What Should Dentists Know about Medicine...

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Learning Outcomes

1. Medical Conditions and Their Impact on Dental Care.
2. Medical Emergency & Resuscitation in the Dental Practice.
3. The Special Care Needs Patient.
4. Geriatrics: Oral Medicine and the Ageing Patient.
5. Management of the Oncologic Patient.
6. Oral Soft Tissue Lesions, Temporomandibular Disorders and Orofacial Pain.
7. Infections, Infectious Diseases and Dentistry.
8. Nutrition and Oral Health.
9. Clinical & Applied Pharmacology and Dental therapeutics.

Pharmacology & Therapeutics in Dentistry

- We are all dealing with an increasing ageing population who are retaining their teeth well into old age. A large proportion of this population will be taking one or two medicines to enable them to continue with their normal daily activities.
- Certain drugs are the mainstay of dental practice. These include antibiotics, analgesics, local anesthetics, and agents to control anxiety.

Pharmacology & Therapeutics in Dentistry

- Many of our patients are medically compromised and this raises three important issues with respect to the delivery of routine dental care:
  1. Can the patients medication cause an adverse reaction in the mouth and associated structures?
  2. Can the drugs that I wish to prescribe interact with their current medication?
  3. What medical emergencies are likely to arise in this population and how should they be dealt with?

Local Anaesthesia

- The improvements in agents and techniques for local anaesthesia are possibly the **most important advances in dental science** to have occurred in the past 100 years. The agents currently available in dentistry have most of the characteristics of an **ideal** local anaesthetic:
  1. Administration is non-irritating
  2. Anaesthetic has little or no allergenicity
  3. Rapid onset and adequate duration of anaesthesia
  4. Provides anaesthesia that is completely reversible
  5. Minimal systemic toxicity
  6. Selective to nocioception (pain) pathways

Local Anaesthesia

- Today's anaesthetics can be administered with **minimal irritation and little concern for stimulating allergic reactions**.
- A variety of agents are available that provide **rapid** onset of surgical anaesthesia with **adequate duration**.
- Persistent nerve impairment and systemic toxicity are **rarely reported**.
- Unfortunately, local anaesthetic agents that **selectively** inhibit pain pathways ***without*** interrupting transmission of other sensory pathways are not currently available.

Local Anaesthesia: Learning Outcomes

1. A brief **review** of the local anaesthetic agents, and formulations used in dentistry.
2. Important **considerations regarding the clinical pharmacology of vasoconstrictors**.
3. **Adverse reactions** related to local anaesthetic formulations used in dentistry will be presented in a separate article.

Clinical Pharmacology of Local Anaesthetics

- For the **past 20 years**, the primary local anaesthetics used in dentistry are those classified as **amides**. Lidocaine and mepivacaine, two of the most commonly used dental anaesthetic agents, have a 50-year history of effectiveness and safety for dental therapies.
- Practitioners prefer the **amide** agents over the **ester** agents (i.e., procaine and propoxycaine) because they are more rapidly and reliably produce profound surgical anaesthesia.
- The availability of effective amide agents that provides anaesthesia of **varying duration** has dramatically improved patient care, permitting the development of many of the sophisticated surgical outpatient procedures now available in dentistry.

Clinical Pharmacology of Local Anaesthetics

Anesthetic	Brand names	Formulations	Duration
Surgical anesthetics			
Articaine	Ultracaine®, Septocaine®	4% with epinephrine	1.5–3 hours
Lidocaine	Xylocaine®	2% with epinephrine	1.5–3 hours
Mepivacaine	Carbocaine®	3% plain	1–2.5 hours
		2% with levonordefrin	1.5–3 hours
Prilocaine	Citanest®	4% plain	1–2.5 hours
		4% with epinephrine	1.5–3 hours
Long-acting agents			
Bupivacaine	Marcaine®	0.5% with epinephrine	4–8 hours
Etidocaine	Duranest®	1.5% with epinephrine	4–8 hours

Clinical Pharmacology of Local Anaesthetics

- **Onset of action**, **potency**, and **duration** of action are determined by the specific local anaesthetic's:
  - **pKa**,
  - **lipid solubility**,
  - **protein binding**,
  - **tissue pH**, and
  - **vasodilatory effects**.
- Increasing the dose by administering a high concentration **shortens onset**, while increasing **potency** and **duration of action**, as well as **increasing possibility for the adverse/toxic reactions**.

Clinical Pharmacology of Local Anaesthetics

- **Onset of Action**
  1. pKa is the primary factor that determines onset of action.
  2. Lower pKa **increases** tissue penetration and shortens onset of action; this is due to increased lipid solubility of non-ionized (uncharged) particles.
  3. pKa that is closer to pH optimizes penetration.
  4. **Inflammation in the extracellular space may decrease pH and may slow onset of action**.
  5. Site of administration influences onset (i.e., prolonged in areas with increased tissue or nerve sheath size).

Clinical Pharmacology of Local Anaesthetics

- **Potency**
  1. Local anaesthetics with **high** partition coefficients that **increase** lipophilic properties easily pass into the lipid nerve membrane.
  2. **Degree of vasodilation** promotes vascular absorption, thereby reducing locally available drug and **decreases** potency.
  3. Addition of **epinephrine** or **sodium bicarbonate increases pH**, thereby **increasing nonionized particles, which are more lipid soluble**.
  4. Generally, local anaesthetic solutions that contain premixed epinephrine contain preservatives; in these solutions, **the pH is adjusted lower to maintain the stability of epinephrine and antioxidants.**

Clinical Pharmacology of Local Anaesthetics

- **Duration of Action**
  1. Addition of epinephrine to some local anaesthetic solutions **prolongs duration of action by causing vasoconstriction and decreasing systemic absorption**.
  2. Degree of protein binding **primarily determines duration of action**; **high protein binding increases duration.**
  3. Increasing pH (addition of epinephrine or sodium bicarbonate) also **prolongs duration of action**.

Clinical Pharmacology of Local Anaesthetics

- Variations in **physical** and **clinical characteristics** of local anaesthetics can be attributed to differences in **chemical properties of their molecular structures**.
- The **pKa** of an anaesthetic determines the pH at which the drug's ionized (charged) and non-ionized (uncharged) forms are in equal concentrations.
- This is critical for effective anaesthesia because the uncharged form of a local anaesthetic **can readily diffuse across lipid nerve sheaths and cell membranes**, whereas ***only*** the charged form **can diffuse through the extracellular fluid and intracellular cytoplasm**.

Clinical Pharmacology of Local Anaesthetics: Clinical Characteristics

1. An agent's **pKa** is therefore the most important factor in determining an agent's **diffusion properties** and **RATE OF ONSET**.
   - Procaine, with a **pKa** of **8.9**, is **98% ionized** at a **normal tissue pH of 7.4** – Most of this drug is in a charged state and unable to cross cell membranes. The **onset** of procaine anaesthesia is therefore **unacceptably prolonged**.
   - Amide anaesthetics having **pKa** in the range of **7.6–8.0** have less of the drug in an ionized state and therefore **diffuse through tissue more readily** .

Clinical Pharmacology of Local Anaesthetics: Clinical Characteristics

2. The **lipid solubility** characteristics of a local anaesthetic best **PREDICTS POTENCY**.
   - Procaine is one of the least lipid-soluble and least potent local anaesthetics, whereas bupivacaine is **very** lipid-soluble and therefore the most potent.
3. **Protein binding** characteristics are a primary determinant of the **DURATION OF ANAESTHESIA**.
   - Agents that attach to protein components of nerve membranes are less likely to diffuse from the site of action and into the systemic circulation.
   - Lidocaine's **short** duration and bupivacaine's **long** duration are caused, in part, by their distinctly different protein binding characteristics .

Clinical Pharmacology of Local Anaesthetics: Clinical Characteristics

- But factors such as:
  1. the site of injection,
  2. drug and vasoconstrictor concentration,
  3. volume of injection, and
  4. inherent vasoconstrictive properties of the anaesthetic

...will all also influence the clinical performance of a local anaesthetic.

Ester Anaesthetics: Procaine / Propoxycaine

- A combination of ester anaesthetics, procaine and propoxycaine, was available in **dental cartridges until 1989** – the formulation in dental cartridges was the combination of **0.4%** propoxycaine (Ravocaine®) and **2%** procaine (Novocain®) with 1:20,000 levonordefrin as a vasoconstrictor.
- Procaine is a **potent** vasodilator and is **not** effective if used without a vasoconstrictor.
- Ester anaesthetics are generally **less effective** than amides because they have poor diffusion properties.
- Procaine has significant allergenicity and has been known to **affect both the patient and practitioners** – termination of effect through hydrolysis by plasma and cholinesterases to **para-aminobenzoic acid** (PABA) and **diethylamino alcohol**. **The PABA appears to be the allergen associated with procaine's allergenicity.**

Ester Anaesthetics: Procaine / Propoxycaine

- In the 1980s, there was some concern about the use of amide anaesthetics with patients diagnosed with "malignant hyperthermia."
- This rare genetic syndrome causes a rapid and potentially fatal rise in body temperature during general anaesthesia.
- Ester anaesthetics at one time were **considered to be the local anaesthetic agents of choice for these patients**.
- Recent evidence has determined, however, that this concern is unfounded and the use of an amide anaesthetic for patients at risk for malignant hyperthermia is no longer contraindicated.

Amide Anaesthetics: Lidocaine Hydrochoride

- Lidocaine hydrochloride (Xylocaine®, Octocaine®) was introduced into practice in the **1950s** and, because of its excellent efficacy and safety, has become the **prototypic dental local anaesthetic**.
- Lidocaine has limited allergenicity with **fewer than 20 reports of allergic reactions in the literature in the past 50 years** – given the frequent use of local anesthesia in dentistry (**500,000 – 1,000,000 injections a day in the United States and UK**), the rare incidence of hypersensitivity reactions is an extremely important clinical advantage.

Amide Anaesthetics: Lidocaine Hydrochoride

- Lidocaine is formulated in cartridges as:
  - 2% lidocaine with 1:50,000 epinephrine,
  - 2% lidocaine with 1:100,000 epinephrine, and
  - 2% lidocaine with 1:200,000 epinephrine.
- The **2% lidocaine with 1:100,000 epinephrine** is considered the standard for comparison with newer anaesthetics.
- Lidocaine with epinephrine rapidly induces oral anaesthesia and provides surgical anaesthesia that last **90–180 minutes**.

Deciphering Anaesthetic Concentration and Dilution

- Drug **concentration** is expressed as a percentage (e.g., bupivacaine 0.25%, lidocaine 1%).
- Percentage is measured in grams per 100 mL (i.e., 1% is 1 g/100 mL [1000 mg/100 mL], or 10 mg per mL).
- Calculate the mg/mL concentration quickly from the percentage by moving the decimal point 1 place to the right:
  - Bupivacaine 0.25% = 2.5 mg/mL
  - Lidocaine 1% = 10 mg/mL

Deciphering Anaesthetic Concentration and Dilution

- When epinephrine is combined in an anaesthetic solution, the result is expressed as a **dilution** (e.g., 1:100,000).
  - 1:1000 means 1 mg per 1 mL (i.e., 0.1%)
  - 1:10,000 means 1 mg per 10 mL (i.e., 0.01%)
  - 1:2000 means 1 mg per 2 mL (i.e., 0.05%)
  - 1:20,000 means 1 mg per 20 mL (i.e., 0.005%)
  - 0.1 mL of 1:1000 epinephrine added to 10 mL of anaesthetic solution = 1:100,000 dilution or 0.01 mg/mL

Epinephrine Content Examples

Solution Volume	1:100,000 (1 mg/100 mL)	1:200,000 (1 mg/200 mL)
1 mL	0.01 mg	0.005 mg
5 mL	0.05 mg	0.025 mg
10 mL	0.1 mg	0.05 mg
20 mL	0.2 mg	0.1 mg

What does 2% concentration Xylocaine® in a 1.8mL cartridge signify?

- 2% concentration lidocaine is (2000mg of the solution in 100mL of diluent) 20mg/ml.
- therefore 1.8mL will have 20 x 1.8 = **36mg** of lidocaine per cartridge of LA

What does a 1:100,000 dilution of epinephrine (adrenaline) in a 1.8mL cartridge of Xylocaine® signify?

- 1:100,000 dilution represents (1000mg of the solution in 100,000mL of diluent) 0.01mg/mL.
- therefore 1.8mL will have 0.01 x 1.8 = **0.018mg** of epinephrine (adrenaline) per cartridge of LA

Amide Anaesthetics: Mepivacaine Hydrochloride

- Mepivacaine hydrochloride (Carbocaine®, Polocaine®) has an important place in dental anaesthesia because it has minimal vasodilating properties and can therefore provide profound local anaesthesia ***without*** being formulated with a vasoconstrictor such as epinephrine or levonordefrin.
- The availability of a 3% formulation **not containing a vasoconstrictor** is a valuable – available in dental cartridges as:
  - 3% mepivacaine plain or
  - 2% mepivacaine 1:20,000 levonordefrin.
- Recent investigation suggests that although **pulpal durations** of mepivacaine **plain** are **shorter** than 2% lidocaine with epinephrine, **soft tissue anaesthesia** for both are nearly identical *(Hersh EV et al 1995)*

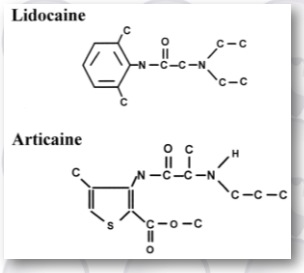
Amide Anaesthetics: Prilocaine Hydrochloride

- Prilocaine hydrochloride (Citanest®) can provide excellent anaesthesia with or without a vasoconstrictor.
- One of its metabolic products, toluidine, has been associated with the development of **methemoglobinemia**.
- It is available in preparations of:
  - 4% prilocaine plain and
  - 4% prilocaine with 1:200,000 epinephrine.
- The formulation containing epinephrine **has anaesthetic characteristics similar** to 2% lidocaine 1:100,000 epinephine.
- The 4% prilocaine **plain** formulation provides a **slightly shorter duration** of surgical anaesthesia.
- Although the pH of the solution in dental cartridges is **less acidic**, there is little indication that prilocaine causes less discomfort upon injection.

Amide Anaesthetics: Articaine Hydrochloride

- Prilocaine hydrochloride (Citanest) Articaine hydrochloride (Ultracaine®, Septanest®, Septocaine®) has been available in **Europe (1976)** and **Canada (1982)** for several decades - recently, the USA FDA approved it in the **USA**.
- Because of its unique chemistry and pharmacologic profile, 4% articaine with epinephrine may provide practitioners with an alternative.
- Formulation contains 4% articaine hydrochloride 1:100,000 epinephrine bitartrate in a sterile 1.7 mL.
- The molecular structure of articaine additionally contains a **thiophene (sulfur-containing) ring** and an **ester side chain** – as articaine is absorbed from the injection site into the systemic circulation, it is rapidly inactivated by hydrolysis of the ester side chain to **articainic acid and therefore has an extremely short plasma half-life (27 minutes)**.

Molecular Structures of Lidocaine and Articaine



Amide Anaesthetics: Articaine Hydrochloride

- The onset time, duration, and anaesthetic profundity of articaine is comparable to 2% lidocaine with 1:100,000 epinephrine.
- Articaine and prilocaine have been associated with a **slightly higher incidence of mandibular and lingual paresthesia**.
- Articaine does **not** appear to have a greater allergenicity – probably because the ester metabolite is not the allergen PABA.

Amide Anaesthetics: Articaine Hydrochloride

- Reports of toxicity reactions following the use of articaine **are extremely rare** – the rapid inactivation of articaine by plasma esterases may explain the apparent lack of overdose reactions reported following its administration, even though it is marketed as a 4% solution.
- When **reinjection** of anaesthesia is anticipated because of **long appointments required** for **cosmetic dentistry**, **full mouth restoration**, **full mouth periodontal surgery**, or **multiple implant placements**, articaine may be considered as a desirable anaesthetic.

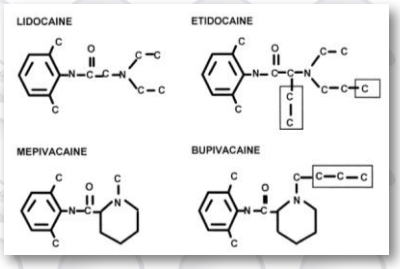
Amide Anaesthetics: Articaine Hydrochloride

- The 4% articaine solution with epinephrine has been reported to have an onset of **1.5-3.0 minutes for maxillary infiltrations**, and only **slightly longer** for inferior alveolar blocks.
- The duration of soft tissue anaesthesia ranges from **2-3 hours for maxillary infiltration** anaesthesia and **3-4 hours for mandibular** block anaesthesia.
- Little data to support the claim that **articaine has superior diffusion properties** or **that lingual/palatal anaesthesia can be induced following buccal infiltration** – the establishment of maxillary and mandibular pulpal anaesthesia following buccal infiltration with articaine has been **compared** with prilocaine using electrical stimulation of tooth pulp and lingual soft tissue.
- No statistically significant differences between articaine and prilocaine in their ability to induce anaesthesia for any tissue at any site tested.

Long-acting Amide Anaesthetics: Bupivacaine and Etidocaine

- Bupivacaine and etidocaine play a valuable role in the overall management of surgical and postoperative pain associated with dental care.
- They are **chemical analogues** of lidocaine and mepivacaine.
- Bupivacaine (1-butyl-2', 6'pipecoloxylidide) (Marcaine®) is **identical** to mepivacaine **except** for a butyl (4 carbon) substitution of the methyl (1 carbon) group at the aromatic amine.
- Etidocaine (2-N-ethylpropylamino-2'butyroxylidide) (Duranest®) is identical to lidocaine **except** for a propyl (3 carbon) substitution and an ethyl (2 carbon) addition.
- These **provide enhanced lipid solubility** and, especially, **protein-binding properties** as compared with their shorter-acting analogues.

Comparison of the Molecular Structures of Standard Anaesthetics to Long-acting Anaesthetics



Long-acting Amide Anaesthetics: Bupivacaine and Etidocaine

- Although both bupivacaine and etidocaine may provide adequate surgical anaesthesia, they are **most useful for postoperative pain management**.
- Bupivacaine **has a slightly longer onset** time than conventional anaesthetics. The **profundity** of anaesthesia, however, is comparable – **Onset** times and **profundity** are **optimized** when preparations of bupivacaine include epinephrine.
- Etidocaine appears to have an **onset** time slightly more rapid than bupivacaine (**less than 1 minute difference**) when the agents were compared in endodontics and oral surgery. The **profundity** of ***mandibular anaesthesia*** provided by etidocaine with epinephrine appears to be **equivalent to conventional agents**. The **profundity** of etidocaine anaesthesia following ***maxillary infiltrations*** may be somewhat less.

Long-acting Amide Anaesthetics: Bupivacaine and Etidocaine

- **Duration** of soft-tissue anaesthesia (inferior alveolar blocks) using bupivacaine have durations **2–3 times those of lidocaine and mepivacaine**. As might be expected, **durations** are **somewhat shorter when maxillary infiltrations are evaluated**.
- Bupivacaine provided soft tissue anaesthesia for **4–5 hours after infiltration**, and **5–8 hours following nerve blocks**.
- Etidocaine provides **similar increases in soft-tissue anaesthesia duration following block injections**.
- Because the low epinephrine concentrations formulations of bupivacaine and etidocaine, **increased bleeding during surgery has been demonstrated**.

Long-acting Amide Anaesthetics: Bupivacaine and Etidocaine

- The use of long-acting local anaesthetics to **alleviate pain** following **third molar extractions** has been consistently and repeatedly demonstrated *(Moore PA 1984; Davis WM et al, 1984; Dionne RA et al, 1984; Trieger N et al, 1979)*
- Patients undergoing **third molar extractions** involving **bone removal were administered** 0.5% bupivacaine without epinephrine, 0.5% bupivacaine 1/200,000 epinephrine, or 3% mepivacaine. The patients receiving bupivacaine with epinephrine had a mean duration of anaesthesia of **7.0 hours (versus 2.9 hours for mepivacaine)** and **required the fewest doses of postoperative narcotic analgesics** *(Trieger N et al, 1979)*
- **My Practice:** A combination strategy for managing **postoperative pain** using a **nonsteroidal anti-inflammatory drug (NSAID)** *prior* to surgery and a **long-acting anaesthetic** may provide MAXIMAL COMFORT *(Dionne RA et al, 1984)*

Long-acting Amide Anaesthetics: Bupivacaine and Etidocaine

- Some patients may be concerned about prolonged anaesthesia (**possible dysesthesias caused by surgical trauma**).
- Delays in recovery following local anaesthetic using long-acting agents beyond 10 hours are not uncommon.
- **Patient preparation and a thorough explanation of this pain control strategy are essential**.
- Bupivacaine and etidocaine have been used in the **overall management of chronic pain** either as **symptomatic**, **diagnostic**, or **definitive therapy**:
  1. Prolonged anaesthesia and pain relief may **facilitate physical therapy** of certain skeletal muscle disorders.
  2. Some **myofascial pain dysfunction syndromes** may benefit from injection of a long-acting local anaesthetic into **"trigger points."**
  3. Injections of long-acting agents, sometimes repeatedly over a course of weeks, may be useful in **stimulating complete recovery from postherpetic neuralgias** and **reflex sympathetic dystrophies** *(Burney RG et al, 1983)*

Vasoconstrictors: Indications and Precautions

- Since 1901, when Braun first combined cocaine and epinephrine, **vasoconstrictors have been added to local anaesthetic solutions to increase the quality and duration of anaesthesia, to aid in hemostasis**, and, presumptively, to **reduce toxicity of the local anaesthetic**.
- With the exception of cocaine, all local anaesthetics are **potential vasodilators**.
- Epinephrine (Adrenaline®) and levonordefrin (Neo-Cobefrin®) are the most widely used vasoconstrictors.
- Felypressin, a non-catecholamine vasoconstrictor, is also available.

Mechanism of Action

- Epinephrine and levonordefrin **stimulate** adrenergic receptors (also referred to as **adrenoceptors**) that are responsible for their **vasoconstrictive** and other properties.
- There are two basic categories of adrenergic receptors:
  - α, which usually have **excitatory actions**, and
  - β, which **stimulate the heart** but otherwise are **mostly inhibitory**.
- The α and β adrenoceptors **have been further divided** into α_1 (α_{1A}, α_{1B}, α_{1D}) and α_2 (α_{2A}, α_{2B}, α_{2C}), and β1, β2, and β3 subtypes, respectively.

Adrenergic Receptor Activities

Effector organ or function	Receptor[a]	Response
Cardiovascular system		
Heart rate	β_1, β_2	Increased[b]
Contractile force	β_1, β_2	Increased
Coronary arterioles	α_1, α_2/β_2	Constriction/dilation[c]
Automaticity	β_1, β_2	Increased
Conduction velocity	β_1, β_2	Increased[b]
Peripheral resistance	α_1, α_2/β_2	Increased/decreased
Capacitance veins	α_1/β_2	Constriction/dilation
Respiratory system		
Bronchial smooth muscle	β_2	Relaxation
Bronchial glands	α_1/β_2	Decreased secretion/increased secretion
Pulmonary arterioles	α_1/β_2	Constriction/dilation[c]
Gastrointestinal tract		
Motility and tone	α_1, α_2, β_1, β_2	Decreased
Sphincters	α_1	Contraction
Visceral arterioles	α_1/β_2	Constriction/dilation
Liver		
Glucose metabolism	α, β_2	Glycogenolysis, gluconeogenesis
Arterioles	α_1/β_2	Constriction/dilation

Adrenergic Receptor Activities

Fat		
Lipolysis	α, β_1, β_3	Lipolysis
Arterioles	α_1/β_2	Constriction/dilation
Pancreas		
Insulin secretion	α_2/β_2	Decreased/increased
Genitourinary system		
Urinary bladder sphincter	α_1	Contraction
Detrusor muscle	β_2	Relaxation
Trigone muscle	α_1	Contraction
Uterine tone	α_1/β_2	Contraction/relaxation[d]
Renal arterioles	α_1, α_2, β_1, β_2	Constriction/dilation
Skeletal muscle		
Neuromuscular transmission	α, β_2	Increased
Arterioles	α/β_2	Constriction/dilation
Salivary glands		
Secretion	β	Mucous secretion
Arterioles	α_1, α_2	Constriction
Skin and mucosa		
Arterioles	α_1, α_2	Constriction

Mechanism of Action

- Vasoconstrictors **differ in their affinity for adrenergic receptors**.
- One might assume that a vasoconstrictor added to a local anaesthetic would ideally have only α-agonistic activity, but epinephrine, the most commonly used vasoconstrictor, is also the **least selective**, exerting both strong α and β actions.
- Epinephrine is a **highly effective vasoconstrictor** for intraoral use in concentrations of 1:200,000–1:50,000 (5–20 μg/mL) because of the predominance of a adrenoceptors in the oral mucosa, submucosa, and peridontium.
- Levonordefrin is relatively specific for the α_2 receptor. It **has about one sixth the vasoconstrictor potency of epinephrine** and is therefore marketed in a 1:20,000 concentration (50 μ g/mL).

Relative Receptor Potencies of Adrenergic Vasoconstrictors

	α_1	α_2	β_1	β_2
Epinephrine	+++	+++	+++	+++
Levonordefrin	+	++	++	+

Symbols indicate the relative potency: +++ = high, ++ = intermediate, + = low.

Mechanism of Action

- Felypressin, a nonsympatho-mimetic vasoconstrictor, is a **synthetic analogue of vasopressin**, otherwise known as **anti-diuretic hormone**.
- It stimulates V_{1a} receptors on vascular smooth muscle.
- Because it **does not significantly influence the heart directly** and **invokes other effects that limit increases in peripheral resistance** (e.g., by inhibiting sympathetic neurotransmitter release), felypressin in standard doses has little effect on **blood pressure**, **heart rate**, or **cardiac rhythm**.
- It may, however, cause clinically **significant coronary vasoconstriction in patients with heart disease**.
- Felypressin is relatively **ineffective as a haemostatic agent**.

Indications

- Several benefits accrue from **adding vasoconstrictors** to local anaesthetic solutions:

1. Most important for dentistry is the enhancement of local anaesthesia in **quality** and **duration**.
2. Vasoconstrictors have also been used to assist in haemostasis.
3. Finally, it has been suggested that inclusion of a vasoconstrictor increases local anaesthetic safety.

Indications: Enhancement of Local Anaesthesia

- **Most** local anaesthetics cause vasodilation clinically, and the **addition of a vasoconstrictor opposes this effect** – increase local blood flow and their own absorption into the systemic circulation.
- These effects are **especially true in dentistry**, where local anaesthetics are injected into **highly vascular tissues**.
- Lidocaine produces **unreliable pulpal anaesthesia without a vasoconstrictor** – with the addition of epinephrine, however, at a concentration of 1:100,000, 2% lidocaine blocks pulpal nerve fibers for **60–90 minutes, depending on the site of injection**.
- Procaine is ineffective for pulpal anaesthesia without a vasoconstrictor.

Indications: Enhancement of Local Anaesthesia

- Mepivacaine and prilocaine, are available without a vasoconstrictor.
- These two local anaesthetics **cause less vasodilation than lidocaine** or **procaine** and can be used without a vasoconstrictor for short procedures.
- A maxillary tooth can be reliably blocked for about 20 minutes after supra-periosteal injection. **But with the addition of a vasoconstrictor, the duration of pulpal anaesthesia rises to 40 minutes with prilocaine and 50 minutes with mepivacaine.**
- Bupivacaine, is also a **powerful vasodilator**.
- Because it is highly **lipid-soluble (or hydrophobic)** and tends to be sequestered in nerve membranes for a prolonged period, it is capable of providing **protracted pulpal anaesthesia without a vasoconstrictor**. Even so, the addition of a vasoconstrictor increases its duration of anaesthesia.

Effect of Catecholamine Vasoconstrictors on the Duration of Pulpal Anaesthesia After Inferior Alveolar Nerve Blockade

Local anesthetic	Duration (min)
2% Lidocaine	40 (unreliable)
2% Lidocaine with 1:100,000 epinephrine	85
3% Mepivicaine	40
2% Mepivicaine with 1:20,000 levonordefrin	75
4% Prilocaine	55
4% Prilocaine with 1:200,000 epinephrine	60

Indications: Haemostasis

- Intra-operative haemostasis is **important** for optimal results when performing surgical procedures in the oral cavity.
- Infiltration of a local anaesthetic containing epinephrine can help:
  - **reduce blood loss** during surgery and
  - **improve visualization** of the operative field.
- For local haemostasis, an epinephrine concentration of **1:50,000 with 2% lidocaine** is **more effective** than a **1:100,000 strength**.

Indications: Haemostasis

- Lidocaine partially **counteracts the vasoconstrictive effect** of epinephrine and **enhances its systemic absorption**.
- A more rational, if less convenient, approach to control bleeding may be to **inject less concentrated solutions of epinephrine without local anaesthetic**.
- Practitioners should also be aware that rebound hyperaemia can occur (**primarily from tissue ischemia and the accumulation of vasodilatory metabolites**) once the vasoconstriction has dissipated, which can accentuate postoperative blood loss.

Indications: Haemostasis

- Epinephrine-impregnated **gingival retraction** cord is still used by some practitioners **as a haemostatic agent**.
- Such retraction cord **may contain racemic epinephrine** in amounts up to **1mg/ inch**.
- When the retraction cord is placed in the gingival sulcus, especially in **abraded**, **inflamed tissue**, the potential exists for systemic uptake of large quantities of epinephrine.

Indications: Increased Safety

- The addition of a vasoconstrictor **can protect** against systemic local anaesthetic toxicity *(Glover J et al, 1968)*
- By **decreasing blood flow** in the injected tissues, a vasoconstrictor **slows the rate at which the local anaesthetic enters the circulation** – the **metabolic inactivation** of the local anaesthetic is **more able to keep pace with absorption**, and that the resulting **smaller** peak plasma concentrations of drug elicit fewer adverse effects.
- These ***presumptions*** are reflected in the fact that the maximum **manufacturer's recommended dose of lidocaine is 4.5 mg/kg** up to a maximum of **300 mg without a vasoconstrictor** but **7 mg/kg** up to a maximum of **500 mg with epinephrine** *(Jastak JT et al, 1995)*

Indications: Increased Safety

- Peak plasma concentrations of lidocaine are **reduced** by about **30–40%** when it is **co-administered** intra-orally with epinephrine.

...But

- There is **NO** evidence of a reduction in local anaesthetic toxicity with vasoconstrictor use *(Åström A et al, 1964; Yagiela JA, 1985)*
- Animal studies suggest that **vasoconstrictors increase the relative distribution of large doses of local anaesthetics into the brain** even as they retard drug absorption from the injection site *(Yagiela JA et al, 1999)*
- Thus, **there is little direct proof that the addition of a vasoconstrictor makes a local anaesthetic safer by retarding systemic absorption**.

Indications: Increased Safety

- Even though the addition of a vasoconstrictor may not **moderate maximum plasma concentrations** of a local anaesthetic, it **may be useful in reducing the amount of local anaesthetic needed for adequate pain relief**.
- In the case of mepivacaine, a 2% solution is highly effective when combined with levonordefrin, but a 3% solution (representing 50% more drug) is needed in the absence of a vasoconstrictor.
- Furthermore, because a local anaesthetic solution with vasoconstrictor often **provides a longer duration of effect**, there is a **diminished need for reinjection** and **less likelihood for drug accumulation**.

Precautions

- As with any medication being considered for use, the **potential risks** of vasoconstrictors must be weighed against their **expected benefits**.
- For **adrenergic vasoconstrictors**, the greatest potential for adverse effects resides in patients with:
  - **cardiovascular disease** and who are **taking certain interacting drugs**.
  - Concerns are also sometimes expressed about vasoconstrictor usage during **pregnancy** and in
  - patients with sulfite intolerance.

Precautions: Cardiovascular Disease

- There has been enduring debate.
- Arguments have been expressed that the **amounts of catecholamines released endogenously** in response to inadequate pain relief and/or the stress of dental treatment are **much greater than those commonly injected for dental procedures** *(Glover J et al, 1968; Pērusse R et al, 1992)*
- It has also been suggested that a local anaesthetic with vasoconstrictor is **desirable** in patients with cardiovascular disease because of the **greater pain relief afforded by the combination** *(Hirota Y, 1986)*

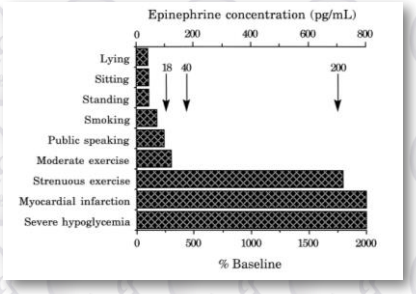
Precautions: Cardiovascular Disease

- Historical progression of this issue is reflected in several official pronouncements.
- **In 1955,** a special committee of the New York Heart Association (AHA) **recommended 0.2 mg as the maximum dose of epinephrine** that should be used in local anaesthesia for patients with heart disease *(New York Heart Association. Use of epinephrine in connection with procaine in dental procedures: report of the Special Committee of the New York Heart Association, Inc., on the Use of Epinephrine in Connection with Procaine in Dental Procedures. J Am Dent Assoc 1955;50(1):108.)*
- **In 1964,** the American Dental Association and the AHA jointly stated that **vasoconstrictors were not contraindicated for patients with cardiovascular disease** when administered **carefully, slowly**, and with **preliminary aspiration to avoid intravascular injection** and **The maximum strength of epinephrine that should be used was 1:50,000.** *(Management of dental problems in patients with cardiovascular disease: report of a working conference jointly sponsored by the American Dental Association and American Heart Association. J Am Dent Assoc 1964;68:334–42.)*
- Lastly, **in 1986,** the AHA emphasized safety by concluding, "Vasoconstrictor agents **should be used in local anaesthesia** solutions during dental practice only when it is clear that the procedure will be **shortened** or the **analgesia rendered more profound**. When a vasoconstrictor is indicated, **extreme care** should be taken to avoid intravascular injection. The **minimum** possible amount of vasoconstrictor should be used" *(Kaplan EL, editor. Cardiovascular disease in dental practice. Dallas (TX): American Heart Association; 1986.)*

Precautions: Cardiovascular Disease

- Epinephrine is normally released from the adrenal medulla at a basal rate of 2.5–7.5 ng/kg per minute.
- This endogenous amount may **rise twenty to forty fold** in times of stress.
- A single cartridge of 2% lidocaine with 1:100,000 epinephrine **significantly increases plasma epinephrine** over **resting values**, and that **two cartridges yield a concentration equivalent to that of mild physical exertion**.
- It is logical to conclude that ambulatory patients, including those with cardiovascular disease, **should be able to tolerate these doses** of vasoconstrictor because they are **already doing so during the course of daily life**.

Influence of various activities and conditions on venous plasma epinephrine concentrations



Precautions: Cardiovascular Disease

- Unfortunately, certain individuals have special risk for cardiovascular problems during dental treatment.
- These patients **include** those with:
  1. **unstable angina pectoris** (chest pain without exertion),
  2. **recent heart attack** or **stroke** (within 6 months),
  3. **severe untreated or uncontrolled hypertension**, and
  4. **uncontrolled or untreated congestive heart failure**.

Precautions: Cardiovascular Disease

- The **American Society of Anesthesiologists' (ASA)** physical status score classifies patients from ASA I (healthy patients with no systemic disease) to V (moribund patients with little chance of survival over the next 24 hours).
- The patients listed above would mostly be ranked as **ASA IV**, having severe systemic disease that is constantly life-threatening.
- Patients in this category should **NOT** receive **invasive dental treatment** until they have been **stabilized medically** *(Pallasch TJ et al, 1998)*
- Even then, **vasoconstrictors should be avoided if at all possible** because of the threat posed by accidental intravascular injection or rapid systemic absorption of the drug.

Precautions: Cardiovascular Disease

- **Heart transplants** have created a special group of patients who are **supersensitive to injected catecholamines**.
- When a heart is transplanted, it is of **necessity surgically denervated**.
- The **loss** of sympathetic nerves to the heart eliminates the adrenergic nerve terminals that both release nor-epinephrine and take it back up for later reuse (**by a transport system known as uptake$_1$**).

Precautions: Cardiovascular Disease

- This reuptake process is also the principal means by which the actions of epinephrine and levonordefrin molecules reaching the cardiac adrenoceptors.
- The resulting increased exposure to these drugs **MAGNIFIES** cardiac stimulation in these patients.
- The dentist **should be cautious in their use, administering local anaesthetic solutions in small divided doses and monitoring the heart for any changes in rate or rhythm**.

Precautions: Pregnancy

- Prudence dictates that **elective dental procedures** be **deferred** when a patient is pregnant.
- When delay is not possible, **necessary treatment** must be provided in an **optimally safe manner for both mother and fetus**.
- Potential concerns regarding epinephrine involve the drug's effects on **uterine muscle tone** and **blood flow**.
- EXPERIMENTALLY, **stimulation** of **α1-adrenergic** receptors causes **contraction of uterine muscle strips**. *But* the principal effect of CLINICALLY used doses of epinephrine during pregnancy is **uterine relaxation during the third trimester**, a **β2-adrenoceptor effect**.
- Because it only weakly stimulates α1 and β2 adrenoceptors, levonordefrin probably has little effect on uterine tone.

Precautions: Pregnancy

- As with many vascular beds, epinephrine can **cause vasoconstriction and decrease uterine blood flow**.
- This effect has been examined in pregnant women receiving epidural local anaesthesia for labour.
- Most studies have shown that uterine and umbilical blood flow are **NOT** compromised by epinephrine.
- A ***possible* exception** includes women whose pregnancies are complicated by hypertension – in this case, epinephrine may increase vascular resistance in the utero-placental circulation, indicating impaired blood flow.

Precautions: Pregnancy

- Even so, there is **no evidence of increased deleterious effects**.
- Because the use of a vasoconstrictor can **reduce the amount of local anaesthetic administered and concomitantly reduce fetal drug exposure**.
- **Vasoconstrictors are appropriate when local anaesthesia is administered to a pregnant woman .**

Precautions: Drug Interactions

- With the growing variety and number of drugs patients are taking, and the rising use of multiple medications, drug interactions are of increasing concern.
- The most important and best characterized **interactions with vasoconstrictors** include:
  - the tricyclic antidepressants,
  - nonselective β-adrenergic blocking agents,
  - certain general anaesthetics, and
  - cocaine.

Precautions: Drug Interactions

- The potentiation of epinephrine with TCAs is about **threefold**, at least early in TCA therapy. The potentiation is **six- to eightfold** with levonordefrin.
- It is recommended that levonordefrin **not** be used with patients on TCAs because of the **acute hypertension** and **cardiac dysrhythmias** that might occur.
- Epinephrine impregnated gingival retraction cord is **also contraindicated** because of the large amounts of epinephrine available for absorption.
- If a local anaesthetic with epinephrine is to be used, it should have **no more than 1:100,000 epinephrine**, and the maximum recommended dose should be reduced by one-third.

Precautions: Drug Interactions

- When epinephrine is administered to a patient with non-selective β blockade, unopposed α-adrenergic stimulation may lead to a **serious rise in blood pressure** and **reflex bradycardia.**
- patients taking non-selective β blockers should receive a minimal initial dose such as one half of a cartridge of local anaesthetic with 1:100,000 epinephrine and then be monitored for systemic effects at 5 minutes before additional drug is administered.
- Special **care** should also be taken to avoid intravascular injection.
- **This interaction is not evident in patients receiving selective β1 blockers**

Precautions: Drug Interactions

- The inhalation agent halothane (Fluothane®) has the greatest potential to potentiate **dysrhythmias** associated with the administration of vasoconstrictors – epinephrine should not be administered in single doses over 2 µg/kg (14 mL of a 1:100,000 epinephrine solution) when used with halothane.
- The intravenous anaesthetic thiopental (Pentothal®) is likewise capable of enhancing the **dysrhythmic** activity of adrenergic drugs (epinephrine administered in single doses reduced to 1 µg/kg)
- Gingival retraction cord containing epinephrine is best avoided in all patients receiving general anaesthesia.

Precautions: Drug Interactions

- Cocaine and epinephrine possess a potentially lethal interaction.
- Cocaine is a stimulant that **blocks** the **reuptake** of norepinephrine, dopamine, and 5-hydroxytryptamine at **pre-synaptic nerve terminals**.
- **Serious adrenergic stimulation leading** to hypertension, myocardial infarction, and even sudden death may ensue in patients actively abusing cocaine.
- Therefore, patients who are under the influence of cocaine should have elective dental treatment postponed for at least 24 hours after the last drug exposure.

Precautions: Drug Interactions

- The monoamine oxidase inhibitors (MAOIs) illustrate a widely mentioned interaction that actually has little clinical relevance for adrenergic vasoconstrictors used in dentistry - **a MAOI interaction is not clinically significant with epinephrine or levonordefrin as used in dentistry.**
- Because catechol-O-methytransferase (COMT) is directly involved in the metabolism of epinephrine and levonordefrin, care should be taken when using local anaesthetics with vasoconstrictors – **recommended that** no more than the equivalent of one cartridge of lidocaine with 1:100,000 epinephrine be administered initially and that the patient's heart rate and blood pressure be checked 5 minutes afterward before giving more local anaesthetic.

Drug interactions involving catecholamine vasoconstrictors

Drug class	Examples	Mechanism	Effect	Recommendation
Tricyclic antidepressants and related drugs	Amitriptyline (Elavil®), doxepin (Sinequan®), imipramine (Tofranil®), maprotiline (Ludiomil®)	TCAs block the uptake of catecholamines by sympathetic nerve terminals, increasing their actions	Potentiation of cardiovascular effects	Use epinephrine cautiously, avoid levonordefrin and gingival retraction cord with epinephrine
Nonselective β-adrenergic blockers	Nadolol (Corgard®), propranolol (Inderal®)	Unopposed α-adrenergic stimulation of catecholamines	Hypertension and reflex bradycardia	Use epinephrine and levonordefrin cautiously; avoid gingival retraction cord with epinephrine
Volatile general anesthetics	Desflurane (Suprane®), enflurane (Ethrane®), halothane (Fluothane®)	Potentiation of the dysrhythmic potential of catecholamines	Ventricular dysrhythmias	Use epinephrine and levonordefrin cautiously after informing anesthesiologist; avoid gingival retraction cord with epinephrine
Intravenous general anesthetics	Thiopental (Pentothal®)	Potentiation of the dysrhythmic potential of catecholamines	Ventricular dysrhythmias	Use epinephrine and levonordefrin cautiously after informing anesthesiologist; avoid gingival retraction cord with epinephrine
Recreational drugs	Cocaine	Cocaine potentiates sympathetic nervous system activity and blocks the uptake of catecholamines by sympathetic nerve terminals, increasing their actions	Hypertension, myocardial infarction, ventricular dysrhythmias	Have patient abstain from cocaine for 48 hours before treatment; avoid catecholamines if emergency dental treatment necessary
COMT inhibitors	Entacapone (Comtan®), tolcapone (Tasmar®),	Metabolism of catecholamines by COMT is inhibited, increasing their actions	Potential of cardiovascular effects	Use epinephrine and levonordefrin cautiously; avoid gingival retraction cord with epinephrine
Antiadrenergic agents	Guanadrel (Hylorel®), guanethidine (Ismelin®), methyldopa (Aldomet®)	Uptake of catecholamines is inhibited and/or target tissue responsiveness is increased	Possible potentiation of cardiovascular effects	Use epinephrine and levonordefrin cautiously; avoid gingival retraction cord with epinephrine
Nonselective α-adrenergic blockers	Chlorpromazine (Thorazine®), clozapine (Clozaril®), haloperidol (Haldol®), olanzapine (Zyprexia®)	Unopposed β_2-adrenergic stimulation of catecholamines	No interaction with normal doses of interacting drugs; hypotension with large doses	No special precautions in ambulatory patients; avoid epinephrine when treating hypotensive emergencies
Digitalis glycosides	Digoxin (Lanoxin®)	Additive dysrhythmogenic effects	Potentially dangerous dysrhythmias with large doses of vasoconstrictor	Use epinephrine and levonordefrin cautiously; avoid gingival retraction cord with epinephrine
Thyroid hormones	Desiccated thyroid (Armour Thyroid®), levothyroxine (Synthroid®), liothyronine (Cytomel®)	Additive dysrhythmogenic effects	Potentially dangerous dysrhythmias with large doses	No special precautions in euthyroid patients; use epinephrine and levonordefrin cautiously and avoid gingival retraction cord with epinephrine in hyperthyroid patients
MAO inhibitors	Furazolidone (Furoxone®), linezolid (Zyvox®), phenelzine (Nardil®), selegiline (Eldepryl®), tranylcypromine (Parnate®)	Exogenously administered catecholamines are not inactivated by monoamine oxidase	No interaction	None

COMT, catecholamine-O-methyltransferase; MAO, monoamine oxidase; TCAs, tricyclic antidepressants.

Precautions: Sulfite Intolerance

- Numerous reports exist of alleged allergic reactions to local anaesthetics.
- The **majority of true allergic reactions** to amide local anaesthetic solutions are **probably responses to the methyparaben preservative used in multidose vials**.
- Reactions have also been attributed to **sulfites**, most notably, **sodium metabisulfite**.

Precautions: Sulfite Intolerance

- Sulfites are found naturally in many common foods and beverages.
- Sulfites are also added to prevent or delay undesirable changes in the colour, taste, or texture of such edibles.
- Sulfites are used in local anaesthetic solutions as **antioxidants** to **prevent the breakdown of the vasoconstrictor components**.
- Local anaesthetics with vasoconstrictors can contain as much as **2 mg/mL of sulfite salts**.

Precautions: Sulfite Intolerance

- Allergic-like reactions to sulfites are most commonly seen in **asthmatic adults** who react to inhaled or ingested sulfites through a non-immunologic pathway.
- These individuals are **NOT particularly sensitive to small amounts of injected sulfites**.
- In fact, documented **anaphylactic reactions to sulfites**, which would be expected to be more intense with an injected allergen, are quite rare.
- Most patients who describe themselves as being sulfite-sensitive can receive intraoral injections of sulfite-containing solutions safely.

Precautions: Sulfite Intolerance

- whenever a patient reports a history of "allergy" to a local anaesthetic, the **treating dentist must include sulfite intolerance** in the differential diagnosis.
- **Local anaesthetics with adrenergic vasoconstrictors are absolutely contraindicated in the rare patient with a true sulfite allergy.**

Precautions: Sulfite Intolerance

- whenever a patient reports a history of "allergy" to a local anaesthetic, the **treating dentist must include sulfite intolerance** in the differential diagnosis.
- **Local anaesthetics with adrenergic vasoconstrictors are absolutely contraindicated in the rare patient with a true sulfite allergy.**

Adverse Effects

- Adverse effects are usually caused by **high plasma concentrations of local anaesthetic** drug that result from:
  1. inadvertent intravascular injection,
  2. excessive dose or rate of injection,
  3. delayed drug clearance, or
  4. administration into vascular tissue.

Local Anaesthetic Agents Used Commonly for Infiltrative Injection

Agent	Duration of Action	Maximum Dosage Guidelines (Total Cumulative Infiltrative Injection Dose per Procedure*)
Esters		
Procaine (Novocain)	Short (15-60 min)	7 mg/kg; not to exceed 350-600 mg
Chloroprocaine (Nesacaine)	Short (15-30 min)	Without epinephrine: 11 mg/kg; not to exceed 800 mg total dose With epinephrine: 14 mg/kg; not to exceed 1000 mg
Amides		
Lidocaine (Xylocaine)	Medium (30-60 min)	Without epinephrine: 4.5 mg/kg; not to exceed 300 mg
Lidocaine with epinephrine	Long (120-360 min)	With epinephrine: 7 mg/kg
Mepivacaine (Polocaine, Carbocaine)	Medium (45-90 min) Long (120-360 min with epinephrine)	7 mg/kg; not to exceed 400 mg
Bupivacaine (Marcaine)	Long (120-240 min)	Without epinephrine: 2.5 mg/kg; not to exceed 175 mg total dose
Bupivacaine with epinephrine	Long (180-420 min)	With epinephrine: Not to exceed 225 mg total dose
Etidocaine (Duranest) No longer available in United States	Long (120-180 min)	Without epinephrine: 0.4 mg/kg; not to exceed 300 mg total dose With epinephrine: 8 mg/kg
Prilocaine (Citanest)	Medium (30-90 min)	Body weight <70 kg: 8 mg/kg; not to exceed 500 mg Body weight >70 kg: 600 mg
Ropivacaine (Naropin)	Long (120-360 min)	5 mg; not to exceed 200 mg for minor nerve block

Adverse Effects

- The toxicity of local and infiltration anaesthetics can be classified by **local** and **systemic levels** of manifestations.
- The **local adverse** effects of anaesthetic agents include **neurovascular manifestations such as prolonged anaesthesia and paresthesias**, which may become **irreversible**.
- **Systemic toxicity** of anaesthetics involves:
  - the **central nervous system (CNS)**,
  - the **cardiovascular system**, and
  - the **immune system**.

Adverse Effects

- In relatively rare instances (<1%), the effects on the **immune system** can produce immunoglobulin E (IgE)–mediated allergic reaction.
- Most cases are associated with the use of **amino esters**.
- Some anaesthetics, particularly benzocaine, are associated with **hematologic effects**, namely methemoglobinemia.
- **Cardiovascular effects** are primarily those of direct myocardial depression and bradycardia, which may lead to cardiovascular collapse.

Adverse Effects

- Note that toxicity of anaesthetics may be **potentiated** in patients with renal or hepatic compromise, respiratory acidosis, pre-existing heart block, or heart conditions.
- Toxicity may be **potentiated** during pregnancy, at the extremes of age, or in those with hypoxia.
- However, **inadvertent intravascular injection is the most common cause of local anesthetic toxicity** even if anesthetic was administered within the recommended dose range.

Minimum Intravenous Toxic Dose of Local Anaesthetic in Humans

Agent	Minimum Toxic Dose (mg/kg)
Procaine	19.2
Tetracaine	2.5
Chloroprocaine	22.8
Lidocaine	6.4
Mepivacaine	9.8
Bupivacaine	1.6
Etidocaine	3.4

Signs or Symptoms as a Possible Sign of Toxicity

1. **Central Nervous System**

- Initial symptoms
  - Lightheadedness
  - Dizziness
  - Visual and auditory disturbances (difficulty focusing and tinnitus)
  - Disorientation
  - Drowsiness
- Higher-dose symptoms
  - Often occur after an initial CNS excitation followed by a rapid CNS depression
  - Muscle twitching
  - Convulsions
  - Unconsciousness
  - Coma
  - Respiratory depression and arrest
  - Cardiovascular depression and collapse

Signs or Symptoms as a Possible Sign of Toxicity

2. **Cardiovascular**

- Direct cardiac effects
  - Toxic doses of local anaesthetic agents can cause myocardial depression (tetracaine, etidocaine, bupivacaine), cardiac dysrhythmias (bupivacaine), and cardiotoxicity in pregnancy.
  - Several anaesthetics' also have negative inotropic effects on cardiac muscle that lead to hypotension. Bupivacaine is especially cardiotoxic.
- Peripheral effects
  - Vasoconstriction at low doses
  - Vasodilatation at higher doses (hypotension)
- The range of signs and symptoms of cardiovascular toxicity include the following:
  - Chest pain
  - Shortness of breath
  - Palpitations
  - Lightheadedness
  - Diaphoresis
  - Hypotension
  - Syncope

Signs or Symptoms as a Possible Sign of Toxicity

3. **Hematological**
   Methemoglobinemia has been frequently reported in association with benzocaine use; however, lidocaine and prilocaine have also been implicated. O-toluidine, the liver metabolite of prilocaine, is a potent oxidizer of haemoglobin to methemoglobin. At low levels (1-3%), methemoglobinemia can be asymptomatic, but higher levels (10-40%) may be accompanied by any of the following complaints:
   - Cyanosis
   - Cutaneous discoloration (gray)
   - Tachypnea
   - Dyspnea
   - Exercise intolerance
   - Fatigue
   - Dizziness and syncope
   - Weakness

Signs or Symptoms as a Possible Sign of Toxicity

- **Allergic Manifestations**
- Amino esters are derivatives of ***para* -aminobenzoic acid (PABA)**, which have been associated with acute allergic reactions.
- Previous studies indicate a 30% rate of allergic reactions to procaine, tetracaine, and chloroprocaine.
- Amino amides are **not associated with PABA** and **do not produce allergic reactions with the same frequency**.
- However, preparations of amide anaesthetics may sometimes contain **methylparaben**, which **is structurally similar to PABA** and, thus, may result in allergic reactions.
- Patients who **report an allergy to lidocaine are likely allergic to the methylparaben preservative**.

Signs or Symptoms as a Possible Sign of Toxicity

- Allergic manifestations of local anaesthetics include **rash and urticaria**.
- **Anaphylaxis** due to local anaesthetics is **very rare** but should be considered if the patient is wheezing or in respiratory distress following administration.

Signs or Symptoms as a Possible Sign of Toxicity

- **Local Tissue Manifestations**
- In addition to numbness and paresthesias, which is expected in the normal range of local anaesthetic application, very high doses of local anaesthetics can produce **irreversible conduction block within 5 minutes**.
- **Peripheral neurotoxicity**, such as prolonged sensory and motor deficits, has also been documented.
- It is hypothesized that a **combination of low pH** and **sodium bisulfite** in the mixture can **be partially responsible for these changes**.
- Reversible skeletal muscle damage has also been reported.

Thank You

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