next morning hale and hearty and went for an hours walk.
- By 3pm I had a strong pressure on my skull, and became rather dizzy when I stood up…All these symptoms vanished when I lay down flat…
- Meanwhile….
- Dr Hildebrandt went to bed at 11pm and woke at midnight with a violent headache that quickly became unsupportable. At 1am he began to vomit… The next morning he felt very ill but was able to perform his service duties of operating and changing dressings.
- It lasted for 3-4 days … Dr Hildebrandt's tibia became painful and bruises developed in several places…

Local SAR - What are the below chemicals?

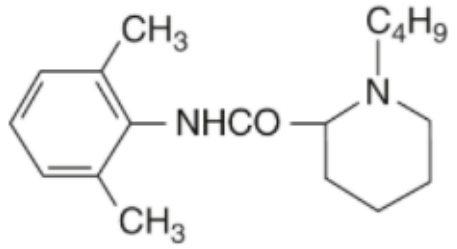
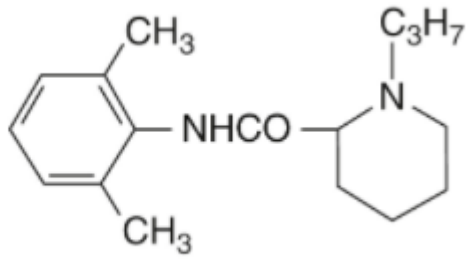


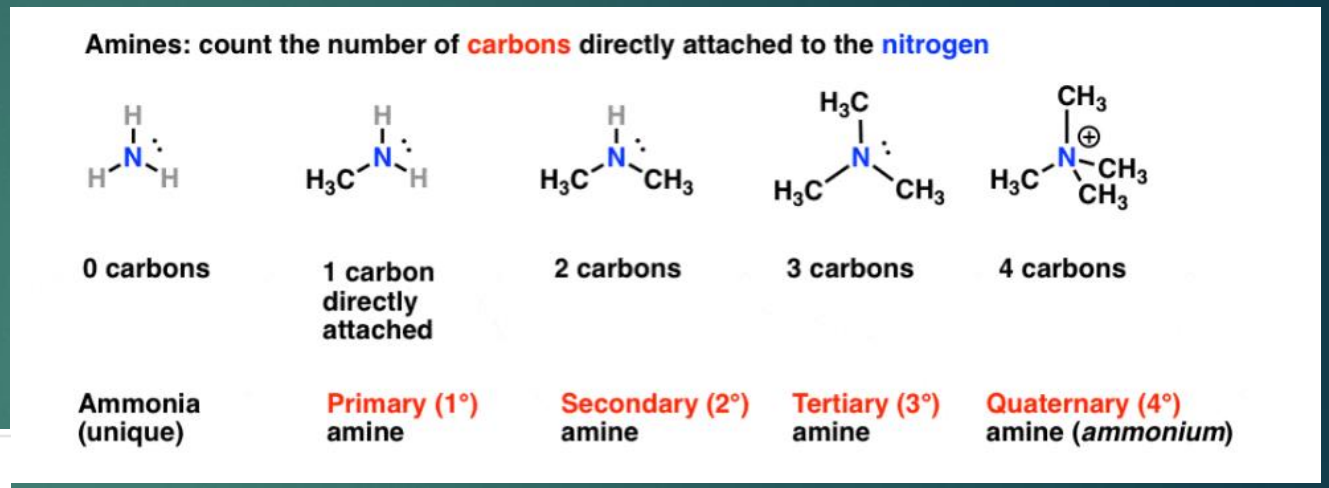
Local Structure Activity Relationship



- Amide bond or ester bond linking a substituted aromatic ring (lipophilic) with a substituted tertiary amine group (hydrophilic)
- Note the hydrophilic tertiary amine is variably protonated
- Aromatic ring is a 6 carbon ring
- Tertiary amine is a 3 carbon attachment to the nitrogen – hydrophilic especially as partially protonated in physiologic range

SAR contd…

Bupivacaine (Marcaine)	
Ropivacaine (Naropin)	



What is chirocaine? How does it vary from bupivacaine?

- Isomer is when a chemical has the same atomic formulae but different 3D structure.
- Subtypes:
  - 1. **Structural isomer** – different order of bonds but same formulae

    (eg prednisolone and aldosterone)
  - **2. Stereoisomerism** – same chemical formulae and bond structure order, but different 3D configuration (eg levobupivacaine and bupivacaine)

- Subtype of stereo isomerism:

a. **Geometric** – a molecule has different group attached with a double bond or ring structure(they can be cis (same) or trans (opposite) sides of the double bond. Eg cis-atracurium

b. **Optical isomer** is when a carbon or quaternary amine has 4 groups attached but are different mirror image structure… next slide

Levobupivacaine

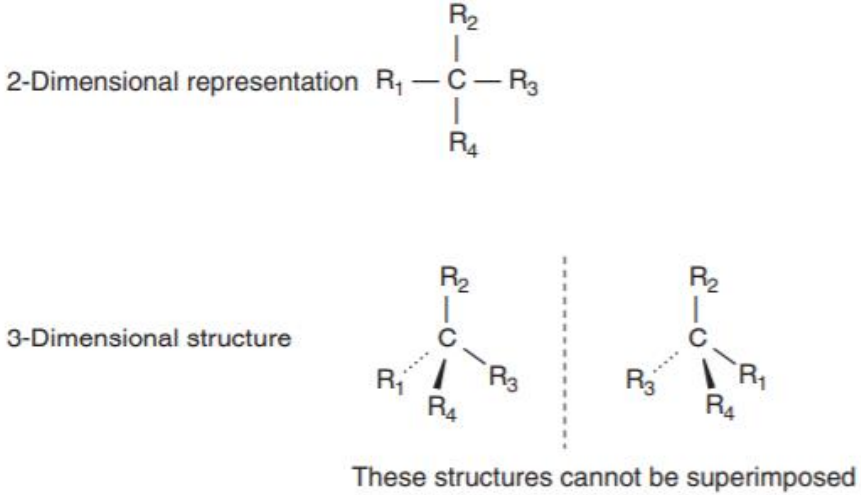


Figure 5.2 Chiral centres.

- Initially classified dextro or levo based on how they rotate polarised light in a lab …
- Hence levobupivacaine
- Now usually classified R or S based on clockwise or anticlockwise order of MW if lowest MW group is placed at R4 behind the page.
- Each type is called enantiomer
- Levo- bupivacaine is enantiomer pure
- Naturally not possible, many natural drugs are racemic mixtures or even split of enantiomers (adrenaline, ketamine, bupivacaine)

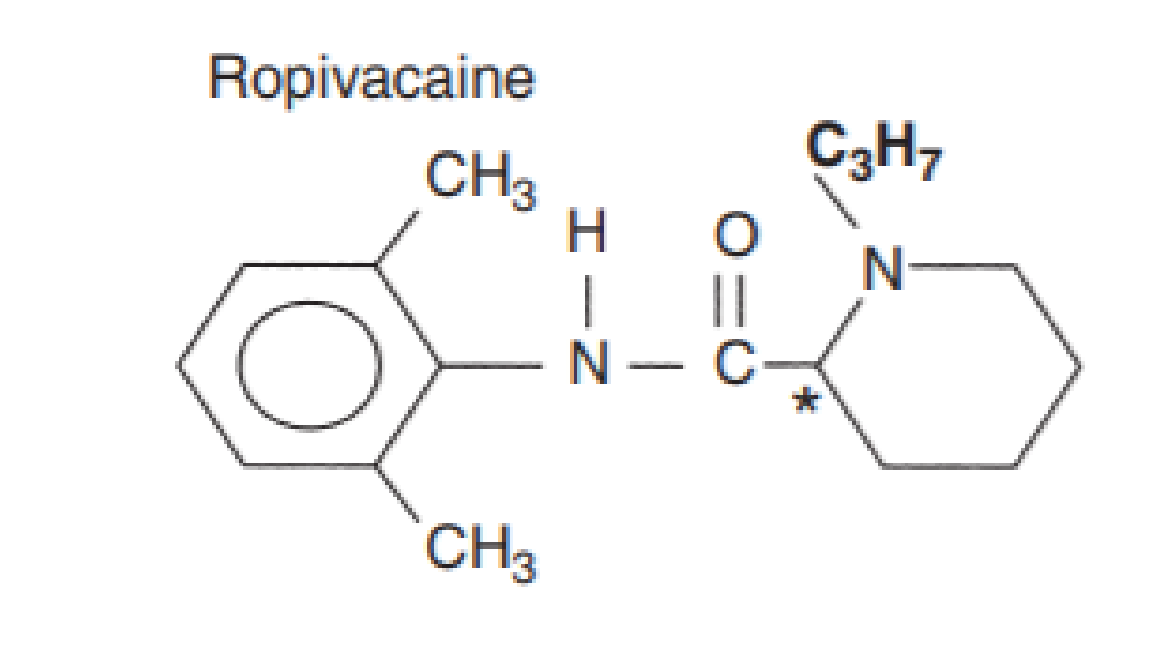
Peck, Hill et al Pharmacology for Anaesthesia and ICU 2014 Ed 4

Stereoisomer – levobupivacaine advantages and disadvantages

- Chirocaine (levobupiv) is the s-enantiomer of bupivacaine.
- Less likely to cause seizure and CNS excitation sx
- Myocardial depression via cardiac K channels occurs at much higher dose with levo bupivacaine
- 13% less potent
- Slightly longer onset time for motor blockade
- Hepatic metabolism
- Renal (75%)and faecal excretion

Ropivacaine

- What is ropivacaine in regard to what we have just discussed and what are its relative advantages to bupivacaine?



Ropivacaine

- Produced as a pure S enantiomer like levo bupivacaine
- S enantiomers are though to be less cardiotoxic and neurotoxic than racemic mixtures.
- Higher clearance than bupivacaine when metabolised by cyt p450 in liver → shorter half life and less chance of systemic toxicity → higher max dose possible.
- Less potent
- Also highly bound to AAG (alpha 1 acid glycoprotein)

Lignocaine

EMLA - what is it?

EMLA

- **Eutectic mixture of lignocaine and prilocaine.**
- **Eutectic** = when 2 compounds are combined to have properties as though they were a single substance.
- Mixture of 2.5% lignocaine crystals and 2.5% prilocaine crystals.
- When combined they drop their melting point and become an oil.
- It is presented in a white oil: water emulsion.

- Apply to skin under occlusive dressing for 60 mins.
- Absorption : do not use of mucous membranes as rapid absorption.
- Prilocaine has low potency(0.5 – 2%) and low pKa 7.7 → rapid onset
- Metabolism :

Hepatic, renal and lung → short half life.

Amide so mostly hepatic

O- toluidine is a metabolite → methaemoglobinemia if large doses.

Caution in children Rx methylene blue

Neonates at increased risk as lack methaemoglobin reductase.

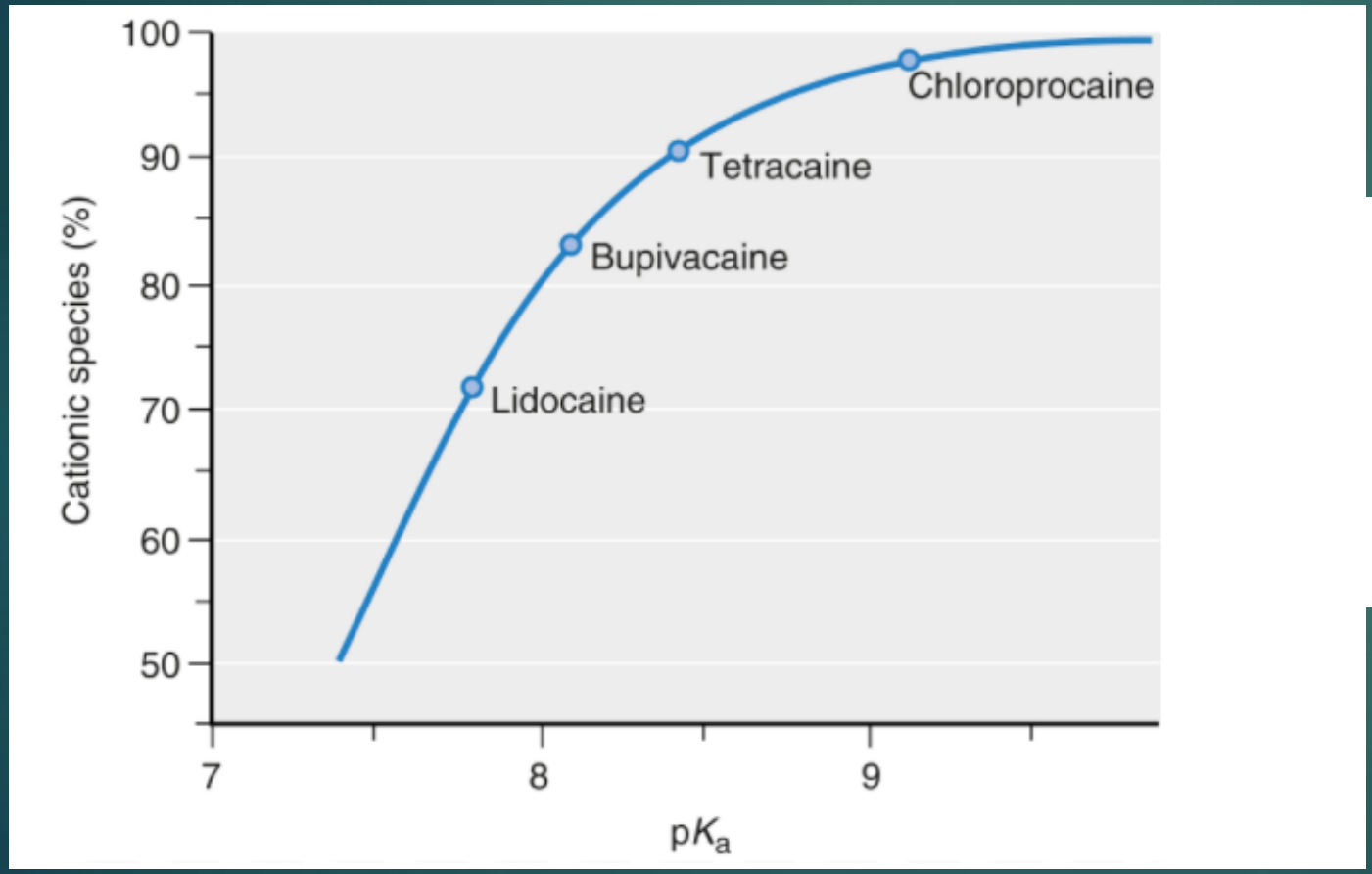
NB Low protein binding (55 %) → prilocaine use in Bier's block

Peck, Hill 4th Edition

Amethocaine

- Ester local anesthetic for topical anaesthesia
- 0.5% - 1% drops for eye surgery
- 4% cream for topical anaesthesia to skin like EMLA cream.
- Faster onset - 30 mins
- Lasts 3-4 hours
- Intrinsic venodilation which helps cannulating
- Avoids methaemoglobinemia issue
- PABA

pKa –?Meaning of graph pH = 7.4 …. What about Inflamed tissue?



$$pH = pK_a + \log \frac{[A^-]}{[HA]}$$

Figure 7. The Henderson-Hasselbach equation.

$$\frac{[BH^+]}{[B]} = 10^{pK_a - pH}$$

Lidocaine: $pK_a = 7.9$

At pH 7.4

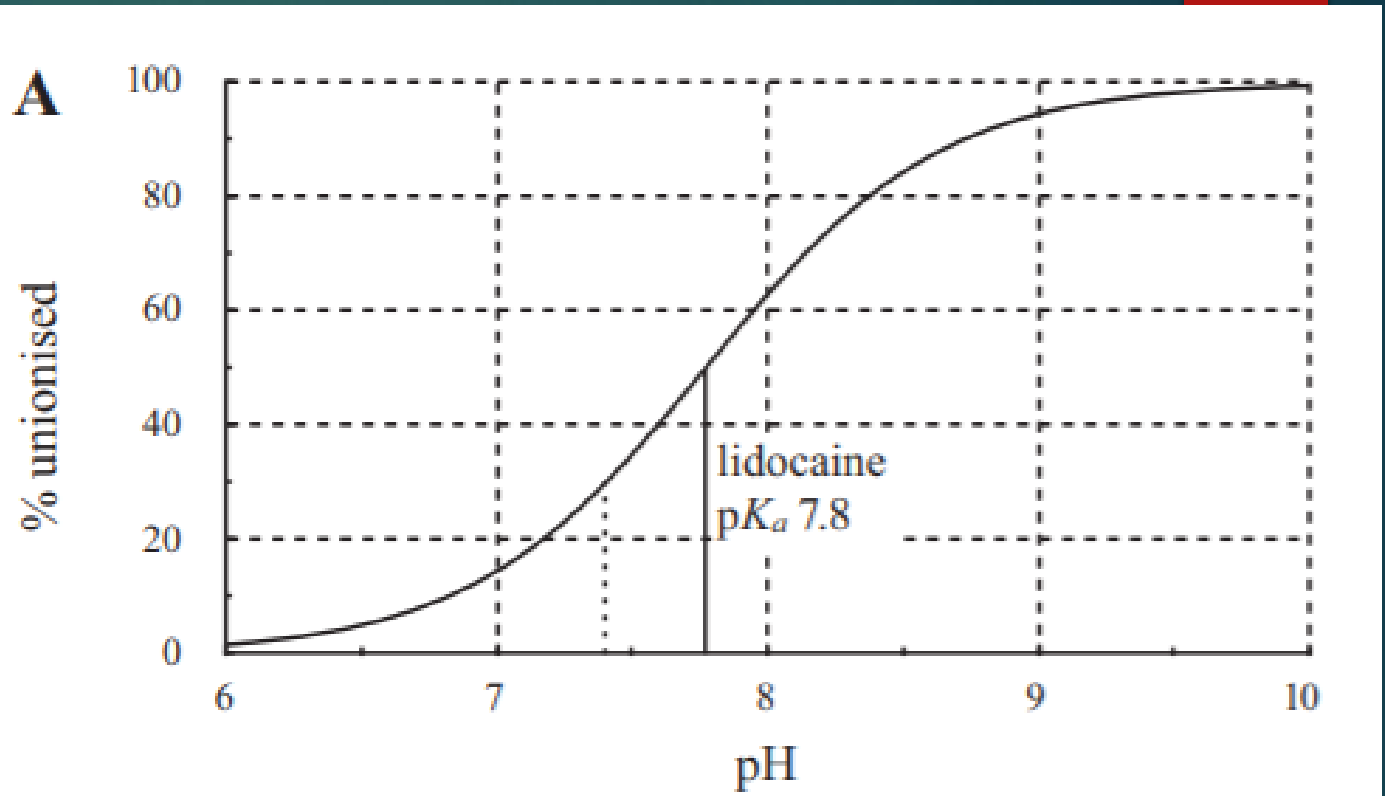
$$pH = pKa + \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$7.4 = 7.9 + \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$-0.5 = \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$0.3 = \left\{\frac{[B]}{[BH^+]}\right\}$$

so 75% ionized and 25% unionized.



At pH of 7.1

$$7.1 = 7.9 + \log\left\{\frac{[B]}{[BH^+]}\right\}$$

$$0.16 = \left\{\frac{[B]}{[BH^+]}\right\}$$

so 86% ionized and 14% unionized (i.e. less available to penetrate nerves).

Answers:

- Ka is a dissociation constant or how easily an acid gives up its proton or H+ in solution.
- pKa is the – log Ka
- Strong acids have a low pKa and strong bases have a higher pKa
- When pH is the same as the pKa the local anesthetic exists equally in the protonated and unprotonated form. (log 1 =0)
- In inflamed tissue the pH tends to be lower.
- Hence the local anaesthetics tend towards the protonated form.
- Hence penetrate tissue relatively poorly.

Common pKa

Drug	Relative Conduction-Blocking Potency *	Physiochemical Properties	
		p K_a †	Hydrophobicity †
Low Potency			
Procaine	1	8.9	100
Intermediate Potency			
Mepivacaine	1.5	7.7	136
Prilocaine	1.8	8.0 ‡	129
Chloroprocaine	3	9.1	810
Lidocaine	2	7.8	366
High Potency			
Tetracaine	8	8.4	5822
Bupivacaine	8	8.1	3420
Etidocaine	8	7.9	7320

Ropiv pka = 8.1

Local anaesthetic presented in vial in acid environment (3.5 – 5.5) – prolongs shelf life, especially of adrenaline.

Almost completely in charged or ionised form – hence stable in solution and increase shelf life to 3-5 years.

Scenario 2 - Rural Hospital – "Way out West"

- Surgical registrar in a small country hospital.
- You are required to assist with the obstetrician for LSCS cases when on call.
- The town is staffed by 3 GP anaesthetists.
- Linda is away at Ningaloo Reef Eco Resort – uncontactable.
- Keith is in town but away for the weekend on his property playing diesel ball with his kids.
- Barry is on call and places an epidural in a primip.
- The FHR 2 hours later drops to 60. It is unresponsive to repositioning.
- What do you do?

Scenario 2 Continued

- Terbutaline fails.
- Cat 1 LSCS called
- Midwife – calls Barry, paramedic answers the phone – he has hit a kangaroo on the way home. He is unconscious at the scene and Careflight have been called to take him to Perth.
- You look at the epidural.
- The mother remains stable and comfortable on ropiv 0.1% PIEB + PCEA and the FHR is still 60 – 80.
- What do you do with the epidural and why?

Answer

- Local anaesthetics to work must have some molecules in ionised and unionised form.
- Alkalisation of solution will result in more rapid onset and less painful of injection (useful in kids) with emla
- Too much can precipitate out solution so care
- Time saved is small in all scenarios except urgent epidural top-up
- Use lignocaine with adrenaline as has lower pKa 7.9 and lower potency resulting in faster onset time.

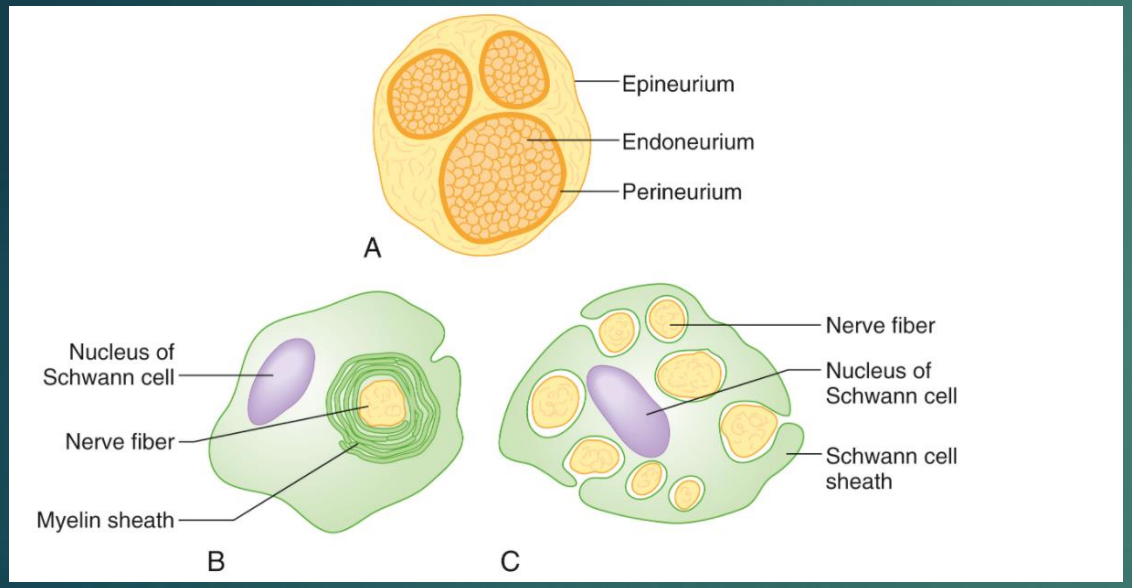
Table 1 Alkalinisation of local anaesthetic solutions[2]

Anaesthetic solution	Volume of 8.4% sodium bicarbonate to be added to 20 mL
Lignocaine 1% or 2%	2 mL
Bupivacaine 0.25% or 0.5%	0.1 mL*
Ropivacaine 0.2% ‡	0.1 mL* (must be used within 5–10 minutes)

* The small volume of 8.4% sodium bicarbonate to be added requires great care as adding too much will cause precipitation

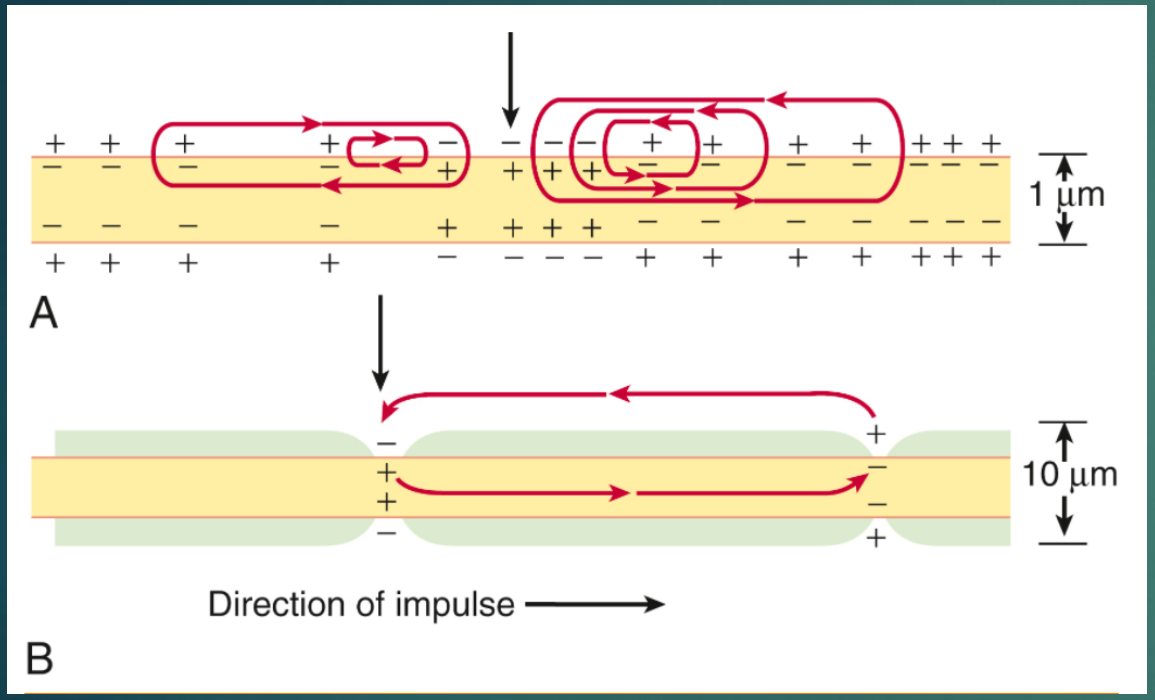
‡ Higher concentrations of ropivacaine (for example 0.75%) precipitate at a pH greater than 6 so are not suitable for alkalinisation[6]

Structure of a nerve



- Perineurium collects nerve axons into fascicles
- 60% CSA is nonneural tissue
- B. Each myelineated fibre is wrapped in 1 Schwann cell wrapped many times by a myelin sheath. Length it covers is x100 axon diameter with node of Ranvier in which most of Na channels are found.
- C. Nonmyelinated fibres bundled into groups of 5 -10 axons with a Schwann cell.

Structure of a neuron



- A. Non myelinated C fibre, slow transmission of current.
- B. Myelinated fibre – current "jumps "from node to node and travels faster.
- Charge is negative inside at rest and positive during action potential
- Usually depolarise a few nodes at a time
- Block a larger myelinated nerve need ~ 1cm of local anaesthetic

Structure of Axonal Membrane

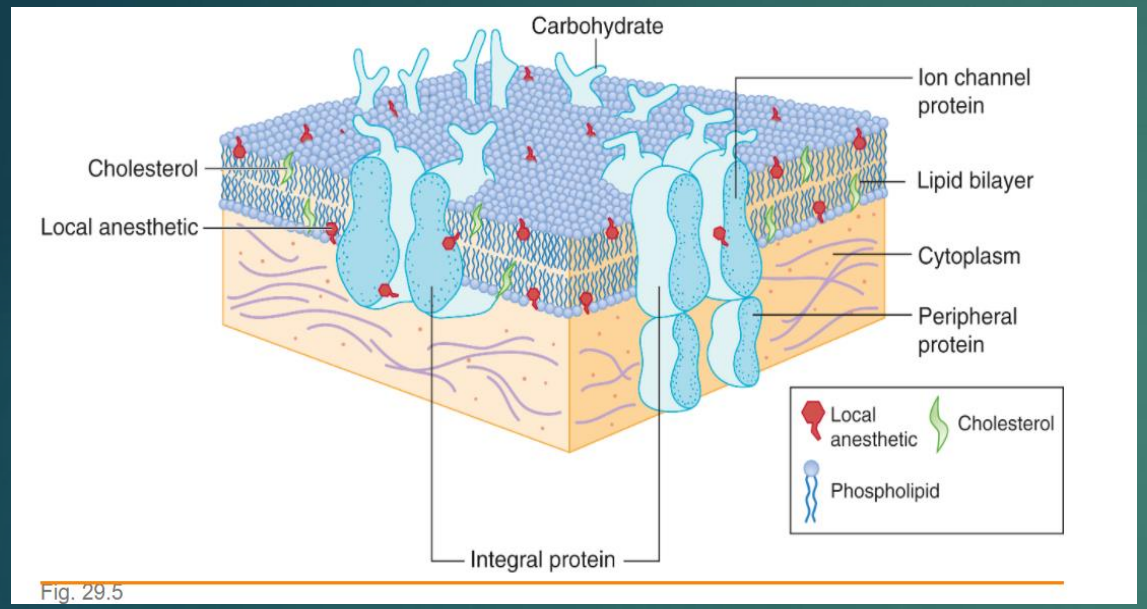


Fig. 29.5

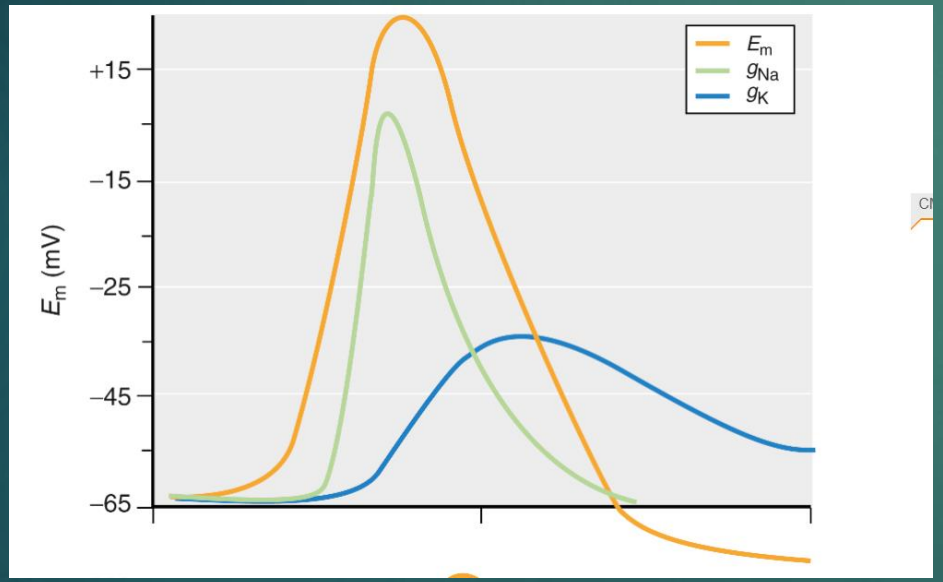
- Membrane structure with lipid bilayer embedded with integral proteins that act as ion channels – often fixed to internal cytoskeleton structure
- Lipid interior of the wall – with zwitterionic (positive and negative charge present) hydrophilic outer edges

Basic Nerve Physiology

- Action potential occurs when ions permeate through these specialised protein pores in the membrane (ion channels)
- At rest the Na – K ATPase pump maintains a resting state of -60 to -90 mV relative to the outside.
- Pumps brings in K and pumps out Na (K is 150 : 5)
- At rest relatively impermeable to Na but permeable to K

Action Potential

- Influx of Na occurs through Na channels
- Depolarisation occurs down the membrane to the next node – passively trigger depolarisation in the next node.
- Some depolarisations are too weak to reach the threshold shown next slide and don't propogate an action potential



- Small depolarisation will trigger Na and K channels to open.
- Na channel open faster and cause an influx of Na into cell – rendering it more positive, triggering more Na channels to open…
- They then enter an inactivated closed phase
- K channels are opening at this point and rebalancing things until a net inward current is balanced and cell then enters a repolarisation phase.

- If excitability is reduced eg by local anesthetics then a signal is less likely to be propagated.
- If impulse jumps two block nodes but triggers 3rd and then can continue – but will be in a reduced fashion for many centimetres on the nerve.
- This can occur as block wears in or off …

Storage and preparation

- Stored as hydrophilic salts as free base form is sparingly soluble in water – generally acidic solution to preserve it in ionised form
- Injected into tissue – tissue pH and pKa will determine % that converts to free base form vs ionised form. (positive charged cation)
- Tissue uptake by liphophlic absorption.
- Onset is also determined by concentration gradient –with highly potent local anaesthetic in a lower concentration form – hence slowing the onset.
- Tissue binding
- The unionised form dissolves better through the surrounding membranes and is the rate limiting step – hence the effect of alkaline solutions.

Mechanism of action over view

- 1. Solution of local anaesthetic deposited near the nerve
  - Removal of free drug from this locus is a function of tissue binding, local hydrolysis of aminoesters, removal by circulation.
  - Remaining free drug penetrates the nerve sheath.
- 2. Local anaesthetic permeates the axon membrane and stay in the axoplasm. Speed of this depends on lipophilicity of base and cation species and its pKa.
- 3. Binding of local anaesthetic to Na channel prevents the conformational change that allows channel activation and Na influx.
- 4. During onset and wear off blockade still occurs with stimulation (phasic block)
- 5. One binding site accounts for tonic (at rest) and phasic block.
- 6. Onset and offset of effect is governed by the diffusion in and out of the whole nerve (hours) not by the binding and dissociation from the Na channel each time (seconds)

Mechanism of action – extra info

- The actual binding occurs to the Na channel from the cytoplasmic side after dissolving through the lipid membrane.
- Binding occurs with the aromatic moiety to the Na channel.
- Charged portion of the local anaesthetic protrudes into channel lumen.
- Charged form dissociate slowly from the ion channel, but neutral unionised form act faster.
- In brief – the unionised form helps the onset of the effect, but the ionised form keeps it there bound to the receptor.

Sodium Channel Structure

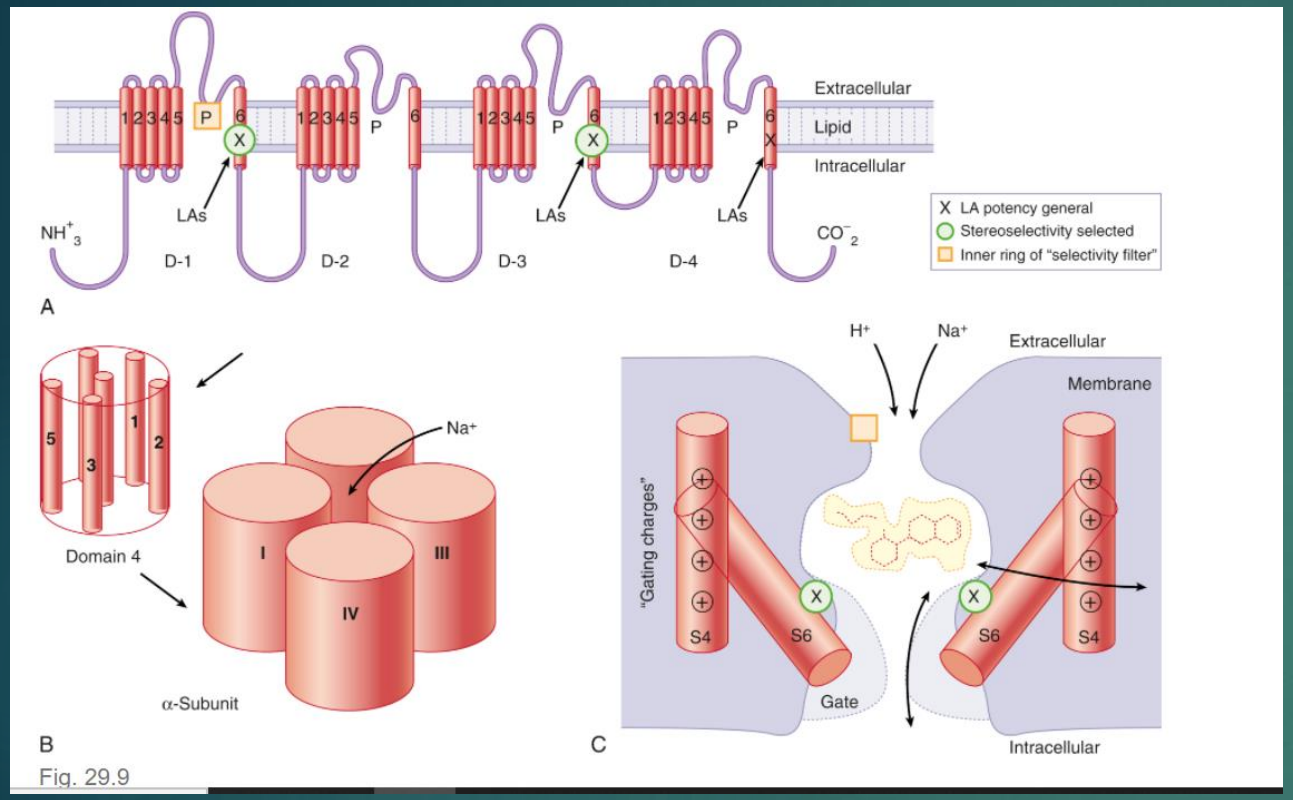


Fig. 29.9

Structure of Na channel and LA interaction

a. Alpha subunit of the Na channel is a single peptide

b. Alpha subunit is made of 4 domains (D1-D4) – each domain is made of 6 helical regions S1-S6 that span the core of the membrane.

c. Local anaesthetic binds to site X which is known as site 9 on the S6 and S5 projections into the pore.

Each part of the P segment contributes to ¼ of the pore or the narrowest segment of the ion channel.

Depolarisation of the membrane triggers a movement in the S4 segment rendering it voltage sensitive. This triggers rearrangement of S6 and channel opens.

Nerve susceptibility and differential block

3 main types of nerves

- A fibres – myelinated, larger 4-20 micron diameter
  - A alpha – largest, motor innervation skeletal muscle
  - A beta – sensory- touch,pressure, proprioception
  - A gamma – smaller again muscle spindle tone
  - A delta – thinnest, pain and cold temperature
- B fibres – myelinated preganglionic fibres 1-2 micron diameter
- C fibres – nonmyelinated, 1-2 micron diameter, pain, temp, post ganglionic autonomics

- Alpha is fast pain, C is slow pain
- Pain is complex along multiple pathways and pressure and light touch can be misinterpreted in anxious patients especially if windup/central sensitisation.

- Differential block is when pain sensation blocked and /or sensation but motor function is recovered or preserved.

- Take home point: **Size does not matter (despite traditional textbooks to contrary)**

Cousin's and Bridenbaugh Neural Blockade in Clinical Anaesthesia and Pain Medicine

Nerve susceptibility

Nerve type	Susceptibility to Pain
A alpha	++
A beta	++
A gamma	+++
A delta	+++
B	++
C	+

Pharmacoceutics /Presentation

- Solution – clear colourless
- Gel
- Nasal spray
- Patch - emulsion
- EMLA – eutectic mixture of lignocaine and prilocaine
- Amethocaine – gel
- Eye drops

Pharmacokinetics - What is your general structure in a viva?s

How to bluff the examiner when you can't remember the specifics

1. **Absorption** – remember different routes including transdermal

Remember 1st pass metabolism

2. **Distribution** -

3 groups generally

a. Plasma – large and can't cross endothelium or very protein bound.
b. Limited distribution – can cross into muscle with fenestrated capillaries – polar, poorly lipid soluble, bulky eg NMBA
c. Extensive distribution – highly lipid soluble. Not restricted to plasma – distribution is based on blood flow with initial redistribution to vascular organs (eg heart, lung, adrenals) – then moderate (muscle) and finally low (fat).

3. **Metabolism -** Usually reduces activity of a drug (though not if a prodrug) and generally converts it to a water soluble polar drug that ban be excreted in urine or bile. Remember phase 1 and 2.
4. **Excretion –** removal from body (not to be confused with elimination)

Pharmacokinetics – General

- The concentration of local anaesthetic in the blood is determined by:
  - the amount injected
  - Rate of absorption from site injected
  - Rate of tissue distribution
  - Rate of biotransformation
  - Rate of excretion
  - Age, cardiovascular status, renal and hepatic function

Absorption of local anaesthetics

- **<u>Determined by site of injection – vascularity of site.</u>** Single number not meaningful. (Less than 10mg of lignocaine injected directly into carotid or vertebral A can cause coma, resp or cardiac arrest)
- Dose of injection
- Volume injected
- Intrinsic properties of local anaesthetic
- **Additive used – adrenaline will reduce primary peak of lignocaine**
- Primary plasma level peak from injection, related to dose and vascularity.
- Intercostal most vascular with highest peak → Caudal → Lumbar epidural → Brachial plexus → Subcutaneous tissue.
- Later usually lower secondary peak from reabsorption from lipid compartment

Distribution

- 2 compartment model for LA
- Primary phase redistribution → highly vascular organs
- Secondary phase related to the compound uptake in the liver and lung.
- Bound to plasma protein (AAG)
- Bupivacaine ropivacaine, lignocaine are 95%, 94, 70 respectively.
- AAG increases post operatively as acute phase reactant - protective

Biotransformation and Metabolism

Aminoamides

- Amino amides (lignocaine, bupivacaine, ropivacaine) are degraded enzymatically in liver (lignocaine fastest of the 3) by amidases. Slow process cf esters
- Reduced hepatic blood flow and function alters this process
- Renal excretion of metabolites.
- 5% of drug is renally excreted unchanged.

Esters (eg procaine)

- Metabolised in plasma by pseudocholinesterases and other esterases to inactive compounds
- PABA (para-aminobenzoate) is one on main metabolites and sensitivity to this triggers most hypersensitivities in atopic people
- Cocaine exception – hepatic hydrolysis to water soluble metabolites → excreted in urine

Toxicity

CNS

- Initial excitatory symptoms such as tinnitus, perioral tingling, metallic taste and onto seizures reflect blockade of excitatory pathways increasing glutamate in the brain.
- Higher levels → seizure ceases and respiratory depression or arrest occurs with inhibition of all neuronal function.
- Higher CO2 → cerebral vasodilation → more LA delivered to brain.
- Higher CO2 → creates intracellular acidosis → converts local anaesthetic from free base to ionised form → traps the drug intracellularly → exposing the neuron to higher levels.
- Higher CO2 → reduces binding of local anaesthetic to plasma proteins → higher unbound fraction.

Toxicity – Cardiac – multiple mechanisms

- Blockade of Na channels → decreased conduction in Purkinje fibres → see prolonged PR and QRS duration
- Higher doses → depress cardiac function by blocking Ca release from sarcoplasmic reticulum which has negative inotropic effect.
- Also block mitochondrial function. Not emphasised in traditional texts but emphasised in recent reviews in literature (see later)

Local Anaesthetic Toxicity Sx

TABLE 3. Progression of signs and symptoms of toxicity as the local anesthetic dose (or concentration) gradually increases.

- Vertigo
- Tinnitus
- Ominous feelings
- Circumoral numbness
- Garrulousness
- Tremors
- Myoclonic jerks
- Convulsions
- Coma
- Cardiovascular collapse

Most LA cause seizure at x3 less concentration than cardiac arrest.

TABLE 4. Convulsive versus lethal doses of local anesthetics in dogs.

	Lidocaine	Bupivacaine	Tetracaine
Dose producing convulsions in all animals (mg/kg)	22	5	4
Dose producing lethality in all animals (mg/kg)	76	20	27

Toxicity in clinical practice - bolus

Properties of local anaesthetics

Local anaesthetic	pKa	Onset	Protein binding (%)	Duration of action	Maximum dose (mg/kg)
Bupivacaine	8.1	Medium	95	Long	2
Levobupivacaine	8.1	Medium	95	Long	2
Ropivacaine	8.1	Medium	94	Long	3
Prilocaine	7.7	Fast	55	Medium	6 (8 with adrenaline)
Lidocaine	7.7	Fast	65	Medium	3 (7 with adrenaline)
Articaine	7.8	Very fast	70	Medium	7
Amethocaine	8.5	Slow	75	Long	1.5
Procaine	8.9	Slow	6	Short	12
Cocaine	8.6			Short	1.5

- True maximum doses are not well known and depend on vascularity of the site, protein binding in the patient.
- Rough rule of thumb numbers vary considerably between countries but are useful to prevent inadvertent overdose.
- UK and Australian max doses are the same.

What does 3mg/kg mean? Say patient is 10 kg…
How much can you inject of ropivacaine 0.75 or 0.2%?

- 0.75% weight/vol

= 0.75 g/ 100ml

= 7.5 g/L

= 7.5mg/ml

Dose for 10 kg = 30 mg max.

30/7.5 =

- Therefore Ropivacaine 1% = 10mg/ml
- Ropivacaine 0.2% = 2mg/ml
- Marcaine 0.5% = 5mg/ml

Factors Affecting Local Anaesthetic in vivo

Dose and concentration of local anaesthetic

- Increasing dose or concentration given a specific volume will result in a shorter latency, higher rate of successful analgesia and longer duration of sensory blockade.
- Increasing the volume as an isolated variable will increase the spread of local anesthetic around the nerve or dermatomal cover of an epidural injection
- Ultrasound trials with more precise needle placement now demonstrate much lower volumes required and landmark injection – though extreme dose reduction will affect duration.

“How much can you give topically (Eg to airway mucosa)?”

Answer

- 8-9mg/kg of topical lignocaine – safest LA in higher dose

ASA/ANZCA statement on AFOI 2012

Additives we use - what are they and what are their effects?

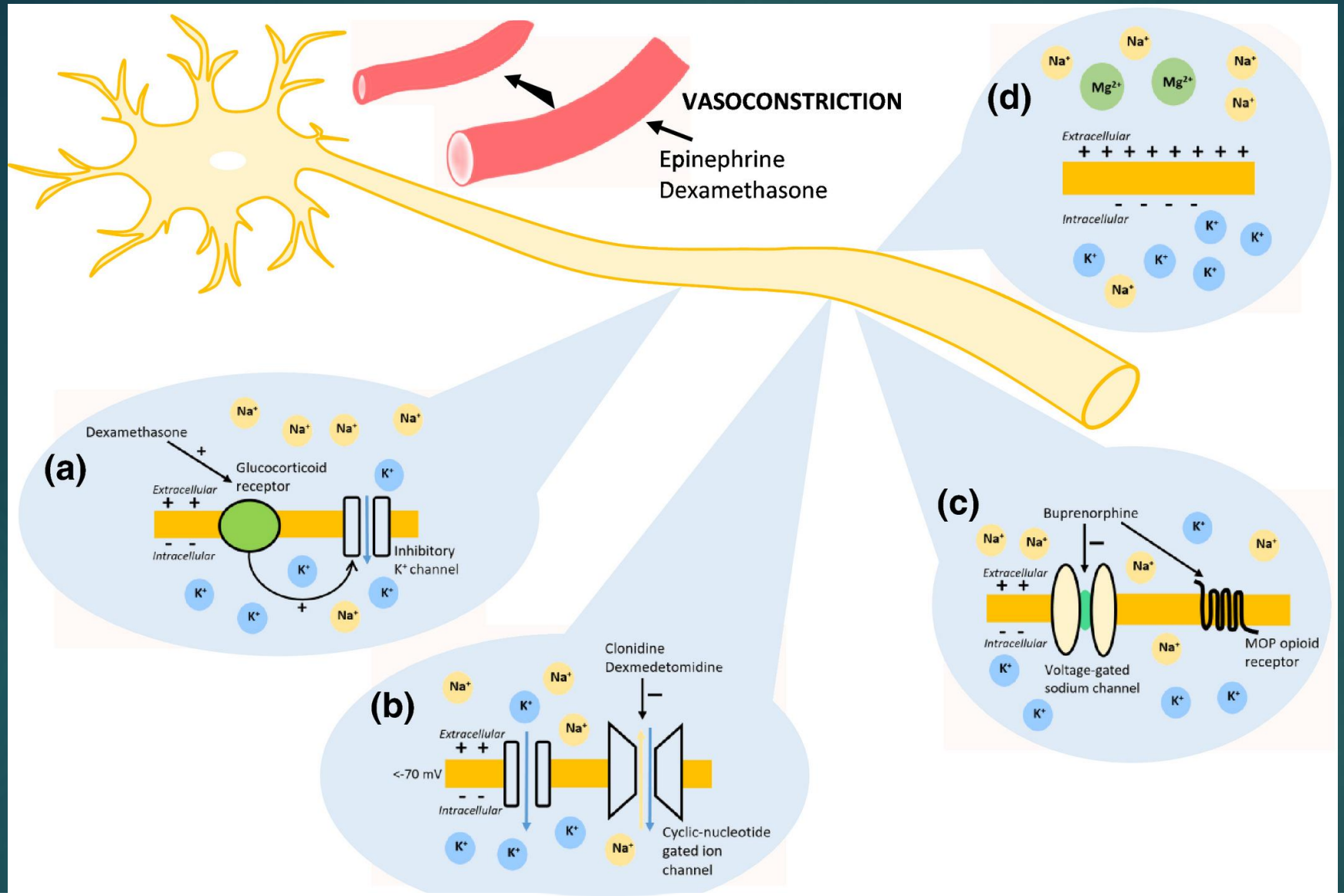


Figure 1 Mechanisms of action of local anaesthetic adjuncts on the cell membrane of neurones and the blood vessels. (a) Dexamethasone stimulates glucocorticoid receptors, increasing the expression of inhibitory potassium channels and decreasing the excitability of neurones. (b) Clonidine and dexmedetomidine inhibit the hyperpolarisation-activated nucleotide-gated channels, maintaining the neurone at a more negative potential and hence hyperpolarised state. (c) Buprenorphine inhibits voltage-gated sodium channels, preventing the generation of action potentials, and interacts with MOP (μ) receptors. (d) Magnesium results in the hyperpolarisation of the neurone secondary to the interaction between its positive divalent charge and the neuronal membrane.

Factors affecting local anaesthetic in vivo contd…

Additives to local anaesthetic

- **Adrenaline** – Decreases vascular absorption and allows more of the local anaesthetic molecule to reach the nerve target.
- This improves latency, depth and duration of anaesthesia (minimal). Duration prolonged lignocaine but not much effect on bupiv or ropiv.
- Useful as a marker of inadvertent intravascular injection. However can be masked in parturient, GA or beta blocked case
- 5 mcg/ml or 1:200,000 is a compromise between efficacy and systemic side effects of adrenaline (arrhythmias) and local toxicity exacerbation(eg neuropathy)

- **Clonidine –** Alpha 2 agonist but these rceptors are not present on peripheral nerves.
- Causes hyperpolarisation of cell, locking it in refractory phase blocking currentI/AP Prolongs block duration ~ 2 hours.
- Block alpha 1 receptors → locallised vasoconstriction (220:1)
- Limit 0.5- 1 mcg / kg to avoid hypotension, bradycardia and sedation.
- **Dexmedetomidine** – More selective alpha 2 agonist. Longer duration of block (4hr) but similar side effect profile to clonidine though less bradycardia. No risk of neurotoxicity (1620:1 alpha 2:1)
- Optimal dose 50-60mcg perineural
- Increased differential block

Factors affecting in vivo contd…

More additives

- **Dexamethasone** - Most effective agent for block prolongation – up to 10 hours. (analgesia), 8 hr sensory, 4 hr motor.
- Mechanism: glucocorticoid receptor perineural → incr inhibitory K channel expression → reducing nerve excitability
- Lesser effect but still present when given systemically.
- Dose 4 – 10mg in adults
- (?ceiling 4mg IV perineural?)
- Systemic 0.1 – 0.2mg/kg IV
- Mixing drugs is off label

- **Carbonation** – discussed earlier

Rapid onset not useful with ultrasound, but still useful in obstetrics, only weak evidence in perineural blocks.

Mixtures – mixed results, can show faster onset and longer duration but toxicity is ***additive*** and usual limits do not apply.

Factors affecting in vivo contd…

Site of injection

- **Distance from nerve** –

Further from nerves with more tissue barriers will result in slower onset eg injection outside brachial plexus sheath cf intrathecal injection of local anaesthetic

- **Pregnancy** – hormonal effects increase suspectibiltiy of nerves to local anaesthetic in parturient.

Toxicity in clinical practice - infusions

- Paediatric data:
- 0.3 mg/kg/hour in < 6months.
- 0.4mg/kg/hr > 6 months.
- Epidural extrapolation in adults is 0.4mg/kg/hr.
- Afghanistan trauma data allows higher safely but ASA large Caucasian male studies with normal cardiac, renal and liver function. (Trauma also increases AAG levels from stress response.)
- Site specificity needs to be considered and lack of extrapolation cf no limit problems.
- Cases of toxicity at levels lower than this in medically complex cases.
- Dose reduce by 10 -20% in the following = uremia, CCF, hepatic impairment, hypoalbuminema
- Poor data

Mechanism of LAST

- Mitochondrial metabolism is most important target of LAST.
- Multiple effects on metabotropic and ionotropic receptors.
- Hence highly aerobic organs such as brain and heart most affects.
- Oxidative phosphorylation is inhibited in mitochondria→ depletion of ATP → anaerobic metabolism instead.

LAST narrative review Anaesthesia 2021; 76: Supp 1:26-39

LAST prevention – ASRA guidelines

No single measure can prevent it completely

Use lowest effective dose = (concentration x volume)

3-5ml aliquots pausing approx 15 – 30 sec between each, wait 30 45sec with fixed needle technique. Also wait longer for lower limb blocks.

Less important for ultrasound guided block – especially as frequent needle reposition and direct visualization of injectate.

Aspirate needle before each injection – be aware 2% false negative rate.

When injecting potentially toxic dose use adrenaline as an intravascular marker (adrenaline 1:200,000) Classic test dose is 10-15mcg of adrenaline and positive is regarded as HR incr > 10 bpm. SBP > 15 mmHg.

Be aware that elderly, pregnant, beta blocked patients may miss.

Auditory changes, metallic taste, perioral tingling and excitation and agitation often occur but will not occur in sedated patients.

In children adrenaline dose > 0.5mcg/kg look for SBP > 15mmHg increase.

LAST diagnosis

- Agitation
- Seizure
- Cardiac toxicity (arrhythmias)
- Cardiac depression (brady)
- < 60 sec = intravascular – brain
- 1-5 min = lower limb, intermitten vascular
- Can present > 15 min

TABLE 3. Recommendations for Diagnosing LAST

- Classic descriptions of LAST depict a progression of subjective symptoms of CNS excitement (agitation, auditory changes, metallic taste or abrupt onset of psychiatric symptoms), followed by seizures then CNS depression (drowsiness, coma, or respiratory arrest). Near the end of this continuum, initial signs of cardiac toxicity (hypertension, tachycardia, or ventricular arrhythmias) are supplanted by cardiac depression (bradycardia, conduction block, asystole, decreased contractility). However, there is substantial variation in this classic description, including:
  - Simultaneous presentation of CNS and cardiac toxicity
  - Cardiac toxicity without prodromal signs and symptoms of CNS toxicity
  - Thus, the practitioner must be vigilant for atypical or unexpected presentation of LAST (I; B).
- The timing of LAST presentation is variable. Immediate (<60 s) presentation suggests intravascular injection of local anesthetic with direct access to the brain, whereas presentation that is delayed 1–5 mins suggests intermittent intravascular injection, lower extremity injection, or delayed tissue absorption. Because LAST can present >15 mins after injection, patients that receive potentially toxic doses of local anesthetic should be closely monitored for at least 30 mins after injection (I; B).
- Case reports associate LAST with underlying cardiac, neurologic, pulmonary, renal, hepatic, or metabolic disease. Heightened vigilance may be warranted in these patients, particularly if they are at the extremes of age (IIa; B).
- The overall variability of LAST signs and symptoms, timing of onset, and association with various disease states suggests that practitioners should maintain a low threshold for considering the diagnosis of LAST in patients with atypical or unexpected presentation of CNS or cardiac signs and symptoms after receiving more than a minimal dose of local anesthetic (IIa; B).

The class of recommendation and level of evidence for each intervention are given in parenthesis (Table 1).

LAST treatment

Stop injection and call for help….

- Secure airway and ventilate
- More important than adult cardiac arrest as hypoxia and acidosis will exacerbate toxicity and treatment of this will prevent progression in some cases.
- Terminate seizures with benzo's. Best drug as does not depress cardiac contractility, if not available small dose of propofol or thio can be used but consider myocardial depression with these
- Persistent seizures paralyse with NMBA to prevent worsening of acidosis with muscular contractions.

- Cardiac arrest → ALS with following modifications:
- 1. Use less adrenaline up to 1mcg/kg or 10 – 100mcg – arrhythmogenic and increases lactate
- 2. Avoid vasopressin (very poor outcome in animal models secondary to pulmonary haemorrhage) due to intense vasoconstriction and reduced perfusion
- Intralipid 1.5ml /kg bolus --> 0.25ml/kg/min infusion 10 minutes

Then repeat bolus 0.5ml/kg/min

- Max 10ml/kg over 30 min.
- ECMO if this is failing

Neal et al ASRA guidelines RAPM; 2010

Intralipid mechanism

- Acts a a shuttle not a sink.
- Shuttles the local anaesthetic away from the well perfused organs (heart and brain) and ultimately transfers it to less well perfused organs.
- Reduction in cardiac concentration → improves the depressed cardiac output, at lower levels intralipid itself may boost cardiac output.

Picard et al Editorial Anaesthesia 2016; 71: 879 - 882

Local toxicity

- Neurotoxicity – does occur at clinically relevant concentrations.
- Correlated with intra neuronal – intra fascicular injections.
- Especially high pressure (> 20 psi)
- Use standardised syringe size (esp 20 ml)
- USS equivocal

- Local skin necrosis – direct and secondary to vasoconstrictors if added – can be a volume effect

Tumescent local anaesthesia

- Injection of large amounts of local anaesthetic subcutaneously with adrenaline and other additives
- Up to 35 – 55 mg /kg lignocaine have shown to have safe plasma levels (< 5mcg/ml) in some case series
- Case reports of reactions as per scenario 1
- Usually concomitant comorbidities or additional sedation
- Needs further research

Miller's Ed 9

Neuropathic pain and lignocaine infusions

Cocaine toxicity

- Early signs:
- Headache
- Nausea, vomiting and abdominal pain
- Excitement, confusion, restless, hallucinations
- Central and peripheral adrenergic stimulation :
  - Tachycardia
  - Hypertension
  - Aortic dissection
  - Arrhythmias – even VF
  - Accelerated coronary artery disease (chronic)
  - Coronary spasm
  - Infarction
  - Sudden death
- Intracerebral vasospasm causing:
  - Seizures
  - Stroke
  - Rigidity
  - Hyperreflexia
  - Hyperthermia
- Inhalational of cocaine:
  - Alveolar haemorrhage
  - Pulmonary oedema
- Crack is heat stable free base form of cocaine → can smoke it

Cocaine 1% - 10% solution

- Local anaesthetic and indirect sympathomimetic
- Dose 1.5mg/kg
- Toxic dose 3mg/kg

- Easy to exceed recommended dose in gauze ribbon inserted into nose
- Action – onset 1 min, max in 5mins.
- Duration 20-30 minutes.

Cocaine Perioperative Management

- Consider HDU preoperatively if need emergency surgery whilst acutely intoxicated.
- Treat life threatening side effects of vasospasm with vasodilators, antiarrhythmic agents and alpha/beta blockade combination with invasive monitoring.
- Avoid local anaesthetic and vasopressors intraoperatively
- Delay non urgent surgery
- T1/2 = 90 minutes.
- Not available in POW public or private pharmacy
- Used still in private by ENT (esp St Lukes)
- Limited stock at SCH – 1% solution used for oral and nasal mucositis in kids with chemotherapy(especially teenagers)

Questions?

Main References

- Miller's Anaesthesia – Edition 9. 2020. Chapter 29 Local Anaesthetics.
- Neal et al ASRA Practice Advisory on LAST. RAPM 2010; 32:152-161
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