Episode 20 - Local Anaesthetic Systemic Toxicity

Presentations

Immediate, e.g. intravascular injection
Delayed, e.g. continuous infusion, wound infiltration (overdose)

Adverse drug reactions to local anaesthetics

Antigens	Para-amino benzoic acid (plasma cholinesterase breakdown of ester local anaesthetics) leading to allergic reactions
Metabolites	O-toluidine (product of Prilocaine metabolism) leading to methaemoglobinaemia.
Direct effects	Local anaesthetic systemic toxicity (LAST). Incidence

Mechanism of action

Local anaesthetics block voltage-gated sodium channels in excitable tissues (nerve and muscle). Toxicity therefore primarily leads to dysfunction of the central nervous system (seizures and coma) and cardiovascular system (arrhythmias and reduced myocardial contractility). Skeletal muscle and smooth muscle rely more on calcium for contraction and are less affected by the direct effects of local anesthetics. Note however, that since all nerves will be affected (not just the CNS) and thus symptoms and signs may reflect sensory, motor or autonomic dysfunction.

Risk factors

Anything that predisposes to high concentrations in the blood. a) Volume of distribution - Larger doses and smaller patients. Skeletal muscle forms a sort of reservoir in which local anaesthetic can be deposited so it stands to reason that individuals with less skeletal muscle are at higher risk of toxic plasma concentrations (the elderly, frail, chronically or critically unwell). b) Protein binding determines the free drug fraction. Thus patients with reduced levels of alpha-1-acid glycoprotein are therefore at higher risk. This includes pregnant women, neonates and infants, and the elderly. Any frail or cachectic patient for that matter. c) Potency - lipid soluble, potent local anaesthetics (i.e. Bupivacaine) have a greater likelihood of causing toxicity. Bupivacaine has a greater affinity for cardiac sodium channels than either Lidocaine or Levo-bupivacaine.

Metabolism and excretion. These affect how quickly local anaesthetic is cleared from the plasma in relation to how quickly it is entering the plasma. Liver disease or a liver that doesn't work means that levels of amide local anaesthetic can build up over time. Renal disease doesn't affect things too much. Although excretion may be impaired, renal patients actually have relatively normal levels of alpha-1-acid glycoprotein. In fact, surprisingly, so too do patients with quite advanced liver failure. The difference being that liver failure really does affect how the drugs are metabolised.

Route of administration

The vascularity of the tissue being infiltrated has an effect on how quickly plasma levels rise following administration.

Field blocks (fascial plane blocks)	Highest risk (vascular tissues)
Intercostal block Intrapleural Paravertebral	
Epidural injection (including caudal)	Moderate risk (intravascular injection)
Upper limb blocks	
Lower limb blocks	Lowest risk

Peripheral nerve blocks

Using ultrasound for peripheral nerve blocks reduces the risk four-fold (visualisation of blood vessels and spread of local anaesthetic around the nerve - permits the use of smaller doses). The best way to inject local anaesthetic for a peripheral nerve block is in small aliquots of 3-5 ml waiting for about 15-30 seconds between.

Symptoms and signs

Central nervous system	Tinnitus, perioral tingling, diplopia, a metallic taste, slurred speech, tremor, confusion, agitation, seizures, coma, respiratory depression.
Cardiovascular	Hypertension and tachycardia, myocardial depression, bradycardia, peripheral vasodilation, hypotension, arrhythmia, cardiac arrest.

Management

Lipid emulsion (intralipid) - acts as a sink for circulating local anaesthetic. It sequesters local anaesthetic, levels of free drug in the plasma fall, and the local anaesthetic that is bound to sodium channels moves away from these binding sites. Large volumes of lipid can lead to pancreatitis and the patient must be followed up to monitor for this. Laboratory biochemistry tests will be inaccurate due to high lipid levels (magnesium, calcium, phosphate, creatinine, liver enzymes, Bilirubin, and amylase and lipase).

Seizures	Benzodiazepines, Levetiracetam (as for status epilepticus).
Arrhythmias	Amiodarone (avoid beta-blockers and calcium channel antagonists - interfere with cardiac conduction pathways)
Cardiac arrest	Use a smaller dose of Adrenaline (1 mcg/ml) since larger doses can worsen arrhythmia. Prolonged resuscitation (it takes time for local anaesthetic to be metabolised).

Intralipid

Made up of soya bean oil, egg phosphatides, and glycerine. 20% emulsion (200 g of soya oil per litre). Dosing in millilitres: 1.5 ml/kg bolus followed by an infusion of 15 ml/kg/hr. If required two more boluses at 5 minute intervals (so three doses in total) after the second bolus and you can double the infusion rate to 30 ml/kg/hr. The maximum cumulative dose however is 12 ml/kg (about 750 to 1000 ml for an adult). Infusion time is 15-45 minutes depending on boluses and infusion rate.