The Autonomic Nervous System and Toxic Syndromes

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Objectives

- Review the anatomy and physiology of the autonomic nervous system
- Improve understanding of medications that affect the autonomic nervous system
- Use clinical findings to predict potential causes of toxic syndromes
- Go over a bunch of tox cases and make this lecture slightly more enjoyable than a hernia

Autonomic Nervous System

- Temperature regulation
- Fluid and electrolyte balance
- Metabolism rate
- Digestion and excretion
- Cardiovascular function

Autonomic Nervous System

- Responsible for control of involuntary responses
- Two functional divisions:
  - Sympathetic (adrenergic)
  - Parasympathetic (cholinergic)
- Preganglionic fibers – from spinal cord to ganglia
- Postganglionic fibers – from ganglia to target organs
- Synapses – space between nerve cells (endings)
- Neurotransmitters – chemical messengers
  - Norepinephrine (NE)
  - Acetylcholine (Ach)

Physiologic Receptors in the Autonomic Nervous System

CHOLINERGIC (Acetylcholine)
Nicotinic: autonomic ganglia, adrenal medulla, striated muscle
Muscarinic: heart, smooth muscle, glands

ADRENERGIC (epinephrine, norepinephrine)
Alpha – 1: blood vessels, eyes, reproductive organs
Alpha – 2: regulate neurotransmitter release
Beta – 1: heart and kidneys
Beta – 2: salivary glands, eyes, lungs, GI tract, arterioles of hear, lungs, skin, skeletal muscle

DOPAMINERGIC
CNS and renal vasculature

Autonomic NS Receptors

Autonomic Pharmacology

- Sympathetic
  - Agonist: sympathomimetic / adrenergic (epinephrine)
  - Antagonist: sympatholytic
    - Alpha receptor blockers (phentolamine)
    - Beta blockers (propranolol, metoprolol)
- Parasympathetic
  - Agonist: cholinergic (acetylcholine)
  - Antagonist: parasympatholytic, anticholinergic
    - Muscarinic receptor blocker (atropine)
    - Nicotinic antagonist (neuromuscular blockers, ganglionic blockers)

Toxic Syndromes

- Physical signs
- Patient symptoms
- Characteristic odors, color
- Laboratory findings
- Suggests, <u>but does not confirm</u>, a diagnosis

TOXIC SYNDROMES – CASE 1

A 34 y/o female presents with confusion, disorientation and somnolence

HR	140	BP	130/80
RR	16	T	101.6

ANTICHOLINERGIC SYNDROME

- Antihistamines: pyrilamine, doxylamine, diphenhydramine, dimenhydrinate
- Phenothiazines, cyclic antidepressants
- Antiparkinson agents: benztropine, trihexiphenidyl
- Plants
  - Jimson weed (*Datura stramonium*)
  - Deadly nightshade (*Atropa belladonna*)
- Some Mushrooms (muscimol, ibotenic acid)
- Atropine, scopalamine
- Antispasmodics (belladonna, hyoscamine)

ANTICHOLINERGIC SYNDROME

Blind as a bat

Dry as a bone

Red as a beet

Hot as Hades

Mad as a hatter

TOXIC SYNDROMES – CASE 2

A 24 y/o male presents with seizures and coma.

HR	160
BP	190/100
RR	24
T	102

Pupils, dilated, reactive Marked diaphoresis
Bowel sound hypoactive

SYMPATHOMIMETIC SYNDROME

- Mixed alpha and beta adrenergic effects
- Clinical effects:
  - Tachycardia
  - Hypertension
  - CNS stimulation
  - Diaphoresis

- Decreased GI motility
- Miosis/Mydriasis

SYMPATHOMIMETIC SYNDROME

Dx: **cocaine toxicity**

Other agents:

- Amphetamines
- Ephedrine
- Pseudoephedrine
- Anoretics (Fen-Phen)
- Propylhexadrine
- Tyramine

TOXIC SYNDROMES – CASE 3

A 22 y/o male presents with lethargy, confusion, and complaining of severe crampy abdominal pain, vomiting and severe diarrhea.

HR	60
BP	110/70
RR	28, labored
T	99

Diaphoretic, cyanotic, drooling
Marked respiratory distress with rales
Bowel sounds hyperactive
Incontinent of bowel and bladder

CHOLINERGIC SYNDROME

- Excess acetylcholine at muscarinic and nicotinic receptors

- Dx: Organophosphate insecticide

- Other Agents:
  - Carbamate insecticides
  - Physostigmine
  - Nicotine insecticides
  - Tobacco
  - Mushroom (Clitocybe, Inocybe)

CHOLINERGIC SYNDROME

D	diarrhea, diaphoresis
U	urination
M	miosis
B	bradycardia
B	bronchorrhea
E	emesis
L	lacrimation
S	salivation, sweating

TOXIC SYNDROMES – CASE 4

A 19 y/o male presents with headache and lethargy. No history of vomiting or diarrhea.

HR	60	BP	210/120
RR	16	T	99.9

Pupils dilated, sluggishly reactive
Skin slightly moist
Bowels sounds decreased

ALPHA ADRENERGIC SYNDROME

- Dx: Phenylpropanolamine (PPA) Overdose

- Other agents:
  - Phenylephrine
  - Methoxamine
  - Imidazolines
    - Tetrahydrozaline (Visine)
    - Oxymetazoline
    - Naphazoline
    - Xylometazoline

Alpha Adrenergic Drugs

ALPHA AGONISTS

- Dobutamine
- Dopamine
- Ephedrine

- Epinephrine
- Ergot alkaloids
- Methoxamine (Vasoxyl)
- Phenylephrine (Neo-synephrine)
- Phenylpropanolamine (PPA)
- Pseudoephedrine (Sudafed)

ALPHA ANTAGONISTS
- Doxazosin (Cardura)
- Prazosin (Minipress)
- Terazosin (Hytrin)
- Phentolamine (Regitine)
- Phenoxybenzamine
- Tolazoline (Priscoline)
- Induramine (Baratol)
- Urapidil
- Labetalol (alpha & beta)

TOXIC SYNDROMES – CASE 5

A 2 y/o male presents with agitation and bizarre behavior.

HR	190
BP	80/60
RR	24
T	99.8

Tremulous, irritable
Pupils normal size, reactive
Skin and bowel sounds normal

BETA-ADRENERGIC SYNDROME

- Dx: Albuterol overdose

- Other agents:
  - Terbutaline
  - Metaproterenol
  - Isoproterenol
  - Theophylline
  - Caffeine

Beta Adrenergic Drugs

BETA AGONISTS
- Albuterol (Proventil, Ventolin)
- Bitolterol (Tornalate)

- Dobutamine
- Dopamine
- Epinephrine
- Isoetharine (Bronkosol)
- Isoproterenol (Isuprel)
- Metaproterenol (Alupent)
- Norepinephrine
- Ritodrine (Yutopar)]
- Salmeterol (Serevent)
- Terbutaline (Bricanyl, Brethrine)

BETA BLOCKERS
- Acebutolol (Sectral)
- Atenolol (Tenormin)
- Betaxolol (Kerlone)
- Bisoprolol (Zebeta)
- Esmolol (Brevibloc)
- Metoprolol (Lopressor)
- Carteolol (Cartrol)
- Nadolol (Corgard)
- Penbutolol (Levatol)
- Pindolol (Visken)
- Propranolol (Inderal)
- Sotalol (Betapace)
- Timolol (Blocadren)
- Labetalol (Normodyne, Trandate)

Beta Blocker Toxicity

- **Bradycardia**
- **Hypotension**
- A-V block
- Heart failure
- CNS depression
- Seizures

TOXIC SYNDROMES – CASE 6

A 2 y/o female presents with extreme lethargy.

HR	72	Dusky appearance
BP	70/50	Lips cyanotic
RR	10	Shallow respirations
T	98	Skin Dry

Bowel sounds decreased, present

SYMPATHOLYTIC SYNDROME

- Clonidine
- Methyldopa
- Guanabenz
- Sedative / hypnotics
- Opioids
- Alcohol

Imidazolines

- **Antihypertensives:**
  - **Guanfacine (Tenex)**
  - **Guanabenz (Wytensin)**

- **Decongestants**
  - **Tetrahydrozoline (Visine)**
  - **Oxymetazoline (Afrin)**
  - **Naphazoline (Clear Eyes)**

TOXIC SYNDROMES – CASE 7

A 45 y/o male presents comatose and cyanotic.

HR	68	BP	110/60
RR	8, shallow	T	97.8

Pupils constricted
Needle marks on left arm
Bowel sounds decreased

OPIOID SYNDROME

- Dx: Heroin Overdose
- Triad: coma, respiratory depression, miosis
- Other agents
  - Opiates
  - Clonidine
  - GHB or analogue

TOXIC SYNDROMES – CASE 8

A 35 y/o female presents with confusion and lethargy. No nausea or vomiting.

	HR	110				
	BP	120/80	PE unremarkable except for drowsy,			
	RR	32	confusion and tachypnea.			
	T	99				
Labs:	Na	142	Cl 96	BUN	27	Glucose 100
	K	4.1	Bicarb 8	Cr	2.2	

Other labs?

ABG: 7.02 / 96 / 25 Measured osmolality = 380. ETOH = 0.

TOXIC SYNDROMES- CASE 9

The police bring in a 28 y/o female with drowsiness who says she just wants to die. There is a suicide note.

HR	130	Skin warm and dry
BP	120/80	Bowel sounds decreased
RR	16	Pupils slightly,reactive
T	98	

TCA Clinical Toxicity

- Lethargy ± agitation
- Sinus tachycardia

- Then:
- Seizures, hypotension, ventricular dysrhythmias

Cyclic Antidepressants

- Inhibit catecholamine reuptake
  - NE, 5-HT, DA
- Block ACH_M receptors
- Block fast Na^+ cardiac channels
- Block alpha- adrenergic receptors
- Block K^+ efflux from cardiac cells
- Indirect GABA antagonist
- Block H_1 and H_2 receptors

TOXIC SYNDROMES – CASE 10

A 22 y/o female presents with a severe toothache for one week, and mild nausea and vomiting for 3 days. She is seeking pain medication for the persistent toothache. Her friends told her that her eyes were turning yellow.

Vital signs normal
Mild scleral icterus
Right upper quadrant tenderness
Severely abcessed tooth

TOXIC SYNDROMES – CASE 11

A depressed 17 y/o female presents with acute onset of nausea, abdominal pain, hematemesis and diarrhea.

HR 115
BP initially normal but falls to 80/50

Anion gap metabolic acidosis is present

Iron Poisoning

- Direct GI irritant → corrosive
- Decreased venous return → fall in CO
- Elevated lactate, release of protons as Fe++ converted to Fe+++
- Catalyzes free radical formation and lipid peroxidation (hepatotoxicity)
- Hyperglycemia, leukocytosis

TOXIC SYNDROMES – CASE 12

A 44 y/o female presents with dyspnea, nausea, vomiting and lethargy. It is difficult to obtain a history because the patient is hard of hearing.

HR 96 BP 130/90
RR 28 T 100.6

PE: consistent with advanced rheumatoid arthritis

Salicylates

- **Analgesics**
  - **ASA, Fiorinal**
  - **Goody, BC powders**
- **Pepto-Bismol**
- **Topical liniment analgesics (Ben Gay)**

- **Suppositories**
- **Chewing gum**
- **Flavorings (oil of wintergreen)**
- **Plants (acacia, hyacinth, calycanthus)**
- **Chinese / herbal products**

Salicylates

- GI irritant
- Stimulates respiratory center
  - Hyperventilation/respiratory alkalosis
- May alter capillary permeability
  - Cerebral/pulmonary edema
- Uncouples oxidative phosphorylation
  - Causing lactic acidosis, ketoacidosis
- Inhibits cyclo-oxygenase
  - Loss of gastric mucosal barrier
  - Platelet dysfunction

TOXIC SYNDROME – CASE 13

A 44 y/o female presents with severe nausea and vomiting.

HR	140, irregular	
BP	110/70	
RR	18	Agitated, tremulous
T	99	Skin, pupils, bowel sounds are normal

Cardiac monitor shows sinus tach with narrow QRS complex and occasional PADS and PVDS. Before any further information can be obtained the patient has a seizure which is not controlled with diazepam and phenytoin.

Theophylline

- Mechanism of Action
  - Inhibition of phosphodieterase
  - Adenosine receptor antagonism
  - Release of catecholamines

- Clinical Effects
  - Gastric acid and pepsin secretion
  - Stimulation of respiratory & vomiting centers in medulla
  - Positive inotropic and chronotropic effects
  - Reduction of peripheral arteriolar resistance
  - Relaxation of bronchial smooth muscle
  - Increase GFR and RBF
  - CNS stimulation

TOXIC SYNDROMES – CASE 14

A 48 y/o male alcoholic presents with confusion and blurred vision.

HR	100
BP	140/90
RR	32
T	99

Confused, lethargic, disoriented

Labs:	Na 144	Cl 100	Bicarb 10
	K 3.9	Glu 100	BUN 18
	Cr 1.2		

ETOH = 0 Measured osmolality = 350

TOXIC SYNDROMES – CASE 15

A 19 y/o male is brought in by 6 policemen for severe agitation and disruptive behavior.

Hypertensive

Nystagmus

Severe agitation alternating with coma

TOXIC SYNDROMES – CASE 16

A 55 y/o male alcoholic presents with lethargy, confusion, nausea, vomiting and abdominal pain.

HR 95 – remainder of vital signs normal

Mild epigastric tenderness

Labs:	Na 140	Cl 110	Bicarb 24
	K 3.8	BUN 21	Cr 1.2
	Glucose 100		

ETOH = 0

Measured osmolality = 372

A 4 y/o girl is found comatose in a closet in her home. She is dressed in her mother's clothes, shoes and jewelry. Also in the closet are her doll, several suitcases and several cans of cleaning fluids and pesticides.

In the ED, she is comatose, with a regular HR of 108 bpm and BP 80 mm Hg by palpation. She has pinpoint pupils, dry skin and clear lungs. No bowel sounds are audible.

The parents are certain that all medications in the home are secured in a medicine cabinet, and all other toxic chemicals are locked under the kitchen sink

The child is stabilized in the ED. The HR decreases to 96 and the BP rises to 90 mm Hg. She becomes awake, alert and her pupils dilate to normal size after receiving a dose of 2 mg naloxone IV.

The parents still emphatically deny the use of any natural or synthetic opiates at home.

Upon returning home, the father, while searching through the closet, discovers an open bottle of Lomotil tablets in an open suitcase. The antidiarrheal medication had been left there after a foreign trip.

Lomotil

- Diphenoxylate 2.5mg + atropine 0.025mg
- Lethargy reported after ingestion of 1 tablet
- CNS depression may be delayed up to 18 hours
- Treatment is supportive
  - Naloxone for opioid effects
  - Physostigmine has been used for anticholinergic toxicity

A mother runs into your office with her 2 year-old son, anxiously stating that he is difficult to arouse. He awoke that morning and had breakfast as usual, then "fell asleep" two hours later. The child has now been "sleeping" for about an hour.

No one witnessed trauma.
Only medications in the house are APAP and ASA – both stored in the bathroom medicine cabinet.
No history of previous similar episodes.
No family history of metabolic disorders.

Pulse 110, BP 90/60, RR 8, T 36 (96.8)
Obtunded, responding only to painful stimuli by crying and moving purposelessly.

Skin cool, slightly diphoretic.
Pupils midsize, neuro exam non-focal and symmetric, with slight hyporeflexia in all extremities.

At the end of the exam the child has a generalized, tonic-clonic seizure.

Conclusions

- Safe use of cardiovascular and other resuscitation drugs requires understanding of autonomic nervous system
- Assessment for “toxidromes” can assist in diagnosis of intoxication when lab testing is not available
- Call the Poison Center – it’s a free call and not a sign of weakness!!

CNS Depression

- Alcohols
- Antihistamines
- Anticonvulsants
- Antidepressants
- Asphyxiants
- Barbiturates
- Benzodiazepines
- Carbon Monoxide
- Dextromethorphan
- GHB
- Hypnotics
- Muscle relaxers
- Neuroleptics
- Opiates / opioids

Common Toxic Causes of Convulsions

- Amphetamines
- Antidepressants
- Antidysrhythmics

- Beta blockers
- Camphor
- Carbon monoxide
- Cocaine
- Cyanide
- Isoniazid
- Narcotics
- Organophosphate
- PCP
- Physostigmine
- Theophylline

Common Toxic Causes of Altered Heart Rate

BRADYCARDIA

- Beta blockers
- Calcium channel blockers
- Clonidine
- Digitalis
- Opioids
- Ach estersae inhibitors

TACHYCARDIA

- Anticholinergics
- Cocaine
- Dextromethorphan
- Iron
- Phencyclidine
- Sympathomimetics
- Theophylline

Common Toxic Causes of Altered Temperature

HYPOTHERMIA

- Carbon monoxide
- Hypoglycemic agents
- Opioids
- Phenothiazines
- Sedative-hypnotics

HYPERTHERMIA

- Anticholinergics
- Cocaine
- LSD, PCP
- Salicylates
- Sympathomimetics
- NMS, SS