



Clinical Pharmacology & Toxicology Pearl of the Week

~ Toxicologic Hyperthermic Syndromes, Part 1 ~

Hyperthermic syndromes are a diverse group of clinical entities that cover both toxicologic and non-toxicologic diagnoses. This pearl will focus on the toxicologic causes.

It is important to refer to these patients as hyperthermic rather than febrile. The mechanism of temperature increase is different than in a febrile patient, and antipyretics such as acetaminophen do not work in managing the hyperthermia.

Toxicologic differential diagnosis of the hyperthermic patient:

- Serotonin Syndrome
- Neuroleptic malignant syndrome
- Sympathomimetic toxidrome
- Antimuscarinic toxidrome
- Malignant hyperthermia
- GABAminergic withdrawal
- Thyroid hormone toxicity
- Cutaneous ADRs (e.g. DRESS syndrome)
- Uncouplers (e.g. salicylate poisoning, dinitrophenol)
- Less common and not covered here: strychnine and propofol-related infusion syndrome

1. Serotonin syndrome

- Occurs most commonly with addition of new serotonergic agents on top of a patient's pre-existing serotonergic medications
- Overstimulation of 5-HT_{2A} and 5-HT_{1A} receptors
- Many drugs implicated:
 - Drugs that inhibit the breakdown of serotonin (MAOIs, linezolid, methylene blue)
 - Drugs that block serotonin reuptake (DXM, bupropion, meperidine, fentanyl, tramadol, SSRIs, clomipramine, nefazodone, trazodone, venlafaxine, duloxetine, cocaine)
 - Serotonin precursors or agonists (tryptophan, LSD)
 - Drugs that enhance serotonin release (amphetamines, buspirone, cocaine, lithium, mirtazapine)
- Triad of autonomic instability + neuromuscular findings + mental status changes
- Other findings: myoclonus, hyperreflexia, tremor, diarrhea, increased tone (lower > upper extremity), ocular oscillations/opsoclonus
- Sternbach and Hunter are two lists of criteria used to establish diagnosis (Sternbach were the first ones developed, Hunter more sensitive)
- Treatment largely supportive (fluids, cooling, intubation/ventilation, benzos), consider cyproheptadine if benzos/supportive care fails
- Most mild-moderate cases resolve within 24 hours after offending drug is removed

2. Neuroleptic malignant syndrome

- Rare, reported incidence = 0.2-1.4%
- Abrupt reductions in central dopaminergic neurotransmission in? striatum and hypothalamus → altered core temperature set point → impaired thermoregulation and autonomic dysfunction

- Can occur with therapeutic use of a dopamine D2 receptor antagonist (older antipsychotics), or discontinuation/change in treatment with dopamine agonists (levodopa, tolcapone, entacapone, pergolide, bromocriptine).
- Aka: “Parkinsonian-hyperpyrexia syndrome” reflecting symptoms that occur with drug holidays from antiparkinsonian drugs, especially when hospitalized for infectious processes (e.g. pneumonia)
- Risk factors: young age, male, volume depletion, higher potency antipsychotic, depot preparations, co-treatment with lithium, multiple drugs in combination, rapid dose escalation
- Tetrad of: altered mental status + muscular rigidity (“lead pipe”) + hyperthermia + autonomic dysfunction
- Lab findings non-specific (increased CK, leukocytosis, renal failure, acidosis, increased PT, hyponatremia)
- Treatment largely supportive (ABC’s, fluids, cooling). Benzos first line for agitation and autonomic hyperactivity.
- If muscular rigidity is a prominent feature or if supportive care fails, consider bromocriptine (dopamine D2 receptor agonist) 2.5-10 mg TID-QID or dantrolene (dantrolene 2-3 mg/kg IV bolus and repeat q15min until hypermetabolism features are reversed or 10 mg/kg reached, then 1 mg/kg q4h for 24 h)

3. Antimuscarinic toxidrome

- Inhibition of muscarinic receptors in sympathetic and parasympathetic nervous system
- Clinical features:
 - Vitals: tachycardia, hypertension, hyperthermia
 - CNS: agitated, delirium, seizures
 - Pupils: mydriasis
 - Skin: dry and flushed
 - Bowel sounds: decreased
 - GU: urinary retention
- Mnemonic:
 - Decreased sweating → “Dry as a bone”
 - Decreased sweating → “Hot as a hare”
 - Flushed skin → “Red as a beet”
 - Mydriasis → “Blind as a bat”
 - Delerium → “Mad as a hatter”
 - Tachycardic → “Heart runs alone”
 - Urinary retention → “Full as a flask”
- Rx:
 - Cardiac monitoring
 - i. Watch for dysrhythmias (Na⁺ channel blockade with 1st generation antihistamines)
 - Control agitation with chemical restraint (goal = patient asleep, rouses to verbal stimuli)
 - i. Benzodiazepines
 - Lorazepam 1-2 mg IV Q10-15 min
 - Diazepam 5-10 mg IV Q 10-15 min
 - ii. Haloperidol 2nd line: 2.5-5.0 mg IV Q15-30 min (watch for prolonged QT)
 - Physostigmine if no contraindications

4. Sympathomimetic toxidrome

- Increased norepinephrine and epinephrine effects at postsynaptic alpha and beta receptors as well as in the CNS
- E.g. cocaine, methamphetamine, amphetamine, methylphenidate
- Clinical features:
 - Vitals: tachycardia, hypertension, hyperpyrexia
 - Mental status: agitated
 - Pupils: mydriasis
 - Skin: diaphoretic
 - Bowel sounds: normal or increased
 - Misc: tremor, seizures
- Management:
 - ABC's
 - Decontamination = charcoal if oral exposure, WBI if body packer
 - Elimination = no role
 - Find an antidote = no specific antidote
 - General mgmt = benzodiazepines for agitation and seizures, haloperidol (with caution) if ongoing agitation

The table below summarizes some of the similarities and differences between some toxicologic causes of hyperthermic syndromes (Modified from Boyer et al, N Engl J Med 2005;352:1112-20)

Etiology	Precipitant	Time of onset	Vital signs	Pupils	Skin	Muscle tone	Reflexes	Mental status	Special features
Serotonin syndrome	Proserotonergic drug	Mins-hours	Hypertension, tachycardia, tachypnea, hyperthermia	Mydriasis	Wet	Lower extremity rigidity, hyperkinesia	Hyper-reflexia, clonus	Agitation, coma	Ocular clonus, shivering, startling
Antimuscarinic toxidrome	Antimuscarinic agent	Hours	Hypertension, tachycardia, tachypnea, hyperthermia	Mydriasis	Hot, dry	Normal unless agitated	Normal	Agitated delirium	Picking at air, lilliputian hallucinations
Sympathomimetic toxidrome	Sympatho-mimetic drug	Mins-hours	Hypertension, tachycardia, tachypnea, hyperthermia	Mydriasis	Wet	Normal unless agitated	Normal	Agitated delirium	Choreo-athetotic movements with some drugs of abuse
GABAminergic withdrawal	Withdrawal from etOH, benzos, GHB, baclofen	<12h-7 days	Hypertension, tachycardia, tachypnea, hyperthermia	Normal	Wet	Normal unless agitated	Normal	Agitated delirium	Auditory or visual hallucinations
Neuroleptic Malignant Syndrome	Dopamine antagonist	1-3 days	Hypertension, tachycardia, tachypnea, hyperthermia	Normal	Wet	"Lead pipe rigidity", bradykinesia	Brady-reflexia	Stupor, coma	Catatonia, mutism, bradykinesia
Malignant Hyperthermia	Inhalational anesthetic or succinylcholine	30 min-12 h	Hypertension, tachycardia, tachypnea, hyperthermia	Normal	Wet	Rigor-mortis like rigidity	Hypo-reflexia	Agitation	Mottled skin
Salicylate poisoning	Salicylate OD (acute or chronic)	Hrs-Days	Tachycardia, tachypnea, hyperpnea, hyperthermia (late)	Normal	Normal	Normal	Normal	Normal (early), altered (late)	Mixed resp alk/met acidosis on blood gas

The Clinical Pharmacology (CP) physician consultation service is available Mon-Fri, 8am-5pm. The on-call physician is listed in ROCA on the AHS Insite page. CP consultations are also available through Netcare e-referral and Specialist Link. You can also find us in the [Alberta Referral Directory](#) (ARD) by searching "Pharmacology" from the ARD home page. Click [HERE](#) for more details about the service.

The Poison and Drug Information Service (PADIS) is available 24/7 for questions related to poisonings. Please call 1-800-332-1414 (AB and NWT) or 1-866-454-1212 (SK). Information about our outpatient Medical Toxicology Clinic can be found in [Alberta Referral Directory](#) (ARD) by searching "Toxicology" from the ARD home page.

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