ARTICLE

The hot patient: acute drug-induced hyperthermia

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SUMMARY

Drugs can cause dysregulation of the hypothalamic–pituitary–adrenal axis which can result in a rise in core temperature. This type of hyperthermia is unresponsive to antipyretics and can be complicated by rhabdomyolysis, multi-organ failure and disseminated intravascular coagulation.

Organic causes of fever such as infection must be ruled out. Syndromes associated with drug-induced fever include neuroleptic malignant syndrome and anticholinergic, sympathomimetic and serotonin toxicity.

The class of offending drugs, as well as the temporal relationship to starting or stopping them, assists in differentiating between neuroleptic malignant syndrome and serotonin toxicity.

Immediate inpatient management is needed. The mainstay of management is stopping the drug, and supportive care often in the intensive care unit.

Introduction

Drugs that alter the neurotransmitters noradrenaline (norepinephrine), dopamine and serotonin can affect thermoregulation by the hypothalamic–pituitary–adrenal axis.[1,2] In drug-induced hyperthermia the core temperature is at least 38.3 °C.[3] Hyperthermia can be complicated by peripheral factors such as increased heat production (e.g. with 3,4-methylenedioxymethamphetamine (MDMA/ecstasy) and other sympathomimetics) and decreased heat loss (e.g. with anticholinergic drugs). Excessive heat production can result in life-threatening complications such as rhabdomyolysis and secondary hyperkalaemia, metabolic acidosis, multi-organ failure and disseminated intravascular coagulation.[1]

The most commonly used drugs that affect thermoregulation include antipsychotic drugs, serotonergic drugs (especially when taken in combination), sympathomimetic drugs, anaesthetics and drugs with anticholinergic properties (Table 1).

Non-drug-induced causes of hyperthermia

There are numerous causes of complicated hyperthermia that are not due to drug exposure (Table 2). Non-drug causes should always be considered and excluded. Lethal catatonia (which can develop over weeks), central nervous system lesions or infections, and tetanus can all cause hyperthermia associated with muscle rigidity. The diagnosis is based on the history and clinical picture.

Thyrotoxicosis and phaeochromocytoma should be considered in the differential diagnosis of hyperthermia. However, they are rarely associated with muscle rigidity.

Table 1 **Drugs commonly known to cause hyperthermia and associated muscle rigidity**

Drug-induced syndrome	Associated drugs
Neuroleptic malignant syndrome	Antipsychotics (haloperidol, olanzapine), some antiemetics (metoclopramide), withdrawal of antiparkinson drugs
Serotonin toxicity	Serotonin reuptake inhibitors, monoamine oxidase inhibitors, dextrometorphan, tramadol, tapentadol, linezolid, St John's wort (toxicity most often occurs when the drugs are used in combination)
Anticholinergic toxicity	Antispasmodics, anticholinergic drugs, plant alkaloids (such as belladonna, *Brugmansia*) and mushrooms (e.g. *Amanita*)
Sympathomimetic syndrome	Phenthylamines, e.g. amphetamines, methamphetamines (MDMA), cocaine, monoamine oxidase inhibitors
Malignant hyperthermia	Volatile anaesthetics and depolarising muscle relaxants, e.g. suxamethonium
Uncoupling of oxidative phosphorylation	Salicylates in overdose, dinitrophenol

Table 2 **Non-drug causes of hyperthermia and muscle rigidity**

Non-drug-induced causes	Associated features
Severe catatonia	Severe rigidity accompanied by psychosis, severe affective disorder, stupor
Heat stroke	Extreme dehydration, exercise or stress in hot, humid environments particularly in patients taking diuretics
Central nervous system infection	General malaise, neurological deterioration, meningeal irritation
Tetanus	Trismus, muscle spasm starting from the neck down, profuse sweating, spasticity intensified by stimuli
Thyrotoxicosis	Tachycardia, tremor and hypertension
Phaeochromocytoma	Tachycardia, hypertension and tremor, diaphoresis, agitation

Drug-induced hyperthermia and hypermetabolic state

Differentiating the conditions associated with drug-induced hyperthermia can be difficult, however the time course of symptom development can assist in diagnosis (Table 3). The drug history is vital.

Neuroleptic malignant syndrome

Neuroleptic malignant syndrome can be a life-threatening idiosyncratic reaction to therapeutic doses of all antipsychotics. The risk is thought to be higher with high-potency antipsychotics (e.g. haloperidol). Neuroleptic malignant syndrome can also be caused by dopamine antagonists (e.g. domperidone) or the sudden withdrawal of dopaminergic drugs (e.g. bromocriptine, levodopa). Men are affected twice as often as women.[4] It is characterised by:

- autonomic instability (systolic blood pressure changes ≥30 mmHg and heart rate changes ≥30 beats/min within the first 24 hours)
- hyperthermia (without another cause, although hypothermic variants have been described)
- encephalopathy (which can range from mild delirium to coma)
- extrapyramidal syndrome (there can be cog-wheel rigidity, or lead-pipe rigidity where the same level of muscle resistance is felt in all directions).

Along with the time course of onset, the presence of diaphoresis, rigors, fever, tremor, in combination with laboratory evidence of muscle injury (elevated creatinine kinase) and leucocytosis, can help distinguish neuroleptic malignant syndrome from other drug toxicities.[5,6]

Neuroleptic malignant syndrome can emerge any time from starting the drug to many years later. Symptoms develop gradually over a period of days and can take a similar time to resolve.

Risk factors include dehydration, agitation, exhaustion, escalation of an antipsychotic dose and previous episodes of neuroleptic malignant syndrome. Organic brain injury and polypharmacy with other psychotropic drugs have also been identified as risk factors.

Morbidity and mortality result from secondary medical complications. These include sepsis, aspiration pneumonia, pulmonary embolism, myoglobinuric renal failure secondary to rhabdomyolysis,[7] metabolic acidosis and electrolyte abnormalities including hyperkalaemia and hypo- or hypernatraemia.

Serotonin toxicity

Symptoms of serotonin toxicity (or serotonin syndrome) can range from mild to severe. The onset of toxicity is normally rapid and apparent within six hours of taking serotonergic drugs. The extent of symptoms relates directly to synaptic serotonin concentrations. Toxicity is usually not severe following an overdose of a single serotonergic drug, but is more serious with a combination of serotonergic drugs. Combinations of a single tablet of monoaminoxidase inhibitor with a serotonin reuptake inhibitor are potentially fatal.[8]

Severe serotonin toxicity is a medical emergency and is characterised by a triad of:

- neuromuscular excitation (manifesting as ankle and/or ocular clonus, hyperreflexia, myoclonus and rigidity)
- autonomic excitation (tachycardia, hyperthermia)
- altered mental state (e.g. agitation, confusion).[9]

The presence of clonus helps in differentiating serotonin toxicity from sympathomimetic or anticholinergic toxicity or neuroleptic malignant syndrome. The Hunter Serotonin Toxicity Criteria can be used to predict cases likely to progress to severe toxicity and guide treatment.[10]

Other non-serotonergic drugs such as some opioids (e.g. tramadol) or over-the-counter medicines such

Table 3 **Clinical features of neuroleptic malignant syndrome, serotonin toxicity, anticholinergic syndrome and sympathomimetic syndrome**

	Neuroleptic malignant syndrome	Serotonin toxicity *	Anticholinergic toxicity	Sympathomimetic syndrome
Onset	Slow (1–3 days)	Rapid (minutes–hours)	Rapid	Rapid
Autonomic system: †				
Instability	♦♦♦	♦	–	–
Hypertension	Labile (SBP >30 mmHg above baseline)	♦	♦♦	♦♦
Tachycardia	Labile (>30 bpm above baseline)	♦♦♦	♦♦	♦♦♦
Diaphoresis	♦♦♦	♦♦	–	♦♦
Hyperthermia	♦♦♦	♦♦	♦♦♦ ‡	♦♦
Mental state:				
Confusion	♦♦♦	♦ (late stage)	♦♦♦	♦
Agitation/restlessness	Akathisia	♦♦♦	♦♦♦	♦♦♦
Coma	♦♦	–	♦	–
Motor system:				
Bradykinesia	♦♦	–	–	–
Tremor	♦	♦♦♦	–	♦♦♦
Rigidity	♦♦	♦	–	–
Hypertonia	–	♦♦	♦	–
Hyperreflexia	–	♦♦♦	♦	♦♦♦
Clonus (ankle/eye)	–	♦♦♦ (lower limb more than upper limb)	–	♦
Myoclonus	–	♦	–	–
Seizures	–	♦ (rare)	–	♦♦
Others:				
Rhabdomyolysis	♦♦♦	♦♦	–	♦♦
Mydriasis	–	♦♦♦	♦♦	♦♦

– No effect
♦ mild
♦♦ moderate
♦♦♦ severe
SBP systolic blood pressure

* Mechanism is excess serotonin.
† These features are non-specific and do not assist in differentiation between syndromes.
‡ Mechanism is inability to sweat and unopposed dopamine centrally leading to dysregulation.
bpm beats per minute

as St John's wort can precipitate serotonin toxicity (Table 1). A thorough history is imperative to identify contributing drugs that may have been stopped weeks earlier but have a long half-life (e.g. fluoxetine).

Anticholinergic toxicity

Anticholinergic toxicity occurs either as a result of antagonism at the muscarinic receptors or a reduction in cholinergic transmission. Toxicity can be caused by eating plants containing atropine-like alkaloids. It is also associated with multiple classes of drugs, such as antiparkinson drugs and tricyclic antidepressants, both in acute overdose or chronic use. The result is central and peripheral clinical effects that are a consequence of the relative cholinergic deficiency at the muscarinic receptors.[11]

The most commonly observed peripheral effects include dry mucous membranes, tachycardia, urinary retention, blurred vision and reduced gastrointestinal motility (ileus). Fever may result from decreased heat loss (due to the absence of sweating), increased heat production (due to agitation and activity) and central nervous system temperature dysregulation.[12] Central symptoms are predominantly agitation, confusion and hallucinations.

Sympathomimetic syndrome

Psychostimulants such as methamphetamines cause an increase in the effects of the neurotransmitters nor/adrenaline (nor/epinephrine), dopamine and serotonin by increasing their release or blocking their reuptake (such as methylphenidate).[13] Toxicity results from an excess of these catecholamines.

Patients may present with agitation, repetitive movements, akathisia, delirium, pressured speech, hypertension, tachycardia and hyperthermia. Additional sympathomimetic features include mydriasis, diaphoresis and neuropsychiatric manifestations such as paranoid psychosis. Complications can damage almost all organ systems. For example, they may involve the cardiovascular, central nervous and gastrointestinal systems (causing myocardial vasospasm, seizures and mesenteric ischaemia).

The degree of monoamine release is substance specific so presentations can be variable. For example, amphetamines release a greater degree of noradrenaline (norepinephrine) compared to MDMA/ecstasy which causes a greater increase in serotonin and therefore carries a greater risk of serotonin toxicity.

Hyperthermia results from central dysregulation, as well as increased heat production from increased physical activity. It is exacerbated by stimulation of peripheral alpha-adrenergic receptors and impaired vasodilation. Rhabdomyolysis is thought to be multifactorial and related to possible overuse of skeletal muscles as a result of excited delirium or repetitive behaviours as well as extreme vasoconstriction.[14]

Management

In all cases of drug-induced hyperthermia with associated rigidity, the principal management is prompt discontinuation of the offending drug and supportive management of the symptoms in hospital. Specifically, this includes active cooling in intensive care, correction of electrolyte abnormalities, intravenous fluids, early thromboprophylaxis and monitoring for aspiration. Muscle rigidity and agitation are responsive in most cases to judicious use of benzodiazepines. Antipyretics have no therapeutic benefit in drug-induced hyperthermia, as the central controlling mechanisms for temperature are not functioning normally.[15]

In the case of neuroleptic malignant syndrome, pharmacotherapy is reserved for complicated cases with moderate rigidity and hyperthermia. The dopamine agonist, bromocriptine, has been reported to be useful in case reports. Dantrolene should be considered in extreme cases of hyperthermia and muscle rigidity. Patients should be monitored for its adverse effects of hepatitis and respiratory impairment.[5,16] A cautious reintroduction of an alternative antipsychotic can be considered after two weeks, once symptoms have completely resolved. However, recurrence has been reported in up to a third of cases of neuroleptic malignant syndrome.[17,18]

Serotonin toxicity is managed largely supportively, as most symptoms subside based on the half-life of the offending drugs. Symptoms therefore usually resolve within 24–72 hours of stopping the drug. In severe cases of toxicity, management consists of sedation (with benzodiazepines), paralysis and intubation to reduce muscle activity, and adequate cooling. These measures need to be started before the patient deteriorates. Chlorpromazine and cyproheptadine (serotonin ($5HT_{2a}$) antagonist) are recommended in moderate to severe cases of toxicity.[9]

Moderate to severe anticholinergic toxicity may require pharmacological intervention based on the persisting symptoms. The reversal of toxicity can be achieved by increasing acetylcholine concentrations with physostigmine. This requires specialist advice from a toxicologist and has the adverse effects of bradycardia and potential seizures. Droperidol can be used for severe agitated delirium.

Conclusion

Drug-induced hyperthermia and rigidity can be a medical emergency and usually requires hospital admission. The clinical assessment and differential diagnosis should always rule out other causes. Stop the offending drug and give supportive care. Severe cases may require adjunctive pharmacotherapy. Specialist toxicological support will be required in most cases. ≺

Nazila Jamshidi was the editorial registrar for Australian Prescriber *in 2018.*

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