

Toxidrome Case 1

HPI: Previously healthy 16 month old girl is brought to the ED by her parents after becoming unresponsive. She was playing in the yard and suddenly collapsed. Parents could not revive; though she was still breathing and had a pulse. On the way to hospital parents report “eye rolling”, “foaming at the mouth/nose”, production of a large amount of mucous stool, and “becomes limp”. Upon arrival at the ED, the patient suffers a seizure lasting 30 minutes, eventually controlled by phenytoin and diazepam, after which she passes another bloody, mucous stool. Intubated due to respiratory distress ($O_2\text{sat} < 80$).

Abbreviated PE (on presentation):

Well-nourished, unresponsive with VS: RR 35, HR 105, Temp 98 °F, BP 125/75.

Skin warm and diaphoretic. Prominent nasopharyngeal/oral mucous discharge evident

Pupils constricted.

Lungs: scattered rhonchi/wheezes bilaterally

Heart: regular; no murmur

Abdomen: soft, non-distended, bowel sounds prominent

Hyporeflexic with decreased muscle tone.

Summary: Unresponsive, otherwise healthy 16 month old female with diaphoresis, mucous discharge, bowel incontinence, constricted pupils, respiratory distress, and hyperactive bowel sounds.

Diagnosis: cholinergic activation: muscarinic mushroom (pilocarpine and muscarine) vs. acetylcholinesterase inhibition. Note that nicotinic receptor agonists are paralyzing agents, with approximately balanced autonomic effects.

Muscarinic effects: (SLUDGE) salivation, lacrimation, urination, defecation, hyperactive bowel sounds, emesis, miosis (small pupils), bradycardia, increased secretions, diaphoresis, hypotension.

Nicotinic effects: tachycardia, hypertension, muscle fasciculation, paralysis.

In muscarinic poisoning hypotension & bradycardia are more prominent; paralysis and fasciculation uncommon. With acetylcholinesterase inhibition cardiovascular effect is more variable and usually mild (due to conflicting activation), paralysis and fasciculation more common.

Further questioning of family reveals recent application of pesticide containing organophosphates. Mechanism is inhibition of acetylcholinesterase, leading to excessive acetylcholine levels in neuronal synapses.

Lab testing to confirm pesticide poisoning: serum pseudocholinesterase – undetectable (normal 560 – 1480 U/L).

Toxidrome Case 2

HPI: 62 y.o. man presents to ER after suffering an episode of syncope. According to his wife, while eating lunch (a soup made from special “greens” he got at a local grocery store) he complained of feeling hot, appeared anxious, and said his mouth felt very dry. He subsequently stood up, said he felt dizzy, and lost consciousness.

PMH is notable for CAD s/p inferior wall MI five years prior; recently developed HTN but responded to treatment

Meds: Lopressor Bid; Lipitor QD; Aspirin 325 mg QD; Tricor 160 mg QD; Zantac 150 mg Bid.

Allergies: PCN

Physical Examination

VS: T 100.5, RR 15, P 75, BP 102/54 lying, 60/40 standing

General: Drowsy, confused and mildly combative, oriented to person & place, but not date.

Skin: red, warm, dry.

HEENT: tongue dry, pupils dilated (9 mm), no response to light

Chest: Lungs CTA, heart normal R/R.

Abd: non-tender, non-distended, bowel sounds present, no HSM

Neuro: no focal deficits

G/U: no urine output, distended bladder

Summary: 62 y.o. man with history of cardiovascular disease and HTN suffers a syncopal episode and is currently confused, drowsy, with dilated pupils, dry mucous membranes, dilated pupils, urinary retention, mild tachycardia and urinary retention. Note lack of hypertension, but on Lopressor (metoprolol, a selective β_1 -antagonist).

Diagnosis: anticholinergic toxidrome, caused almost exclusively by muscarinic receptor antagonists, either classic (atropine, scopolamine, etc.) or unrelated drugs with anti-muscarinic activity (antihistamines, antipsychotics, TCAs).

Urine sent for toxicological analysis. Typical drugs of abuse absent. However, large “spot” seen on thin layer chromatography identified as atropine (smaller spot identified as scopolamine). On further questioning, determined that source of the “special greens” included Jimsonweed, a plant with high levels of atropine, scopolamine, and other anti-muscarinic alkaloids.

Important point of discussion: hypertension vs. hypotension. See page 54 in Course Syllabus.

Toxidrome Case 3

HPI: 65 y.o. man presents to ED after an episode of syncope and emesis at his birthday party. On presentation, he is anxious, diaphoretic and complains of non-pleuritic chest pain and headache.

PMH: HTN, CAD (CABG x 2, 5 years ago), Type II DM, depression.

Meds: Cozaar (losartan, angiotensin II receptor antagonist), Aspirin, Paxil (paroxetine, SSRI).

Physical Examination:

VS: T 98.5, P 115, RR 22, BP 210/150

General: Anxious, diaphoretic, slightly overweight man

HEENT: Pupils dilated to 9 mm, no JVD

Skin: warm, moist.

Chest: Lungs CTA. Heart: S1S2, tachycardic, bounding pulse.

Abdomen: soft, non-distended, non-painful, no hepatosplenomegaly, absent bowel sounds.

Summary: 65 y.o. man with episode of syncope and emesis presents anxious, diaphoretic, with non-pleuritic chest pain, headache, elevated blood pressure, tachycardic, dilated pupils and absence of bowel sounds.

Diagnosis: Sympathomimetic Toxidrome.

All of the below are likely potential agents

MAOIs: tranylcypromine, phenelzine, pargyline

Reuptake inhibitors: cocaine & TCAs (~~amitriptyline, nortriptyline, imipramine, desipramine, doxepin~~)

(TCAs primarily present with anti-cholinergic presentation)

Displacing agents: amphetamine, tyramine, methamphetamine, methylphenidate

(Mostly) non-specific agonists: epinephrine, norepinephrine, isoproterenol, dopamine, dobutamine

What about the selective agonists?

Selective α_1 -agonists (phenylephrine, methoxamine, metoprolol) – will cause hypertension but not tachycardia

Selective α_2 -agonists (clonidine, guanabenz, guanfacine, methyldopa) – causes hypotension

Selective β_2 -agonists (albuterol, salmeterol, metaproterenol, terbutaline, ritodrine) – do cause anxiety and tachycardia, but also cause hypotension

Explanation: patient ran out of Paxil and took “some of my old pills” which turned out to be an MAOI (Iproniazid). Combined with the food/drink (tyramine-containing) at the party led to unrestrained sympathetic activation.

Treatment: IV Fenoldopam (D_1/α_2 -agonist)

Case 4

10 y.o. male in post-operative recovery from routine appendectomy for which he underwent generalized anesthesia. However, nearly five hours post-op, the anesthesiologist is unable to extubate due to prolonged paralysis.

Succinylcholine given at beginning of surgery to induce paralysis (via “depolarizing blockade”).

Acetylcholinesterase (“True” cholinesterase)

RBC’s, lungs, spleen, nerve endings, gray matter

Degrades acetylcholine at nerve endings

Degrades short-acting neuromuscular blockers used in anesthesia

Acylcholine acylhydrolase (Butyrylcholinesterase, Pseudocholinesterase or Plasma cholinesterase)

Liver, pancreas, heart, white matter, serum

Biological function unknown

Hydrolizes (metabolizes) succinylcholine

Therefore a cholinesterase deficiency is the most likely cause of prolonged paralysis. Although highly unlikely, poisoning by a cholinesterase inhibitor (organophosphates, carbamates, snake venom) is a possibility. There are also reported acquired causes of pseudocholinesterase deficiency including infection, pulmonary embolism, renal failure and pregnancy. However, a pseudocholinesterase genetic deficiency is most likely. Essentially represents the first known pharmacogenetic variation.

Genotypes include Usual, Atypical (dibucaine resistant), Fluoride-resistant, and Silent (U, A, F & S).

Laboratory Evaluation

Serum cholinesterase activity: measured by monitoring loss of benzoylcholine; reference range: 560 – 1480 U/L

However, due to the high interindividual variability in total activity, resistances to two inhibitors are used as a surrogate to genotype identification.

Genotypes	Phenotypes	Activity	DN	FN	Frequency	Time to Recovery
E1uE1u	UU	95	80	59	ca. 96%	5 – 10 minutes
E1aE1a	AA	38	22	27	ca. 0.05%	Hours
E1fE1f	FF		66	35	very rare	Hours
E1sE1s	SS	0	0	0	ca. 0.001%	Many hours
E1uE1a	UA	57	62	48	ca. 3.6%	5 – 60 minutes
E1uE1f	UF	62	74	50	very rare	5 – 60 minutes
E1uE1s	US	50	80	59	rare	5 – 60 minutes
E1aE1f	AF		49	33	very rare	Hours
E1aE1s	AS	20	22	27	very rare	Hours
E1fE1s	FS	61	67	43	very rare	Hours

Table shows the different phenotypes of cholinesterase variants at so called E1 locus.

Serum cholinesterase refers to a group of related enzymes found in serum, all of which have the ability to hydrolyze acetylcholine. Acetylcholine is a neurotransmitter which is synthesized at nerve endings and acts to transmit impulses from nerve to muscle fiber. Cholinesterase destroys the acetylcholine after the impulse transmission has been mediated

so that additional impulses may be transmitted if needed. Otherwise the nerve would remain electrically charged and further contraction would not be possible.

Pseudocholinesterase is present in liver, pancreas, heart, white matter of the brain as well as in serum. It hydrolyzes various substrates, one of which is succinylcholine (suxamethonium), a drug used in surgery as a muscle relaxant. Physiological effects of the drug ordinarily persists for only 30-50 minutes. However patients with low enzyme activity usually takes a longer time to recover from the effects of this drug and consequently may enter a period of prolonged apnea (suspension of respiration). Low enzyme activity could be attributed to genetic origin or to contact or exposure to organic phosphorus compounds (e.g., insecticides).

The presence of abnormal enzyme activity due to atypical genetic variant may be confirmed by determining the Dibucaine and Fluoride numbers which indicate the percentage inhibition of enzyme activity toward specified substrates. This distinguishes the genetic origin (typical homozygous, heterozygous, atypical homozygous). Genotype is of mostly academic interest. An exception is the patient with slow recovery from succinylcholine, but low normal cholinesterase activity. An unusual genotype indicates possible poor metabolism of succinylcholine, despite low normal activity with benzoylcholine.

Decreased levels of serum enzyme are also found in patients with acute infections, pulmonary embolisms, muscular dystrophy, chronic renal disease, pregnancy and after surgical procedures.

Serum Cholinesterase activity is depressed after poisoning with organophosphate or carbamate insecticides (Note that carbamate inhibition is potentially reversible in vitro). Interpretation of the result is made problematic by the wide reference range. Symptoms are unlikely unless activity has been reduced by greater than 50%. Severe poisoning is usually accompanied by reductions of greater than 90%. Unless a baseline level is available for the individual, determination of the percent of inhibition cannot be readily done. A retrospective determination may be possible if pseudocholinesterase levels are measured subsequent to recovery to baseline values (Note this may take six weeks for full recovery). Because serum cholinesterase levels are easy to perform this should be the first test used to screen for possible poisoning. If poisoning seems likely, erythrocyte cholinesterase levels should also be measured since these reflect actual inhibition of acetylcholinesterase and will correlate better with extent of poisoning as well as response to therapy with pralidoxime. Erythrocyte cholinesterase levels also recover more slowly than serum cholinesterase and are more useful for making a presumptive diagnosis of a temporally remote exposure.