

Local anaesthetics

Sodium channel blockers that stop nerve conduction at the site applied, safe by design because their effect stays local - until systemic absorption produces local anaesthetic systemic toxicity, the hazard that defines how this class is dosed.

Online guide: <https://www.medguideglobal.com/pharmacology/analgesia-and-anaesthesia/local-anaesthetics>

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Quick revision

One Liner: Local anaesthetics block voltage-gated sodium channels in a use-dependent manner, preventing conduction at the site applied; their principal danger is systemic absorption producing CNS and then cardiovascular toxicity, not a local tissue effect.

1. Mechanism: block voltage-gated sodium channels (VGSCs), preventing sodium influx and impulse transmission, with more frequently firing channels blocked preferentially (use-dependent block). [1]
2. Chemically divided into amino amides (lidocaine, bupivacaine, ropivacaine), metabolised hepatically by cytochrome P450, and amino esters (procaine, tetracaine, benzocaine), hydrolysed rapidly by plasma pseudocholinesterase. [1]
3. Local anaesthetic systemic toxicity (LAST) follows a predictable sequence: CNS signs first (metallic taste, circumoral numbness, agitation, seizures), then cardiovascular signs (hypotension, dysrhythmia, cardiovascular collapse). [1]
4. First-line LAST treatment is 20% IV lipid emulsion, given as an initial bolus followed by a continuous infusion, alongside standard resuscitation. [1]
5. Bupivacaine has high affinity and slow dissociation from cardiac sodium channels, making it disproportionately more cardiotoxic than the less potent lidocaine, which produces mainly neurologic toxicity. [2]
6. Ester agents carry a higher allergic-reaction risk than amides because their metabolism produces para-aminobenzoic acid (PABA); a reaction to one ester predicts cross-sensitivity to others in the ester group. [1]
7. Benzocaine and prilocaine are the two local anaesthetics most associated with methaemoglobinaemia; benzocaine accounts for roughly two-thirds of reported local-anaesthetic-related cases. [3]
8. Epinephrine added to a local anaesthetic reduces systemic absorption and extends duration of action by 50 to 100%, but is avoided in the digits, nose, ears and penis. [1]

Overview

1. Local anaesthetics produce reversible loss of sensation in a defined area by blocking voltage-gated sodium channels, preventing the nerve impulse from ever forming at the site applied. Chemically they split into two groups: amino amides (lidocaine, bupivacaine, ropivacaine), metabolised in the liver by cytochrome P450 enzymes, and amino esters (procaine, tetracaine, benzocaine), hydrolysed rapidly by plasma pseudocholinesterase - a distinction that predicts both duration of action and the class's principal allergy risk. [1]
2. The class is unusually safe when it stays local, because the whole point of the mechanism is confined-area conduction block. The danger appears when the drug is absorbed systemically in sufficient quantity: local anaesthetic systemic toxicity (LAST) produces a predictable sequence of CNS effects - metallic taste, circumoral numbness, agitation, seizures - followed by cardiovascular effects up to collapse. First-line treatment is 20% intravenous lipid emulsion. [1]
3. Within the class, two agents illustrate the risk this way of learning tries to teach. Bupivacaine binds cardiac sodium channels with high affinity and dissociates slowly, making it disproportionately cardiotoxic compared with the less potent lidocaine, which produces mainly neurologic toxicity. Benzocaine and prilocaine are separately notable for causing methaemoglobinaemia, a distinct hazard unrelated to sodium channel blockade at all. [2][3]

Classification and drug examples

Intro: Best learned by chemical class, since ester versus amide status predicts metabolism, duration and - critically - the allergy risk pattern, more reliably than potency alone.

1. Name: Amino amides

1. Note: Hepatic cytochrome P450 metabolism; longer shelf stability; true allergic reaction is rare.

1. Name: Lidocaine

Lignocaine

1. Route: Infiltration/topical/IV/regional

1. Note: The reference amide agent; LAST from lidocaine is predominantly neurologic rather than cardiac. [2]

2. Name: Bupivacaine

2. Route: Infiltration/regional/epidural

2. Note: High cardiac sodium channel affinity with slow dissociation, giving it disproportionate cardiotoxicity relative to its neurologic toxicity. [2]

3. Name: Ropivacaine

3. Route: Infiltration/regional/epidural

3. Note: Structurally related to bupivacaine but with a somewhat different cardiotoxicity profile, developed partly to reduce that risk. [1]

4. Name: Prilocaine

4. Route: Infiltration/topical

4. Note: One of the two agents most associated with methaemoglobinaemia. [3] [1]

2. Name: Amino esters

2. Note: Rapid plasma pseudocholinesterase hydrolysis; shorter duration; higher allergic reaction risk through the shared PABA metabolite.

1. Name: Benzocaine

1. Route: Topical

1. Note: The single agent most associated with local-anaesthetic-related methaemoglobinaemia, accounting for roughly two-thirds of reported cases. [3]

2. Name: Procaine

2. Route: Infiltration

2. Note: An older ester agent, largely superseded in routine practice by amides. [1]

3. Name: Tetracaine

3. Route: Topical/spinal

3. Note: Used topically and for spinal anaesthesia; shares the ester group's allergy risk pattern. [1] [1]

Mechanism of action

Summary: Local anaesthetics block voltage-gated sodium channels, most effectively when the channel is in its inactivated state, preventing sodium influx, depolarisation and action-potential propagation in the nerve at the site of application. The block is use-dependent, favouring rapidly firing fibres - the same fibres that carry pain signals.

Target: Voltage-gated sodium channels (alpha subunit)

Cidal Static: Not applicable - this class blocks nerve conduction rather than acting on an organism.

Kill Kinetics: Not applicable in the antimicrobial sense; block intensity tracks local drug concentration and channel state.

1. Step: 1

1. Title: The drug reaches the nerve membrane in its neutral, un-ionised form

1. Detail: Local anaesthetics are weak bases; the neutral form crosses the nerve membrane more readily than the ionised form. [1]

2. Step: 2

2. Title: Intracellular re-ionisation and channel binding

2. Detail: Once inside the axoplasm, the drug re-ionises and binds the voltage-gated sodium channel from within, preferentially when the channel is in its inactive state. [1]

3. Step: 3

3. Title: Sodium influx is blocked

3. Detail: Channel binding prevents sodium influx, which stops the membrane from depolarising past threshold. [1]

4. Step: 4

4. Title: Use-dependent block accumulates in rapidly firing fibres

4. Detail: Channels that open and close more frequently are blocked more effectively, giving the drug a degree of selectivity for actively signalling pain fibres over quiescent tissue. [1]

5. Step: 5

5. Title: Impulse transmission along the nerve is halted

5. Detail: With enough channels blocked along a segment of nerve, the action potential cannot propagate past that point, producing the local loss of sensation. [1]

Major clinical uses

1. Drug: Lidocaine

1. Indication: Infiltration anaesthesia, topical anaesthesia, regional nerve blocks, and IV use in select antiarrhythmic and analgesic contexts

1. Line: first-line, most versatile agent

1. Note: Also used systemically for other indications outside this class's core anaesthetic use. [1]

2. Drug: Bupivacaine

2. Indication: Regional and epidural anaesthesia, particularly where a longer duration of action is wanted

2. Line: targeted

2. Note: Cardiotoxicity risk is the key consideration governing dose and monitoring. [2]

3. Drug: Tetracaine

3. Indication: Topical ophthalmic anaesthesia and spinal anaesthesia

3. Line: targeted

3. Note: Ester metabolism carries the class's allergy risk pattern. [1]

4. Drug: Benzocaine

4. Indication: Topical mucosal anaesthesia, e.g. oral and throat products

4. Line: over-the-counter topical use

4. Note: Methaemoglobinaemia risk is the dominant safety concern, especially in young children. [3]

Pharmacokinetics

1. Drug: Lidocaine

1. Route: Infiltration/topical/IV/regional

1. Absorption: Depends on site, vascularity and whether epinephrine is co-administered

1. Csf Penetration: Not applicable to peripheral local use

1. Metabolism: Hepatic, cytochrome P450

1. Elimination: Renal, as metabolites

1. Half Life: See prescribing reference

1. Dose Adjust: Hepatic impairment reduces clearance; maximum dose limits apply and depend on site/technique [1]

2. Drug: Bupivacaine

2. Route: Infiltration/regional/epidural

2. Absorption: Depends on site and vascularity

2. Csf Penetration: Not applicable to peripheral use; used directly in epidural/spinal technique

2. Metabolism: Hepatic, cytochrome P450

2. Elimination: Renal, as metabolites

2. Half Life: See prescribing reference

2. Dose Adjust: Narrower safety margin than lidocaine because of cardiotoxicity; maximum dose limits are strictly observed [2]

1. This page gives no dose regimens by design. Maximum local anaesthetic dose depends on the specific agent, whether epinephrine is co-administered, the site injected, and patient weight and comorbidity, and must come from a current prescribing reference and the treating clinician.

2. Every setting using a local anaesthetic in quantities capable of producing LAST should have resuscitation equipment and 20% lipid emulsion immediately available. [1]

Adverse effects

Effect: Local irritation, transient numbness beyond the intended area, or minor injection-site discomfort

Detail: Expected, self-limited effects at the site of administration. [1]

1. Effect: Local anaesthetic systemic toxicity (LAST)

1. Detail: CNS signs (metallic taste, circumoral numbness, agitation, seizures) typically precede cardiovascular signs (hypotension, dysrhythmia, cardiovascular collapse).

1. Action: The injection is stopped, help is called, and 20% IV lipid emulsion is administered as a bolus followed by a continuous infusion, alongside standard resuscitation. [1]

2. Effect: Methaemoglobinaemia

2. Detail: Most associated with benzocaine and prilocaine; reduces the blood's oxygen-carrying capacity and can be life-threatening, with neonates more susceptible.

2. Action: Severe cases are treated with intravenous methylene blue; G6PD deficiency is a contraindication to methylene blue. [3]

3. Effect: Allergic reaction

3. Detail: More common with ester agents because of the PABA metabolite; cross-sensitivity within the ester group is expected.

3. Action: Avoid the whole ester group after a confirmed ester reaction, and consider an amide alternative under guidance. [1]

1. Drug: Bupivacaine

1. Effect: Disproportionate cardiotoxicity relative to its neurologic toxicity, from high-affinity, slow-dissociating cardiac sodium channel binding. [2]

2. Drug: Lidocaine

2. Effect: LAST from lidocaine is predominantly neurologic rather than cardiac. [2]

Contraindications, precautions and interactions

Known hypersensitivity to the specific agent or, for an ester agent, to any ester local anaesthetic. [1]

1. Epinephrine-containing formulations in end-arterial territories: digits, nose, ears and penis. [1]

2. G6PD deficiency, if methylene blue might be needed for methaemoglobinaemia treatment. [3]

3. Cardiac conduction abnormalities, with bupivacaine specifically, given its cardiotoxicity profile. [2]

1. With: Other sodium channel blocking drugs (e.g. certain antiarrhythmics)

1. Effect: Additive sodium channel blockade and toxicity risk. [1]

2. With: Oxidising drugs, with prilocaine or benzocaine

2. Effect: Additive methaemoglobinaemia risk. [3]

Comparison tables

Title: Amide versus ester local anaesthetics

Caption: The chemical distinction that predicts metabolism, duration and allergy risk. A prescribing reference and the treating clinician govern actual therapy.

1. Key: feature
1. Label: Feature
2. Key: amides
2. Label: Amino amides
3. Key: esters
3. Label: Amino esters
1. Feature: Examples
1. Amides: Lidocaine, bupivacaine, ropivacaine
1. Esters: Procaine, tetracaine, benzocaine [1]
2. Feature: Metabolism
2. Amides: Hepatic, cytochrome P450
2. Esters: Plasma pseudocholinesterase (rapid hydrolysis) [1]
3. Feature: Allergic reaction risk
3. Amides: Rare
3. Esters: Higher, via the PABA metabolite; cross-sensitivity within the group [1]

High-yield exam pearls

1. Pearl: "Use-dependent" block is the key phrase for this mechanism.
1. Why: Local anaesthetics preferentially block sodium channels that are firing frequently - which is exactly the pattern of a pain-signalling nerve - giving the class its useful selectivity between conducting and quiescent tissue. [1]
2. Pearl: LAST has a predictable order, and that order is testable.
2. Why: CNS signs (metallic taste, circumoral numbness, agitation, seizure) precede cardiovascular collapse. Recognising the CNS phase early, before cardiovascular signs appear, is the whole point of monitoring during a regional block. [1]
3. Pearl: Bupivacaine's cardiotoxicity is a receptor-kinetics story, not just a potency story.
3. Why: Bupivacaine binds cardiac sodium channels with high affinity and dissociates slowly, so it accumulates block between heartbeats in a way lidocaine does not - this, not simply 'it's a stronger drug,' is why bupivacaine causes disproportionate cardiac toxicity relative to lidocaine. [2]
4. Pearl: Ester allergy is a class effect, amide allergy usually is not.
4. Why: Ester local anaesthetics are hydrolysed to para-aminobenzoic acid (PABA), a known allergen; a patient allergic to one ester should be assumed allergic to the whole ester group, whereas true amide allergy is rare and does not imply cross-reactivity within the amide group in the same way. [1]
5. Pearl: Benzocaine is the leading local-anaesthetic cause of methaemoglobinaemia.
5. Why: Benzocaine accounts for roughly two-thirds of reported local-anaesthetic-related methaemoglobinaemia cases, prompting repeated FDA advisories against benzocaine-containing oral products, especially in young children. [3]

Common exam traps

1. Trap: "Adding epinephrine to a local anaesthetic is always beneficial and never contraindicated."
1. Correction: Epinephrine reduces systemic absorption and prolongs duration, but it is avoided in end-arterial territories - the digits, nose, ears and penis - because of ischaemia risk from vasoconstriction with no collateral supply. [1]

2. Trap: "Lidocaine and bupivacaine carry the same cardiac risk because both are amide local anaesthetics."
2. Correction: Bupivacaine's slow dissociation from cardiac sodium channels makes it disproportionately more cardiotoxic; lidocaine's toxicity profile is predominantly neurologic rather than cardiac. Being in the same chemical class does not mean the same toxicity profile. [2]
3. Trap: "LAST always starts with cardiovascular collapse."
3. Correction: The typical sequence is CNS signs first (metallic taste, circumoral numbness, agitation, seizures), with cardiovascular signs following. Waiting for cardiovascular collapse to suspect LAST misses the earlier warning window entirely. [1]
4. Trap: "A local anaesthetic allergy to lidocaine means avoiding all local anaesthetics."
4. Correction: True IgE-mediated amide allergy is rare, and cross-reactivity between amides is not the pattern seen with esters. The bigger, better-documented cross-reactivity risk is within the ester group, driven by shared PABA metabolite formation. [1]

Self-test questions

1. Question: What is the core mechanism by which local anaesthetics prevent nerve conduction?
 1. They block voltage-gated sodium channels, preventing sodium influx and action potential generation, preferentially in frequently firing channels
 2. They open potassium channels to hyperpolarise the nerve permanently
 3. They inhibit acetylcholinesterase at the neuromuscular junction
 4. They antagonise NMDA receptors in the peripheral nerve
1. Explanation: Local anaesthetics block voltage-gated sodium channels, preventing sodium influx and thus action potential generation. The block is use-dependent, meaning channels that fire more frequently - such as those carrying pain signals - are blocked preferentially. [1]
2. Question: Why is bupivacaine considered disproportionately more cardiotoxic than lidocaine?
 1. Bupivacaine is metabolised entirely by the kidney, unlike lidocaine
 2. Bupivacaine has high affinity for and slow dissociation from cardiac sodium channels, allowing block to accumulate between heartbeats, unlike the more rapidly dissociating lidocaine
 3. Bupivacaine has no effect on cardiac sodium channels at all
 4. Lidocaine is actually more cardiotoxic than bupivacaine
2. Explanation: Bupivacaine binds cardiac sodium channels with high affinity and dissociates slowly, so a meaningful fraction of channels stays blocked between action potentials - an accumulating effect that the more rapidly dissociating lidocaine does not share, explaining why lidocaine toxicity is predominantly neurologic while bupivacaine toxicity is predominantly cardiac. [2]
3. Question: What is the typical clinical sequence of local anaesthetic systemic toxicity (LAST)?
 1. Cardiovascular collapse occurs first, followed later by CNS symptoms
 2. CNS symptoms (metallic taste, circumoral numbness, agitation, seizures) typically precede cardiovascular symptoms (hypotension, dysrhythmia, collapse)
 3. Only cardiovascular symptoms occur; CNS symptoms are not part of LAST
 4. Symptoms are entirely unpredictable and follow no typical pattern
3. Explanation: LAST typically follows a predictable sequence: CNS manifestations appear first, followed by cardiovascular manifestations. Recognising the early CNS phase is what allows intervention before cardiovascular collapse develops. [1]
4. Question: What is the first-line treatment for local anaesthetic systemic toxicity?
 1. High-dose intravenous naloxone
 2. 20% intravenous lipid emulsion, given as a bolus followed by a continuous infusion
 3. Intramuscular epinephrine only
 4. Oral activated charcoal

4. Explanation: 20% intravenous lipid emulsion is the recognised first-line antidote for LAST, administered as a bolus followed by a continuous infusion alongside standard resuscitation measures. [1]
5. Question: Why are ester local anaesthetics more associated with allergic reactions than amides?
 1. Esters are metabolised by plasma pseudocholinesterase into para-aminobenzoic acid (PABA), a recognised allergen, and cross-sensitivity within the ester group is expected
 2. Esters have no metabolism at all and accumulate in tissue
 3. Amides are actually more allergenic than esters
 4. Ester local anaesthetics contain penicillin as an excipient
5. Explanation: Ester local anaesthetics are hydrolysed by plasma pseudocholinesterase, and one metabolic product is para-aminobenzoic acid (PABA), a known allergen. A hypersensitivity reaction to one ester predicts sensitivity to others in the ester group. [1]
6. Question: Which local anaesthetic is most associated with methaemoglobinaemia, and in what population is this especially relevant?
 1. Lidocaine; relevant mainly in elderly patients
 2. Benzocaine, accounting for roughly two-thirds of reported local-anaesthetic-related cases; neonates are more susceptible to methaemoglobinaemia generally
 3. Bupivacaine; relevant only in cardiac patients
 4. Ropivacaine; relevant only during labour epidurals
6. Explanation: Benzocaine is the causative agent in roughly two-thirds of reported local-anaesthetic-related methaemoglobinaemia cases, prompting repeated FDA advisories, particularly regarding benzocaine-containing oral products. Neonates are recognised as more susceptible to methaemoglobinaemia in general. [3]

Frequently asked questions

1. Question: Why do local anaesthetics only numb the area they are injected into?
 1. Answer: Their mechanism - blocking voltage-gated sodium channels to stop a nerve impulse forming - only works where the drug reaches sufficient concentration in the nerve. Problems arise only when enough drug is absorbed into the bloodstream to reach other excitable tissue, such as the brain or heart, which is what local anaesthetic systemic toxicity describes. [1]
2. Question: Why is bupivacaine considered more dangerous than lidocaine if both are amide local anaesthetics?
 2. Answer: Bupivacaine binds cardiac sodium channels with high affinity and releases them slowly, so its block can accumulate between heartbeats in a way lidocaine's more rapidly reversible block does not. That is why bupivacaine toxicity leans cardiac while lidocaine toxicity leans neurologic, even though both work through the same basic mechanism. [2]
3. Question: What are the warning signs of local anaesthetic systemic toxicity?
 3. Answer: Early signs are neurological: a metallic taste, numbness around the mouth, ringing in the ears, agitation or confusion, which can progress to seizures. Cardiovascular signs - low blood pressure, abnormal heart rhythm, or collapse - can follow. Anyone experiencing these symptoms during or after a procedure using local anaesthetic should alert medical staff or seek emergency care immediately. [1]
4. Question: Why do some local anaesthetic mouth or throat sprays carry a warning about a blood disorder?
 4. Answer: Benzocaine-containing topical products are the most common local-anaesthetic cause of methaemoglobinaemia, a condition that reduces the blood's ability to carry oxygen. Young children are especially susceptible, which is why the FDA has issued repeated advisories about these products. [3]

References

- [1] Topical, Local, and Regional Anesthesia and Anesthetics (StatPearls). StatPearls Publishing / NCBI Bookshelf 2025. <https://www.ncbi.nlm.nih.gov/books/NBK430894/>
- [2] Bupivacaine (StatPearls). StatPearls Publishing / NCBI Bookshelf 2026. <https://www.ncbi.nlm.nih.gov/books/NBK532883/>

[3] Methemoglobinemia (StatPearls). StatPearls Publishing / NCBI Bookshelf 2025.
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