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Mini Review

Medication-Induced Anticholinergic Syndrome During Perioperative Encounters

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Abstract

Medication-induced anticholinergic syndrome is an iatrogenic syndrome that results from the simultaneous administration of a single or multiple pharmacological agent/s with high potency anticholinergic effects. Many of these pharmacological agents play an important role during the perioperative period and commonly used during in the operating room and during the postoperative recovery period. The anticholinergic syndrome presents with a constellation of symptoms that can be erroneously categorized as perioperative delirium or sepsis.

Keywords: *Anticholinergic Syndrome; Anticholinergic Burden; High Anticholinergic Potency; Physostigmine; Perioperative Delirium*

Introduction

Anticholinergic Syndrome is a multi-system disorder that develops as a result of the administration of a one or more pharmaceutical agents with anti-cholinergic effects. These agents are commonly used during anesthesia, in the postoperative recovery period and in the intensive care unit (ICU). Anticholinergic syndrome is a very serious disorder that needs to be recognized and treated in a timely manner [1]. It contributes to the increased morbidity and mortality of the affected patients, increases the rate of ICU admission of these patients and leads to prolonged ICU stay and overall duration of hospitalization. Many physician specialists including anesthesiologists, intensivists, and surgeons, are not familiar with this iatrogenic condition, or of its existence as a separate entity. Consequently, anti-cholinergic syndrome can go undiagnosed or mislabeled. According to the published literature, the incidence of anti-cholinergic syndrome following the administration of anesthetic medications alone varies between1% and 40%. The incidence in ICU settings is probably much higher still because of the greater need to institute polypharmacy. The incidence of anticholinergic syndrome is highest in the geriatric population [2,3]. The elderly and critically ill patients are more likely to have a high sympathetic output during the perioperative period. Consequently, they are more prone to suffer from decreased cholinergic reserve and many have a reduced number of central as well as peripheral muscarinic cholinergic receptors, hence they have a higher risk of developing anticholinergic syndrome [4].

Toxic anticholinergic effects manifest in a wide range of symptoms. Old pharmacology textbooks ascribed the anticholinergic toxidrome to administration of belladonna derivatives with the well-known mnemonic: Mad as a hatter (delirium, psychosis), Hot as hare (fever, hyperthermia), Dry as a bone (dry skin, dry mouth, urinary retention), Red as a beet (flushed skin), Blind as a bat (mydriasis). Historically, anticholinergic symptoms were attributed mainly to belladonna derivatives, such as scopolamine, atropine, and hyoscyamine. The latest surveys implicates an excess of six hundred pharmacological agents in potentially causing this syndrome [5-8]. It is nowadays well known that many of the commonly used classes of medications possess clinically significant anticholinergic properties. including antihistamines, sedatives, opioid narcotics [5,9-11], anesthetic agents, anti-depressants, antipsychotics, appetite stimulants, antiparkinsonian drugs, antiemetics, spasmolytic agents, muscle relaxants, and antimuscarinic agents used for control of overactive bladder or diarrhea.

The cumulative effect of taking multiple medicines with anticholinergic properties is known as the anticholinergic burden [6]. A high anticholinergic burden can adversely impact cognition and mental capacity, and may impair the function of multiple organ systems, leading to increased morbidity and mortality [4,12-13]. It is not uncommon to encounter elderly patients with a high anticholinergic burden during the perioperative period and or in the ICU settings, where they are prescribed multiple medications for management of underlying as well as surgical conditions. The current clinical practice encourages the routine use of risk scales in order to quantify the anticholinergic burden in patients, including those enrolled in new clinical research trials [7]. These risk scales rank the anticholinergic activity of medications into four categories, ranging from no anticholinergic activity to definite or high potency anticholingeric activity. The aim of this systematic review is to compare anticholinergic burden quantified by the anticholinergic risk scales and to evaluate the relationship between a high anticholinergic burden and the incidence of adverse outcomes.

The practice of critical care medicine in the US includes physicians from diverse medical backgrounds such as anesthesiology, internal medicine, cardiology, pulmonology, surgery, emergency medicine, or hospital medicine. Most intensive care units rely on standardized treatment methods and protocols for the management of the various commonly encountered clinical scenarios. Patients presenting with anticholinergic syndrome in the post-anesthesia care units or in the ICU often have symptoms that mimic a variety of other commonly encountered or expected post-surgical disorders. Many clinicians are either unfamiliar with the existence of anticholinergic syndromes as a clinical entity, since it mimics other neurological and systemic disorders, or they will consider anticholinergic syndrome only as a diagnosis of exclusion. However, given the high likelihood of patients receiving multiple pharmacological agents with high anticholinergic potency during the perioperative period, it is prudent that perioperative and critical care physicians familiarize themselves with the anticholinergic syndrome symptomatology and management. Elderly patients and patients with underlying co-morbidities tend to be more susceptible to suffer from the anticholinergic side effects, especially during the perioperative period [7,8].

Discussion

Symptomatology of the anticholinergic syndrome affects various organ systems including the central nervous system, respiratory, gastrointestinal, urological, and cardiovascular systems.

Central anticholinergic effects on the brain can manifest as lack of concentration, confusion, restlessness, attention deficit, agitation, memory impairment, delirium, delayed emergence from general anesthesia [14,15], altered mental status, psychosis, hallucinations, and seizures. Prolonged and continued exposure to anticholinergic effects may cause permanent deterioration and post-operative cognitive dysfunction (POCD) or dementia in susceptible patients [16-20].

Gastrointestinal symptoms related to anticholinergic activity include loss of appetite, decreased salivary gland output and secretions manifesting as dry mouth and infections in the oral cavity. Blocking the parasympathetic system output in the GI tract can cause imbalance of the autonomic nervous system and may result in prolonged ileus. Other GI anticholinergic effects include decreased bowel activity, decreased gastric acid secretion, decreased motility with absent bowel sounds, abdominal distension, bloating resulting in increased abdominal girth, discomfort and pain, poor absorption of fluids and enteral feeds mimicking bowel obstruction. In extreme cases, bowel distension may increase intraluminal pressure inside the bowel, resulting in anastomotic leak, or even perforation. Ileus and abdominal distension may result in intra-abdominal hypertension, which can lead to intra-abdominal compartment syndrome if pressure is not relieved.

Intra-abdominal distension can cause pulmonary embarrassment resulting in increased work of breathing, low lung volumes, atelectasis and aspiration pneumonia. These pulmonary complications place patients at an increased risk of needing endotracheal intubation and mechanical ventilation. The administration of additional sedatives to intubated patients may place patients in a vicious cycle and worsening of the anticholinergic symptoms. Other direct anticholinergic effects on the respiratory system include bronchoconstriction and drying of secretions, which may lead to serious problem with pulmonary toilet, especially for mechanically ventilated patients.

Anticholinergic syndrome affects other systems as well. Anticholinergic effects on the cardiovascular system include tachycardia, hypertension, and dysrhythmias. Ophthalmological effects causing dilated pupils or mydriasis, blurred vision and failure of visual accommodation, which often is the cause of the increased incidence of falls. Anticholinergic effects on the sweat glands manifests as hyperthermia due to impaired production of sweat. Perioperative hyperthermia due to increased anticholinergic activity is often worked up as infectious in nature or categorized as sepsis, especially when accompanied by tachycardia and altered mental status.

Effects on the urinary system include urinary retention that may require urinary bladder catheterization, urinary sphincter spasm, which can cause significant pain and distress.

A number of studies reported on the adverse effects associated with a higher anticholinergic burden, citing it as a strong predictor of cognitive and physical impairments in older people. A retrospective study conducted in Finland indicates that the use of medications with anticholinergic properties is a strong independent predictor of mortality in older people. More recently several studies reported an association between exposure to a high anticholinergic burden and increased rate of hospital admission and prolonged hospitalization in the in the geriatric population [4,6].

Pathophysiology

Anticholinergic medications are competitive antagonists of the neurotransmitter acetylcholine at receptor sites within the cholinergic system. The cholinergic system has two major categories of receptors namely muscarinic and nicotinic. Muscarinic receptors are plasma membrane-bound G protein-coupled receptors, and the nicotinic receptors are ligand-gated ion channel receptors. Nicotinic receptors are found in the postganglionic dendrites, the nerve bodies of the autonomic nervous system and on the motor endplate of the neuromuscular junction. Muscarinic receptors are found in the target organ cells of parasympathetic nervous system and sweat glands in the sympathetic nervous system. Brain has both nicotinic and muscarinic receptors. Medications with anticholinergic activity presenting as anticholinergic syndrome affect predominantly the muscarinic receptors.

Differential diagnosis

Anticholinergic syndrome must be distinguished from other clinical conditions such as serotonin syndrome, neuroleptic malignant syndrome, malignant hyperthermia, encephalitis or meningitis [21,22].

Serotonin syndrome is commonly seen in patients receiving antidepressants that affect the availability of serotonin between neurons, such as Selective Serotonin Reuptake Inhibitors (SSRI), Serotonin Norepinephrine Reuptake Inhibitors (SNRI). It is also seen with Mono-Amine Oxidase (MAO) Inhibitors, tricyclic antidepressants and herbal products such as St. John's wort. It presents with fever, hyperreflexia and diarrhea.

Neuroleptic malignant syndrome presents with rigidity, muscle stiffness, fever and a history of administration of anti-dopaminergic agent including butyrophenones such as haloperidol, phenothiazines such a chlorpromazine and other antipsychotic agents. It responds well to the administration of bromocriptine and dantrolene sodium.

CNS infections such as meningitis and encephalitis present with fever, chills, photophobia, neck stiffness, rash and are usually require radiographic studies and cerebrospinal fluid analysis to confirm the diagnosis.

Management

Physostigmine is a useful medication to confirm the diagnosis of anticholinergic syndrome and to manage its symptoms [23,24]. It counters the iatrogenic anticholinergic side effects and provides relief of symptomatic and supportive treatment. Physostigmine is a tertiary amine that rapidly crosses the blood-brain barrier and is an acetylcholinesterase inhibitor. It improves both the central and

peripheral symptoms associated with anticholinergic toxicity. It is preferred over other cholinergic agents due to its rapid onset of action and short half-life. Physostigmine has a short half-life, may require repeated administration if symptoms recur. The usual dose of physostigmine is 1 - 2 mg given IM or 0.02 mg/kg IV. Patients receiving Physostigmine are kept under monitoring and close observation for few hours until anticholinergic syndrome symptoms improve. Rapid improvement following physostigmine injection is evidenced by improved cognition, decreased tachycardia, and improved hydration status [25,26]. Mydriasis may take days to fully resolve, even with continued physostigmine treatment. Pilocarpine drops may helpful to treat mydriasis. Patients receiving physostigmine treatment need to be observed for cholinergic symptoms which may signal the development of cholinergic syndrome.

In summary, anticholinergic syndrome is an iatrogenic disorder of serious consequences frequently encountered in the perioperative setting and in the ICU [27,28]. It follows the administration of multiple agents that exert anticholinergic side effect. The geriatric age group and frail patients with multiple underlying co-morbidities are most affected. Early recognition of symptoms and diagnosis is crucial and can help reduce complications associated with on-going anticholinergic effects.

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