ALLERGIC REACTIONS AND HIGH BLOOD LEVELS IN ANESTHESIA

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THE STATISTICS

- 6-10% of all adverse drug reactions
- 5% population allergic 1 or more drugs
  - Most common penicillin
- Physiologic definition
  - Sudden 30% ↓ in BP with ↑ in HR in temporal relationship to medication being given.
- Drug sensitivity implicated 4% anesthesia related deaths.

- Incidence of patient allergen sensitivity doubles in last 30 years (54%)
  - Teen dies from kissing boyfriend
    - Residual peanut allergen
  - 150 – 200 anaphylactic food deaths in US
  - Anaphylaxis represents 0.02% of all ER admissions

USA Today, Nov 29, 2005

LIFE-THREATENING ALLERGIC RX

- Estimated
  - 1:10-12,000 anesthetics.
  - 10% of anesthetic complications
  - Rare
  - Incidence increasing
    - Longer list of chemicals used
- Regional anesthesia may worsen Reaction
  - Interfere with epinephrine release from adrenal glands.

DEFINING THE TERMS ALLERGIC REACTION

- Anaphylactic –
  - Immunologically mediated reactions.
  - Usually fast onset < 5 minutes
  - Greek – backward protection
  - Prior exposure
    - Antigen-antibody complex
      - Mast cell have 40-100,000 IgE attachment sites
      - Interaction of antigen with antibody or specific receptor cell.
    - Antigen : molecules capable of stimulating an immune response when contact occurs by injection or exposure.
    - Antibody : complex large protein molecules produces by plasma cells and capable of binding with antigens.
DEFINING THE TERMS ALLERGIC REACTION

- Anaphylactoid –
  - 1st exposure
  - Pharmacologic idiosyncrasy, by direct toxicity or drug overdosage, or by drug interaction.
  - Indistinguishable from anaphylactic
    - May be less severe
  - Different pathophysiology
    - Drug has direct effect on mast cells and Basophils causing reaction and release of histamine.
    - Not dependent on production of antibodies.
    - Not immunologically mediated.
    - Medications with basic PH more prone to effect.
      - Rapid administration will increase severity.

CLASSIFICATION OF ALLERGIC TERMS

- Complement mediated
  - Hypersensitivity - having the specific or general ability to react with characteristic symptoms to application or contact with certain substances (allergens) in amounts innocuous to normal individuals.
  - If know antigen-antibody mediated call anaphylactic otherwise allergic reaction

WHAT IS THE COMPLEMENT SYSTEM?

- 20 plasma proteins
  - Principle humoral effector of immunologically induced inflammation
  - Act to identify and destroy foreign antigens.
  - Drug-antibody (IgG and IgM) complex initiates complement cascade sequence by activating the C1 complement protein.
  - Various activated proteins have cytotoxic capabilities
    - Some cause mast cell degranulation.
    - Does not require previous exposure.
  - Proteins are produced primarily in hepatocytes.
  - Some such as macrophages may produce these proteins as well.
  - These proteins are found in most bodily fluids.
CHEMICAL MEDIATORS RELEASED

<table>
<thead>
<tr>
<th>Substance</th>
<th>Physiologic Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>Histamine</td>
<td>• Bronchospasm</td>
</tr>
<tr>
<td></td>
<td>• Increased capillary permeability</td>
</tr>
<tr>
<td></td>
<td>• Peripheral vasodilation</td>
</tr>
<tr>
<td>Leukotrienes</td>
<td>• 1000x more potent than histamine</td>
</tr>
<tr>
<td></td>
<td>• Increased capillary permeability</td>
</tr>
<tr>
<td></td>
<td>• Intense bronchospasm</td>
</tr>
<tr>
<td></td>
<td>• Negative ionotropic effects,</td>
</tr>
<tr>
<td></td>
<td>• Coronary vasoconstriction and ischemia</td>
</tr>
</tbody>
</table>

Prostaglandins

- Bronchospasm

Tryptase

- No physiologic effect
- Only way to get into circulation is degranulation
- Allergic reaction marker
- Elevated to 4 hours
- Not elevated in vancomycin anaphylactoid rx.

PERIOPERATIVE DIAGNOSIS

- More difficult
  - Loss of subjective complaints (signs)
  - Absence of cutaneous clues (draping)
  - Use of multiple drugs (masking)
  - Overdependence on technology.

TESTING

- Skin tests still most sensitive
  - Help patient find appropriate consultant.
  - Interdermal testing
    - Best time several weeks after event
    - May be depletion of mediators giving negative skin test.

TISSUES OF THE IMMUNE SYSTEM
PHYSIOLOGY OF ALLERGIC REACTIONS

- Immune system
  - Thymus
  - Lymph nodes
  - Tonsils
  - Spleen
- Responsible for protections from infections and foreign substances
- Can react inappropriately to produce hypersensitivity or allergic reaction

ALLERGIC REACTIONS

- Types of reactions
  + Type 1 - Anaphylactic or Immediate
    - Produced by release of physiologically active mediators
    - Primarily from mast cells and Basophils
    - Follows specific antigen binding, IgE antibodies, with cell membranes
    - Angioedema, Anaphylaxis
  + Type 2 - Antibody dependent cytotoxic hypersensitivity
    - Mediated by IgG or IgM antibodies directed against antigens on the surface of foreign cells.
    - Damage may include:
      - lysis of cells following complement cascade activation
      - increased phagocytosis by macrophages
      - killer T-cell lymphocytes producing antibody dependent cell mediated cytotoxic effects,
      - i.e. ABO incompatibility
  + Type 3 - Immune Complex Reaction
    - Results in circulating soluble antigens and antibodies that bind to form insoluble complexes that become lodged in microvasculature of organs.
    - Complement system is activated
    - Tissue damage is produced by polymorphonuclear leukocytes localized at the site of complement deposition
    - i.e. snake bite
  + Type 4 - T-Cell mediated immunity
    - Results following interaction of sensitized lymphocytes to specific antigens.
    - No complement or antibody involvement
    - Predominantly mononuclear and slow to develop
      - First appears 18-24 hours
      - Maximum effect 48-80 hours
      - Disappears in 72-90 hours
  + Type 4 - Cell mediated immunity
    - Antigen binding to lymphocytes produce lymphokine synthesis
    - Lymphocyte proliferation and generation cytotoxic T-cells
    - T-cells kill target cells that bear antigens identical to those that trigger reaction
    - Important in tissue rejection
    - Contact dermatitis
ALLERGIC REACTIONS

- Types of immunity
  - Hormonal immunity
    - Mediated by B-lymphocytes
    - Antibodies are plasma proteins designated immunoglobulins.
  - Cellular immunity
    - Mediated by T-lymphocytes - most abundant in adults
    - 2 types - Helper (OKT4) and Suppressor (OKT8)
      - Regulate antibody production by B-cell lymphocytes
      - Activated by helper T-lymphocytes balanced by suppressor T-cell lymphocytes

ALLERGIC REACTIONS

- Effects of surgery
  - Depression of both T-cells and B-cell responsiveness.
  - Effects short-lived.

ALLERGIC REACTIONS

<table>
<thead>
<tr>
<th>IgG</th>
<th>IgA</th>
<th>IgM</th>
<th>IgD</th>
<th>IgE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Location</td>
<td>Plasma</td>
<td>Amniotic fluid</td>
<td>Plasma Saliva Tears</td>
<td>Plasma</td>
</tr>
<tr>
<td>Half-life (Days)</td>
<td>23</td>
<td>6</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Function Immunity</td>
<td>&amp; defense against infection</td>
<td>Topical defense against infection</td>
<td>Lysis of bacterial cell walls</td>
<td>Not known</td>
</tr>
<tr>
<td>Function</td>
<td>Immunity &amp; defense against infection</td>
<td>Topical defense against infection</td>
<td>Lysis of bacterial cell walls</td>
<td>Not known</td>
</tr>
</tbody>
</table>

Does it really matter?

ANAPHYLACTIC VS. ANAPHYLACTOID

RECOGNITION OF ANAPHYLAXIS DURING REGIONAL AND GENERAL ANESTHESIA

<table>
<thead>
<tr>
<th>Systems</th>
<th>Signs</th>
<th>Symptoms</th>
<th>Dyspnea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Respiratory</td>
<td>Bronchospasm - not majority</td>
<td>Dizziness</td>
<td>Acute respiratory failure</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Hypotension - 90%</td>
<td>Malaise</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Neurovascular</td>
<td>Loss of consciousness</td>
<td>Angina</td>
<td>Cardiac arrest</td>
</tr>
<tr>
<td>Vascular</td>
<td>Vasodilatation (H$_2$ receptor mediated)</td>
<td>Vasodilatation</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Digestive</td>
<td>Tachycardia</td>
<td>Tachycardia</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>Dystrophias</td>
<td>Dystrophias</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Dermatological</td>
<td>Decreased systemic vascular resistance</td>
<td>Decreased systemic vascular resistance</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Respiratory</td>
<td>Pulmonary edema</td>
<td>Pulmonary edema</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Increased pulmonary compliance</td>
<td>Increased pulmonary compliance</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Neurological</td>
<td>Laryngeal edema</td>
<td>Laryngeal edema</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Dysnea</td>
<td>Dysnea</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Skin</td>
<td>Wheezing</td>
<td>Wheezing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Eye</td>
<td>Sneezing</td>
<td>Sneezing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Ear</td>
<td>Coughing</td>
<td>Coughing</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Nose</td>
<td>Laryngeal edema</td>
<td>Laryngeal edema</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Throat</td>
<td>Increased pulmonary compliance</td>
<td>Increased pulmonary compliance</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Neck</td>
<td>Fulminant pulmonary edema</td>
<td>Fulminant pulmonary edema</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Head</td>
<td>Acute respiratory failure</td>
<td>Acute respiratory failure</td>
<td>Pulmonary hypertension</td>
</tr>
</tbody>
</table>

- ANAPHYLACTIC
  - Systems: Respiratory, Cardiovascular, Neurovascular, Vascular, Digestive, Musculoskeletal, Dermatological, Respiratory, Cardiovascular, Neurological, Gastrointestinal, Skin, Eye, Ear, Nose, Throat, Neck, Head
  - Signs: Bronchospasm, Hypotension, Loss of consciousness, Vasodilatation, Tachycardia, Dystrophias, Decreased systemic vascular resistance, Pulmonary edema, Increased pulmonary compliance, Laryngeal edema, Wheezing, Coughing, Sneezing, Coughing, Laryngeal edema, Increased pulmonary compliance, Fulminant pulmonary edema, Acute respiratory failure

- ANAPHYLACTOID
  - Systems: Respiratory, Cardiovascular, Neurovascular, Vascular, Digestive, Musculoskeletal, Dermatological, Respiratory, Cardiovascular, Neurological, Gastrointestinal, Skin, Eye, Ear, Nose, Throat, Neck, Head
  - Signs: Dizziness, Malaise, Angina, Vasodilatation, Tachycardia, Dystrophias, Decreased systemic vascular resistance, Pulmonary edema, Increased pulmonary compliance, Laryngeal edema, Wheezing, Coughing, Sneezing, Coughing, Laryngeal edema, Increased pulmonary compliance, Fulminant pulmonary edema, Acute respiratory failure
**RECOGNITION OF ANAPHYLAXIS DURING REGIONAL AND GENERAL ANESTHESIA**

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<thead>
<tr>
<th>Systems</th>
<th>Symptoms</th>
<th>Signs</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cutaneous</td>
<td>Itching</td>
<td>Urticaria (hives)</td>
</tr>
<tr>
<td></td>
<td>Burning</td>
<td>Flushing</td>
</tr>
<tr>
<td></td>
<td>Tingling</td>
<td>Periorbital edema</td>
</tr>
<tr>
<td></td>
<td>Angioedema</td>
<td>Personal edema</td>
</tr>
</tbody>
</table>

**MANAGEMENT OF ANAPHYLAXIS DURING GENERAL AND REGIONAL ANESTHESIA**

Initial Therapy
1. Stop administration of antigen
2. Maintain airway and administer 100% O2 – VQ abnormalities.
3. Discontinue all anesthetic agents
4. Start intravascular volume expansion (2 – 4 L of crystalloid/coil with hypotension).
   Hypovolemia rapidly ensues.
   *Loss 40 – 50% volume in as little as 10 minutes!*
5. Give epinephrine (5–10 µg iv bolus with hypotension, titrate as needed; 0.1–1.0 µg/min iv with cardiovascular collapse) $\beta_2$ receptor stimulation

**HISTAMINE RECEPTORS**

- Receptors
  - $H_1$ receptors: mediate contraction of smooth muscle in GI tract and lungs.
  - Only cardiac effect: delayed conduction in AV node.
  - Increased capillary permeability and relaxation vascular smooth muscle.
  - $H_2$: increased myocardial contractility and rate.
  - Increased capillary permeability and relaxation vascular smooth muscle.

**HISTAMINE EFFECTS ON ORGAN SYSTEMS**

- **Airway**
  - $H_1$ receptors: constrict bronchiole smooth muscle while $H_2$ causes relaxation of bronchi.
  - Normally bronchoconstrictor action negligible.
  - In patients with obstructive airway disease (asthma or bronchitis) likely to develop increases in airway resistance.
- **Gastric Hydrogen Ion Secretion**
  - Evokes copious secretion of gastric secretions with high concentrations of hydrogen ions (acidic).

**H$_1$ RECEPTOR ANTAGONISTS**

- Resemble histamine
  - Contain substituted ethylamine group
  - Unlike histamine contain tertiary amino group linked to two aromatic substitutes.
- Pharmacokinetics
  - Readily absorbed by GI tract
  - Reach maximal plasma concentration in 1-2 hrs
  - Elimination half-life 3.5 hrs
- Side effects
  - Sedation, dry mouth, tachycardia

**H$_2$ RECEPTOR ANTAGONISTS**

- Not recommended in acute anaphylaxis
  - May precipitate vasoconstriction
- Cimetidine
  - Selective and competitive $H_2$ antagonist.
  - Blocks histamine induced secretion of $H^+$ ions by gastric cells.
  - No significant effect on gastric emptying, lower esophageal tone or pancreatic secretions.
MANAGEMENT OF ANAPHYLAXIS DURING GENERAL AND REGIONAL ANESTHESIA

Secondary Treatment

1. Antihistamines (0.5–1 mg/kg diphenhydramine)
   • H₁ receptors mediate many adverse effects of histamine.
   • Does not inhibit anaphylactic reaction degranulation but competes with histamine for receptor sites.

2. Catecholamine infusions (starting doses: epinephrine, 4–8 µg/min; norepinephrine, 4–8 µg/min; or isoproterenol, 0.5–1 µg/min as a drip; titrated to desired effects)

3. Aminophylline (5–6 mg/kg over 20 min with persistent bronchospasm)
   • Bronchodilates and decreases histamine release from mast cells or Basophils.
   • Increases right and left ventricular contractility and decreases PVR.

4. Corticosteroids (0.25/g hydrocortisone; alternatively, 1–2 g methylprednisolone)
   • Best for complement activated
   • May alter activation and migration of inflammatory cells.

5. Sodium bicarbonate (0.5–1 mEq/kg with persistent hypotension or acidosis)
   • Acidosis diminishes effects of epinephrine.

6. Airway evaluation (prior to extubation)
   • Laryngeal edema possible sequela.

PROPHYLAXIS

1. Pretreat patients with history of allergic reaction.
   • H₁ receptor antagonists (antihistamines)
     » diphenhydramine 0.5–1 mg/kg night before surgery and day of exposure
     » H₂ receptor antagonists
       » cimetadine 4–6 mg/kg or ranitidine 1–2 mg/kg orally night before surgery and day of exposure
   • Corticosteroids
     » Prednisone 1 mg/kg every 6 hours for 4 doses prior to surgery

H₂ RECEPTOR ANTAGONISTS

- Cimetadine
- Pharmacokinetics
  + Absorbed by GI tract with peak concentration 60-90 min.
  + Therapeutic concentrations maintained for 4 hrs with 90% suppression of H⁺ ion secretion for 5-7 hrs.
  + Excreted by kidneys
    » 50-70% excreted unchanged within 24 hrs.
- Uses
  » Treatment gastric ulcer
  » Increase gastric pH prior to induction anesthesia
    » 300 mg P.O. 1-2 hours prior to induction
  » Effect on gastric volume variable
  » Has no effect on pH of existing gastric fluid
  » Preoperative preparation of patient with likelihood of allergic reactions.
H₂ RECEPTOR ANTAGONISTS

- **Ranitidine**
  - Similar to cimetidine but no imidazole ring.
  - 5-8 times more potent.
  - No effect on gastric emptying.
- **Pharmacokinetics**
  - Absorbed orally (150 mg) with peak in 30-60 min.
  - Bioavailability 50% compared to 70% for cimetidine.
  - More hepatic first pass clearance.
  - Changes gastric H⁺ concentration for 8-12 hrs.
- **Ranitidine**
  - Pharmacokinetics
    - 50% excreted by kidney unchanged.
    - 30% metabolized by liver.
    - Elimination half-life 2-3 hrs.
    - May produce anaphylactoid reaction.

H₂ RECEPTOR ANTAGONISTS

- **Cromolyn**
  - Inhibits antigen induced release of histamine from mast cells.
  - Suppresses secretory response elicited by interaction between cell bound IgE and specific antigen.
  - Does not relax bronchial or vascular smooth muscle.

H₁ & H₂ ANTAGONISTS

<table>
<thead>
<tr>
<th>H₁ Antagonist</th>
<th>Sedative effects</th>
<th>Anti-cholinergic activity</th>
<th>Anti-emetic effects</th>
<th>Duration of action (hrs)</th>
<th>Adult dosage (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diphenhydramine</td>
<td>Marked</td>
<td>None</td>
<td>None</td>
<td>3-6</td>
<td>50</td>
</tr>
<tr>
<td>Prisrimine (Benadryl)</td>
<td>Mild</td>
<td>None</td>
<td>None</td>
<td>3-6</td>
<td>25-50</td>
</tr>
<tr>
<td>Chlorphenamine (ChlorTrimeton)</td>
<td>Mild</td>
<td>Marked</td>
<td>None</td>
<td>4-12</td>
<td>2-4</td>
</tr>
<tr>
<td>Promethazine (Phenergan)</td>
<td>Moderate</td>
<td>Marked</td>
<td>Marked</td>
<td>4-24</td>
<td>25-50</td>
</tr>
<tr>
<td>Cimetadine (Tagamet)</td>
<td>Mild</td>
<td>None</td>
<td>None</td>
<td>5-7</td>
<td>300</td>
</tr>
<tr>
<td>Ranitidine (Zantac)</td>
<td>Mild</td>
<td>None</td>
<td>None</td>
<td>8-12</td>
<td>150</td>
</tr>
</tbody>
</table>

**Sedative effects**
- Diphenhydramine: Marked
- Prisrimine: Mild
- Chlorphenamine: Mild
- Promethazine: Moderate
- Cimetadine: Mild
- Ranitidine: Mild

**Anti-cholinergic activity**
- Diphenhydramine: None
- Prisrimine: None
- Chlorphenamine: None
- Promethazine: Marked
- Cimetadine: None
- Ranitidine: None

**Anti-emetic effects**
- Diphenhydramine: None
- Prisrimine: None
- Chlorphenamine: None
- Promethazine: Marked
- Cimetadine: None
- Ranitidine: None

**Duration of action (hrs)**
- Diphenhydramine: 3-6
- Prisrimine: 3-6
- Chlorphenamine: 4-12
- Promethazine: 4-24
- Cimetadine: 5-7
- Ranitidine: 8-12

**Adult dosage (mg)**
- Diphenhydramine: 50
- Prisrimine: 25-50
- Chlorphenamine: 2-4
- Promethazine: 25-50
- Cimetadine: 300
- Ranitidine: 150

AGENTS IMPLICATED DURING ANESTHESIA

- Impossible to do prospective research.
- True anaphylactic reaction rare, usually anaphylactoid.
- Rely on case report.
  - If you have an occurrence, write it up!!
  - Administer multiple drugs with induction.

Distribution of reactions to causative agents

- Opioids, 1.4%
- Latex, 12.1%
- Hypnotics, 3.7%
- Others, 2.9%
- Antibiotics, 8.9%
- Opioids, 2.7%

AGENTS IMPLICATED DURING ANESTHESIA

- Induction agents - barbiturates, etomidate, ester local anesthetics.
  - PABA preservative
- Muscle relaxants - succinylcholine, pancuronium, d-tubocurare, atracurium
  - 70% of reactions with induction
  - Quartenary ammonium common antigenic component
- Narcotics - demerol, morphine, fentanyl
  - Probably anaphylactoid

AGENTS IMPLICATED DURING ANESTHESIA

- Antibiotics - cephalosporines, penicillin, vancomycin
  - Some cross-sensitivity
  - 3 strategies
    - Select another drug
    - Administer cephalosporine if negative skin test
    - If benefit out-weighs disadvantage then give
    - Vancomycin – 15-30 minutes by infusion

AGENTS IMPLICATED DURING ANESTHESIA

- Blood products - whole blood, packed cells, fresh frozen plasma, platelets, cryoprecipitate
  - 1% of patients receiving (plasma proteins)
  - Usually not life-threatening, antihistamine & continue
- Bone cement - Methylmethacrylate
- Cyclosporine
- Insulin
- Latex
  - 1% of general population and 10% health care workers
  - #1 cause today especially in children
  - Can react to inhaled latex antigens over the day
- Mannitol
- Protamine

AGENTS IMPLICITED DURING ANESTHESIA

- Radiocontrast dye
  - Probably anaphylactoid
- Colloid volume expanders - dextran, albumin, hydroxyethyl starch (hetastarch), gelatins
- Others
  - Aprotinin, providone iodine, methylene blue, ranitidine (anaphylactoid)

AGENTS IMPLICITED DURING ANESTHESIA

- Preservatives
  - Sodium metabisulfate
    - Generic propofol and many other drugs
DECISION ALGORITHM FOR PATIENTS WITH HYPERSENSITIVITY

ETIOLOGY OF REACTIONS TO BLOCKS

- Allergy to drug employed
- High blood levels of injected drug

ALLERGY TO DRUG EMPLOYED

- Systemic reactions to local anesthetic drugs applied to mucous membranes are usually not of the allergic type.
  - Due to rapid absorption of highly concentrated solutions.
  - High blood level type reactions.

HIGH BLOOD LEVEL OF DRUG

- Cause majority of “allergic” reactions (99%)
  - High level for one may not be high level for another.
- More likely to occur in blocks where large volumes of highly concentrated drugs need to be injected.
  - Peripheral nerve blocks, caudal, epidural

CLASSIFICATION OF HIGH BLOOD LEVEL

- Intravascular injection - intravascular injection of large volume, high concentration, or both is a frequent cause of high blood level. Aspiration mandatory.
- Injection into highly vascular regions - absorption almost as rapid as intravenous injection. Include: head, neck, mucous membranes, urethra, inflamed tissue.

CLASSIFICATION OF HIGH BLOOD LEVEL

- Injection in individuals with substandard detoxification - rate of detoxification governs the duration of a systemic toxic reaction once it had occurred. Liver
- Administration of excessive amounts or concentrations - toxicity increases in geometric, not arithmetical, progression with increasing amounts & concentrations.
CLASSIFICATION OF HIGH BLOOD LEVEL

- Injection of wrong concentration - improper mixing of solutions.
- Injection of drug with narrow margin of safety - drugs with higher ED95 have greater safety.

CLASSIFICATION OF HIGH BLOOD LEVEL

- Injection of solution with spreading factor - some drugs, hyaluronidase, increase absorptive area immensely - higher blood level in shorter time.
- Injection of drug without epinephrine - if drug does not contain epinephrine absorption is more rapid.

PRECAUTIONS TO AVOID HIGH BLOOD LEVELS

- Avoid overmedication with barbiturates or other drugs.
  - Patients may not be able to report paresthesia.
- Avoid overdosage of local anesthetics
  - High ED95
  - Do not exceed recommended doses
  - Use weakest concentration & volume
  - Aspiration prior to injection

PRECAUTIONS TO AVOID HIGH BLOOD LEVELS

- Monitor patient
- Have equipment & drugs ready to treat reaction
- Choose local anesthetic carefully
- Avoid spreading agents
  - Especially when large volumes are injected
- Stop Injection

PRECAUTIONS TO AVOID HIGH BLOOD LEVELS

- Apply a tourniquet
  - May prevent generalized circulation of the drug
  - When reaction controlled, intermittently release the tourniquet
- Skin wheel test
  - Not highly conclusive
- Adequate personnel

SIGNS & SYMPTOMS OF TOXIC REACTION

Central Nervous System Effects
- Stimulation of
  - Cerebral cortex
    - excitement, disorientation, slurred speech, convulsions
  - Medulla
    - Cardiovascular - hypertension, tachycardia
    - Respiratory - Increased rate and variations in rhythm
    - Vomiting center - N&V
SIGNS & SYMPTOMS OF TOXIC REACTION

Central Nervous System Effects
- Depression of
  - Cerebral cortex
  - Unconsciousness
- Medulla
  - Vasomotor - hypotension, syncopy
  - Respiratory - variations in respiration, apnea

PERIPHERAL EFFECTS
- Cardiovascular
  - Heart
    - Bradycardia - depression from direct action of local anesthetic on myocardium
  - Blood vessels
    - Vasodilatation from direct action of local anesthetic on blood vessels

Allergic Responses
- Skin - urticaria
- Respiration - depression
- Circulation - depression

Miscellaneous Reactions
- Psychogenic
- To other drugs - vasoconstrictors

ONSET
- Delayed
  - Occurs seconds to minutes after injection
  - Usually inadvertent intravascular injection
  - Collapse is rapid and total

- Immediate
  - Occurs after repeated reinforcing doses
  - Leads to tonic/clonic seizures
  - Results from
    - Slow build-up
    - Slow hydrolysis, detoxification
    - Combination of above

Plasma Levels of Local


< 20 mg/kg local yields plasma level < 2.75 mcg/ml
### TREATMENT OF HIGH BLOOD LEVEL
- Stopping s&s of overstimulation
- Supplemental Oxygen
  - combat tissue hypoxia from increased cell metabolism
- Correcting central of cortex and medullary centers
- Reversing peripheral cardiovascular collapse
- Re-establishing circulation

### TREATMENT OF CORTICAL MANIFESTATIONS
- Oxygen by bag & mask
  - Cell metabolism increases greatly, therefore oxygen demand increases
  - ↓O₂ & ↑CO₂ may lead to cardiovascular collapse &/or convulsions
- IV fluids
- Make sure airway clear
- Stop convulsions
- Raise blood pressure

### EQUIPMENT OF IMMEDIATE TREATMENT
- Oxygen bag & mask
- Suction apparatus
- Airways & intubation equipment
- Intravenous apparatus
- Electrocardiograph
- Defibrillator
- Drugs

### DRUGS
- Vasoconstrictors drugs
- Succinylcholine
- Barbiturates - treat convulsions
- Diphenhydramine - allergic reactions
- Calcium chloride
- Potassium chloride
- Procainamide (Pronestyl)

### RULES TO REMEMBER WHEN PERFORMING REGIONAL ANESTHESIA
- Carefully observe patient for at least 30 minutes following completion of block.
- Objectively evaluate any type of reaction, NO MATTER HOW MILD!!!
- Be prepared to treat any type of reaction.
- Do not overtreat or undertreat reactions.

### RULES TO REMEMBER WHEN PERFORMING REGIONAL ANESTHESIA
- Tell the patient they have a reaction.
- Do not exceed maximum recommended doses
- Do not rely on premedications to prevent systemic toxic reactions.

VOMITING CAN BE CATASTROPHIC!!!
SIGNS & SYMPTOMS OF GENERALIZED SYSTEMIC ALLERGIC REACTION

- Generalized edema
- urticaria
- pruritus
- hypotension
- joint pains

- asthmatic breathing
- nausea & vomiting
- hypotension
- laryngeal Edema
- dermatitis

ALLERGIC REACTION TRUE LIFE-THREATENING EVENT QUESTIONS??