Poison-induced hyperthermic syndromes: mechanisms and management

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Introduction

• Fever is probably one of the most common signs observed in the clinical practice
• Fever may be considered as a normal host defense reaction against infection, but is also reflecting inflammatory processes
• Uncommon etiologies of fever may be sometimes considered: exertional fever or drug-induced fever
• The prognosis is usually related to the underlying disease and not to the fever
• Two major exceptions: exertional fever (« heat stroke ») and drug-induced fever
  – The patient dies really from the consequences of hyperthermia (ventricular fibrillation, clotting disorders)
  – When central temperature is > 43.5°C, the mean survival time is less than 30 minutes!
Background

- An increasing number of patients are prescribed simultaneously several neuropsychiatric drugs (antidepressants, antipsychotics) which could interfere with temperature regulation.
- The main causes of drug-related hyperthermic syndromes are: serotonin syndrome, neuroleptic malignant syndrome, anticholinergic syndrome and sympathomimetic syndrome (malignant hyperthermia following general anesthesia is now exceptional).
- The common experience is that the diagnosis remains difficult as fever, one of the key symptoms, is often erroneously ascribed to infectious complications.
- The diagnosis is also difficult when the offending drug does not belong exactly to a defined category:
  - Weak opioids and serotonin syndrome
  - Anti parkinsonian drugs withdrawal and « neuroleptic-like » malignant syndrome
- Even in case of difficult differential diagnosis, supportive therapy remains essential.
Clinical case: post-operative hyperthermic syndrome

• 72-yr-old woman: obesity, hyperlipidemia, arterial hypertension and diabetes
• Current medications: duloxetine (60 mg/d) for chronic neuropathic pain + insulin, metformin, verapamil,…
• Urgent surgery for hip replacement
• Postoperative pain: paracetamol 4g/d and, after 48h, in combination with tilidine/naloxone
• Day 4: hyperthermic syndrome with unconsciousness and respiratory failure leading to mechanical ventilation, without muscle rigidity or clonus
• Admitted to the ICU: GCS 3/15, HR 128/min, BP 111/67 mmHg, rectal temperature 42.2°C

(Vinetti et al., Clin Toxicol, 2013)
Clinical case: post-operative hyperthermic syndrome

- Cooling blanket + neuromuscular blocker $\implies$ fall of temperature
- EEG: diffuse slowing 3-4 Hz
- Lab: CK 1318 IU/l, mixed acidosis, mild renal impairment (crea 2.52 mg/dl)
- MRI:
  - hyperintensity in the corpus callosum corresponding to cytotoxic edema
- Full neurological recovery after 5 days
Consequences of life-threatening hyperthermia

- Drug-induced severe hyperthermia has probably the same consequences as « heat stroke », at least at the last stage
- What is the critical value? When T 41.6 to 42°C: 45 min to 8 hours, survival < 30 min for T 43.5°C
- Death is the consequence of multiple organ failure
  - Encephalopathy, rhabdomyolysis, acute renal failure, acute respiratory distress syndrome, myocardial injury, hepatocellular injury, intestinal ischemia, pancreatic injury, hemorrhagic complications, disseminated intravascular coagulation
- The pathophysiology has been mainly investigated in exertional or environmental « heat stroke »
  - Acute phase response, heat shock response
  - Is the same cascade involved in drug-related severe hyperthermic syndromes?
Hyperthermia is not fever

• *Fever* is different from *hyperthermia*: mediated by pyrogenic cytokines triggering the acute phase reaction
  – Consequences: changes in the thermal set point and systemic responses

• In *hyperthermia*, the thermoregulatory control mechanisms are impaired, disabled or overwhelmed. They are intact in fever

• Hyperthermia means elevation of the temperature within the established physiological range
  – Mammals: brain temperature during sleep 36°C, at rest 37.3°C and up to 39°C during stress or exercise

• Do we measure temperature accurately? What is core temperature? Temperature is often not measured in the brain as a potential target organ…
Morbidity related to hyperthermia

• What is the cut-off value for heat stroke? Usually a rectal temperature of 40.6°C
  – Acute mortality may be still around 20%, with 33% of moderate to severe impairment on discharge

• When core T > 40°C, disturbed level of consciousness and brain edema

• In vitro: in neural cells, mitochondrial and plasma membranes demonstrate irreversible changes in proteins around 40°C

• Intervention is required within minutes when core temperature is reaching 40°C
Effect of temperature on blood-brain barrier permeability

• High temperature (>40.0°C) has destructive effects on metabolically active brain cells (neuronal, glial, endothelial and epithelial cells)

• Increased BBB permeability and vasogenic edema are observed after extreme environmental warming or after drug intoxication

• Brain damage may be due to hyperthermia or associated factors (oxidative stress, alterations in cerebral blood flow, hypoxia)

• Can we differentiate « high temperature » as a physical factor from other possible contributors?
Rat model, anesthesia by pentobarbital
Passive warming from 32 to 42°C

(Kyiatkin et al., Int Rev Neurobiol, 2012)
Rat model, anesthesia by pentobarbital
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Serotonin and thermoregulation

- No single neural area acts as the center for thermoregulation. Rather, there appears to be a hierarchy of structures extending through the hypothalamus, brainstem and spinal cord.
- Animals with genetically near-complete absence of central 5-HT neurons maintain temperature control under baseline conditions but develop hypothermia during cold challenge.
- 5HT neurons modulate descending synaptic drive from the hypothalamus to effector organs for thermogenesis, but are not part of the direct pathway for either heat generation or conservation.

Pre-optic anterior hypothalamus
Hyperthermia and serotonin overstimulation

• 5HT2A overstimulation: hyperthermia (central), incoordination, neuromuscular excitement

• 5HT1A overstimulation: hyperactivity, hyperreflexia, anxiety

• + other symptoms linked to 5HT1A overstimulation in the medulla
Acetylcholine and dopamine and thermoregulation

- **Antipsychotics on Ach and DA**
  - Antagonists (D2 mediated) tend to increase body temperature
  - DA agonism in the preoptic area triggers heat loss
    - !!! Some DA agonists, bromocriptine, are also 5HT2A agonists => worsening of hyperthermia
    - Apomorphine is a DA agonist and 5HT2A antagonist
  - Central cholinergic M2 receptor agonism increases heat dissipation
    - ! Some antipsychotics with antimuscarinic properties
- **However, overdoses with antipsychotics do not give rise to significant temperature elevation !**
Alteration in brain temperature induced by selective stimulation and blockade of dopamine receptor

- Link between dopamine and motor and behavioral activation
  - Dopamine antagonist => decrease of motor activity
  - Dopamine agonist => increase of motor activity
- Logically, under physiological conditions, there is a coupling between locomotor activation and increased brain metabolism
- This relation is significantly different with pharmacological interventions interfering with DA transmission
  - Rat model with recording of brain temperature
  - Agonist DA and antagonist DA
  - Influence on motor activity and brain activation and temperature

(Kiyatkin, Psychopharmacology, 2013)
• DA antagonist reduced motor activity but increased slightly brain temperature
• Effect of brain T less pronounced when brain T is ~ 38.5°C

• DA agonist increased motor activity but decreased brain temperature
• Changes in brain T more pronounced when basal T was high

Dopamine is modulating brain activation and metabolism
The hidden side of drug action: Brain temperature changes induced by neuroactive drugs

Eugene A. Kiyatkin

• Hypothesis: the effect of MDMA on temperature homeostasis may be influenced not only by the dose, but also by experimental conditions (social interaction, warm environment)

• Experimental model:
  – Rats exposed to various doses of MDMA (1,3 and 9 mg/kg) or saline at ambient temperature 22-23°C, at rest
  – Rats exposed to 9 mg/kg MDMA or saline, with social interaction
  – Rats exposed to 9 mg/kg MDMA or saline, at warm ambient temperatures
  – Temperature was recorded in the brain (nucleus accumbens), in the temporal muscle and in the skin
    • Brain heat production, heat dissipation by the skin
Modest temperature and motor-activating effects of MDMA under quiet resting conditions at standard ambient temperatures (22–23°C).


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Potentiation of MDMA effects on temperature and locomotion during social interaction (I).

Fatal potentiation of MDMA-induced brain hyperthermia at warm ambient temperatures (I).

Main mechanisms in drug-induced hyperthermia

Serotonin syndrome
- 5HT2A central stimulation + 5HT1A medullar stimulation with increased muscle tone and rigidity

Neuroleptic malignant syndrome
- Action on central D2 receptors + increased muscle tone

Sympathomimetics
- Complex interactions between dopamine and serotonin
- Role of ambient temperature, motor activity, metabolic regulation, autonomic vascular changes

Anticholinergics
- Combination of central and peripheral manifestations resulting from the blockade of muscarinic acetylcholine receptors

Do we need a specific pharmacological approach?
Thermoregulation and consequences for management

(Musselman et al., Am J Health Syst Pharm, 2013)
Pharmacological management

- Identify and stop the offending agent
- NSAIDs and acetaminophen are ineffective (not prostaglandin-mediated)
- Agitation?
  - Avoid medications antagonizing dopamine and acetylcholine transmission (all the major or even recent antipsychotics)
  - Prefer the use of titrated doses of benzodiazepines (midazolam, diazepam) with as endpoints the control of psychomotor agitation and normalisation of vital signs. Also effective for myoclonus and seizures
- Increased muscle tone?
  - Paralysis with a nondepolarizing agent, caution for underlying seizure activity
Pharmacological management

• Do we need more specific, oriented therapy?

1. Serotonin syndrome
   – Serotonin inhibitors: cyproheptadine (histamine-1 receptor blocking agent with non-specific antagonist properties at 5HT-1A and 5HT-2 receptors) from 4 to 32 mg? Some experimental evidence, limited experience in humans and mainly in mild to moderate forms. Available orally, few side effects
   – Chlorpromazine also as 5-HT2A inhibitor: should be avoided, may exacerbate muscle rigidity and lower epileptic threshold
   – Propranolol: inconstant
   – Dantrolene: acting peripherally, not logical
   – Bromocriptine may be deleterious
Pharmacological management

• Do we need more specific, oriented therapy?

  2. Neuroleptic malignant syndrome
     – Consider reintroduction of the drug when withdrawal of a dopaminergic agent is the possible etiologic factor
     – Levodopa or bromocriptine logically proposed, until symptoms resolve, with a progressive tapering down, but no direct scientific evidence that superior to supportive care
     – Dantrolene not indicated

  3. Anticholinergics
     – Hyperthermia alone is not considered an indication for physostigmine therapy

  4. Sympathomimetics
     – Dantrolene not indicated
Cooling techniques

- No validated clinical studies
- Treatment now commonly applied in patients in out-hospital cardiac arrest
- Induction
  - 30 ml/kg of iced (4°C) saline
- Maintenance
- Core plus external cooling
  - fan + ice + cooling blanket
Cooling techniques

- Resides in Inferior Vena Cava
- 8.5 Fr shaft
- 38 cm long - Insert to manifold
- Polyurethane and PET
- Duraflo® coated
- Radiopaque

• Typical time to <34 °C is 90 minutes
• 50 ICU patients with an indication for controlled mild hypothermia or strict normothermia

• 5 groups analyzed
  – Conventional cooling with a rapid infusion of 30 ml/kg lactate Ringer at 4°C, combined by surface cooling using ice and/or coldpacks
  – Water-circulating cooling system with a two water-circulating cooling blankets
  – Air-circulating cooling system with a single blanket
  – Gel-coated external cooling system
  – Intravascular cooling system
While water-circulating, gel-coated or intravascular cooling systems appear more effective than conventional or air-circulating cooling systems, the mean speed of cooling was not exceeding 1.5°C/hour.
Cooling techniques

- **Potential advantages:**
  - inexpensive
  - adaptable in the ER
  - speed of cooling
- **Potential disadvantages:**
  - excessive cutaneous vasoconstriction and shivering limiting heat dissipation
  - patient’s discomfort
  - difficulties of monitoring or treatment (intubation, defibrillation)

Ice water submersion
Cooling techniques

- Recently published experience about 2 cases (4-fluoroamphetamine, cocaine)
- Peak temperature respectively 41.4° and 44.4°C
- With ice water submersion: cooling rate 0.18°C/min and 0.28°C/min

(Laskoski et al., Clin Toxicol, 2015)
Conclusion

• Hyperthermia, not fever, is a life-threatening complication in a limited number of patients treated by neuropsychiatric drugs or using recreative drugs
• Dysregulation of serotonin or dopamine neurotransmission is largely involved in temperature homeostasis
• The role of environmental conditions should not be underestimated!
• The severity of the reaction is usually not dose-related
• Treatment: mainly supportive, with aggressive temperature control based on physical principles, eviction of the offending drug, myorelaxation, and, when indicated, more specific pharmacological agents influencing either central or peripheral mechanisms of thermoregulation