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Drug-induced hyperthermia in critical care

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Abstract

Fever is common in critically ill patients and the cause is frequently not infection. Drug fevers occur in the intensive care and there are many pharmacological agents, by a variety of mechanisms, which increase body temperature beyond normal range. This article is a review of the common classes of drugs that can induce hyperthermia, highlighting the deleterious effects of a sustained high temperature and outlining available treatments.

Keywords

Intensive care medicine, fever, pyrexia, drug, hyperthermia

Introduction

The finding of raised temperature in the critically ill is common. Up to half of all patients are pyrexial during intensive care admission.[1] Sepsis is not the only trigger and up to two-thirds of fevers in hospital patients may be due to non-infectious reasons.[2] Where infection is excluded, the diagnosis may not be made in as many as 97% of cases.[2] While the mortality from a non-infectious cause is lower than from sepsis it remains significant and unlike in sepsis, a higher temperature is associated with a worse outcome.[3]

A non-infectious cause of raised temperature is important to consider for these reasons. Table 1 lists the non-septic causes.

Hyperthermia has various definitions. The American College of Critical Care Medicine and the Infectious Diseases Society of America define 'fever' as a temperature of greater than 38.2°C,[4] based partly on 37.7°C being the upper limit of normal human temperature.[5] In this article, we define hyperthermia similarly as a core temperature of 38.2°C or higher. This article will concentrate on drug-induced hyperthermia only.

Pharmacological agents may cause fever by a number of pathophysiological mechanisms. These include interference with the physiological mechanisms of heat loss from the peripheries, interference with central temperature regulation, direct damage to tissues, stimulation of an immune response or pyrogenic properties of the drug.

Causes of hyperthermia

Malignant hyperthermia (MH)

MH is a life-threatening condition usually triggered by exposure to volatile anaesthetic agents or the depolarising neuromuscular blocker succinylcholine. It affects 1:5000–1:100,000 patients, is reported twice as commonly in males and frequently in young people. However all ages groups, including neonates, are at risk.[6] It has also been observed in other species such as dogs, cats, horses and pigs. When skeletal muscle is exposed to the causative agent, oxidative metabolism increases suddenly and markedly. Oxygen delivery, carbon dioxide removal and thermoregulation are insufficient to match the hypermetabolism. Collapse, multi-organ failure and death follow if it is not rapidly treated.

MH is often inherited as an autosomal dominant disorder. Mutation in the ryanodine receptor (RYR) accounts for up to 70% of cases, with some newer genetic abnormalities also having been identified.[7] RYRs form calcium channels and are the main mediators of calcium-induced calcium release in animal cells. RYR1 is found in the sarcoplasmic reticulum of skeletal muscle. RYR1 usually opens in response

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Table 1. Table of causes of non-septic hyperthermia.

Category
Drug reactions
Heat illness (e.g. classical heat stroke, exertional heat stroke)
Immunological and inflammatory diseases
Malignancy
Metabolic disorders (e.g. gout, porphyria)
Reaction to incompatible blood products
Tissue destruction (e.g. haemolysis, surgery, infarction, rhabdomyolysis)
Thrombo-embolic disease

to increases in intracellular calcium mediated by L-type calcium channels, which results in a larger increase in intracellular calcium levels and muscle contraction. In MH, the RYR functions abnormally meaning calcium is released in a much higher amount. Heat is generated during the processing of this excess calcium. The increased energy demands deplete adenosine triphosphate (ATP) and myocytes are damaged by the loss of ATP and the hyperthermia. The intracellular constituents leak into the circulation. These include myoglobin, creatine, phosphate and creatine kinase. In the acute phase, patients therefore develop an oxygen debt, hyperthermia, hypercarbia and tachycardia due to hypermetabolism, and hyperkalaemia and rhabdomyolysis due to cell breakdown. Acute kidney injury and disseminated intravascular coagulation (DIC) are also a risk.

The first documented survivor of MH in Australia in 1961 was a young man requiring surgery for a fractured tibia. Ten of his family members had previously developed uncontrolled hyperthermia and died during general anaesthesia with ether. Halothane had been recently introduced and was therefore used instead, but after 10 min the patient developed MH. The halothane was discontinued and he was packed in ice and subsequently recovered uneventfully.[8]

There are no pathognomonic features for MH and currently no single diagnostic test. The genetic abnormality and the clinical features vary between patients. The MH Clinical Grading Score quantifies the severity of muscle rigidity, muscle breakdown, respiratory acidosis, temperature increase, cardiac involvement and other features. The higher the score, the more likely it is MH.[9] The triggering agent should be discontinued and the patient actively cooled. Dantrolene, a skeletal muscle relaxant originally developed for managing spasticity is the treatment of choice. With early recognition and treatment, mortality has now fallen to less than 5%. Following recovery, referral to a specialist centre for susceptibility testing is recommended.

Exertional heat stroke (EHS) is becoming increasingly common in endurance athletes.[10] It was first described in 24 BC, in a Roman account during an expedition to Egypt when it was noticed 'the desert, the sun and the water, which had some peculiar nature, all caused his men great distress so that the larger part of the army perished'.[11] Rhabdomyolysis, DIC, renal and liver failure, and neurocognitive failure are often seen. Current recommended treatment is immediate cooling, rather than the 'olive oil and wine, both taken as a drink and used as an ointment' as originally suggested. HS has clinical and biochemical similarities to MH, and there are case reports of patients with both conditions. While some patients with EHS display mutations in the RYR1 gene, the genetic basis is probably different to MH, although some authorities advise that heat stroke patients should be considered for testing for susceptibility to develop MH.[12] Recently, there has been some interest in another similar sarcoplasmic skeletal muscle protein called calsequestrin (CASQ1), which appears to modulate RYR1 function. Ablation of this protein in mice increases the risk of MH-like episodes when exposed to both heat and halothane, raising the possibility that there is also a genetic basis to EHS and a similarity to MH.[13]

Neuroleptic malignant syndrome (NMS)

NMS is most often caused by an adverse reaction to neuroleptic or antipsychotic drugs. It is probably related to central dopaminergic (DA2) receptor blockade and other dopaminergic antagonists, including metoclopramide, have been implicated. The incidence of NMS may be up to 2%.[14] Other studies with newer drugs or using different diagnostic criteria report a lower incidence.[15] Mortality is currently around 11%,[16] but was previously significantly higher at up to 76%.[14] Development of renal failure is a strong predictor of mortality, associated with a mortality rate of 50%.[14]

The criteria vary, but the features are often grouped into four: hyperthermia; changes in the level of consciousness; autonomic instability (for example, unstable blood pressure, tachycardia, diaphoresis, incontinence); and muscle rigidity,[17] Leucocytosis and an elevated CK may be present. The hyperthermia is incompletely understood and is probably related to the blockade of heat loss pathways in the hypothalamus and the heat production from the muscle rigidity. The muscle rigidity is due to exaggerated calcium release from the sarcoplasmic reticulum in a similar manner to MH. NMS usually presents after hours or days of the drug intake, compared with MH, where symptoms usually develop within minutes. The elevated white cell count and CK, and the muscle rigidity distinguish it from serotonin syndrome. Treatment is supportive, and includes active cooling. Dantrolene or bromocriptine (a dopamine agonist) may be used, but evidence of their efficacy is limited.[18]

Serotonin syndrome

The neurotransmitter serotonin is found widely in the peripheral and central nervous systems (CNS). Serotonin syndrome is caused by an increased level of serotonin in the CNS, and is therefore a predictable consequence of therapeutic or recreational drugs moderating serotonin pathways, rather than an idiopathic drug reaction. Agonism at the 5-HT_{1A}, and 5-HT_{2A} receptors is thought to be responsible.[19,20]

The symptoms can be grouped into three:

- Neuromuscular hyperactivity (tremor, myoclonus, ataxia, hyper-reflexia)
- Neurocognitive symptoms (agitation, confusion, hallucinations, coma)
- Autonomic effects (hyperthermia, sweating, tachycardia, nausea)

Of these, clonus is a particularly sensitive and specific feature. Clonus, combined with a history of intake of a suitable drug, forms the basis of the Hunter Serotonin toxicity criteria.[21] If spontaneous clonus, or inducible clonus in combination with agitation or sweating is present, then serotonin syndrome is diagnosed. Tremor and hyper-reflexia, or a combination of hypertonia, hyperthermia and clonus also fulfil the criteria. Serotonin syndrome is a clinical diagnosis, but the Hunter criteria are valuable, being 84% sensitive, and 97% specific. Serotonin syndrome may develop within minutes or hours of starting the culprit drug,[18] distinguishing it from NMS.

Patients may become hyperpyrexic in life-threatening cases. Complications are similar to other hyperpyrexic states, and include metabolic acidosis, rhabdomyolysis, seizures, renal failure and DIC.

A large number of medications either alone in high dose or in combination can produce serotonin syndrome (see Table 2). Many of these are commonly used in intensive care.

Management is based primarily on stopping the usage of the precipitating drugs and treating complications. Serotonin receptor antagonists, for example, cyproheptadine, are sometimes suggested, but evidence for their use is poor. Supportive care, including controlling agitation, autonomic instability and hyperthermia, is important.

Table 2. Examples of causes of serotonin syndrome.

Class	Drugs
Antidepressants	Monoamine oxidase inhibitors, tricyclic antidepressants, selective serotonin reuptake inhibitors, serotonin-noradrenaline reuptake inhibitors, bupropion
Opioids	Tramadol, pethidine, fentanyl, pentazocine, buprenorphine oxycodone, hydrocodone
CNS stimulants	MDMA, amphetamines, sibutramine, methylphenidate, methamphetamine, cocaine
Psychedelics	5-Methoxy-diisopropyltryptamine, lysergide
Herbs	St John's Wort, Syrian rue, Panax ginseng, nutmeg, yohimbine
Others	Tryptophan, L-Dopa, valproate, buspirone, lithium, linezolid, chlorpheniramine, risperidone, olanzapine, antiemetics (ondansetron, granisetron, metoclopramide), ritonavir, sumatriptan

Propofol infusion syndrome

Propofol infusion syndrome (PRIS)[22] is a rare syndrome, and was originally described in children in the 1990s who were sedated with propofol. Cardiac dysfunction and metabolic acidosis are common features of PRIS. Rhabdomyolysis, renal failure, hyperkalaemia, hypertriglyceridemia and hepatomegaly are also seen. Thirty-eight percent of patients receiving propofol develop hyperthermia although the criteria for PRIS may not otherwise be met.[23] The mortality is high, reported to be 30% overall, but as high as 83% dependent upon the clinical manifestations.[24] The mortality is higher in males compared with females, younger patients and those with more severe clinical features.[24] PRIS is thought to be caused by the effect of propofol inhibiting the mitochondrial respiratory chain or impairing mitochondrial fatty acid metabolism. It occurs more often with high doses and long-term use of propofol (>4 mg/kg/h for more than 48 h) and in patients receiving catecholamines and glucocorticoids. The electrocardiogram (ECG) may show a right bundle branch block with ST elevation in the right praecordial leads similar to a Brugada pattern. This may progress to a refractory bradycardia and asystole.[25]

Anticholinergic syndrome

Anticholinergic drugs cause hyperthermia through peripheral muscle activation, reduction in the ability of the body to lose heat and a central action if they enter the CNS (for example atropine). Hyperthermia is a feature seen in over 25% of cases.[26] Children are more likely to develop hyperthermia than adults, probably because of their reduced ability to lose heat.[27] Other CNS features include agitation and CNS depression with coma. Peripheral manifestations are sinus tachycardia, anhydrosis, functional ileus, urinary retention, hypertension, tremulousness, and myoclonic jerking or, 'red as a beet, dry as a bone, blind as a bat, mad as a hatter and hot as a hare' Like many of the previous conditions, treatment is supportive, including active cooling. Physostigmine, a cholinesterase inhibitor, is often used.

A large number of drugs, many commonly used in intensive care, have anticholinergic properties. Some plants and foods, for example, deadly nightshade, tomatoes and potatoes, also have anticholinergic properties. Causative agents include:

- anticholinergics (atropine, glycopyrrolate),
- antihistamines (chlorpheniramine),
- antipsychotics (olanzapine, quetiapine),
- antispasmodics (oxybutynin),
- cyclic antidepressants (amitriptyline, doxepin) and
- mydriatics (tropicamide).

Sympathimometic syndrome

Sympathomimetic agents are widely used in prescription drugs, for example in those used to treat asthma. They are also commonly found in non-prescription drugs such as cold remedies (containing ephedrine), illegal street drugs (e.g. cocaine, amphetamines, methamphetamine ('ecstasy'), mephedrone) and dietary supplements (e.g. ephedra alkaloids). Signs and symptoms include bronchospasm and wheezing from crack cocaine, hypertension causing headache, hypertensive encephalopathy and intracranial haemorrhage, and hyperthermia from agitation and seizures. Hyperthermia may be worsened by the hot and humid environments (for example, dance clubs) where these drugs are taken. Other features include cardiac arrhythmias, myocardial ischaemia and cardiomyopathy, confusion, agitation and delirium.

These drugs have their pharmacological effects by a variety of mechanisms. Some sympathimometics directly stimulate α- and β-adrenergic receptors. Amphetamines appear to have multiple actions to increase the synaptic levels of a number of neurotransmitters, including noradrenaline and serotonin. Cocaine and the tricyclic antidepressants prevent the presynaptic reuptake of noradrenaline. Other sympathimometics prevent the breakdown of the catecholamine neurotransmitters, usually through the inhibition of the enzyme monoamine oxidase. 3,4-Methylenedioxy-methamphetamine (MDMA) appears to have several mechanisms. It probably partly acts as an indirect serotonergic agonist, acting on the serotonin transporter and increasing the amount of serotonin available to be released into the synapse. It also enhances the release of dopamine and noradrenaline, probably in a similar manner to serotonin, has effects on monoamine reuptake, and may act as an agonist on various receptors, including 5HT2, α2-adrenergic, M1 muscarinic cholinergic and D1 and D2 dopamine receptors.

MDMA is probably the commonest sympathimometic to cause hyperthermia. It was originally produced in 1912 as a precursor to a haemostatic drug in development.[28] It was not until the 1920s that its similarities to adrenaline were noted. There was some interest in the 1950s and 1960s in whether it could be used as a stimulant or as an interrogation tool and in the late 1960s it was discovered to have psychoactive properties. A number of psychiatrists noted that it helped patients overcome emotional barriers and it gained some use in psychotherapy as a result. It earned the nickname 'penicillin for the soul' until the 1980s, when its illicit street use became more widespread and it was subject to class A restrictions.

Piperazine compounds

Piperazine compounds[29] are rarely used in medical practice with the exception of the anti-emetic cyclizine and anti-helminths. Piperazine derivatives are predominantly found in 'club drugs', having effects similar to MDMA and amphetamines. Common names include 'Legal X', 'Legal E' and 'Frenzy', and they are class C drugs often used as legal alternatives to Ecstasy. Various derivatives of piperazine have been synthesised, and probably generally prevent the re-uptake of dopamine and stimulate release of noradrenaline.[30] Common effects include agitation, sweating, dizziness and seizures, and in severe cases, metabolic acidosis and hyponatraemia. Hyperthermia and multi-organ failure have also been reported.[29] Symptoms can persist beyond 24 h.

Synthetic cathinones

Cathinone occurs naturally in the *Catha edulis* (khat) plant, which is a flowering plant native to East Africa and the Arabian Peninsula. Khat chewing has been social custom in local communities for thousands of years. Cathinone is a monoamine alkaloid similar to amphetamine which causes excitement, loss of appetite and euphoria. In 1980, it was classified by the World Health Organization (WHO) as a drug of abuse which can produce some psychological dependence but is less addictive than tobacco or alcohol. Synthetic cathinones[29] are generally street drugs (mephedrone, 'meow-meow'), and are classified as Class B. The anti-depressant and anti-smoking drug bupropion is a cathinone derivative. These drugs increase noradrenaline, dopamine and serotonin levels. Symptoms are usually mild, and include sweating, palpitations and headache. More serious complications include hyperthermia, serotonin syndrome and hyponatraemia.

Cannabinoids

Although not normally associated with cannabinoid use, hyperthermia has been reported.[31] It is more common to find a lowering of the core temperature in relation to use of this drug.

Problems of extreme hyperthermia

Despite the myriad conditions causing hyperthermia the systemic effects are similar, raising the possibility that at least some of the effects are due to hyperthermia *per se*, rather than the underlying aetiology. Perhaps in some situations there is a final common pathway and indeed, artificially induced hyperthermia also often produces the same multi-system effects.[32]

Cerebral or cognitive dysfunction is a common feature of hyperthermic states. This may be a recognised side effect of the drug or as a direct result of the hyperthermia. Coagulopathy, liver failure and renal failure are common, and rhabdomyolysis and cell damage also occur. Conversely, a number of drugs cause organ and tissue damage independent of their hyperthermogenic properties. Rhabdomyolysis may develop because of a reduction in blood flow and oxygen delivery, or by impaired ATP production or metabolism and a large number of drugs are implicated.[33] This drug-induced acute renal and liver failures are common, accounting for 20%[34] and 50%[35] of cases, respectively, suggesting that hyperthermia is only one of a number of mechanisms through which these drugs may cause tissue damage.

Cooling

While it appears that lower degrees of hyperthermia have an improved outcome and less morbidity it is not clear whether a 'safe' level of hyperthermia exists. Observational data suggest that the mortality is 13-fold higher at a temperature of 39.5°C compared with normothermia.[3] Whether artificially lowering the temperature has the same effect is not known. Antipyretics, for example paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs), are unlikely to work as it has a heat generation problem and not a hypothalamic-driven one. Furthermore, NSAIDs are likely to contribute to both the clotting abnormalities and the gastrointestinal cellular dysfunction that develop in hyperthermia.[36]

Measuring a core rather than peripheral temperature is recommended, as a peripheral temperature may under-read by up to 2°C in hyperthermia.[37]

Conclusions

A raised temperature from a non-septic cause is common in the critically ill, but is often poorly recognised and diagnosed. Many of the drugs that are used in the intensive care unit (ICU) have the potential to cause hyperthermia. With emerging evidence that hyperthermia causes multi-system effects and can lead to death, increased effort should be made to identify the cause of the temperature and understand the mechanisms better. Cooling is probably important; however, the optimum temperature is currently unknown.

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