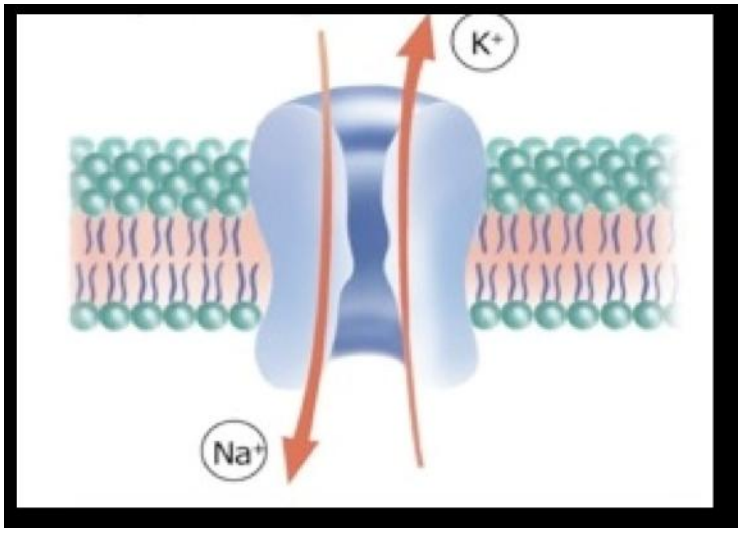
Local Anaesthetic Toxicity and Tumescent Anaesthesia

Local anaesthetics are important tools used in the everyday practice of medicine. The first local anaesthetic was cocaine. In 1884, Koller used topical cocaine in the eye and was credited with the introduction of local anaesthesia into clinical practice[1]. Though they have a relatively safe safety profile when used within the recommended dosage regimens, in overdose or inadvertent intra arterial or intravenous injection they can be lethal and very difficult to manage. A lot of my discussion will revolve around lignocaine, but I will mention other agents when relevant.

Pharmacology and Physiology of Overdose

Local anaesthetics (LAs) stabilize the membrane of excitable cells through inhibition of the tetrodotoxin sensitive sodium channel, which prevents the transmembrane sodium shifts that cause depolarization. In peripheral nerves, this causes conduction blockade and anaesthesia.

Figure 1. Na^+ Channel Blockade (Permission from Astra Zeneca)



On the heart lignocaine has little effect on normal automaticity or conduction. At higher concentrations, lignocaine can decrease both automaticity and conduction by shortening the action potential and the refractory period of both His-Purkinje cells and healthy ventricular muscle. This can occur at therapeutic concentrations in the presence of sinus node dysfunction, abnormal His-Purkinje conduction, or ischaemia. The net effect being that there is an increased risk of conduction abnormalities and life threatening arrhythmias. After overdose, sodium conduction can be decreased even in normal tissue and can produce wide QRS complex arrhythmias, vasodilatation, low output shock, decreased automaticity, slow ventricular rhythm and asystole.

The duration of action of lignocaine is dependent on many factors including: the dose, rate and site of drug administration, lignocaine concentration before and after injection, the patient's clearance of the drug, percentage of protein

bound lignocaine, patient's physiologic state, the presence of other drugs and the concentration of lignocaine metabolites[2].

Table 1 – Factors affecting local anaesthetic activity

Factors affecting local anaesthetic activity
1. Site of injection and dose – peak plasma concentrations are influenced by the site of injection 2. Addition of vasoconstrictor – prolongs duration of action and decreases systemic absorption with lignocaine but not with bupivacaine or ropivacaine 3. Tissue pH – infection produces acidic tissue and decreases activity of local anesthetics 4. Plasma protein binding is inversely related to the plasma concentration- decreases in pregnancy, protein deficiency, neonate, malignancy. It increases in sepsis, stress and renal failure 5. Hepatic impairment leads to decreased metabolism 6. Hyperkalaemia leads to a increased resting membrane potential and an increased local anaesthetic affect 7. Hypercalcaemia has the opposite effect to hyperkalaemia 8. Pregnancy increases CNS sensitivity to local anaesthetics and increases cardiotoxicity 9. Circulatory state affects systemic absorption 10. Drugs can interfere with the action of local anaesthetics eg.metoprolol, cimetidine

Table 2 - Key Pharmacokinetic Properties of Local Anaesthetics

Agent	pKa (25°C)	Protein Binding (%)	Site of metabolism	$T_{1/2}$ (min)	V_d (L)	Cl (L/min
Prilocaine	7.9	55	Lung, Kidney, Liver	0.5	261	2.84
Lignocaine	7.85	60-80	Liver	1.0	91	0.95
Ropivacaine	8.1	94	Liver			
Bupivacaine	8.1	96	Liver	2.7	72	0.47

Table 3 - Key Pharmacodynamic Properties of Local Anaesthetics

Agent	Onset (min)	Duration (min)	Relative Potency	Max. Dose Plain for 70kg Male (mg)	Max. Dose with Adrenaline For 70kg Male (mg)
Prilocaine 0.5-1%	2-5	15-45	1	500 (7mg/kg)	600 (8mg/kg)
Lignocaine 0.5-1%	2-5	60-120	1	300 (5mg/kg)	500 (7mg/kg)
Ropivacaine 0.2-0.75%	1-15	120-360	4	188 (2.5mg/kg)	188
Bupivacaine 0.25%	2-5	240-540	4	175 (2.5mg/kg)	175

Table 4 – Calculating Local Anaesthetic Doses

Calculation of Local Anaesthetic Doses

Local anaesthetic agents are marketed with drug concentrations expressed as percentages. To ascertain the strength of the solution do the following:
A 1% solution is prepared by dissolving 1g of drug in 100ml of solution
Therefore, 1g/100ml = 1000mg/100ml = 10mg/ml
To calculate the strength from the % quickly, move the decimal point 1 place to the right.
i.e. 0.25% Bupivacaine = 2.5mg/ml
0.5% lignocaine = 5mg/ml
1.0% lignocaine = 10mg/ml

When combined with an anaesthetic solution, adrenaline is usually in a 1:100000 or 1:200000 dilution
1ml of 1:1000 adrenaline = 1mg
0.1ml of 1:1000 adrenaline in 10ml anaesthetic solution = 1:100000 dilution = 0.010mg/ml
0.1ml of 1:1000 adrenaline in 20ml anaesthetic solution = 1:200000 dilution = 0.005mg/ml
e.g.

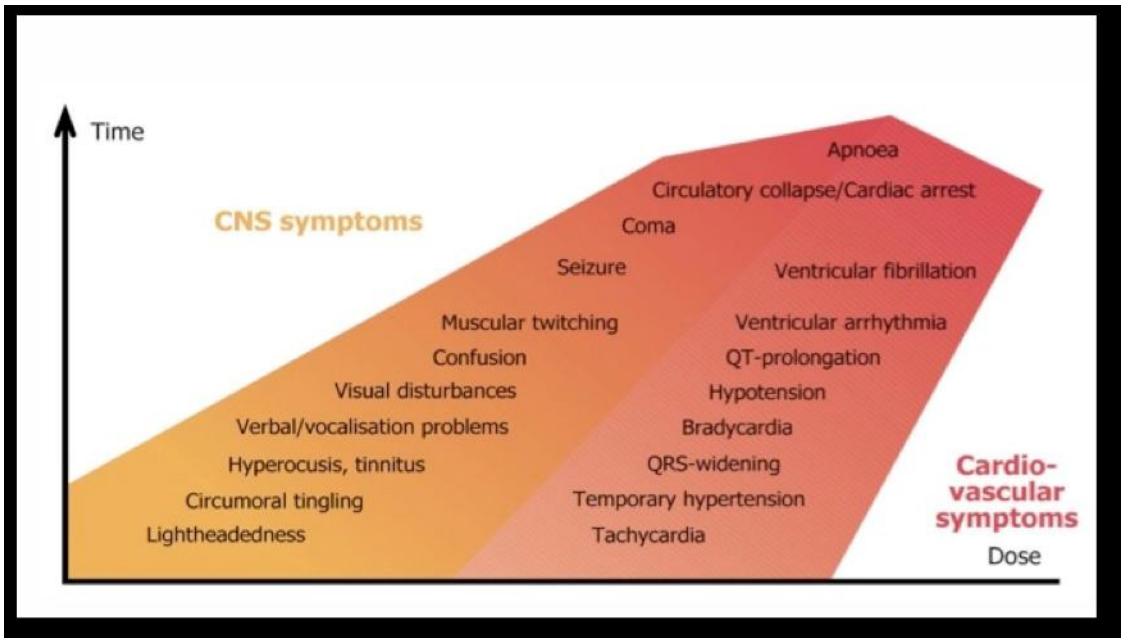
	1:100000	**1:200000**
5ml	0.050 mg	0.025 mg
10ml	0.100 mg	0.050 mg
20ml	0.200 mg	0.100 mg

Local Anaesthetic Toxicity and Management

Toxicity to local anaesthetics and lignocaine can be divided into systemic and local effects.

There are serious effects of lignocaine and its metabolites on the CVS and CNS. GIT, haematologic and immunologic signs are indirect and less common.

Figure 2 – Lignocaine Toxicity by Time and Dose (with permission from Astra Zeneca)



CNS

The dose and blood level of local anaesthetics required to produce CNS toxicity is lower than that resulting in circulatory collapse. The initial CNS symptoms are light-headedness and dizziness followed by circumoral tingling, then by visual and auditory disturbances such as difficulty focussing and tinnitus. Other subjective CNS symptoms include disorientation and drowsiness. Objective signs are usually excitatory and include shivering, muscular twitching, tremors involving facial muscles and distal parts of the extremities. Finally tonic clonic seizures occur. If the patient is given a large enough dose of rapid IV lignocaine or other LA, the initial signs of CNS excitation are followed by a state of generalised CNS depression. Seizure activity stops, respiratory depression and apnoea follow. In some patients CNS depression is seen without a preceding excitatory phase particularly if CNS depressants have been given.

Convulsions from an inadvertent IV bolus of lignocaine or other LA can generally be terminated by small doses of midazolam or thiopentone. Phenytoin does not have a role, as it is a sodium channel blocker, which will only make the seizures worse.

Respiratory or metabolic acidosis increases the risk of CNS toxicity. An increase in $PaCO_2$ from 25 to 40mmHg and from 65 to 80 mmHg decreases the convulsive threshold by 50%[3]. An elevated $PaCO_2$ increases cerebral blood flow, which delivers more local anaesthetic to the brain. In addition diffusion of CO_2 into neuronal cells decreases intracellular pH, which facilitates conversion of the base form of the drug to its cationic. The cationic form does not diffuse well across nerve membranes, so ion trapping will occur which increases toxicity.

Hypercapnia or acidosis (or both) also decreases the plasma binding of lignocaine[4,5]. Therefore an elevation of $Paco_2$ or a decrease in pH will increase the proportion of free drug available for diffusion into the brain. The clinical implications of the above deserve special mention. Seizures produce hypoventilation and a combined metabolic and respiratory acidosis, which will further worsen the CNS toxicity. It is essential to provide rapid assisted ventilation and circulatory support to avoid any worsening of the acidosis and hypoxia. **Clinicians performing major conduction blockade should have the following equipment and drugs available: monitoring equipment (ECG, NIBP and SPO_2), oxygen tank or wall oxygen, airway equipment, bag and mask, midazolam, adrenaline, defibrillator.**

CVS

Extremely high doses of lignocaine will depress spontaneous pacemaker activity in the sinus node resulting in sinus bradycardia and sinus arrest. It also exerts a dose dependent negative inotropic action on cardiac muscle, it is not as potent however as bupivacaine.

Lignocaine and other local anaesthetics exert a biphasic effect on peripheral vascular smooth muscle. So at low doses it causes vasoconstriction and at higher doses vasodilatation.

Lignocaine is a less potent local anaesthetic as compared to bupivacaine or ropivacaine and a higher dose is required to cause cardiovascular and CNS toxicity. The ratio of the dosage required for irreversible cardiovascular collapse (CC) and the dosage that will produce CNS toxicity (convulsions), i.e. the CC/CNS ratio, is lower for bupivacaine than for lignocaine[6].

CC/CNS dose ratio – lignocaine 7.1±1.1

bupivacaine 3.7±0.5

NB this indicates that 7 times as much lignocaine is required to induce irreversible CVS collapse as is needed to produce convulsions

Bupivacaine is more likely to produce severe cardiac arrhythmias than lignocaine. Ventricular arrhythmias are rarely seen with lignocaine[7]. Arrhythmias when they do occur with bupivacaine are difficult to treat because of the very slow reversal of sodium blockade after a cardiac action potential (this is faster with ropivacaine).

No medications are uniformly effective in facilitating resuscitation from bupivacaine - induced cardiac arrest or severe VT. The emphasis is on ALS resuscitation principles.

Hypercapnoea, acidosis and hypoxia potentiate the negative chronotropic and inotropic action of lignocaine and bupivacaine and increase the frequency of cardiac arrhythmias.

Methemoglobinaemia

This is a side effect that is unique to prilocaine overdose (more than 8mg/kg body weight)[8]. It is spontaneously reversible or treated by IV Methylene Blue (1mg/kg over 5 minutes). Remember that prilocaine is a component of EMLA.

Allergies

Allergic reactions are very rare to local anaesthetic agents[9].

Local Tissue Toxicity

All local anaesthetics can produce direct toxicity to nerves if they achieve sufficiently high intraneural concentrations.

Lignocaine has also been associated with poor wound healing and increased risk of wound infection especially when combined with adrenaline.

Local injuries produced by the local anaesthetic needle penetrating an organ or tissue.

Tumescent Anaesthesia

This technique involves the subcutaneous infiltration of very large volumes of dilute local anaesthetic solution (usually containing adrenaline), until the tissues become tense and swollen. The aim is to provide particular conditions primarily for liposuction and other superficial and plastic surgical procedures. The operation may then be undertaken with the patient completely awake, sedated or anaesthetised.

Klein first described tumescent anaesthesia in 1987[10]. Large volumes of isotonic fluid (normal saline or Hartmann's) along with low concentrations of adrenaline and 1% lignocaine (35mg/kg) are infused into the subcutaneous tissues to the point of tissue turgor. The primary benefits behind this technique were to avoid the supposed risks of general anaesthesia, decreased blood loss in liposuction and provide postoperative anaesthesia up to 18 hours[11].

This technique is mainly used in the USA and Germany particularly with office based practitioners working without the assistance of an anaesthetist. In my personal communication with plastic surgeons performing this procedure in Australia, it is done in a hospital environment with an anaesthetist present, who is giving sedation to the patient. They are not using more than the standard recommended maximal dose of whatever local anaesthetic agent that they prefer.

The dose recommended for lignocaine by Klein(35mg/kg) is 5 times the recommended dose to be given with adrenaline. When we consider the potential toxicity of such a dose we have to take into account a number of factors, which affect its absorption. We have to account for the site of administration, plasma concentration following injection, the pattern of

distribution to other tissues and the rates of both metabolism and excretion. Local anaesthetics are absorbed fairly slowly from subcutaneous tissues due to poor vascularity and because much of the drug is initially absorbed into the fat. The vasoconstriction produced by the adrenaline will further slow the process. A proportion (up to 35%) of the lignocaine administered for liposuction is removed by the aspirate[12]. This would still leave a potentially lethal amount of lignocaine, but even this would not matter if absorption was slower than the rate of metabolism and excretion. There have been some studies of plasma lignocaine concentrations with this technique, and the results have been used to make claims of safety[11,13,14]. The concentrations however continue to rise for 16 or even 23 hours[15], long after the patient has been discharged from medical supervision. The sampling times in the studies were also wide and variable. While I think higher does of lignocaine may be safe in tumescent anaesthesia I do not believe the evidence is strong enough yet. More vigorous research needs to be done.

Dr Klein's claims that general anaesthesia imposes unacceptable high risk to patients having liposuction are ridiculous, ill informed and misleading. Australian anaesthetists have deaths due to anaesthesia at least once every 56000 administrations of general anaesthesia[16]. Dr Klein gives figures of 2500 – 10000. He also cites a study of deaths related to sedation with plastic surgery procedures. These again were of cases performed by non-anaesthetists in their rooms.[17]

There are still questions on the safety of tumescent anaesthesia. Even though the proponents claim that it is very safe. In one often quoted study of 15336 patients undergoing tumescent liposuction that reported no complications, has significant flaws. The authors wrote to 1778 Fellows of the American Society of Dermatologic Surgery but only 66 provided data[18]. A response rate of 4% must cast doubt on the validity of the results. Also self-reporting of results by surgeons who have a vested interest in the procedure also colours the results as it is a reporting bias.

In 1999 the NEJM published an article, which reported five deaths after tumescent anaesthesia in New York between 1993 and 1998. The authors linked 2 deaths to lignocaine toxicity, one to fluid overload and 1 to thromboembolic complications. 1 of the deaths could not be fully investigated due to consent issues[19]. Since then several other deaths have been reported in medical journals.[20]

Whether or not the infusion of large amounts of fluid produces good conditions for certain types of surgery is for the surgeons to decide not me. As for the safety of the technique especially when using supra maximal recommended lignocaine doses has not been proven to my satisfaction. More vigorous studies need to be performed. I do not believe it is prudent to perform this procedure in an office type of environment certainly without an anaesthetist being present or having resuscitation equipment available. I also believe that the patient should be monitored for at least 24 hours post procedure as toxicity can be delayed secondary to continuous absorption from the tissues.

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