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Local Anesthetic Toxicity

Practical points you should know

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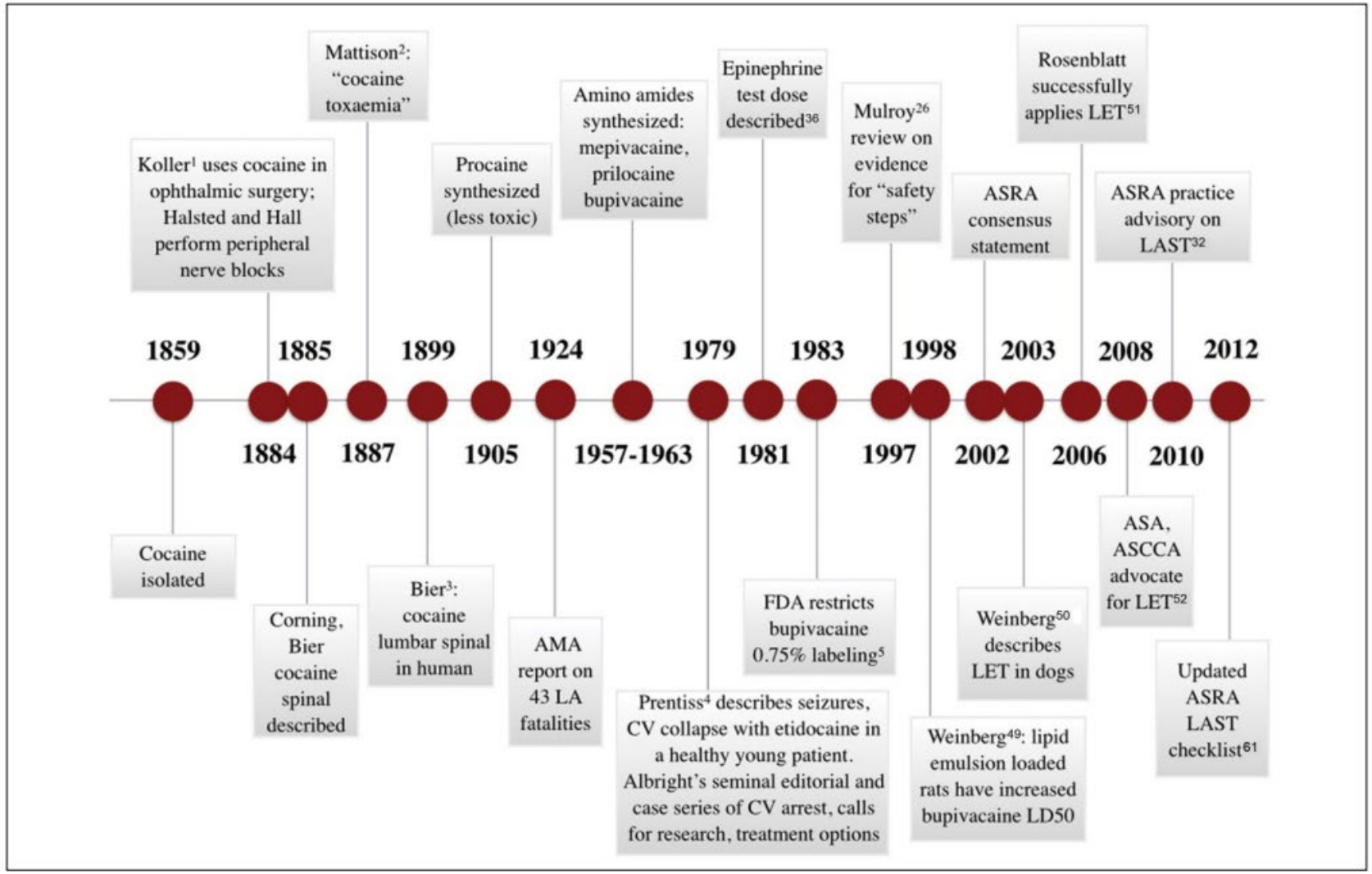
Local Anesthetic Systemic Toxicity



Dickerson DM, Apfelbaum JL. Local anesthetic systemic toxicity. Aesthet Surg J. 2014 Sep;34(7):1111-9.

Class of drugs of Medication errors

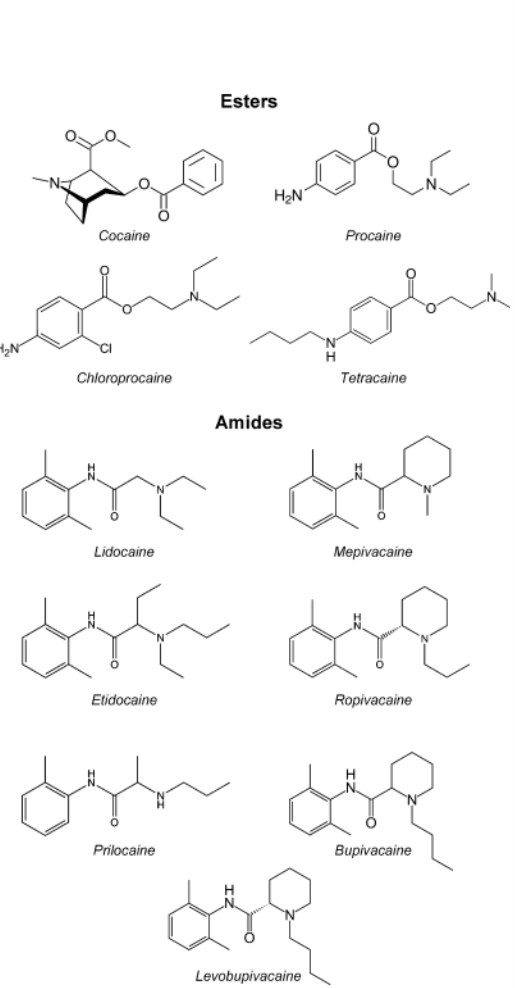
Class of drugs	Number (%)
Local anesthetics	**15 (13.4)**
Cardiology drugs	10 (8.9)
Antipsychotic drugs	10 (8.9)
Bronchodilators	9 (8.0)
Antineoplastic drugs	8 (7.1)

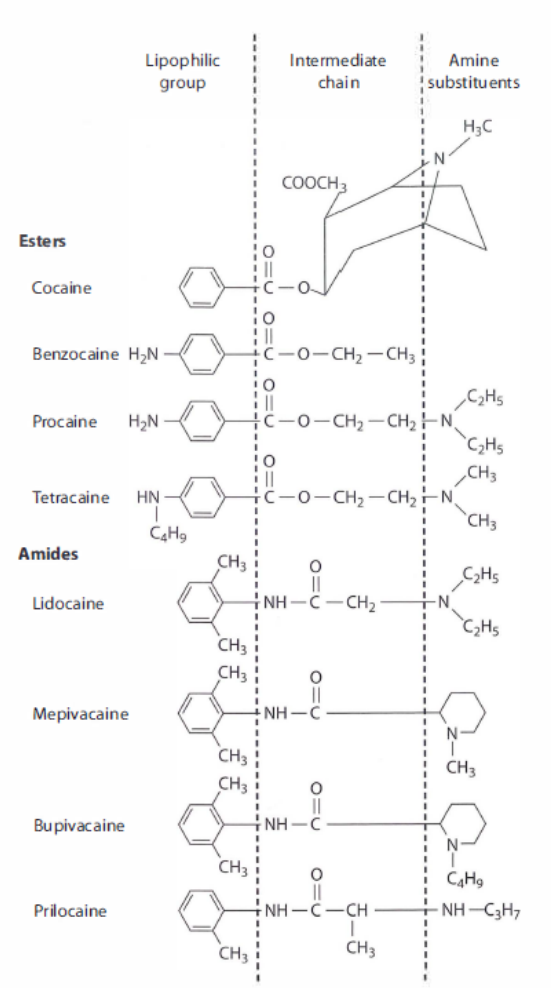
10-year retrospective study (2011-2020) of MEs in adult reported to RPC

Local anesthetics

- Provide analgesia in various parts of the body by
  - Topical application
  - Injection (intradermal, subcutaneous, intravenous ophthalmic, epidural)
- **Iatrogenic poisonings** result from inadvertent injection of
  - Therapeutic dose into a blood vessel
  - Repeated use of a therapeutic dose
  - Unintentional administration of a toxic dose

Pharmacology





https://www.researchgate.net/figure/1-Local-anesthetics-esters-and-amides-with-chemical-structures_fig1_226934971

- **Amino-esters** undergo hydrolysis by plasma cholinesterase to derivatives of para-aminobenzoic acid(PABA), which is a known allergen.
  - Patients with enzymatic mutations or low or absent concentrations of plasma cholinesterase are risk for systemic toxicity.
- **Amino-amides** are extensively metabolized by the liver to a variety of products with very low potential of triggering allergic reactions.
  - Decrease hepatic blood flow or impair hepatic function increase the risk for systemic toxicity.

Pharmacology

Local Anesthetic	Class/Chemical Linkage	pK_a (Onset Time)	Protein Binding (Duration of Action)	Lipophilicity (Potency)	Maximum Dose, mg/kg (Dose With Epinephrine)
Lidocaine[a]	Amide	7.8 (fast)	Moderate	Moderate	4.5 (7)
					Tumescent: 35-55
Bupivacaine[a]	Amide	8.1 (slow)	Long	Potent	2.5 (3)
Ropivacaine[a]	Amide	8.1 (slow)	Long	Potent	3 (3.5)
Prilocaine	Amide	8.0 (fast)	Moderate	Weak	5-7 (7-8.5)
Mepivacaine	Amide	7.7 (fast)	Moderate	Moderate	4.5 (7)
Articaine	Ester	7.8 (fast)	Short	Moderate	4 (7)
2-Chloroprocaine[a]	Ester	8.0 (very fast)	Short	Moderate	11 (14)
Cocaine	Ester	8.7 (slow)	Moderate	Moderate	12
Procaine	Ester	8.9 (slow)	Short	Weak	3

pKa

Protein binding

receptor affinity

- The onset of action of a local anesthetic is dependent on the **pKa.**
- At physiologic pH (7.4), LA with a lower pKa" have more **nonionized form** cross nerve cell membranes, producing a faster onset of action than LA with a higher pKa.
- **Lidocaine with has a more rapid onset of action.**

Pharmacology

- The duration of action of the local anesthetics is a function of **receptor affinity**.
  - LA with a higher receptor affinity (bupivacaine) have a longer duration of action than lower receptor affinity (lidocaine).
- The degree of **protein binding** influences the duration of action of LA.
  - LA with greater protein binding remain associated with the neural membrane for a longer time interval and therefore have longer durations of action.

- When high serum concentrations are achieved, a higher degree of protein binding increases the risk for cardiac toxicity.

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Anesthetic agents

Docaine Jelly 2 %
(ยาชาแบบทา) ขนาด 30g

https://www.tsnphatthana.com/product/54/docaine-jelly-2-%

Xylocain 10% Spray
ขนาด 50ml

https://www.tsnphatthana.com/product/27/xylocain-10-spray

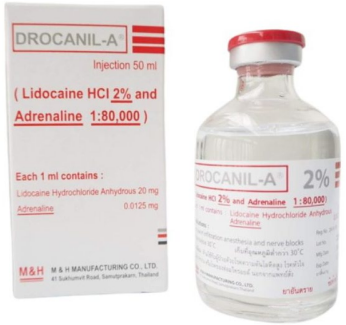
TABLE 36-1 Topical Anesthetic Agents

Agent	Active Ingredients	Application	Time to Effectiveness
Intact Dermis			
Eutectic mixture of local anesthetic agents (EMLA®)	Lidocaine 2.5% Prilocaine 2.5%	Apply thick layer, 5–10 grams (maximum 20 grams), to area to be anesthetized; cover with semiocclusive dressing.	60 min
Tetracaine (amethocaine) gel (Ametop®)	Tetracaine 4%	Apply 1 gram (1 tube) to area to be anesthetized; cover with occlusive dressing.	30 min
Liposome-encapsulated tetracaine	Tetracaine 5%	Apply 0.5 gram to area to be anesthetized.	60 min
Liposome-encapsulated lidocaine (LMX4® and LMX5®)	Lidocaine 4% or 5%	Apply 2.5 grams to area to be anesthetized.	30–60 min
Open Dermis			
Lidocaine, epinephrine, tetracaine (LET)	Lidocaine 4% Epinephrine 0.1% Tetracaine 0.5%	Apply 3–5 mL to gauze pad placed into wound; cover with semiocclusive dressing.	20–30 min
Mucosa			
Topical anesthetic gel (ZAP®)	Benzocaine 18% Tetracaine 2%	Apply 0.2 mL (1 dispenser application) with cotton swab to area to be anesthetized.	5 min
Benzocaine spray (Hurricaine®)	Benzocaine 20%	Apply 1 spray to area to be anesthetized; volume delivered is highly dependent on canister orientation and residual volume.	15–30 s
Viscous lidocaine	Lidocaine 2%	Apply 10 mL to area (e.g., topical anesthesia before upper airway procedures).	2–5 min

TABLE 36-2 Local Anesthetic Agents

Agent	Lipid Solubility*	Protein Binding	Duration† without epinephrine (min)	Onset‡ (min)	Maximum Dose milligrams/kg without epinephrine (with epinephrine)	Concentration (subdermal use)	Concentration (regional anesthesia use)
Amides							
Bupivacaine	High	High	120–240	2–10	3 (5)	0.50%–0.75%	0.25%–0.50%
Lidocaine	Medium	Medium	30–120	<1	4 (7)	0.5%–1.0%	1%–2%
Levobupivacaine	High	High	>1000	10–20	2	0.25%	0.50%
Mepivacaine	Low	Medium	30–120	3–20	4	0.5%–1.0%	1%–2%
Prilocaine	Medium	Medium	30–120	5–6	5	4%	NA
Ropivacaine	Medium	High	120–350	10–45	3	0.5%	0.5%
Esters							
Procaine	Low	Low	15–90	5	7	0.25%–0.5%	0.5%–2.0%
Chloroprocaine	Low	Low	30–60	5–6	8	1%–2%	1%–2%
Tetracaine (amethocaine)	High	High	120–240	7	1.5	NA	0.2%–0.3%
Alternatives for patients with reactions to amides and esters							
Diphenhydramine§			25			1%	NA
Benzyl alcohol with epinephrine§			15–25			0.9%	NA

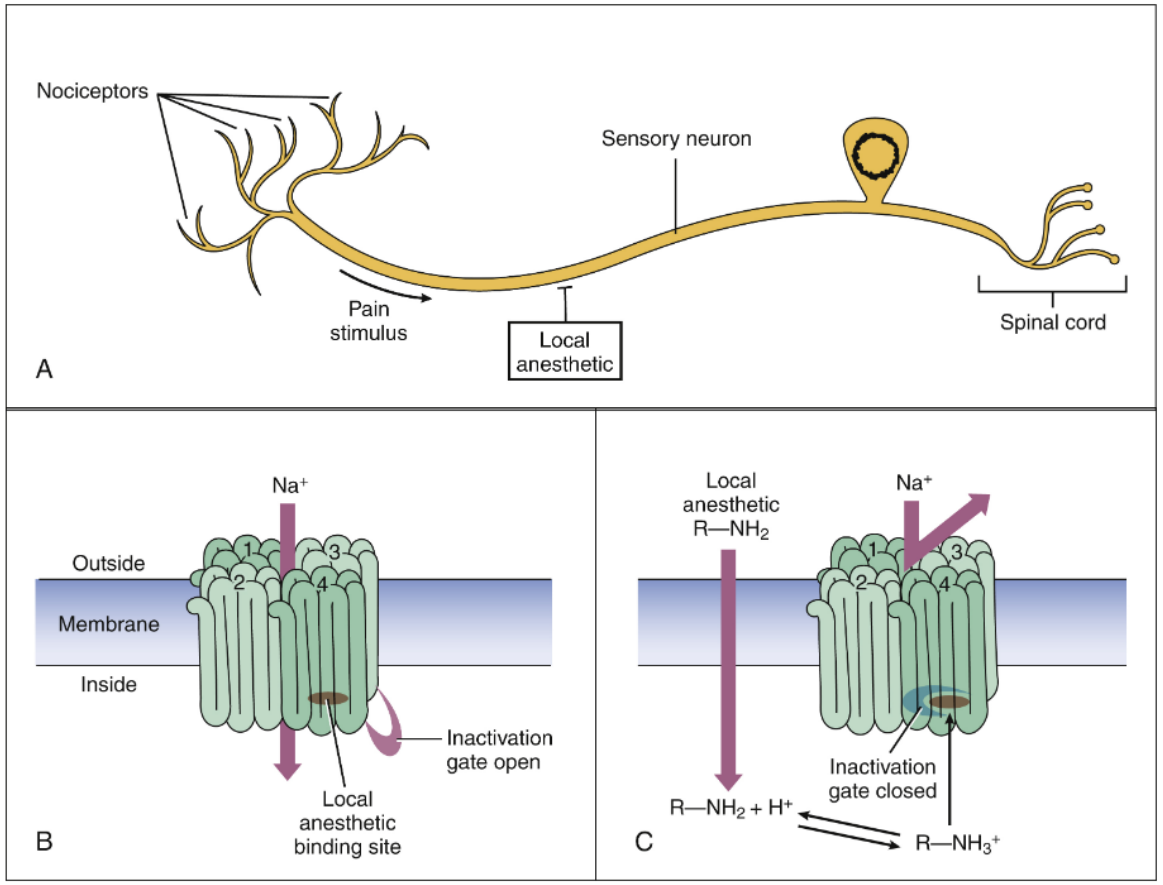
https://www.udl.co.th/product/lidocaine-2-injection/



Dronil-A 2% 50ml
ยาชาแบบฉีด 2% +adrenaline

https://www.tsnphatthana.com/product/87/dronil-a2

Mechanism of Local Anesthetics



https://basicmedicalkey.com/local-and-general-anesthetics-2/

- **Reversible inhibition** of action potential conduction by binding to the **sodium channel** and decreasing the nerve membrane permeability to sodium.
- Binding prevents pain transmission by the peripherally located primary afferent neuron.
- Sodium channel blockade first affects the smaller nerve fibers, causing a reduction in pain and temperature sensation, followed by loss of touch, deep pressure sensation, and, finally, motor function.
- These effects also occur in conductive tissues in the **heart and brain** that rely on sodium current.

PHARMACOKINETICS

- Local distribution is influenced by several factors
  - Spread of local anesthetic by bulk flow
  - Diffusion
  - Transport via adjacent blood vessels
    - Greater blood flow will have more rapid and complete systemic uptake of LA
    - Intravenous (IV) > tracheal > intercostal > paracervical > epidural > brachial plexus > sciatic > subcutaneous.
  - Binding to proximate tissues.

PHARMACOKINETICS

- Aging
  - Newborns with immature hepatic enzyme systems have prolonged elimination of amino amides and associated with seizures when high continuous infusion rates are used
  - In aged 22-26 year-old
    - Lidocaine's half-life after IV administration averaged 80 minutes
  - In aged 61-76 years
    - Lidocaine's half-life after IV administration averaged 138 minutes
- Lidocaine elimination is reduced by congestive heart failure and coadministration of xenobiotics that reduce hepatic blood flow

PHARMACOKINETICS

- LA cause peripheral vasodilation by direct relaxation of vascular smooth muscle.
- Vasodilation enhances vascular absorption
- **Addition of epinephrine** to the LA solution
  - Decreases the rate of vascular absorption
  - Prolonging the duration
  - Decreases bleeding into the surgical field
  - Mitigating risk of systemic toxicity

Dronil-A 2% 50ml
ยาชาแบบฉีด 2% +adrenaline
https://www.tsnphatthana.com/product/87/dronil-a2

Risk factors of Toxicity

- **Drug**
  - High receptor binding
  - A low CC/CNS ratio is associated with more cardiotoxic agents, while LAs with a higher CC/CNS ratio have a greater safety margin.
- **Renal disease**
  - Reduced clearance
- **Cardiac disease**
  - Pre-existing conduction disorders
- **Hepatic dysfunction**
  - Reduced hepatic clearance
- **Age**
  - Neonate
  - Elderly
- **Pregnancy**
  - Reduced plasma concentrations of a-1-acid glycoprotein and an increased cardiac output..

El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: current perspectives. Local Reg Anesth. 2018 Aug 8;11:35-44.

CLINICAL MANIFESTATIONS OF TOXICITY

TABLE 64–3 Types of Local Anesthetic Reactions

Cause	*Major Clinical Features*
Local anesthetic toxicity (intravascular injection)	Immediate seizure or dysrhythmias
Reaction to adjuvant catecholamine	Tachycardia, hypertension, headache
Vasodepressor syncope	Bradycardia, hypotension, pallor rapid onset and recovery, loss of conscientiousness
Allergic reaction	Anaphylaxis
High spinal or epidural block	Bradycardia, hypotension, respiratory distress, respiratory arrest

- Regional Side Effects and Tissue Toxicity
- Systemic Side Effects and Toxicity
  - Allergic Reactions
  - Methemoglobinemia
  - Local Anesthetic Systemic Toxicity
    - Central Nervous System Toxicity
    - Cardiovascular Toxicity

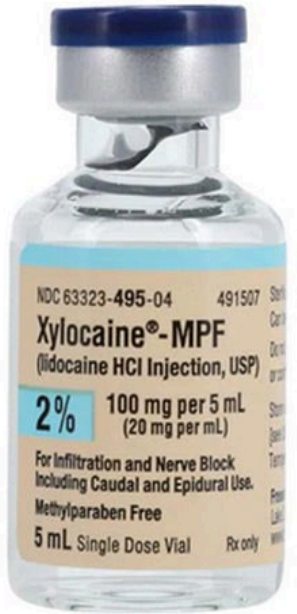
Regional Side Effects and Tissue Toxicity

- Directly cytotoxic to nerve cells but in therapeutic doses, they rarely produce localized nerve damage.

- Nerve damage often is attributed to the use of excessively concentrated solutions or inappropriate formulations.
- Significant direct neurotoxicity results from intrathecal injection or infusion of local anesthetics for spinal anesthesia.
- Several reports of cauda equina syndrome are associated with use of hyperbaric 5% lidocaine solutions for spinal anesthesia.

Systemic Side Effects and Toxicity

- Allergic Reactions
- PABA, most likely the cause of allergic reactions
- **Preservative-free amino amides**, in lidocaine, are appropriate for use in patients who have reactions to drug preparations containing methylparabens.
- Patient with a history of allergic reaction to a particular anesthetic requires a local anesthetic, a paraben preservative-free drug from the opposite class can be chosen



https://www.mountainside-medical.com/collections/local-anesthetics/products/xylocaine-2-for-injection-5ml-mpf-vials-25-tray

Systemic Side Effects and Toxicity

- Methemoglobinemia
  - Frequent adverse effect of topical and oropharyngeal **benzocaine** and is occasionally reported with **lidocaine**, tetracaine, or prilocaine use.
  - Excessive dose or a break in the normal mucosal barrier for topical anesthetics.
- Standard doses of lidocaine-prilocaine cream used for circumcision in term neonates are associated with minimal production of methemoglobin, but risks may be increased in neonates with metabolic disorders.

Local Anesthetic Systemic Toxicity

- LAST : Systemic toxicity correlates with serum concentrations.
- Factors that determine the concentration include
  - Dose
  - Rate of administration
  - Site of injection
  - Presence or absence of a vasoconstrictor
  - Protein binding
  - Fat solubility
  - pKa of LA

Local Anesthetic Systemic Toxicity

- The brain and heart are the primary target organs for systemic toxicity because of
  - High perfusion
  - Lack of diffusion limitations
  - Presence of cells that rely on voltage-gated sodium channels to produce an action potential.

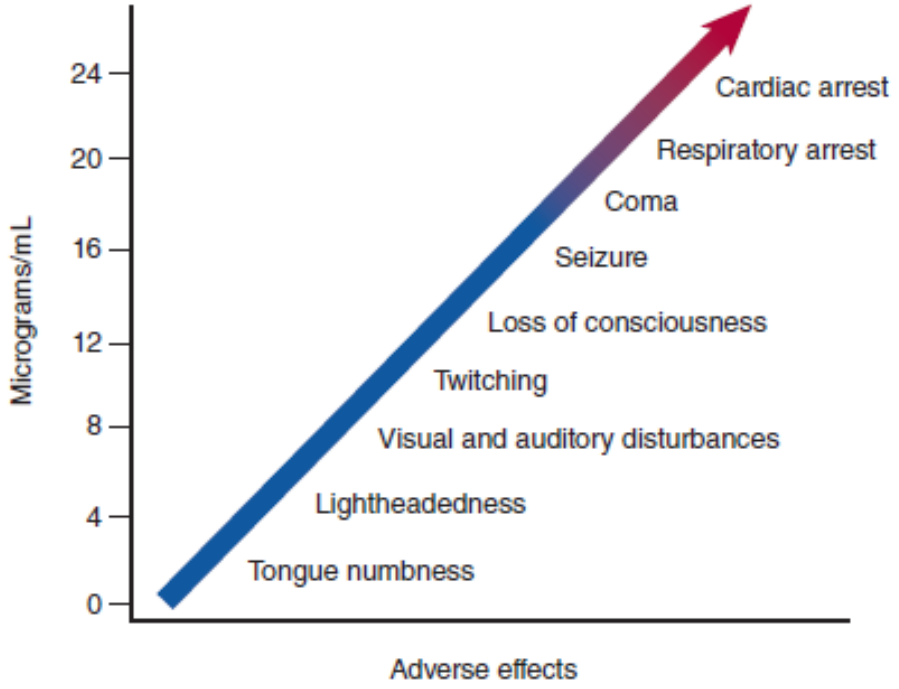


FIGURE 36-1. Adverse effects of local anesthetics. Plasma concentration of local anesthetics versus toxic effects.

Central Nervous System Toxicity

- **Selective sodium channel blockade of cerebral cortical inhibitory pathways in the amygdala** resulting increase in unopposed excitatory activity leads to seizures and as the concentration increases, both inhibitory and excitatory neurons are blocked, and generalized CNS depression ensues.

- A gradually increasing serum lidocaine concentration usually produces a **stereotypical pattern of signs and symptoms**.
- The initial effects include Tongue numbness
  - Occur at serum concentrations between 3 and 6 mcg/mL.
- After that develop, and include shivering, tremors, and ultimately generalized tonic-clonic seizures.
  - Occur at serum concentrations between 5 and 9 mcg/mL.
- Seizures are reported after even small doses injected into the vertebral or carotid artery.

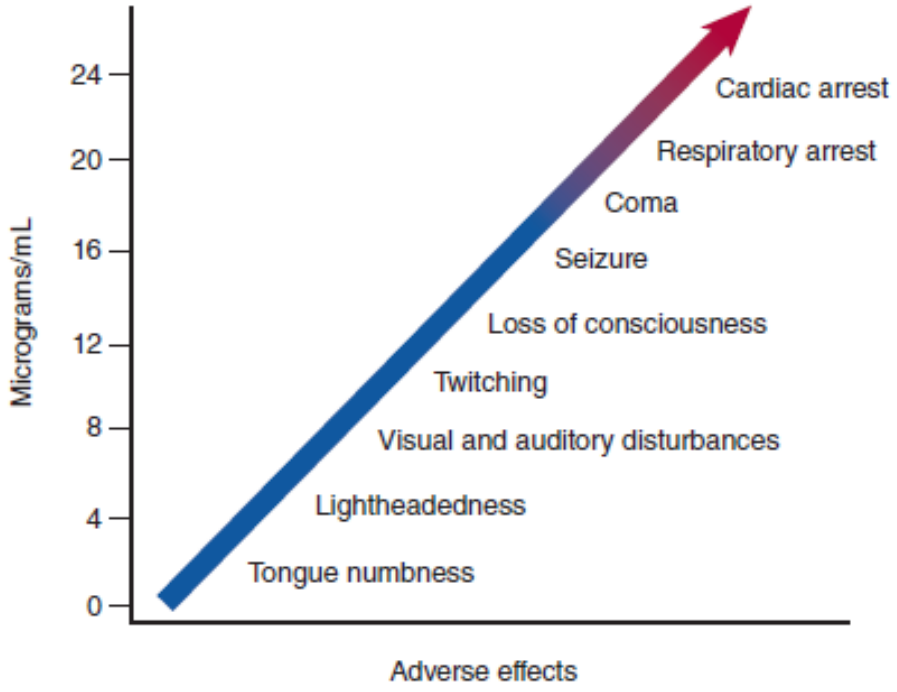
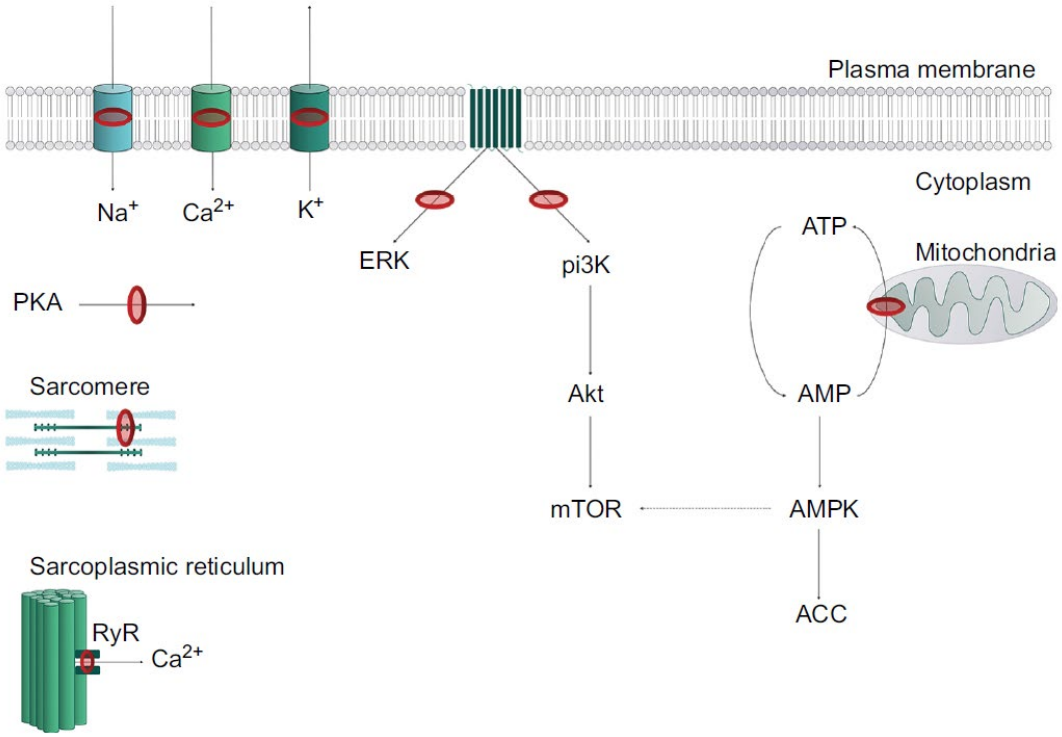


FIGURE 36-1. Adverse effects of local anesthetics. Plasma concentration of local anesthetics versus toxic effects.

Cardiovascular Toxicity



El-Boghdadly K, Pawa A, Chin KJ. Local anesthetic systemic toxicity: current perspectives. Local Reg Anesth. 2018 Aug 8;11:35-44.

- Effect in **conduction disturbances**, **myocardial dysfunction**, and **capable of peripheral vascular tone**.
- The primary effects are likely to arise from rhythm disturbance.
- Normal conduction is disrupted by direct sodium channel blockade, chiefly at the bundle of His.
- By driving the resting membrane potential to a more negative level, action potential is impaired, leading to prolonged PR, QRS, and ST intervals.
- Myocardial dysfunction due to
  - Blockade of Calcium channel and Na+ – Ca2+ exchange pump reduces intracellular calcium stores and, thus, diminishes contractility.
- Result in reduction of intracellular adenosine triphosphate reserves, and impaired cyclic adenosine monophosphate production further contributes to reduced myocardial contractility

Cardiovascular Toxicity

- Shock and cardiovascular collapse are related to effects on **vascular tone, inotropy, and dysrhythmias.**
- At progressively higher LA concentrations,
  - Hypotension, sinus arrest with junctional rhythm, and eventually cardiac arrest occur.
- The cardiovascular collapse: CNS toxicity (CC:CNS) ratio for Lidocaine is approximately 1:7
- **Bupivacaine** is significantly more cardiotoxic than most other LA commonly used, with a CC:CNS ratio of 3:7
- Bupivacaine produces myocardial depression out of proportion and cause more refractory ventricular dysrhythmias.

DIAGNOSTIC TESTING

- Cardiac monitoring to detect dysrhythmias and conduction disturbances.
- Serum electrolytes, blood urea nitrogen, creatinine, and blood gas analysis should be obtained to help assess the cause of cardiac dysrhythmias.

Management

- Decontamination
  - Oral exposure : ingestion of liquid medications within 1-2 hour
    - Gastric lavage
    - Single dose activated charcoal
- Enhance elimination
- Specific antidote : Intralipid Emulsion (ILE)

Management of Central Nervous System Toxicity

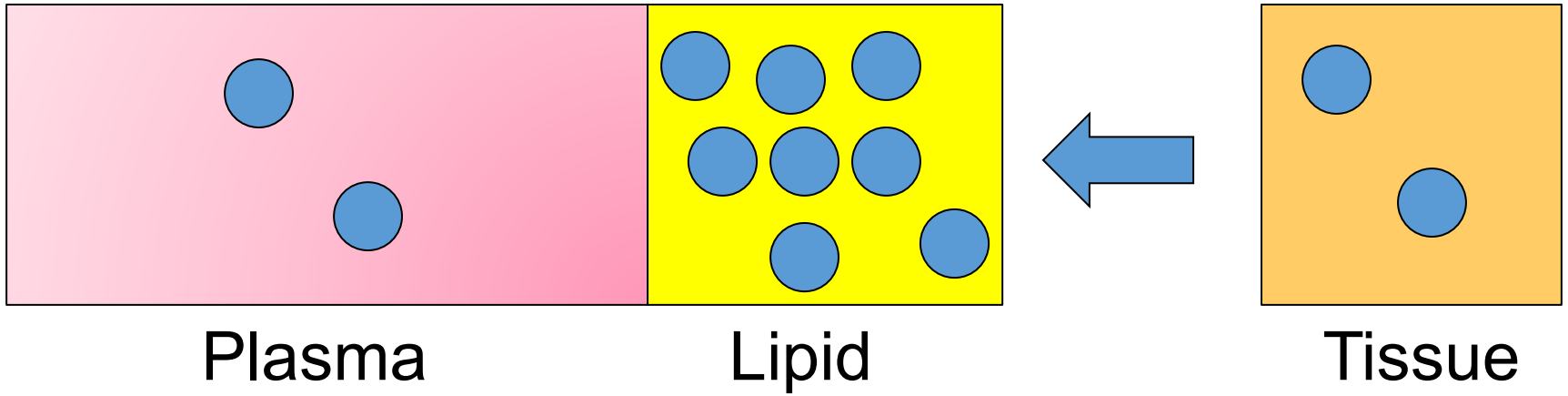
- Stop administration drug
- Protect airway with ventilation supports
- Patients with minor symptoms need to followed closely for progression to more severe effects.
- Benzodiazepines are recommended as the first-line treatment for local anesthetic CNS toxicity.
- **Succinylcholine** is not routinely recommended because of side effects, including hyperkalemia and dysrhythmias.
- Nondepolarizing neuromuscular blockers such as rocuronium are preferentially recommended.

Management of Cardiovascular Toxicity

- Early recognition of potential cardiac toxicity
- Standard Advanced Cardiac Life Support (ACLS) protocols should be followed.
- Bupivacaine-induced dysrhythmias often are refractory to cardioversion, defibrillation, and pharmacologic treatment.
- Extracorporeal membrane oxygenation (VA-ECMO) is being used in the management of critically ill overdose patients

IV Fat Emulsion

- Three proposed mechanisms of action
  - Soaks up lipid-soluble xenobiotic
  - Removes from the site of toxicity
  - May pull the xenobiotics out of the aqueous plasma



ILE : DOSING AND ADMINISTRATION

ASRA PAIN MEDICINE
American Society of Regional Anesthesia and Pain Medicine

The Association of Anaesthetists of Great Britain & Ireland

American Heart Association.

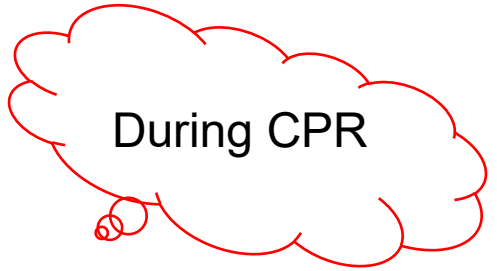
- Recommend dose of 20% ILE 1.5 mL/kg IV bolus over 1 minute followed by 0.25 mL/kg/min or 15 mL/kg/h to run for 30 to 60 minutes.
- They suggest repeating this bolus several times for persistent dysrhythmias and that the infusion rate can be increased if blood pressure decreases.
- Maximum total dose of 10 mL/kg/day

RESUSCITATION: Antidotes

TABLE 176-2 Common Antidotes Used in Resuscitation of the Acutely Poisoned Patient

Antidote	Initial Pediatric Dose*	Initial Adult Dose*	Indication
Calcium gluconate 10% 9 milligrams/mL elemental Ca	0.5–0.45 mL/kg IV	10–30 mL IV	Hypermagnesemia Calcium channel blockers
Cyanide antidote kit Amyl nitrite	Not typically used	Crack vial and inhale over 30 seconds, or place in chamber of ventilation bag and use 30 s on/30 s off	Cyanide
Sodium nitrite (3% solution)	Dosed according to hemoglobin level. If unknown, assume hemoglobin level is 12 g/dL (120 g/L) and dose with 0.33 mL/kg IV	10 mL IV	Cyanide Hydrogen sulfide (use only sodium nitrite)
Sodium thiosulfate (25% solution)	1.65 mL/kg IV	50 mL IV	Cyanide
Dextrose (glucose)	0.5–1.09 gram/kg IV	1 gram/kg IV	Insulin Oral hypoglycemics
Digoxin Fab Acute toxicity	5–10 vials IV	10 vials	Digoxin and other cardioactive steroids
Flumazenil	0.01 milligram/kg IV	0.2 milligram IV	Benzodiazepines
Glucagon	30 micrograms/kg IV over 1–2 min for CCB toxicity and 30–150 micrograms/kg IV over 1–2 min for BB toxicity	5 milligrams IV	Calcium channel blockers Beta-blockers
Hydroxocobalamin	70 milligrams/kg (maximum 5 grams) IV over 15 min	5 grams IV over 15 min	Cyanide Nitroprusside
IV lipid emulsion 20%	1.5 mL/kg IV bolus over 1 min (may be repeated 2 times at 5-min intervals), followed by 0.25 mL/kg per min IV infusion for 20 min	100-mL IV bolus over 1 min (may be repeated 2 times at 5-min intervals), followed by 18 mL/min IV infusion for 20 min	Local anesthetic systemic toxicity Rescue therapy for lipophilic cardiotoxins
Methylene blue	1 milligram/kg IV Neonates: 0.3–1.0 milligram/kg IV	1 milligram/kg IV	Oxidizing toxins (e.g., nitrites, benzocaine, sulfonamides)
Naloxone	As much as required Start: 0.01 milligram IV	As much as required Start: 0.1–0.4 milligram IV	Opioids Clonidine
Pyridoxine	Gram for gram if amount of isoniazid ingested is known, otherwise:		Isoniazid
	70 milligrams/kg IV (maximum 5 grams)	5 grams IV	
Sodium bicarbonate	1–2 mEq/kg IV over 1–2 min followed by 0.3 mEq/kg per hour IV infusion		Sodium channel blockers Urinary alkalinization
Thiamine	5–10 milligrams IV	100 milligrams IV	Wernicke's syndrome Wet beriberi

Tintinalli 9th ed



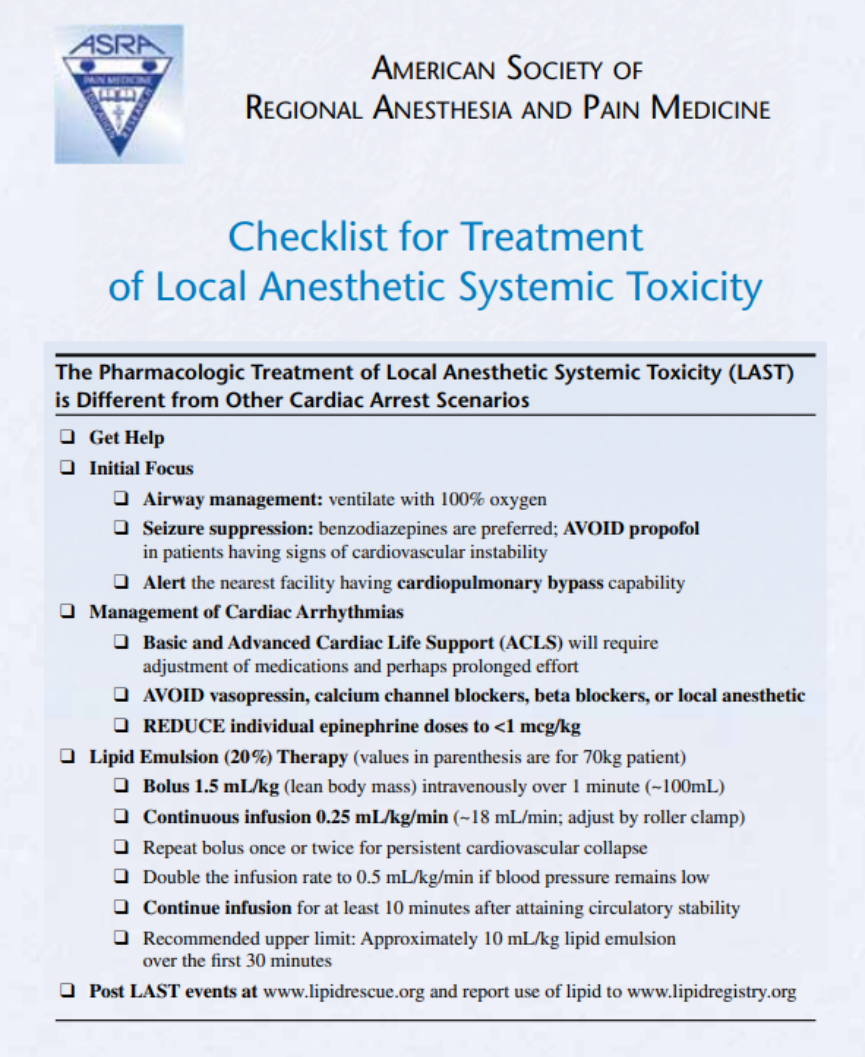
- ILE is recommended with CPR and standard ACLS.
- *Dose of Epinephrine small doses of epinephrine 10 - 100 micrograms
- ILE should be stored for easy and rapid access in operating rooms or in areas where local anesthetics are frequently used.
- ILE should we administration when
  - CNS involvement
    - Agitation, confusion, seizures
  - Cardiovascular system involvement
    - Ventricular dysrhythmias, hypotension, conduction blocks

ADVERSE EFFECTS AND SAFETY ISSUES

- ARDS
  - Occlude the pulmonary vasculature injection over 8 hours resulted increased pulmonary artery pressures, increased pulmonary vascular resistance, and decreased partial pressures of oxygen in the alveoli
- Venous thromboembolism
- Hypersensitivity
- Fat overload syndrome
  - Characterized by hyperlipemia, fever, fat infiltration, hepatomegaly, jaundice, splenomegaly, anemia, leukopenia, thrombocytopenia, coagulation disturbances, seizures, and coma.
- Pancreatitis
  - Large concentration of triglycerides forming large lipid droplets that obstruct the small vessels of the pancreas, leading to ischemia
- Extracorporeal circulation machine circuit obstruction
  - Fat deposition in the VA-ECMO circuit and increased blood clot formation within the circuit
- Increased susceptibility to infection
- **Interfere with Albumin, Amylase, lipase, phosphate, creatinine, total protein, alanine aminotransferase, creatine kinase, and bilirubin and magnesium level interpreted**

Prevention of Systemic Toxicity of Local Anesthetics

- Use the lowest possible anesthetic concentration and volume consistent with effective anesthesia and to avoid a significant intravascular injection.
- Ensuring extravascular placement demonstrated by ultrasonographic guidance and by careful.



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Checklist for Treatment of Local Anesthetic Systemic Toxicity

The Pharmacologic Treatment of Local Anesthetic Systemic Toxicity (LAST) is Different from Other Cardiac Arrest Scenarios

- ❑ **Get Help**
- ❑ **Initial Focus**
  - ❑ **Airway management:** ventilate with 100% oxygen
  - ❑ **Seizure suppression:** benzodiazepines are preferred; **AVOID propofol** in patients having signs of cardiovascular instability
  - ❑ **Alert** the nearest facility having **cardiopulmonary bypass** capability
- ❑ **Management of Cardiac Arrhythmias**
  - ❑ **Basic and Advanced Cardiac Life Support (ACLS)** will require adjustment of medications and perhaps prolonged effort
  - ❑ **AVOID vasopressin, calcium channel blockers, beta blockers, or local anesthetic**
  - ❑ **REDUCE individual epinephrine doses to <1 mcg/kg**
- ❑ **Lipid Emulsion (20%) Therapy** (values in parenthesis are for 70kg patient)
  - ❑ **Bolus 1.5 mL/kg** (lean body mass) intravenously over 1 minute (~100mL)
  - ❑ **Continuous infusion 0.25 mL/kg/min** (~18 mL/min; adjust by roller clamp)
  - ❑ Repeat bolus once or twice for persistent cardiovascular collapse
  - ❑ Double the infusion rate to 0.5 mL/kg/min if blood pressure remains low
  - ❑ **Continue infusion** for at least 10 minutes after attaining circulatory stability
  - ❑ Recommended upper limit: Approximately 10 mL/kg lipid emulsion over the first 30 minutes
- ❑ **Post LAST events at** www.lipidrescue.org and report use of lipid to www.lipidregistry.org

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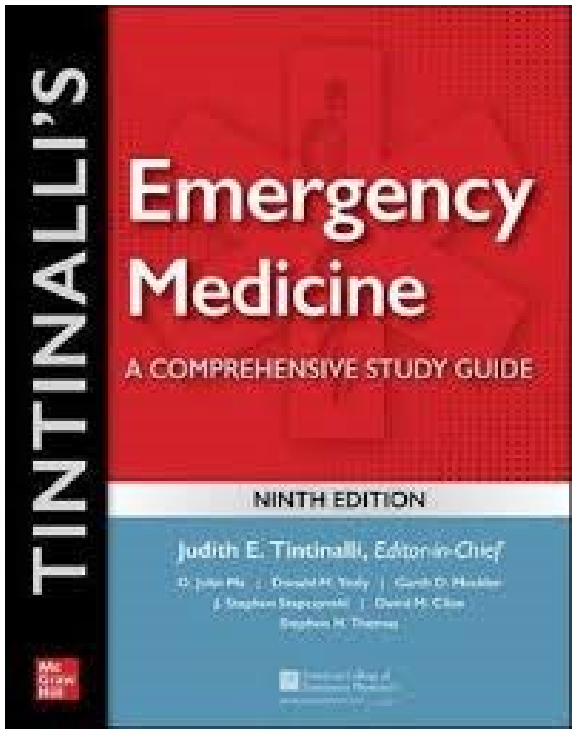
Thank you for your attention

Question ?

E-mail: phantakan.tan@mahidol.ac.th

References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A COMPREHENSIVE STUDY GUIDE
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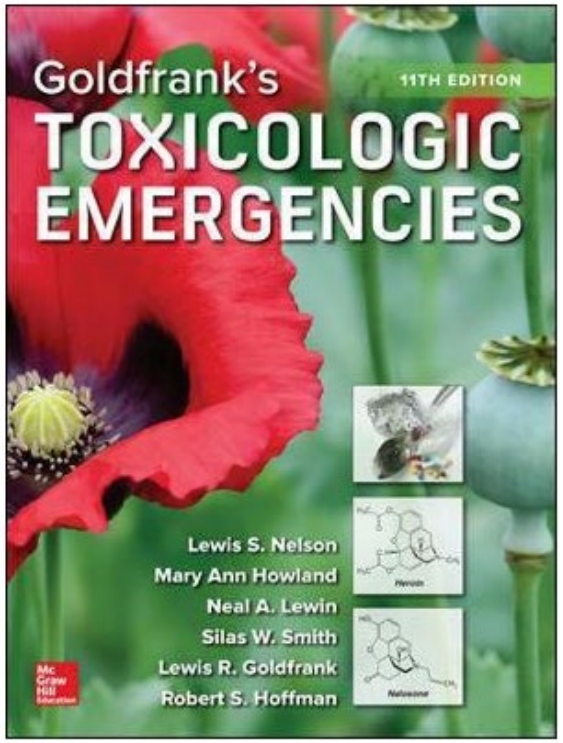
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