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Anticholinergic syndrome in the perioperative period (review). Part 1

Abstract. *Anticholinergic syndrome is a febrile toxidrome characterized by the suppression of cholinergic neurotransmission in muscarinic receptors. A prerequisite for its development is that pharmacological agents must be lipophilic and capable of crossing the blood-brain barrier to block muscarinic cholinergic receptors. Triggers of anticholinergic toxidrome include alkaloids from over 2,000 species of plants and fungi, antipsychotics, antidepressants, antiparkinsonian drugs, antispasmodics, ocular and antihistamine medications, general and local anesthetics, which are often prescribed in combinations, although these drugs vary significantly in their anticholinergic effects within classes. Overdose of anticholinergic compounds can be accidental or intentional. Contributing factors include old age, central nervous system diseases, vitamin B_1 deficiency, genetic predisposition, and polypharmacy. The mechanism of action of anticholinergic compounds is based on the antagonism of the neurotransmitter acetylcholine and its deficiency in the synaptic cleft of muscarinic anticholinergic receptors, which can be due to various factors. Symptoms caused by acetylcholine deficiency can be divided into peripheral and central, depending on whether the triggering substance can cross the blood-brain barrier. In anticholinergic syndrome, rhabdomyolysis is usually not present due to the rare occurrence of severe muscle tone increase or rigidity. The cumulative effect from taking several anticholinergic drugs, known as anticholinergic load, can negatively affect cognitive and physical functions and increase the risk of mortality.*

Keywords: *anticholinergic toxidrome; etiology; pathogenesis; clinical signs*

"Belladonna: in Italy — a beautiful woman, in England — a deadly poison. A striking example of the deep similarity between two languages".
A. Birz

Introduction

Anticholinergic syndrome (ACS) is a febrile toxidrome characterized by the suppression of cholinergic neurotransmission in muscarinic receptors. Until recently, this condition was called "postoperative delirium" or "atropine poisoning" [1]. The cholinolytic toxidrome was first described by V. Longo in 1966 in connection with agitation, disorientation, ataxia, hallucinations, and coma after the administration of an excessive dose of atropine. In the second half of the past century, the term "cholinolytic cumulative effect" was introduced into medical practice, describing the synergistic clinical manifestations of the action of several drugs with different degrees of anticholinergic activity [3–5].

According to the American Association of Poison Control Centers (AAPCC), in 2007, 8,582 cases of anticholinergic syndrome were detected in the USA, 13 of which were life-threatening. In 2008, the number of cases was about 20,000. Anticholinergic toxicity is common in emergency departments but rarely leads to death. According to the AAPCC annual report for 2015, approximately 14,000 cases of ACS were registered, none of which were fatal. However, 51 deaths were registered in previous years [1, 5]. In 2016, the USA recorded 2,159,032 cases of anticholinergic drug overdose. According to the AAPCC report, in 2019, cumulative cholinolytic effects requiring inpatient treatment were registered in 5,316 cases, none of which ended fatally [3, 5, 6]. Antihistamines were recognized as the sixth most common category of substances associated with pathologi-

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cal effects on the human body (4.19 % of all medications). The actual numbers of complications are likely significantly underestimated since most cases of toxidrome are not reported to toxicology centers [3, 5]. ACS is also common in psychiatric practice [1, 5].

Currently, the highest rates of morbidity and mortality from ACS are observed in children aged 13 to 18 years, among whom recreational and suicidal intentions are most common [7, 8].

Evidence gathering. Studies were included in the research if they: 1) were published in Ukrainian, German, Spanish, Polish, or English; 2) reported on anticholinergic toxidrome associated with anesthetic management of surgical interventions; 3) informed about the prevalence of anticholinergic toxidrome from the use of medicinal and non-medical substances; 4) used an observational design (cohort or cross-sectional). A retrospective information search was conducted using a spatial-vector descriptive model system, which was supplemented by a manual search for involved articles.

Synthesis of evidence. This syndrome can be caused by intentional overdose, accidental ingestion of external-use products, violations of medical standards, or geriatric polypharmacy; systemic effects of cholinergic drugs can result from the use of eye drops with a high concentration of atropine and other M-cholinergic blockers (MChB) [3, 9]. Therefore, understanding the risks of side effects from prolonged simultaneous use of several drugs for therapeutic purposes is quite important [3, 5, 6, 10, 11].

The popularity of MChBs is due to their wide range of therapeutic and toxic properties. In Ukraine, they are widely used in outpatient, planned, and urgent medical practice, and these drugs are included in clinical protocols for emergency and critical medical care, anesthesiology, intensive care, neurology, psychiatry, surgery, gastroenterology, ophthalmology, allergy, pulmonology, narcology, cardiology, otolaryngology, nephrology, urology, toxicology (including military), and more. MChBs are also used in folk and alternative medicine, cosmetology, and veterinary practice. This phenomenon is partly due to the use of a wide range of over-the-counter medications [12]. Overdosing on anticholinergic compounds can be accidental or intentional [5].

Substances that can cause ACS. A prerequisite for the development of ACS is that pharmacological agents must be lipophilic and capable of crossing the blood-brain barrier and blocking muscarinic cholinergic receptors, leading to the development of central anticholinergic syndrome symptoms [1, 13].

Most anticholinergic drugs are taken orally, and their effects usually manifest within 2 hours. Some locally applied medications, such as hyoscine, may have an effect for more than 24 hours. The impact of anticholinergic compounds on the central nervous system (CNS) can last more than 8 hours, whereas the initial action on the cardiovascular system typically lasts much shorter [5].

The diversity of effects from MChBs necessitates considering the pharmaceutical properties of the most typical representatives of this group. Medical drugs capable of causing anticholinergic toxidrome include atropine, scopolamine, metacin, platyphylline, pirenzepine (gastrozepin), ipratropium bromide (atrovent), and many others [12].

Cholinergic blockers, primarily affecting M- and N-cholinoreceptors of central nervous system synapses, are used as mild tranquilizers during mental stress, such as mydriatics (amizylum, homatropine), antispasmodics (spasmolytin, cyclodol), and antihistamines (diphenhydramine) [5, 9, 14, 15].

Antipsychotics, antidepressants, antiparkinsonian drugs, antispasmodics, ocular and antihistamine medications, which are often prescribed in combinations, also trigger ACS, although they vary significantly in anticholinergic activity within classes [16].

Alkaloids from nearly 2,000 plant species have anticholinergic properties (belladonna, black henbane, mandrake, datura, brugmansia, scopolia, broad-leaved ragwort, duboisia, and even hawthorn tincture) [3, 5, 8, 12, 16–19].

Alkaloid muscaridine is found in poisonous neurotropic mushrooms (Inocybe fastigiata, Inocybe patouillardii, Clitocybe nebularis). The panther cap (Amanita pantherina) also contains cholinolytics scopolamine and hyoscyamine [20, 21].

Therapeutic doses of anticholinergic drugs are unlikely to significantly change body temperature, at least in healthy subjects in thermally neutral environments, but after overdose or combining several cholinergic agents, hyperthermia may occur. Once sweating stops due to even therapeutic doses of anticholinergic drugs, body temperature may rise sharply in hot environments [16].

The H1 receptor is similar to muscarinic receptors. Therefore, diphenhydramine (dimedrol) also acts as an antimuscarinic agent; it is a competitive antagonist of the muscarinic acetylcholine receptor, which allows us to use it as an antiparkinsonian drug [15]. Antihistamines cause hyperthermia through central (e.g., hypothalamic) and peripheral (suppressing sweating and causing muscle rigidity) effects. Diphenhydramine is a sodium channel blocker. Therefore, combining antihistamines with cocaine use may amplify the molecular-pathophysiological cascade that worsens organ dysfunction [22]. Dimedrol overdose can cause significant toxicity, ranging from agitation and heart arrhythmias to rhabdomyolysis and classic anticholinergic toxidrome [15].

The systemic absorption of the drug can occur through the conjunctiva or nasolacrimal duct, as the nasal mucosa is highly vascularized, with 30–80 % of the dose reaching the general bloodstream after conjunctival instillation. Eye drops can be absorbed by capillaries and reach the brain via the deep cerebral veins and cavernous sinuses. Most cholinolytics have low molecular weight, so they can easily diffuse across the blood-brain barrier [23].

Factors contributing to the development of anticholinergic syndrome

— The main individual factor/modifier for the patient is the reduction of baseline cholinergic function, which is associated with aging or diseases of the CNS [4, 24].

— In the context of Alzheimer's dementia as a neurodegenerative disease, cholinergic neurons have defective projections, which correlate with the classic symptoms of cognitive slowing and decreased neurotransmission [25].

— Previous neuro-muscular diseases and an increase in the permeability of the blood-brain barrier also play a role in enhancing the central anticholinergic effect of drugs [4].

— With age, the retention of various compounds in the body increases due to the suppression of metabolism (reduced drug clearance) [3].

— From 10 to 60 % of elderly take at least one anticholinergic drug, and from 7 to 17 % take several drug forms simultaneously [3].

— 16.1 % of patients had prolonged use of anticholinergic drugs with side effects [26].

— More than 25 % of elderly surgical patients had polypharmacy [26].

— Acquired and hereditary plasma cholinesterase anomalies can lead to significant prolongation of succinylcholine and mivacurium action by reducing their metabolism. The frequency of significant metabolic inhibition of succinylcholine is estimated at one case per 2,800 anesthesias [27, 28].

— Genetic damage to cholinergic neurons of the basal forebrain (long-term effects) increases the effectiveness of isoflurane and propofol [29].

— Vitamin B_1 deficiency may be associated with a deficiency in the cholinergic system due to limited acetylcholine synthesis [4].

— Cumulative cholinolytic effects with signs of hyperactivity were observed in patients receiving prolonged high doses of sedatives who were on mechanical ventilation; prolonged ventilation required additional pharmacological myoplegia [3, 9, 30].

Pathogenesis of ACS

Acute ACS is caused by the suppression of acetylcholine action primarily on muscarinic cholinergic receptors [1, 18]. Muscarinic receptors belong to a superfamily of receptors associated with G proteins. These are membrane receptors with a shared structure, represented by seven transmembrane domains. Currently, five types of cholinoreceptors are known. Activation of M1, M2, and M5 receptors, located in various organs, leads to the activation of Gs proteins, followed by the production of the second messenger cAMP [31].

The mechanism of action of anticholinergic compounds lies in antagonizing the neurotransmitter acetylcholine and its deficiency in the synaptic cleft of muscarinic anticholinergic receptors, which has various causes, including direct inhibition by tropane alkaloids that act as direct antagonists of muscarinic receptors and can inhibit M1 receptor activity. Among the five muscarinic receptors, only M1, which is found exclusively in the central nervous system, is associated with the development of delirium [3–5, 13]. The neurotransmitter acetylcholine is involved in several processes that are disrupted during delirium, such as attention, sleep, and memory. This formed the basis for the hypothesis that cholinergic deficiency may be involved in the pathogenesis of delirium [10].

Common anticholinergic drugs are more accurately called antimuscarinic, as they usually do not block nicotinic receptors [1, 24].

In addition to receptor inhibition, other widely used drugs or their metabolites can also reduce acetylcholine release. Opioids, benzodiazepines, and inhalational anesthetics, as well as substances like cannabinoids or alcohol, can reduce acetylcholine concentration in the synaptic cleft [4, 32].

Clinical signs

British writer L. Carroll in the "Alice's adventures in Wonderland" (1865) showed remarkable knowledge of the clinical toxicology of anticholinergic substances, giving a kind of artistic interpretation to the hallucinatory state and phenomena now referred to as macropsia and micropsia. The classic state of a person suffering from central anticholinergic syndrome was described as "red as a beet" (skin hyperemia), "dry as a bone" (anhidrosis), "hot as a hare" (anhidrotic hyperthermia), "blind as a bat" (dilated pupils), "mad as a hatter" (delirium), and "full as a flask" (urinary retention), without mentioning tachycardia [33, 34].

ACS includes a wide range of mental states, from excitation to depression, as well as various symptoms, such as myoclonus, rigidity, tremor, respiratory depression, and aphasia [35].

Symptoms caused by acetylcholine deficiency can be divided into peripheral and central, depending on whether the triggering substance can cross the blood-brain barrier. CNS symptoms, which also describe individual severity, are decisive for ACS. The mild variant shows only slight neurological signs like restlessness, irritability, and impaired vision. With increasing severity, hallucinations, confusion, and motor restlessness, including seizures or coma, may develop [4, 11, 24, 27]. Clinical symptoms in ACS are divided into central and peripheral [1].

Central nervous system manifestations: hallucinations, macropsia, and micropsia; clouding of consciousness; psychosis with paranoid delusions; psychomotor agitation with sharp myoclonic or choreoathetotic movements (this rarely leads to rhabdomyolysis); seizures (purely antimuscarinic agents do not cause seizures, but other drugs like tricyclic antidepressants or antihistamines may cause this effect); coma.

The depressive type is characterized by coma, drowsiness, stupor, and respiratory depression.

The hyperactive type is characterized by excitation, delirium, hallucinations, ataxia, convulsions, and myoclonus.

The depressive variant usually results from scopolamine action, while the hyperactive variant — from atropine [1].

The comatose form is characterized by drowsiness, apathy, impaired consciousness, and development of a comatose state with respiratory depression.

The agitation form is accompanied by hallucinations, emotional lability, disorientation, psychomotor agitation, and seizures [1, 13].

Peripheral manifestations: hyperthermia; mydriasis, leading to blurred vision; vasodilation; diffuse erythema; warm dry skin and dry mucous membranes; tachycardia; dynamic intestinal obstruction (pseudo-obstruction); bladder atony, acute urinary retention [1, 13, 18, 24, 27, 36, 37].

The manifestations of cumulative anticholinergic effects on the peripheral nervous system are divided into *low-potential* and *high-potential* anticholinergic activity. The first manifests as dry mouth, blurred vision, dizziness, rarely psychomotor reactions, gastrointestinal disorders, and urinary disturbances. For drugs with high-potential anticholinergic activity, there is a characteristic increase in the strength and frequency of all manifestations of low-potential activity, in addition to dysphagia, confusion, cognitive dysfunction, depression, disorientation, delirium, dizziness, headaches,

drowsiness, arrhythmias, constipation, and increased residual urine volume [3, 30].

Awareness of ACS pathophysiology and identification of modifiable risk factors are of primary interest in the process of diagnosing the toxidrome.

In ACS, symptoms of nervous system damage should first be identified. These include headache, dizziness, logorrhea (speech excitement, verbosity, uncontrollable speech production, and accelerated speech tempo), dysarthria (speech articulation disorder), and disturbances in vocal tone, up to complete aphonia. Optic-vestibular disorders include tremors, disequilibrium, flickering of surrounding objects, and chromatic illusions (color perception disturbances). Cerebellar disturbances manifest as instability in Romberg's test with eyes closed, gait ataxia. Motor hypermetria is observed, and the accuracy of performing heel-to-knee and finger-to-nose tests is impaired. The use of anticholinergic drugs may be a risk factor for delirium. Delirium is very common among elderly patients and is associated with poor outcomes, such as functional and cognitive impairment, and increased mortality [4, 10–12, 16, 23, 38–41].

The severity of CNS disorders is assessed by a rating scale [24]:

— 0 points — relaxed, cooperative;

— 1 point — anxious, irritable, trembling;

— 2 points — periodic or moderate disorientation, confusion, hallucinations, moderate agitation, and motor hyperactivity;

— 3 points — incomprehensible speech, pronounced agitation, and motor hyperactivity (requires restrictions);

— 4 points — seizures, deep coma (lack of response to voice or pain).

There is a pronounced erythema of the face, neck, and chest, and in children, a fine-papular redness that sometimes leads to a misdiagnosis of rubella or measles.

Muscle tone decreases. Tendon and abdominal reflexes are suppressed in mild intoxication, while they increase in severe cases. Pathological reflexes of oral automatism, Babinski, and Oppenheim's signs, myoclonia, and hyperesthesia appear. Proprioceptive sensitivity is unaffected. In severe intoxication, there is behavioral inadequacy, psychomotor agitation, and difficulty or inability to make verbal contact with the patient. There is pronounced blurring of vision, mydriasis, exophthalmos, and widening of the palpebral fissure; accommodation and photoreaction are absent. Seizures of the clonic or tonic-clonic type may occur, possibly accompanied by biting of the tongue. Hallucinations appear, with possible seizure attacks, breathing disorders, and involuntary urination. The most dangerous are toxic sopor and coma. Patients lose the ability to react to stimuli. Pale skin, muscle atony, absence of tendon, conjunctival, and corneal reflexes are observed. A constant symptom of ACS is tachycardia, which occurs even in the absence of CNS disturbances. Tachycardia is caused by the blockade of the inhibitory effect of the vagus nerve and the activation of the sympathetic nervous system. Severe intoxication is accompanied by a direct toxic effect on the myocardium and the heart conduction system. With tachycardia, stroke volume decreases and minute blood volume increases, leading to impaired bioelectrical activity of the heart, decreased T-wave amplitude with shortening of PQ, S-T, and T-R intervals, and atrioventricular dissociation with atrioventricular block. Heart tones are loud, and "gallop rhythm" is auscultated with accentuated second tone over the aorta. Blood pressure is variable, most often with increased diastolic pressure, decreased pulse pressure, and increased mean pressure due to increased vascular tone. Dry rales are present against the background of tachypnea as a result of lung atelectasis, and clinically, "silent zones" appear. It has been reported that undiagnosed ACS led to acute lung injury.

Dry mouth, atony of the gastrointestinal tract is observed, which can lead to functional intestinal obstruction. Abdominal bloating, especially in children, can cause a misdiagnosis of acute surgical diseases of the abdominal organs. Atony of the bladder is accompanied by urinary retention [4, 10–12, 16, 17, 23, 36, 38–42].

Currently, there is no laboratory test to confirm ACS [1]. Clinical blood examination shows an increase in erythrocyte sedimentation rate to 20 mm/h, leukocytosis up to $10–15 \cdot 10^9/mm^3$, and sometimes eosinophilic and neutrophilic leukocytosis and monocytosis. The above-mentioned disturbances vary in severity depending on the degree of intoxication [12].

The diagnosis of the cumulative cholinolytic effect often presents significant difficulties, due to both the polymorphism of manifestations and insufficient awareness of clinicians because of the relative rarity of this pathology [3, 30].

A thorough medical history collection and physical examination are crucial for identifying patients with anticholinergic drug poisoning [5, 9].

ACS should not be ruled out in situations when the patient develops neurological manifestations after taking centrally acting anticholinergic drugs. Diagnosis is based on signs and symptoms that are excluded in other toxidromes or in cases with a reduction in ACS symptoms after using physostigmine. Other syndromes are excluded when symptoms disappear within 15 minutes after the administration of a cholinesterase inhibitor. In some cases, there may be overdiagnosis of toxidrome after prolonged general anesthesia. However, failure to diagnose ACS may lead to unnecessary intubation (reintubation) and prolonged mechanical ventilation in the postoperative period [5, 9, 35].

Delirium is a neuropsychiatric syndrome characterized by a sharp decline and fluctuation of attention, cognitive functions, and consciousness disturbance. Its etiology is considered multifactorial. In addition to neuroinflammation and crossing the blood-brain barrier, it has been proven that the imbalance of neurotransmitters in the form of acetylcholine deficiency and dopamine excess is involved in the pathogenesis of delirium [43].

Anticholinergic delirium manifests with agitation, confusion, and "picking" behavior. Factors contributing to anticholinergic delirium include a preference for muscarinic antagonists (atropine, scopolamine, hyoscine, benztropine, plant alkaloids); muscarinic antagonism with other mixed effects (antihistamines, tricyclic antidepressants, neuroleptics); decreased acetylcholine release (carbamazepine, opiates, cannabinoids, ethanol, clonidine) and reduced acetylcholine synthesis (thiamine deficiency). Fever correlates with the severity of delirium [24].

In ACS, rhabdomyolysis is mostly absent due to the infrequent occurrence of severe muscle tone increase or rigidity, but miosis, tachycardia, and paresis of the intestines and bladder are almost always present [16].

The cumulative effect of taking several drugs with anticholinergic properties, known as anticholinergic load, can negatively affect cognitive and physical functions and increase the risk of mortality [44]. ACS can lead to fatal outcomes due to respiratory failure or brain damage [35].

The issues related to the specifics of anticholinergic toxidrome associated with anesthesiologic support for surgical interventions will be discussed in Part 2 of this literature review.

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Антихолінергічний синдром у періопераційному періоді (огляд). Частина 1

Резюме. Антихолінергічний синдром — це гарячковий токсидром, який характеризується пригніченням холінергічної нейротрансмісії в мускаринових рецепторах. Обов'язковою умовою його виникнення є факт, що фармакологічні засоби мають бути ліпофільними та здатними проходити крізь гематоенцефалічний бар'єр і блокувати мускаринові холінергічні рецептори. До тригерів антихолінергічного токсидрому належать алкалоїди понад 2000 видів рослин та грибів, антипсихотики, антидепресанти, протипаркінсонічні препарати, спазмолітики, очні й антигістамінні препарати, препарати для загальної та локальної анестезії тощо, які часто призначають у комбінаціях, хоча ці лікарські засоби значно відрізняються за антихолінергічною дією в межах класів. Передозування сполуками з антихолінергічною активністю може бути випадковим або навмисним. Сприяючими факторами є похилий вік, захворювання центральної нервової системи, дефіцит вітаміну B_1, генетична схильність та поліпрагмазія. Механізм дії антихолінергічних сполук полягає в антагонізації нейромедіатору ацетилхоліну та його дефіциту в синаптичній щілині мускаринових антихолінергічних рецепторів, що може бути обумовлено різними факторами. Симптоми, спричинені дефіцитом ацетилхоліну, можна розділити на периферичні й центральні залежно від того, здатна тригерна речовина подолати гематоенцефалічний бар'єр чи ні. При антихолінергічному синдромі рабдоміоліз зазвичай відсутній через нечасте сильне підвищення м'язового тонусу або ригідність. Кумулятивний ефект від прийому кількох ліків з антихолінергічними властивостями, який називається антихолінергічним навантаженням, може негативно вплинути на когнітивні й фізичні функції та збільшити ризик смертності.

Ключові слова: антихолінергічний токсидром; етіологія; патогенез; клінічні ознаки