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A Patient With a Temperature of 102.5 F and Rigors 3 Hours After Surgery

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Stem Case and Key Questions Content

A 55 y.o. male with a left ankle fracture presents for an open reduction and internal fixation of his ankle. He has a history of depression and has never had surgery before. He denies any family history of anesthetic complications. He is taking Tramadol and citalopram. NKDA. He is 5'9" 85kg and his initial vital signs are BP 130/85, HR 88, SaO2 100 on room air. His airway exam is Mallampati I, with a 5cm thyromental distance with full cervical range of motion, his lungs are clear and his heart regular. He requests a general anesthetic.

1. How would you induce this patient?

You are working with a brand new anesthesia resident and since the patient requested general anesthetic, the plan is to perform a total intravenous anesthetic with midazolam, propofol, dexmedetomidine, fentanyl and rocuronium. Standard and bispectral index monitors and are placed and the patient is induced with midazolam, propofol, fentanyl, and rocuronium. Propofol and dexmedetomidine infusions are started. An hour into the procedure, the vital signs are BP 120/62, HR 69, SaO2 100%, ETCO2 38 mmHg, temperature 36.5 °C and BIS of 78.

2. What is a bispectral analysis number and what does it signify?

3. Would you treat that number and if so, how?

Additional propofol, midazolam, and rocuronium were administered. The vitals now are BP 109/56, HR 72, SaO2 100%, ETCO2 38 mmHg, temperature 36.6, and BIS of 79.

4. Would you treat the BIS now?

Sevoflurane is added to the anesthetic and the BIS drops to 43. Approximately 30 minutes later, as the surgeons are closing, 1g of intravenous acetaminophen is administered, the rocuronium is reversed with neostigmine and glycopyrrolate and the patient is extubated. In the PACU, the patient's vital signs are BP 132/76, HR 88, SaO2 97% on 2LNC, and temperature 36.9 °C. In the PACU, the patient complains of PONV, which is treated with 8 mg of ondansetron and 25mg of promethazine. His pain is well controlled and he doesn't recall anything from the surgery. You are relieved and get the case started. The patient remains in the PACU for 90 minutes before being transferred to the floor.

About an hour into the next case, you get a call from the orthopedics resident telling you that this patient is now "shaking".

5. What do you think is the cause of the "shaking"?

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6. How would you manage this patient?
Ten minutes later, you get a call that the temperature is now 101.5° F. You go up to the floor and the patient is diaphoretic, appears uncomfortable, has rigors and muscle rigidity, and his vitals are HR 119 bpm, BP 156/98, SaO2 96% on 4LNC, respiratory rate 30, temperature 102.8° F.

7. What is the differential diagnosis for hyperthermia following surgery?

8. How will you manage this patient?
The patient is immediately transferred to the Medical ICU, which happened to be on the same floor. In the 20 minutes it took to transfer him, his temperature rises to 103.5 ° F.

9. What is your presumptive diagnosis?

10. Which tests would you order?

11. What would you tell the Medical ICU physician?

12. Would you continue to manage the patient or let the ICU physician take over?

13. How would you manage this patient?
The pharmacy is called to obtain dantrolene. The pharmacist seemed confused with the request. At the same time this is happening, cooling is initiated with a cooling blanket and cold fluids and the medical resident is attempting to place an arterial catheter to obtain arterial blood gases.

14. What is the dose of dantrolene and what is the fastest way to obtain it?

15. What resource is there to help with a hyperthermic crisis?

16. What other medical treatments should be started in conjunction with the dantrolene?

17. Which drug induced hyperthermia (DIH) syndromes can be treated with dantrolene and which DIH is dantrolene contraindicated in?
The charge anesthesiologist is called and asked to bring up the MH cart and some help. A bolus of dantrolene is administered. A few minutes later, the resident finally inserts the arterial line and an arterial blood gas is sent, along with electrolytes and CPK. A Foley catheter is also placed and the urine is a dark amber color. The pharmacy finally brings up the dantrolene infusion and it is started at 1mg/kg/hr. With this therapy, his temperature is brought down to 101.3 ° F. The arterial blood gas results are 7.34/30/156/18/-1, K 4.5.

18. Should dantrolene be given before the blood gas analysis?

19. What are the complications associated with dantrolene?

20. What is your diagnosis? Is it MH or another type of DIH?

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21. What instructions would you give the ICU staff about caring for this patient?
The dantrolene infusion is stopped in the middle of the night and without the dantrolene, his temperature rises to 103.5° F.

22. How would you treat this?

23. What is the role of antipyretics in DIH?

24. How long should this patient be treated with dantrolene if considering MH? If so, at what dose?

25. What other causes of hyperthermia should be considered?
The dantrolene is continued for a total of 3 days. At the end, the hyperthermia resolves and the patient is transferred to the floor.

26. How would you counsel this patient and which tests would you consider to prove your diagnosis?

Model Discussion Content
Hyperthermia is defined as an elevation of core body temperature above 37°C. The differential diagnosis of intraoperative hyperthermia includes iatrogenic overheating, infection, transfusion reactions, adrenal insufficiency, thyrotoxicosis, blood in the fourth ventricle, substance use, including alcohol, and drug induced hyperthermia (DIH).

Core body temperature is regulated by a negative feedback system to maintain a set point, that fluctuates between 36 and 38°C. The exact mechanism that determines the absolute threshold is not known but it is mediated by norepinephrine, dopamine, serotonin, acetylcholine, prostaglandins, and neuropeptides. Thermoregulation consists of three phases: afferent thermal sensing, central regulation, and efferent responses. Thermal sensitive receptors are located in the skin and viscera, where they sense temperature changes. When the core body temperature falls below or rises above the set point, the thermoreceptors send and relay afferent thermal information via the spinal cord to the hypothalamus, the central thermoregulatory control center. In determining the cause of increased temperature, it is important to distinguish between hyperthermia and fever. They both increase core body temperature but have different mechanisms and treatment. Fever, defined as a temperature ≥ 38.3°C, occurs when the hypothalamus increases body temperature in response to an infectious or noninfectious cause. Antipyretics are useful because they reduce the elevated set point within the hypothalamus. Hyperthermia occurs when there is a hypermetabolic state or when there is a failure of the hypothalamus to dissipate heat. Antipyretics are not useful because the hypothalamus is not involved in the mechanism of hyperthermia. The syndromes associated with DIH include serotonin syndrome, neuroleptic malignant syndrome (NMS), serotonin syndrome, anticholinergic syndrome, sympathomimetic syndrome, and malignant hyperthermia (MH) (1). Neuroleptic malignant syndrome (NMS) is a complication of the antidopaminergic agents used

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to treat psychosis, nausea, and vomiting. Medications that have been implicated include the antipsychotics, and the dopamine antagonists, prochlorperazine, metoclopramide, droperidol, and promethazine. NMS can also be seen with abrupt disruption of dopaminergic agonists, such as carbidopa/levodopa, amantadine, and bromocriptine. The risk of developing NMS correlates with the dose, potency, rate, and route of administration. Risk factors include males, who have a higher incidence of schizophrenia, concomitant infection, dehydration, and cotreatment with lithium. The incidence of NMS has been reported between 0.2-12.2%, with a mortality rate between 15-18.8%. Antipsychotics with high serotonergic activity have a decreased incidence of developing NMS.

Although the mechanism for developing NMS is not understood, it is thought to be due to a combination of dopamine depletion or disruption in the hypothalamus, along with a direct effect of calcium transport disruption in skeletal muscle in genetically predisposed patients (2). The administration of antidopaminergic medications reduces dopaminergic transmission in the hypothalamus and striatum, leading to alterations in core temperature, impaired thermoregulation, and autonomic dysfunction. The hypothalamus is unable to dissipate heat and the striatum may produce the muscle rigidity that generates heat.

The clinical presentation of NMS includes altered mental status, hyperthermia, muscular rigidity, and autonomic dysfunction. The initial symptoms are usually rigidity and altered mental status, including agitation, lethargy, and coma. Muscular rigidity is seen as the classic lead pipe or cogwheel rigidity, often seen in Parkinson's patients. Other signs include tachycardia, labile blood pressure, tremors, diaphoresis, incontinence, dysphagia, and sialorrhea.

Abnormal laboratory findings include myoglobinuria, leukocytosis, metabolic acidosis, hyper- or hyponatremia, hepatic and renal impairment, and low serum iron.

The differential diagnosis includes anticholinergic syndrome, SS and MH. Onset time can be used to differentiate NMS from the other hypermetabolic syndromes. The onset time for NMS is from 1-3 days, which is longer than the other hypermetabolic syndromes. The differential also includes rhabdomyolysis from other causes, meningitis, encephalitis, neuroleptic heat stroke, tetanus, intracranial masses, and other drug interactions, including MAOIs.

Death can result from respiratory failure, cardiovascular collapse, renal failure, arrhythmia, and DIC. Morbidity is due to rhabdomyolysis, leading to acute renal injury, aspiration pneumonia, seizures, and arrhythmias.

Treatment consists of stopping the dopamine antagonist, restarting the dopamine agonist, and supportive therapy. Since antipsychotics are metabolized slowly and cannot be filtered by

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dialysis, supportive care may be required for days to weeks in the ICU. Supportive care includes aggressive hydration, oxygen, cooling with ice packs, cool fluid, and cooling blankets, and cardiorespiratory support. If intubation is required, nondepolarizing agents should be used instead of succinylcholine.

Benzodiazepines are the mainstay of treatment and attenuate agitation and sympathetic hyperactivity. These patients are prone to venous thromboembolism and require DVT prophylaxis. Dopamine agonists such as bromocriptine, levodopa, and amantadine have been used to reverse the symptoms of NMS. Bromocriptine, a centrally acting dopaminergic agonist, is administered until symptoms resolve. The dose is 2.5mg TID. In severe cases, dantrolene can be used. Dantrolene is a ryanodine receptor type 1 (RYR1) antagonist that inhibits the release of calcium by the sarcoplasmic reticulum in skeletal muscle, directly inhibiting excitation-contraction coupling, reducing the rigidity that leads to muscle breakdown and rhabdomyolysis. It cannot be used as the sole treatment because it is a peripherally acting agent while NMS is a centrally mediated disease. The dose of dantrolene is 1.0-2.5mg/kg bolus and is continued until the signs of hypermetabolism subside or a cumulative dose of 10mg/kg is administered. Dantrolene is continued at a dose of 1mg/kg every 4-6 hours for at least 24h to prevent symptom recurrence. Common adverse effects of IV or IM dantrolene administration are muscle weakness and phlebitis caused by the highly alkaline solution. The most serious adverse effect associated with dantrolene is liver toxicity and should be avoided in patients with liver disease. Oral dantrolene may be given at a dosage of 4-8 mg/kg/day divided into 4 doses and continued for 1-3 days to prevent the recurrence of symptoms. Symptoms typically resolve within 6-10 days after treatment is initiated. Since the elevated temperature with NMS is not prostaglandin mediated, antipyretics are not indicated.

Serotonin syndrome (SS) is a potentially fatal syndrome of rigidity and hyperpyrexia resulting from the administration of serotonergic agents and presenting with a range of symptoms from mild GI distress to hyperthermia and rigidity. The etiology is thought to be due to an increase of serotonin or a serotonin agonist at the 5-HT2A receptor or when reuptake or oxidation is inhibited. Serotonin syndrome occurs shortly after an increase in the dose of a potent serotonin agonist, an MAOI, a serotonin reuptake inhibitor (SRI), or after the addition of a second serotonergic agent, such as tramadol or dextromethorphan. Other agents that can be implicated include meperidine, methadone, and propoxyphene, which have a weak SRI effects, linezolid and isoniazid have MAOI properties, and sumatripan is a serotonergic agonist. Other drugs that have been associated with SS include herbal supplements, such as ginseng and St. John's wort, tryptophan, TCAs, lithium, fentanyl, valproic acid, and antiemetics, such as ondansetron and metoclopramide because they all increase serotonin concentration. Illicit drugs that can cause SS include ecstasy, cocaine, and amphetamines.

In SS, serotonergic agents can enhance synaptic serotonin (5-HT) concentrations, can inhibit the metabolism or reuptake of 5-HT, potentiate 5-HT activity, or can increase substrate supply.

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Excessive serotonin levels increase the stimulation of both central and peripheral serotonergic receptors, leading to hyperthermia.

SS is characterized by a triad of autonomic hyperactivity, neuromuscular abnormalities, including clonus, muscular rigidity, and hyperreflexia, and altered mental status, including agitation and confusion to delirium, seizures, and coma. In its most severe form, serotonin syndrome rapidly progresses to coma, seizures, multiorgan failure with DIC, and cardiac arrest. Clinical findings associated with serotonin toxicity include hypertension, tachycardia, body temperature > 38°C, mydriasis, diaphoresis, diarrhea, neuromuscular abnormalities, including hyperreflexia, inducible and spontaneous clonus, myoclonus, ocular clonus, nystagmus, tremor, shivering, and peripheral hypertonicity, and mental status abnormalities, including agitation, ataxia, delirium, and seizures. Myoclonus is the most common finding in SS. Muscle rigidity is most prominent in the lower extremities and is symmetric. Autonomic nervous system dysfunction manifests as hyperthermia, diaphoresis, tachycardia, hypertension, tachypnea, and mydriasis. The hyperthermia is due to increased muscle tone and rigidity, leading to increased heat production.

Serotonin syndrome is a clinical diagnosis based on signs, symptoms and medication history. Serum 5-HT concentrations have no correlation with the clinical presentation, urinary 5-HT may possibly be used as a biomarker in serotonin syndrome. The symptoms of serotonin syndrome are similar to the symptoms of NMS, except that the onset of symptoms of SS is rapid and patients with SS are agitated with myoclonus and incoherent speech while patients with NMS are usually mute, stare with a flat affect, and are immobile.

Differential diagnosis includes infection, such as septicemia or meningitis, Ecstacy, cocaine, lithium, or anticholinergic agent overdose, and hypermetabolic syndromes such as NMS. Complications include DIC, seizures, severe hypotension, respiratory distress, renal or hepatic failure, ventricular tachycardia, and death. Approximately 25% of patients require intubation and ventilatory support and most patients show improvement within 24 hours. The mortality rate ranges between 2-12% with the most common cause complications of severe hyperthermia. Treatment consists of discontinuing all serotonergic agents and support care, such as IV fluids and benzodiazepines, which are nonspecific serotonin antagonists. Hyperthermia should be treated with aggressive cooling, and neurologic effects can be treated with benzodiazepines. Cyproheptadine, a 5-HT2A inhibitor, is considered in moderate to severe cases because it is the most effective antiserotoninergic agent. It is administered orally at an initial dose of 4-12mg every 2 hours until a response is seen. If the patients respond, the dose is 4mg every 6 hours for 48h to prevent relapse. Chloropromazine, a parenteral 5HT2A antagonist, can be used as an adjunct. It is not a primary treatment because it can block dopamine receptors, potentiating muscle rigidity. It can also lower seizure threshold and exacerbate NMS. Dantrolene can be used to relax muscles but it does not treat the underlying cause of the disease.

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Sympathetic agonists can also produce hyperthermia through disturbances in central and peripheral thermoregulation, caused by alterations in NE, dopamine, or serotonin levels in the CNS(3). The indirect and mixed agents have adrenergic effects and effects due to behavior. Euphoria, psychomotor agitation, hallucinations, and blunted responses to pain can be seen with amphetamines, cocaine, phencyclidine, and MDMA. This can lead to excessive psychomotor agitation, tachycardia, hypertension, diaphoresis, and increased heat production. MDMA can also cause SIADH, leading to confusion, headaches, and death from hyponatremia. Bath salts contain amphetamine type compounds and can produce hyperthermia, psychomotor agitation, psychosis, and death. The agents most commonly associated with this syndrome are amphetamines, methamphetamine, MDMA, cocaine, and MAO inhibitors.

These patients present with hypertension, tachycardia, psychomotor agitation, and hyperthermia. The hyperthermia is due to increased production and impaired heat dissipation due to vasoconstriction, deteriorating to tremors, psychosis, and seizures. Other signs include mental status changes, electrolyte disturbances such as hyperkalemia and hypo- or hypercalcemia, hypoglycemia, acidosis, dilated reactive pupils and coagulopathy. Death occurs due to hyperthermia, rhabdomyolysis, hypoxia, myocardial dysfunction, DIC, seizures, or multiorgan failure.

Treatment involves supportive care and rapid, aggressive external cooling and control of psychomotor agitation and adrenergic stimulation. Benzodiazepines, used for their anticonvulsant properties, can blunt increased sympathomimetic activity. When benzodiazepines cannot control severe agitation, shivering, or seizures, α adrenergic agents, barbiturates or nondepolarizing paralytics, and mechanical ventilation should be employed to assist with aggressive cooling measures. β-blockers should be avoided because they can cause unopposed vasoconstriction. Dantrolene has been used in treating ecstasy related hyperthermia but its safety and efficacy has not been established. Antipyretics are not effective because the hyperthermia is not prostaglandin mediated.

Anticholinergic agents are a common cause of hyperthermia at therapeutic and toxic doses. Medications with anticholinergic properties, such as antispasmodics, antihistamines, TCAs, antiParkinsonian drugs, neuroleptics, atropine, and belladonna alkaloids can all cause anticholinergic syndrome. TCA overdose also affects the sodium channels in the myocardium, prolonging the QRS. Children are more prone to develop anticholinergic related hyperthermia, because they have a lower sweating rate, which reduces their ability to dissipate heat. Hyperthermia is caused by the blockade of both central and peripheral muscarinic acetylcholine receptors. Central muscarinic blockade effects depend on the ability of the drug to cross the blood brain barrier. Peripheral muscarinic blockade by anticholinergics interferes with cutaneous heat loss by impairing sweat gland function. Hyperthermia results from the combination of heat production from increased muscle activity and the inability to dissipate heat through sweating.

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Symptoms produced by central muscarinic blockade include altered mental status, confusion, tremor, myoclonus, hallucinations, agitation, restlessness, seizures or coma. Peripheral symptoms include dry mouth and axillae, mydriasis, blurred vision, sinus tachycardia, flushing, urinary retention, and decreased bowel sounds. Other abnormalities include hypertension, and mild hyperthermia. The absence of muscle rigidity distinguishes anticholinergic toxicity from other DIH syndromes.

Treatment includes discontinuing the offending agent, restoring hemodynamic stability, manage agitation, prevention of secondary injury such as rhabdomyolysis, supportive care with external cooling and benzodiazepines. Physostigmine, an acetylcholinesterase inhibitor, can be used to accelerate the resolution of anticholinergic symptoms. It can cross the blood brain barrier and by increasing the concentration of acetylcholine, antagonizes anticholinergic effects such as disorientation, agitation, combativeness, and anhydrosis. Since physostigmine can induce bradycardia or seizures, it is reserved for cases where all other treatment options have been exhausted. In severe cases of anticholinergic syndrome involving uncontrolled hyperthermia, the use of paralytics may be necessary. Antipyretic agents are not effective because the mechanism of hyperthermia does not affect the hypothalamus.

MH is a pharmacogenetic autosomal dominant channelopathy of the ryanodine receptor in the skeletal muscle sarcoplasmic reticulum. The incidence of fulminant MH is low, 1 per 250,000 patients, with a mortality rate of 10% but when succinylcholine and inhalational agents are used in combination, the incidence is higher at 1 per 62,000 patients. It is more common in males and most common in the first 3 decades of life with half occurring in patients younger than 15 years. Risk factors include family members of affected individuals, as well as those with myopathic diseases including muscular dystrophies, central cord disease, and hypokalemic periodic paralysis. Mutations in the RYR1 and calcium channel lead to uncontrolled calcium release and sustained muscle contraction. This increase in calcium stimulates the sarcoplasmic calcium ATPase pump to continuously take up the excess calcium, decreasing intracellular ATP. This produces a hypermetabolic state with increased oxygen consumption, decreased mixed venous saturation, hypercarbia, lactic acid production, and rhabdomyolysis with hyperkalemia, hyperthermia, and DIC.

MH occurs after exposure to potent inhalation agents and succinylcholine. In rare cases, nonanesthetic stresses such as vigorous exercise or heat can cause a hypermetabolic response in patients succeptible to MH. MH is a clinical diagnosis. The most potent triggers are the combination of succinylcholine and volatile agents, then succinylcholine and when succinylcholine is not used, halothane is the most potent trigger, followed by sevoflurane, then isoflurane and desflurane, with similar ability to trigger MH (4). Due to the decreased use of succinylcholine and halothane, along with an aging population, MH signs and symptoms occur later in than in the past. The symptoms of MH typically emerge within minutes to hours after exposure to the offending agent. Early signs of MH include tachycardia, tachypnea, muscle

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rigidity, ventricular dysrhythmias, and hypercarbia. Muscle rigidity is usually first noticed in the masseter muscles.

The late clinical findings include muscle rigidity, hyperthermia, and metabolic acidosis, and are all related to the hypermetabolic response. These findings, “the classic clinical triad”, can lead to end organ damage, including myoglobinuria, renal failure, hyperkalemia, liver failure, DIC, arrhythmias, CHF, pulmonary edema, bowel ischemia, neurologic injury, and death. Treatment consists of discontinuing all triggering agents, hyperventilation with 100% oxygen and continuing anesthesia with IV and nondepolarizing agents. Supportive care includes external cooling measures, including cooling blankets and cool IV fluids. Hyperkalemia and rhabdomyolysis should be treated with mannitol, fluids, hyperventilation, and calcium chloride. The pharmacologic treatment is dantrolene, at a dose of 2.5mg/kg up to a maximum dose of 10mg/kg or until symptoms subside. Signs and symptoms of hypermetabolism generally begin to resolve within 30 minutes. To prevent the recurrence, 1 mg/kg every 4-6h can be administered intravenously for at least 24h, followed by the administration of oral dantrolene 4-8 mg/kg/day divided into 4 doses daily for 1-3 days. Since the hyperthermia from MH is not associated with the hypothalamus, antipyretics are not useful.

After the acute crisis has passed, patient and family counseling should occur, including the possibility of testing for a predisposition to MH. At this time, the three tests that are available are the in vitro contracture test (IVCT), the caffeine-halothane contracture test (CHCT), and DNA testing. Both the IVCT and CHCT are considered the “gold standard” but are invasive and are subject to between-center variability (5). They both have limitations in sensitivity and specificity. MH is a complex disease whose complete pathophysiology is still unclear. Although 50-70% of cases can be explained by mutations in the RYR1 receptor, the rest of the genetic disturbances are unclear. There is evidence that calcium release from intracellular stores in skeletal muscle is regulated by the voltage-dependent calcium channel dihydropyridine receptor in the T-tubule membrane, which when depolarized, opens the RYR-1 receptor. Because of the heterogenicity of RYR-1 variants and the potential involvement of other genes, DNA diagnosis for MH susceptibility can only be performed in families with known mutations. If a DNA test is negative, an IVCT is still recommended.

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