

Emergency Diagnosis and Management of Anticholinergic Poisoning

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Abstract: Current review goal was to address and review the evidence in Roles of emergency department/physicians on management of anticholinergic poisoning whether postsurgical or from different etiology. PubMed/Medline, and Embase electronic biomedical databases; were comprehensively searched published articles in English language with human subject up to August, 2017. It's really reliable for emergency situation medical professionals to demonstrates the significance of early recognition and management of anticholinergic disorder, along with understanding the ideal management of consequences. Management of separated anticholinergic poisoning consists of stabilization of breathing, airway, and also circulation, and analysis of glucose. Intravenous gain access to must be acquired with, cardiac monitoring and also continual pulse oximetry, and extra oxygen as required. Gastric decontamination with activated charcoal (Air Conditioner) ought to be thought about for acute intake, although there is restricted information to advise Air Conditioner therapy initiation because of anticholinergic-associated reduced gastrointestinal mobility. Benzodiazepines can be given for anxiety seizures. Physostigmine is the antidote for anticholinergic poisoning Physostigmine, a carbamate acetylcholinesterase prevention, is a relatively easy to fix tertiary amine efficient in crossing the bloodbrain obstacle that can be utilized as an analysis, along with therapeutic, agent for patients offering with moderate to extreme outer or main anticholinergic toxicity.

Keywords: Emergency Diagnosis, anticholinergic poisoning, Physostigmine.

1. INTRODUCTION

Anticholinergic toxicity is often run into in the emergency situation department, as well as hence it is vital that emergency situation medical professionals know with this toxidrome. According the American Association of Poison Control Centers (AAPCC) Annual Report, there were virtually 14,000 direct exposures to anticholinergic compounds including plants, medications as well as antispasmodics in 2015 (624 plants (5 major, or extreme, direct exposures), 10,345 drugs (21 significant), and also 2879 antispasmodics (13 major)) ⁽¹⁾. Regardless of the lot of recorded cases, only 39 of these anticholinergic direct exposures were associated with significant effects and also there were no deaths. This shows a considerable improvement in outcomes compared to previous information where there were 51 fatalities reported ^(2,3,4,5). Emergency situation doctors need to be able to identity and manage timeless physical and neurologic findings of anticholinergic poisoning, such as high temperature, transformed psychological standing, tachycardia, flushing, and completely dry oral membrane layers. Scopolamine hydrobromide is an anticholinergic medicine typically made use of for the prevention of nausea as well as postoperative nausea or vomiting and throwing up (PONV) ⁽⁶⁾. Greater than 600 unique pharmacologic as well as organic substances can trigger anticholinergic effects through their capability to competitively inhibit the binding of acetylcholine to muscarinic acetylcholine receptors ⁽⁷⁾. Common prescription drug categories with high anticholinergic buildings include antihistamines (i.e., diphenhydramine), tricyclic antidepressants ([TCAs] i.e., amitriptyline), sleep helps (i.e., doxylamine), antiemetics (scopolamine), and also cardiac dysrhythmogenic medicines (i.e., atropine). Plants such as jimson weed (*Datura stramonium*) and nightshade (*Atropa belladonna*) likewise have substantial concentrations of belladonna alkaloids, which include both atropine as well as scopolamine and also could create severe anticholinergic poisoning ⁽⁸⁾.

The anticholinergic disorder is a well-documented negative effects of transdermal scopolamine ⁽⁹⁾. There is a situation record defining an intensive care unit (ICU) patient that experienced neurological damage and also bilateral mydriasis 6 hrs after application of a patch consisting of 1 mg of scopolamine to lower bronchial secretions ⁽¹⁰⁾. Signs dealt with after elimination of the patch. Kranke et al. ⁽¹¹⁾ executed a systematic review of randomized controlled trails published between 1984 and also 1996 to examine the efficacy and also security of transdermal scopolamine when utilized for the prevention of postoperative nausea and also vomiting. Based on information from 23 such trials, the writers estimate the occurrence of side-effects to be as complies with: visual disturbances, 18%; completely dry mouth, 8%; wooziness, 2%; as well as anxiety, 1% ⁽¹¹⁾.

Current review goal was to address and review the evidence in Roles of emergency department/physicians on management of anticholinergic poisoning whether postsurgical or from different etiology.

2. METHODOLOGY

PubMed/Medline, and Embase electronic biomedical databases; were comprehensively searched published articles in English language with human subject up to August, 2017. We searched evidence concerning the management of anticholinergic toxicity in emergency department, using following MeSH terms; (anticholinergic poisoning, anticholinergic toxicity, emergency management, emergency department, emergency physicians). Furthermore, references list of the found studies were searched for more relevant articles.

3. DISCUSSION

- **Anticholinergic toxins agents and mechanism of action:**

The use of anticholinergics has a long history that predates medical scientific research. This consists of routine, recreational and restorative use plants including scopolamine, hyoscyamine and also atropine ⁽¹²⁾. Atropa belladonna's name reflected its usage by Italian renaissance females as an appeal help to cause their eyes to expand and sparkle and their cheeks to gain color.

Common anticholinergic agents need to be extra accurately referred to as an antimuscarinics, as these agents do not usually obstruct nicotinic receptors. They are typically responsible for 15 - 20% of severe poisoning admissions ^(13,14), as much as 40% of poisoning admission to critical care unit and 16% of toxin center phone calls ^(15,16,17). 'Anticholinergic' representatives vary and can be considered extensively as being within three classifications (**Table 1**) ⁽¹⁸⁾.

Table 1: Mechanisms contributing to anticholinergic delirium Adapted from ⁽¹⁸⁾

Mechanism	Examples
Predominant muscarinic antagonists	Atropine, scopolamine, hyoscine, benztropine Includes many plants
Muscarinic antagonists with other mixed effects	Antihistamines, tricyclic antidepressants, antipsychotics
Decrease ACh release	Carbamazepine, opiates, cannabinoids, ethanol, clonidine
Decrease ACh synthesis	Thiamine deficiency

Everything may lead to the development of an anticholinergic toxidrome that may have both central as well as peripheral nerves components. Cholinergic deficiency is identified as a most likely adding function to all sources of ecstasy ⁽¹⁸⁾. Antimuscarinic representatives are used to produce pet versions of mental deterioration and delirium. This consequently has actually cultivated considerable study into the pharmacokinetics as well as pharmacodynamics of physostigmine as well as various other therapeutic oral and also transdermal cholinesterase preventions ^(19,20,21).

The timeless anticholinergic medical disorder is an indication of competitive enmity of acetylcholine at outer and also central muscarinic receptors. There go to least five muscarinic subtypes, with distinctive however overlapping tissue distributions ⁽²²⁾. M1 receptors are located primarily in the central nervous system and are associated with understanding, attention and also cognitive performance. Ecstasy is just related to the incongruity of post-synaptic M1 receptors and to date other receptor subtypes have not been implicated ⁽²³⁾. Outer muscarinic receptors become part of the autonomic nervous system and innervated by postganglionic cholinergic nerves. M2 receptors lie in the brain as well as heart, M3 receptors remain in salivary glands and also M4 receptors remain in the mind and lungs ⁽²²⁾.

There is significant diversification in the medical expression of the 'anticholinergic toxidrome'. The major private patient factor/modifier is reduced standard cholinergic function associated with boosting age or main nerves (CNS) illness. The peripheral syndrome consists of completely dry mouth, difficulty in swallowing, blurred vision and photophobia (due to dilated pupils that just weakly tighten with light). Other medicine actions (i.e. from medications with several actions or from co-ingested representatives) lead to reduced student dimension however pupillary reactions will normally still be slow-moving. The skin, consisting of axilla as well as groin, might be dry. Digestive tract audios may be lacking and patients may even present with a paralytic ileus (pseudo-obstruction). Decreased stomach mobility might result in long term absorption, postponed heights and prolonged effects^(24,25). Urinary retention is common and will aggravate the delirium. Sinus tachycardia prevails. High blood pressure could be either low secondary to peripheral vasodilation or elevated as a result of agitation. Fever correlates with seriousness of delirium. It is unclear if this results from high temperature exacerbating delirium or simply that it is an action of anticholinergic effects. Mechanisms for high temperature include lowered warm loss (because of lacking sweating), enhanced warmth manufacturing (because of frustration and also task) and CNS dopamine mediated temperature dysregulation^(26,27).

- **Scopolamine as most common agent causing postoperative anticholinergic toxicity:**

Scopolamine hydrobromide (also called hyoscine hydrobromide) is an antimuscarinic medication which has actually been utilized for the therapy of nausea in a transdermal application, as an anesthetic premedication inducing sedation as well as decrease of secretions in the bronchi and also the oropharynx⁽²⁸⁾. It is the solitary most efficient agent to prevent motion sickness⁽²⁹⁾. Doses differ in accordance with the indicator with a maximum oral everyday dose of 1.2 mg⁽²⁸⁾. Being a tertiary amine, scopolamine hydrobromide is easily soaked up after oral consumption as well as permeates the blood-brain obstacle by passive diffusion. It is necessary to note that scopolamine hydrobromide and scopolamine butylbromide are different in lots of aspects. Both are available as nonprescription items in Australia. Scopolamine butylbromide is a quaternary amine substance that is inadequately absorbed (2% - 10% of an oral dosage) as well as cannot readily pass through the blood-- brain barrier, consequently CNS effects are rare. The maximum daily oral dose is 80 mg each day⁽²⁸⁾.

The pharmacokinetic criteria of scopolamine hydrobromide depend on the dose kind⁽³⁰⁾. It has restricted bioavailability when orally administered with an absolute bioavailability reported to vary in between 3% as well as 27%; a very first pass metabolic rate is believed to occur. Maximum plasma levels have actually happened 23.5 ± 8.2 mins complying with oral management. After eye management, scopolamine hydrobromide is swiftly, successfully as well as systemically taken in. Complying with transdermal application in one research, delivery of scopolamine led to a pattern of systemic availability which was comparable with an intravenous infusion, which recommends a high bioavailability. Scopolamine has actually been used in medical method for several years, data concerning its metabolic rate and also kidney excretion are limited. It appears that glucuronide conjugation is the pertinent path⁽³⁰⁾.

Scopolamine provided in pharmacologically reliable doses, unlike atropine as well as other antimuscarinic representatives, creates CNS depressive results such as sleepiness, amnesia, exhaustion and also dreamless sleep^(30,31). High doses can bring about CNS stimulation (eg, enjoyment, restlessness, irritability, hallucinations, and also ecstasy) which is similar to the result observed with harmful doses of other muscarinic representatives. As a matter of fact, symptoms observed in patients complying with scopolamine intoxication recommend a dose-dependent CNS result⁽³²⁾. Possibly worrying, distinctive reactions might happen with therapeutic dosages of scopolamine hydrobromide^(33,34). The most serious distinctive response is acute psychosis with this referred to as complication, frustration, rambling speech, hallucinations, paranoid behavior, as well as delusions. Other indications could include somnolence, expanded pupils, increased pulse rate, as well as dry skin of the mouth with a husky quality of the voice⁽³⁴⁾.

- **Management anticholinergic toxicity in ED:**

Use of Physostigmine as anticholinergic toxicity, Effectivity & safety:

Management of isolated anticholinergic poisoning includes stabilizing of airway, breathing, and flow, as well as analysis of glucose. Intravenous gain access to ought to be gotten with, cardiac tracking as well as continual pulse oximetry, and also supplemental oxygen as required. Gastric decontamination with turned on charcoal must be thought about for severe ingestion, although there are minimal data to suggest A/C therapy initiation due to anticholinergic-associated decreased stomach mobility. Benzodiazepines can be provided for frustration seizures. Physostigmine is the antidote for anticholinergic toxicity. Physostigmine, a carbamate acetylcholinesterase inhibitor, is a relatively easy to fix tertiary amine with the ability of going across the bloodbrain barrier that can be used as an analysis, as well as therapeutic, agent for patients offering with modest to severe peripheral or central anticholinergic poisoning not managed by helpful care or benzodiazepines^(16,35).

Physostigmine was introduced adhering to monitorings of the test by ordeal conducted by the Efik people in West Africa. The suspicious ingested the physostigmine-containing Calabar bean (*Physostigma venenosum*) leading to a cholinergic dilemma. They were declared innocent if they survived⁽³⁶⁾. The plant was imported to Europe and also physostigmine was isolated in 1864. It was ultimately kept in mind to annoy the results of atropine as well as curare. The earliest use physostigmine to reverse anticholinergic ecstasy remained in 1864 by Kleinwachter that treated detainees that had actually incorrectly consumed atropine⁽³⁷⁾.

Acetylcholinesterase (AChE) inhibitors such as physostigmine reduce the failure of synaptic acetylcholine. Raised concentrations of synaptic acetylcholine complete for binding with the muscarinic villain but additionally promote unblocked nicotinic receptors. Additionally, some cholinesterase preventions such as physostigmine are straight nicotinic receptor agonists at the exact same focus that create cholinesterase inhibition however independent of AChE inhibition^(38,39). Excitement of hippocampal nicotinic receptors is both directly proconvulsant and also assists in the generalization of seizures from various other contaminants⁽⁴⁰⁾.

Restraint of erythrocyte cholinesterase is highly associated with brain AChE restraint in human beings and mice and therefore is often used to quantify anticholinesterase task. There is a straight relationship between physostigmine dose and cholinesterase restraint up until a ceiling impact of optimum inhibition is gotten to^(41,42). This ceiling effect has actually been shown for mind AChE, erythrocyte AChE as well as plasma AChE⁽³⁹⁾.

Since that time doctors have actually revealed a reticence to use physostigmine, though current records again insist its security for anticholinergic toxicity. In 2000, Burns et al.⁽³⁵⁾ published a retrospective research of 52 patients who had actually been described a toxicologist as well as had received either physostigmine, benzodiazepines, or both for a central anticholinergic toxidrome. They discovered that those that obtained physostigmine initially had less problems (7 vs. 47 %) and had their ecstasy reversed more frequently (87 % vs. ineffective) when contrasted with those who received benzodiazepines. In addition, from a functional and expense analysis perspective, no patients in the physostigmine team obtained a head CT, which was particularly associated with clearing up of delirium after the use of physostigmine in a number of patients. Data from Beaver et al. in 2000⁽⁴³⁾, once again demonstrated the family member safety of physostigmine throughout a breakout of anticholinergic toxicity from scopolamine-adulterated heroin along the East Coast. In both of these research studies, ECGs were used to assess for transmission delays that served as an exclusion (QRS period > 100 ms, PR interval > 200 ms) to administration of physostigmine. Further, a testimonial of physostigmine use by a big toxicology solution showed few negative events as well as no cardiac issues over 7 years of information⁽⁴⁴⁾.

4. CONLCUION

It's really reliable for emergency situation medical professionals to demonstrates the significance of early recognition and management of anticholinergic disorder, along with understanding the ideal management of consequences. Management of separated anticholinergic poisoning consists of stabilization of breathing, airway, and also circulation, and analysis of glucose. Intravenous gain access to must be acquired with, cardiac monitoring and also continual pulse oximetry, and extra oxygen as required. Gastric decontamination with activated charcoal (AC) ought to be thought about for acute intake, although there are restricted information to advise AC therapy initiation because of anticholinergic-associated reduced gastrointestinal mobility. Benzodiazepines can be given for anxiety seizures. Physostigmine is the antidote for anticholinergic poisoning Physostigmine, a carbamate acetylcholinesterase prevention, is a relatively easy to fix tertiary amine efficient in crossing the bloodbrain obstacle that can be utilized as an analysis, along with therapeutic, agent for patients offering with moderate to extreme outer or main anticholinergic toxicity.

REFERENCES

- [1] Mowry JB, Spyker DA, Brooks DE, et al. 2015 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 33rd Annual Report. Clin Toxicol (Phila) 2016; 54:924.
- [2] Litovitz TL, Klein-Schwartz W, Dyer KS, et al. 1997 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 1998; 16:443.
- [3] Watson WA, Litovitz TL, Rodgers GC Jr, et al. 2004 Annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2005; 23:589.
- [4] Watson WA, Litovitz TL, Klein-Schwartz W, et al. 2003 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. Am J Emerg Med 2004; 22:335.

- [5] Watson WA, Litovitz TL, Rodgers GC Jr, et al. 2002 annual report of the American Association of Poison Control Centers Toxic Exposure Surveillance System. *Am J Emerg Med* 2003; 21:353.
- [6] Renner UD, Oertel R, Kirch W. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. *Ther Drug Monit* 2005;27: 655–65.
- [7] Dura'n CE, Azermai M, Vander Stichele RH. Systematic review of anticholinergic risk scales in older adults. *Eur J Clin Pharmacol* 2013;69:1485–96.
- [8] Shervette RE 3rd, Schydlower M, Lampe RM, Fearnow RG. Jimson “loco” weed abuse in adolescents. *Pediatrics* 1979;63: 520–3
- [9] Chan YC, Tse ML, Lau FL. Two cases of anticholinergic poisoning from transdermal scopolamine patch. *Hong Kong Journal of Emergency Medicine*. 2006;13(4):221–224.
- [10] Repéssé X, Geeraerts T, Pottecher J, Vigué B, Benhamou D, Duranteau J. Coma with bilateral mydriasis after use of transdermal scopolamine in ICU. *Ann Fr Anesth Reanim*. 2007;26:1070–1072.
- [11] Kranke P, Morin AM, Roewer N, Wulf H, Eberhart LH. The efficacy and safety of transdermal scopolamine for the prevention of postoperative nausea and vomiting: a quantitative systematic review. *Anesth Analg*. 2002;95:133–143.
- [12] López-Muñoz F, Alamo C, García-García P. Psychotropic drugs in the cervantine texts. *J R Soc Med* 2008; 101: 226–34.
- [13] Buckley NA, Whyte IM, Dawson AH, Isbister GK. A prospective cohort study of trends in self-poisoning, Newcastle, Australia, 1987–2012: plus ça change, plus c'Est la même chose. *Med J Aust* 2015; 202: 438–42.
- [14] Hiles S, Bergen H, Hawton K, Lewin T, Whyte I, Carter G. General hospital-treated self-poisoning in England and Australia: comparison of presentation rates, clinical characteristics and aftercare based on sentinel unit data. *J Psychosom Res* 2015; 78: 356–62.
- [15] McMahon A, Brohan J, Donnelly M, Fitzpatrick GJ. Characteristics of patients admitted to the intensive care unit following self-poisoning and their impact on resource utilisation. *Ir J Med Sci* 2013; 183: 391–5.
- [16] Clark D, Murray DB, Ray D. Epidemiology and outcomes of patients admitted to critical care after self-poisoning. *J Intensive Care Soc* 2011; 12: 268–73.
- [17] Bronstein AC, Spyker DA, Cantilena LR, Rumack BH, Dart RC. 2011 annual report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 29th annual report. *Clin Toxicol* 2012; 50: 911–1164.
- [18] Hshieh TT, Fong TG, Marcantonio ER, Inouye SK. Cholinergic deficiency hypothesis in delirium: a synthesis of current evidence. *J Gerontol A Biol Sci Med Sci* 2008; 63: 764–72.
- [19] Bartus R, Dean R, Beer B, Lippa A. The cholinergic hypothesis of geriatric memory dysfunction. *Science* 1982; 217: 408–14.
- [20] Nordberg A, Svensson AL. Cholinesterase inhibitors in the treatment of Alzheimer's disease: a comparison of tolerability and pharmacology. *Drug Saf* 1998; 19: 465–80.
- [21] Darvesh S, Walsh R, Kumar R, Caines A, Roberts S, Magee D, Rockwood K, Martin E. Inhibition of human cholinesterases by drugs used to treat Alzheimer disease. *Alzheimer Dis Assoc Disord* 2003; 17: 117–26.
- [22] Brann MR, Jørgensen HB, Burstein ES, Spalding TA, Ellis J, Jons SVP, Hill-Eubanks D. Studies of the pharmacology, localization, and structure of muscarinic acetylcholine receptors. *Ann N Y Acad Sci* 1993; 707: 225–36.
- [23] Pratico C, Quattrone D, Lucanto T, Amato A, Penna O, Roscitano C, Fodale V. Drugs of anesthesia acting on central cholinergic system may cause post-operative cognitive dysfunction and delirium. *Med Hypotheses* 2005; 65: 972–82.
- [24] Green R, Sitar DS, Tenenbein M. Effect of anticholinergic Drugs on the efficacy of activated charcoal. *J Toxicol Clin Toxicol* 2004; 42: 267–72.

- [25] Livshits Z, Sampson BA, Howland MA, Hoffman RS, Nelson LS. Retained drugs in the gastrointestinal tracts of deceased victims of oral drug overdose. *Clin Toxicol (Phila)* 2015; 53: 113–8.
- [26] Balthazar CH, Leite LH, Ribeiro RM, Soares DD, Coimbra CC. Effects of blockade of central dopamine D 1 and D 2 receptors on thermoregulation, metabolic rate and running performance. *Pharmacol Rep* 2010; 62: 54–61.
- [27] Schwartz PJ, Erk SD. Regulation of central dopamine-2 receptor sensitivity by a proportional control thermostat in humans. *Psychiatry Res* 2004; 127: 19–26.
- [28] Van Sassenbroeck D, Hemelsoet D, Vanwalleghem P, et al. Three cases of substitution errors leading to hyoscine hydrobromide overdose. *Clin Toxicol (Phila)* 2005;43:861–865.
- [29] Spinks AB, Wasiak J, Villaneuva EV, Bernath V. Scopolamine (hyoscine) for preventing and treating motion sickness. *Cochrane Database Syst Rev*. 2007;3:CD002851.
- [30] Renner UD, Oertel R, Kirch W. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. *Ther Drug Monit*. 2005;27(5):655–665.
- [31] Clissold SP, Heel RC. Transdermal hyoscine (Scopolamine). A preliminary review of its pharmacodynamic properties and therapeutic efficacy. *Drugs*. 1985;29:189–207.
- [32] Lauwers LF, Daelemans R, Baute L, Verbraeken H. Scopolamine intoxications. *Intens Care Med*. 1983;9:283–285.
- [33] Scopolamine. *Drug Facts and Comparisons: Pocket Version* [online] Saint Louis: Wolters Kluwer Health; 2008. Cited 2008 October 20. Available from Wolters Kluwer Health, Inc.
- [34] McEvoy GK, editor. AHFS drug information. Scopolamine. Bethesda, MD: American Society of Health-System Pharmacists; 2005. 2005. pp. 1254–1257.
- [35] Burns MJ, Linden CH, Graudins A, et al. A comparison of physostigmine and benzodiazepines for the treatment of anticholinergic poisoning. *Ann Emerg Med* 2000;35:374–81.
- [36] Rygnestad T. Development of physostigmine from a poisonous plant to an antidote. One of the most important drugs in the development of modern medicine? *Tidsskr Nor Laegeforen* 1992; 112: 1300–3.
- [37] Nickalls RWD, Nickalls EA. The first use of physostigmine in the treatment of atropine poisoning. *Anaesthesia* 1988; 43: 776–7.
- [38] Aracava Y, Deshpande SS, Rickett DL, Brossi A, Schönenberger B, Albuquerque EX. The molecular basis of anticholinesterase actions on nicotinic and glutamatergic synapses. *Ann N Y Acad Sci* 1987; 505: 226–55.
- [39] Triggle DJ, Filler R. The pharmacology of physostigmine. *CNS Drug Rev* 1998; 4: 87–136.
- [40] Trivisano M, Terracciano A, Milano T, Cappelletti S, Pietrafusa N, Bertini ES, Vigevano F, Specchio N. Mutation of CHRNA2 in a family with benign familial infantile seizures: potential role of nicotinic acetylcholine receptor in various phenotypes of epilepsy. *Epilepsia* 2015; 56: e53–7.
- [41] Thomsen T, Kaden B, Fischer JP, Bickel U, Barz H, Gusztony G, Cervos-Navarro J, Kewitz H. Inhibition of acetylcholinesterase activity in human brain tissue and erythrocytes by galanthamine, physostigmine and tacrine. *Eur J Clin Chem Clin Biochem* 1991; 29: 487–92.
- [42] Sherman KA, Messamore E. Blood cholinesterase inhibition as a guide to the efficacy of putative therapies for Alzheimer's dementia: comparison of tacrine and physostigmine In: *Current Research in Alzheimer Therapy*. New York: Taylor & Francis, 1988; 73–86.
- [43] Beaver KM, Gavin TJ. Treatment of acute anticholinergic poisoning with physostigmine. *Am J Emerg Med*. 1998;16(5):505–507. doi: 10.1016/S0735-6757(98)90003-1.
- [44] Rasimas JJ, Sachdeva K, Salama AM, Helmick TJ, Donovan JW. A review of bedside toxicologic experience with physostigmine and flumazenil. *Clin Toxicol*. 2010;48(6):648. doi: 10.3109/15563650.2010.505198.