Clinical Pharmacology & Toxicology Pearl of the Week

~ Toxicologic Hyperthermic Syndromes, Part 2 ~

Hyperthermic syndromes are a diverse group of clinical entities that cover both toxicologic and non-toxicologic diagnoses.

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

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., salicylates, dinitrophenol)
- Less common and not covered here: strychnine and propofol-related infusion syndrome

1. Malignant hyperthermia

- Incidence is 1:5000 – 1:60,000 inpatients exposed to anesthetic agents (succinylcholine, inhalational anesthetics).
- Usually occurs in the OR shortly after anesthetic exposure; can also occur after many hours of anesthesia & up to 12h post-op. Recurrence 24-36h after initial episode is also possible.
- Due to defects in an intracellular receptor that regulates calcium release, anesthetic agents trigger abnormal calcium release in skeletal myocytes → sustained, prolonged skeletal muscle contraction.
- Diseases associated: muscular dystrophy, central core disease, King-Denborough syndrome, hypokalemic periodic paralysis, some myotonias.
- Safe drugs: non-depolarizing NMB's, nitrous oxide, propofol, ketamine, etomidate, benzos, barbs, opioids, local anesthetics.
- Clinical features are those of hypermetabolism, ATP depletion, excess heat production, increased O_2 consumption, CO_2 production and lactic acid generation.
- Signs: tachypnea, tachycardia, HTN, labile BP, skeletal/jaw muscle rigidity - hyperthermia and cardiac decompensation are late signs.
- Rx: stop offending agent, ABC's, cooling, fluids, aggressive treatment of hyperkalemia, 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 at least 24h.
- Calcium channel blockers contraindicated if giving dantrolene → may precipitate hyperkalemia and severe hypotension.

2. GABAminergic withdrawal (e.g., ethanol, benzodiazepine, GHB or baclofen withdrawal)

- All share similar features of an imbalance between excitatory neurotransmitters in the CNS (e.g., glutamate) and inhibitory neurotransmitters (e.g., GABA)
  - relative increased effect/amount of excitatory neurotransmitter and a relative decreased effect/amount of GABA
  - up-regulation of excitatory NMDA receptors

- Clinical features reflect CNS stimulation (tremor, hallucinations, seizures) and autonomic hyperactivity (↑ HR, BP, T°, diaphoresis). Treatment involves restoring excitatory:inhibitory neurotransmitter balance in the CNS.

3. Thyroid hormone toxicity

- Clinical effects of levothyroxine toxicity are delayed until the body converts T4 to the more active thyroid hormone, T3. Symptoms typically develop 7-10 days after ingestion but may occur within 12 hours following large overdoses.
- Symptoms of thyroid hormone toxicity in both adults and children include fever, tremor, diaphoresis, flushing, tachycardia, hypertension, dysrhythmias, GI upset, changes in mental status/activity level, & rarely, seizures. Doses that have resulted in symptoms range from 0.5 mg to as high as several hundred mg.
- Treatment for symptomatic thyroid hormone toxicity includes airway protection, rehydration, and control of agitation (benzodiazepines, barbiturates), CV toxicity (propranolol) and hyperthermia (external cooling).

4. Cutaneous adverse drug reactions (e.g., DRESS syndrome)

- DRESS is a severe hypersensitivity reaction to a medication and/or its metabolites.
- It can occur anywhere from 2-6 weeks following drug exposure.
- Mortality is 10-15% in those affected.
- It is thought to arise from:
    - host genetic predisposition
    - immune activation by culprit drugs
    - alterations in drug metabolism
    - drug-induced viral reactivation (HHV-6)
- The most common drugs include:
    - Antiepileptics: carbamazepine, phenytoin, lamotrigine
    - Antibiotics: trimethoprim-sulfamethoxazole, minocycline, dapsone
    - Other: allopurinol, abacavir, sulfasalazine

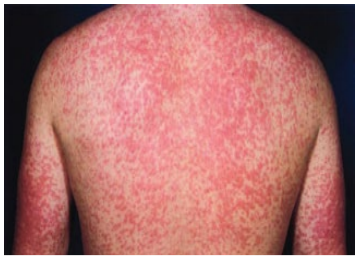

Image 1: Morbilliform rash seen in DRESS

- Most common initial sign is a morbilliform or maculopapular “measles-like” rash (image 1)
- Hematologic, hepatic, renal, pulmonary, cardiac, neurologic, gastrointestinal, and endocrine systems can be affected.
- The diagnosis is clinical, using one of three scoring systems: RegiSCAR, Boquet or J-SCAR
- Differential diagnosis includes:
    - Other drug-related reactions: Stevens-Johnson Syndrome, Toxic Epidermal Necrolysis, Acute Generalized Exanthematous Pustulosis and Hypereosinophilia
    - Viral infections: Epstein-Barr virus, Cytomegalovirus
    - Rheumatologic: Adult-onset Stills Disease
    - Graft-Versus-Host disease
- Treatment: stop the culprit drug, supportive measures, symptom control, corticosteroids for severe disease with organ involvement.
- Patients should be monitored for the complication of hypothyroidism for up to two years following diagnosis of DRESS.

5. Uncouplers (e.g., salicylate poisoning)

- Salicylate toxicity can be life threatening and results from either acute ingestion or excessive therapeutic use. Toxic effects are the result of direct toxicity to the CNS, interference with oxidative phosphorylation, glucose and fatty acid metabolism, and platelet function

- Toxicity can be delayed and prolonged due to several factors: enteric coated (EC) formulation, formation of bezoars (concretions), erratic intestinal absorption, and enzyme saturation. Levels may continue to rise for 12 hours or more, especially with ingestions of EC products
- Acute toxicity usually begins with vomiting, tachypnea, tinnitus, diaphoresis, and lethargy. This may progress to seizures, hypoglycemia, hyperthermia, coma, and pulmonary edema. Blood gas usually reveals a mixed respiratory alkalosis and metabolic acidosis
- The diagnosis of chronic toxicity may be missed, particularly in the elderly, because a specific history of ingestion is usually not apparent and the patient may simply present with delirium, dehydration, and tachypnea. Cerebral and pulmonary edema occurs more frequently than with acute toxicity. Severe poisoning occurs at lower salicylate concentrations, and the mortality rate is higher than in acute poisoning
- Treatment involves decontamination with charcoal, urinary alkalinization, potassium replacement, and dialysis in severe cases
- Salicylate pearls and pitfalls:
    a. Airway – tachypnea is a compensatory mechanism with salicylate toxicity. *Intubation of such patients is a high risk event and should be performed by the most skilled person available*. Any respiratory acidosis during intubation may suddenly increase salicylate absorption into the CNS and result in acute deterioration. Patients who are intubated require frequent monitoring of ventilator settings and blood gases to ensure their minute ventilation matches their pre-intubation state. Such patients are often best treated with hemodialysis post-intubation.

    b. Fluid resuscitation – patients may be volume depleted by several liters on presentation because of vomiting, increased respiratory and metabolic rate. If pulmonary edema is present, intravenous fluids should be restricted; such patients may be best treated with hemodialysis.

    c. Potassium – potassium supplementation must be included in the intravenous fluids to ensure successful urine alkalinization. Oral supplementation may also be required if the patient is hypokalemic on presentation. Patients in oliguric or anuric renal failure should not receive supplemental potassium until the renal failure is corrected.

    d. Glucose – administer supplemental glucose as needed for hypoglycemia or altered mental status in the setting of normal serum glucose.

    e. Imaging – an abdominal X-ray may show radio-opaque material, but a negative x-ray does not rule out salicylate ingestion.

    f. Dialysis – patients who may require dialysis include those with renal failure, congestive heart failure/pulmonary edema, altered mental status, seizures, cerebral edema, worsening acid/base status, unable to alkalinize the urine (urine pH < 7.5), a salicylate concentration > 7.2 mmol/L after an acute overdose, and rising salicylate concentration despite treatment.

    g. Consider transfer to a higher level of care if investigations (q2h salicylate concentrations and electrolytes) or treatment (hemodialysis) are not readily available in your facility.

The table below summarizes the similarities and differences between some toxicologic causes of hyperthermic syndromes:

Etiology	Precipitant	Time of onset	Vital signs	Pupils	Skin	Muscle tone	Reflexes	Mental status	Special features
Serotonin syndrome	Pro-serotonergic drug	Mins – hours	HTN ↑ HR, ↑ RR hyperthermia	Mydriasis	Wet	Lower extremity rigidity, hyperkinesia	Hyper-reflexia, clonus	Agitation, coma	Ocular clonus, shivering, startling
Antimuscarinic toxidrome	Antimuscarinic agent	Hours	HTN ↑ HR, ↑ RR hyperthermia	Mydriasis	Hot, dry	Normal unless agitated	Normal	Agitated delirium	Picking at air, lilliputian hallucinations
Sympathomimetic toxidrome	Sympatho-mimetic drug	Mins – hours	HTN ↑ HR, ↑ RR hyperthermia	Mydriasis	Wet	Normal unless agitated	Normal	Agitated delirium	Choreoathetotic movements with some drugs of abuse
GABAminergic withdrawal	Withdrawal from etOH, benzos, GHB, baclofen	<12h – 7 days	HTN ↑ HR, ↑ RR hyperthermia	Normal	Wet	Normal unless agitated	Normal	Agitated delirium	Auditory or visual hallucinations
Neuroleptic Malignant Syndrome	Dopamine antagonist	1-3 days	HTN ↑ HR, ↑ RR hyperthermia	Normal	Wet	"Lead pipe rigidity," bradykinesia	Brady -reflexia	Stupor, coma	Catatonia, mutism, bradykinesia
Malignant Hyperthermia	Inhalational anesthetic or succinylcholine	30 min – 12 h	HTN ↑ HR, ↑ RR hyperthermia	Normal	Wet	Rigor-mortis like rigidity	Hypo -reflexia	Agitation	Mottled skin
Salicylate poisoning	Salicylate OD (acute or chronic)	Hrs – Days	HTN ↑ HR, ↑ RR hyperthermia (late finding)	Normal	Nor-mal	Normal	Normal	Normal early) Altered (late)	Mixed resp alk/met acidosis on blood gas

(Modified from Boyer et al, N Engl J Med 2005;352:1112-20)

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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