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Modern possibilities of drug therapy for patients with botulism

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ABSTRACT

Botulism is not a commonly encountered infectious disease; however, its severity, the potential use of botulinum toxin as a biological weapon, and the lack of truly effective methods and approaches for treating patients with this pathology prevent it from being regarded as a secondary concern.

Therapeutic measures for botulism, both currently applied in clinical practice and those under development, can be divided into three complementary but unequal groups in terms of volume, complexity of implementation, and effectiveness. The first group of measures aims to neutralize free botulinum neurotoxin in the patient's body—whether in the blood, stomach, or intestines—by any available means. The objective is to prevent further toxin entry into nerve cells and, consequently, the progression of clinical signs of specific intoxication. This objective is primarily achieved through the intravenous (for rapid effect) administration of specific antitoxins—in Russia, this role is assigned to botulinum antitoxin serum. The use of immunoglobulins remains limited, and monoclonal antibodies are still under investigation.

The second group of measures, predominantly in the development phase with varying degrees of maturity, can be characterized as attempts to create drugs for intraneuronal (antidote) therapy aimed at disrupting the sequential intracellular actions of botulinum neurotoxin—from its internalization into the axonal cytoplasm via the endosomal pathway to the damage of the SNARE protein complex. These include guanidine hydrochloride, 4-aminopyridine (4-AP), 3,4-diaminopyridine (3,4-DAP), tousendanin, and other substances. However, these drugs have not progressed beyond laboratory research and isolated clinical cases with inconclusive results. The third group of therapeutic measures focuses on addressing pathological processes and effects already induced by botulinum neurotoxin at the systemic level. Without underestimating the importance of the continually evolving technology of intravenous infusion therapy for various intoxications, it should be noted that these methods primarily address the consequences rather than the cause. In this regard, some authors consider the possibility of intensive correction of homeostatic disorders through the administration of specialized fluids into the gastrointestinal tract as an addition to or alternative for standard therapy—enteral correction.

The use of enteral correction not only detoxifies the gastrointestinal tract but also restores water-electrolyte balance, acid-base homeostasis, hemorheology, microcirculation, pro- and antioxidant balance, intestinal microbiota, and gastrointestinal motility. The elimination of both the intoxication itself and, more importantly, its underlying cause, promotes the activation of reparative processes, including the restoration of neuromuscular transmission through the synthesis of new SNARE proteins.

Keywords: botulism; antibotulinic serum; immunoglobulins; monoclonal antibodies; guanidine; aminopyridines; enteral correction.

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Современные возможности медикаментозной терапии больных ботулизмом

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АННОТАЦИЯ

Ботулизм не относится к часто встречающимся инфекционным болезням, однако тяжесть течения, возможность использования ботулинического токсина в качестве биологического оружия, отсутствие по-настоящему эффективных способов и методов лечения больных данной патологией не позволяют относить проблему к разряду второстепенных. Терапевтические мероприятия при ботулизме, как используемые на практике, так и находящиеся в стадии разработки, можно условно разделить на три взаимодополняющие, но неравнозначные по объёму сложности проведения и эффективности группы. Первая группа мероприятий имеет своей целью любыми путями и методами осуществить нейтрализацию свободного ботулинического нейротоксина в организме пациента (в крови, желудке, кишечнике) и таким образом прекратить дальнейшее поступление ботулинического нейротоксина в нервные клетки и, как следствие, нарастание клинических признаков специфической интоксикации. Этой цели, в первую очередь, служит внутривенное (для быстроты воздействия) введение специфических антитоксинов — в РФ эта функция возложена на противоботулиническую сыворотку. Иммуноглобулины имеют чрезвычайно узкое применение, возможности моноклональных антител изучаются.

Второй блок мероприятий, находящихся в основной своей массе в стадии разработок «разной степени зрелости», можно условно охарактеризовать как попытки создания препаратов для интранейрональной (антидотной) терапии, направленной на разрыв последовательной цепи внутриклеточных действий ботулинического нейротоксина от интернализации в цитоплазму аксона по эндосомальному пути до повреждения комплекса белков SNARE. К ним относятся гидрохлорид гуанидина, 4-аминопиридин (4-AP) и 3,4 диаминопиридин (3,4-DAP) тусенданин и другие вещества. Однако за рамки лабораторного изучения и единичных случаев клинического применения с сомнительными результатами эти препараты не вышли. Третий блок терапевтических мероприятий направлен на устранение уже вызванных ботулиническим нейротоксином патологических процессов и явлений на организменном уровне. Не умаляя значимости постоянно совершенствующейся технологии внутривенной инфузионной терапии при различного рода интоксикациях, следует отметить, что данные методы и методики в случае ботулизма призваны бороться со следствием, но не с причиной. В этой связи ряд авторов в качестве её дополнения или альтернативы рассматривают возможность интенсивной коррекции нарушений гомеостаза с помощью введения специальных жидкостей в желудочно-кишечный тракт — энтеральной коррекции.

Кроме детоксикации путём очищения желудочно-кишечного тракта, при использовании энтеральной коррекции наблюдается улучшение водно-электролитного баланса, кислотно-основного состояния, гемореологии, микроциркуляции, про- и антиоксидантного равновесия, микробиоценоза кишечника и моторной функции желудочно-кишечного тракта. Устранение как самой интоксикации, так и, что более важно, её причины способствует оживлению репарационных процессов, в том числе восстановлению нервно-мышечной передачи за счёт синтеза новых белков комплекса SNARE.

Ключевые слова: ботулизм; противоботулиническая сыворотка; иммуноглобулины; моноклональные антитела; гуанидин; аминопиридины; энтеральная коррекция.

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INTRODUCTION

Botulism remains a serious public health concern, despite the impressive success in the treatment of this condition: at the beginning of the 20th century, the case fatality rate of botulism reached 70% [1], whereas since the 1940s–1950s, it has been steadily declining and currently stands at less than 5% globally, with a continued downward trend directly correlated with the development of modern intensive care methods [1–3].

The current treatment paradigm for patients, even in cases of suspected botulism—including antitoxin infusion and prolonged intensive supportive care with mechanical ventilation—is highly resource-demanding and poorly suited to mass casualty scenarios, as seen in Moscow in June–July 2024. Moreover, the limited capacity of antitoxins to prevent or, more importantly, reverse acute respiratory failure (ARF) further complicates therapeutic strategies, particularly given the small number of healthcare facilities capable of providing high-tech intensive care [4]. However, even if a 100% effective intraneuronal (antidote) treatment were developed, the resolution of neuromuscular paralysis would still be delayed until SNARE proteins are regenerated. In severe cases of botulism accompanied by ARF, this process would inevitably require prolonged respiratory support [5, 6]. In other words, even in theory, no medication can instantly restore botulinum neurotoxin (BoNT)-associated neuromuscular transmission blockade or immediately reverse the clinical manifestations of botulism once they have occurred.

Therapeutic measures for botulism, both those currently employed in clinical practice and those still under development, can be conventionally divided into three complementary yet unequal groups in terms of implementation complexity, scope, and effectiveness.

The first group of measures aims to neutralize free BoNT in the patient's body (in the bloodstream, stomach, or intestines) by any possible means. This approach seeks to halt further entry of BoNT into nerve cells and, consequently, prevent the progression of the clinical signs of specific intoxication.

The second group, most of which is still in the development stage with varying degrees of maturity, can be described as intraneuronal (antidote) therapy aimed at disrupting the sequential intracellular actions of BoNT, from its internalization into the axonal cytoplasm via the endosomal pathway to the cleavage of SNARE complex proteins (see below), ultimately leading to impaired acetylcholine release into the synaptic cleft.

The third group of therapeutic measures is aimed at addressing pathological processes and systemic effects already induced by BoNT (e.g., mechanical ventilation and related interventions) [2].

ANTITOXIC THERAPY

Toxin neutralization can be achieved through both physical and immunological methods, although the potential of either approach is significantly limited. For instance, 5% sodium bicarbonate ($NaHCO_3$) solution is used to chemically degrade BoNT within the gastrointestinal tract lumen (and nowhere beyond), administered either via gastric lavage or cleansing enemas [7]. Understandably, the effectiveness of this method is very low. During the toxin's migration from the intestinal lumen to the target cell, it can (and should) be neutralized by appropriate antitoxic antibodies [2].

The necessity of using specific antitoxic agents in the treatment of patients with botulism became evident following the discovery of the botulism pathogen by Emile van Ermengem in 1897 and the subsequent recognition of the key role of toxemia in the disease pathogenesis [8]. In Russia, the first successful attempts to produce botulinum antitoxin serum (BAS) were made by Konstantsov between 1904 and 1916, and in 1929, Velikanov developed a BAS that matched the quality of its foreign counterparts. In the USSR, BAS produced via horse immunization with anatoxin as per the method proposed by Weinberg and Goy in 1925–1926 entered industrial-scale production as early as 1933.

Currently, the only widely and routinely used specific antitoxic agent worldwide is equine botulinum antitoxin, which in Russia is produced under the name botulinum antitoxin serum [9].

Since 1965, the USSR had been producing an equine BAS for types A, B and E, which was intended for multiple intramuscular administrations. In 1988, a new BAS preparation derived not only from horses but also from cattle was introduced. The spectrum of antitoxins was expanded to include types A, B, C, E, and F, and the administration protocol was revised to a single intravenous dose only. Cattle-derived serum was considered an alternative in cases of intolerance to equine BAS. However, on February 17, 2000, a regulatory document titled "Instructions for the Use of Botulinum Antitoxin Serums…" was approved—and remains in force with no major revisions to date—narrowing the spectrum back to three types (A, B, and E), and the serum obtained through hyperimmunization of cattle is no longer included (and is no longer produced) [2].

As for Western practices, on March 22, 2013, the U.S. Food and Drug Administration (FDA) approved a heptavalent botulinum antitoxin (HBAT) for clinical use, targeting all known BoNT serotypes (A, B, C, D, E, F, and G). HBAT is derived from equine IgG antibodies that have been despeciated by enzymatic removal of the Fc portion, preserving the $F(ab')_2$ fragment (HBAT, Cangene Corporation) [4, 10–12].

In Europe, American-manufactured HBAT is primarily used, alongside the equine trivalent (A, B, and E) antitoxin serum produced by Behring (FRG) [13].

This situation is somewhat questionable: the trivalent BAS clearly lacks a fourth component—antitoxin against BoNT type F—despite documented cases of type F botulism in humans (with confirmed BoNT-F toxemia at the time of hospitalization), often with an unfavorable outcome [14]. Meanwhile, no reports of human disease caused by BoNT

types D or G were found in the available scientific sources, raising reasonable doubts about the necessity of including antitoxins against these two types in the American HBAT formulation.

At the end of the 20th century, an attempt was made (notably in the USSR) to replace equine BAS with donor-derived botulinum immune globulin, aiming not necessarily to increase the effectiveness of specific antitoxic therapy, but at least to reduce the frequency of allergic reactions to foreign (equine) proteins. In the mid-1980s, a homologous (donor-derived) botulinum immune globulin (HBIG) was developed under the supervision of Albitskaya at the bacterial product manufacturing facility of the Tomsk Research Institute of Vaccines and Sera. HBIG represented an immunologically active protein fraction obtained from donor serum or plasma (by ethanol fractionation at low temperatures), collected from individuals previously immunized according to a scheduled protocol: three doses of a sorbed chemical typhoid vaccine combined with a sorbed, purified hexa-anatoxin, followed by a single booster dose of a trivalent botulinum anatoxin (types A, B, and E) [15]. The preparation demonstrated high efficacy comparable to that of equine BAS, with virtually no allergic reactions. However, its production technology permitted intramuscular administration only. Work was initiated to develop an intravenous formulation of HBIG [2], but these efforts were halted by the dissolution of the USSR. Meanwhile, in the United States, similar developments continued.

On October 23, 2003, the FDA licensed a donor-derived botulinum immune globulin for intravenous administration under the name BabyBIG (botulinum immune globulin for infants) for the treatment of infant botulism caused by types A and B [16, 17]. The product is derived from plasma donated by individuals immunized with a pentavalent botulinum toxoid. For the treatment of infant botulism, intravenous infusion of BabyBIG is recommended at a dose of 1 mL/kg (50 mg/kg) [18, 19]. BabyBIG is available in the United States through the Infant Botulism Treatment and Prevention Program (IBTPP). It is administered once via slow intravenous infusion. The risk of anaphylactic shock is extremely low, and the use of the product significantly reduces hospital stay (by almost 50%). However, the cost of BabyBIG is extremely high, approaching $50,000 per dose [20]. As of now, the production scheme of this preparation is undergoing revision [13, 21]. In addition to all the above, the manufacturing of immune sera and immunoglobulins involves complex and labor-intensive production processes [22], requiring rigorous quality assurance and biosafety control.

At the same time, it is clear that, in the long term, the optimal approach would be the development of monoclonal antibodies, as has been achieved in the treatment of patients with COVID-19. Initial attempts to develop such agents for botulism—including monomeric equine immunoglobulin and monoclonal (homologous) human antibodies—date back to the 1980s [23, 24]. However, due to the difficulties associated with their production and, consequently, the extremely high cost, these alternative specific antitoxic agents did not progress beyond clinical trials at that time. Nevertheless, time has brought changes: a substantial number of successful laboratory studies on monoclonal antibodies targeting various subtypes of BoNT have been reported—from the classical types (A, B, and C) [25–29] to type H [30], the independent classification of which remains disputed [31]. The potential use (still at the experimental stage) of a combination of monoclonal antibodies (against BoNT types A and B) even for inhalational botulism [32] is being considered, with explicit regard to the possibility of its use as a biological weapon.

Several monoclonal antibody-based formulations are already under review by the U.S. FDA [23].

Russia is also advancing in this field. On June 26, 2024, the Ministry of Health of the Russian Federation granted approval for clinical trials of a new botulinum toxin type A neutralizing agent developed by the N.F. Gamaleya National Research Center for Epidemiology and Microbiology, based on monoclonal antibodies [33]. Nonetheless, monoclonal antibodies against BoNT have not yet been adopted into routine clinical practice in any country [18].

On the other hand, the potential of serotherapy (immunotherapy, monoclonal antibodies) is far from unlimited and is constrained by the limited window during which antitoxic antibodies can bind the toxin while it remains in the bloodstream [2].

Overall, the following can be concluded.

1. Specific antitoxic therapy had already reached the limits of improving its direct therapeutic efficacy by the mid-20th century. Subsequent research in this field has been primarily focused on reducing the frequency and severity of adverse (undesirable) effects. Nonetheless, survival and recovery still require prolonged use of intensive care resources, which can be substantially reduced through the administration of antitoxins (e.g., BAS, heptavalent botulism antitoxin). A systematic review and meta-analysis of data from 1923 to 2016 demonstrated that antitoxin administration significantly reduced mortality [odds ratio (OR) 0.22; 95% confidence interval (CI): 0.17–0.29], with the greatest effect observed in type E botulism (OR 0.13; 95% CI: 0.06–0.30), followed by type A (OR 0.57; 95% CI: 0.39–0.84). The reduction in mortality for type B botulism was not statistically significant (OR 0.74; 95% CI: 0.27–1.97), possibly due to the generally milder course associated with this toxin type. These findings were based on patients who received trivalent antitoxin targeting types A, B, and E, which, when administered to treat type A, B, or E botulism, significantly reduced overall mortality (OR 0.13; 95% CI: 0.04–0.38) [1].
2. The reduction in mortality from nearly 70% in the first half of the 20th century (despite the availability of antitoxins) to below 2%–8% today—in the absence of significant qualitative changes in the composition of currently used

specific antitoxic agents (whether BAS or HBAT)—can be attributed solely to the development of modern intensive care methods, particularly mechanical ventilation [1, 3].

INTRANEURONAL (ANTIDOTAL) THERAPY

It is well known that the transmission of a nerve impulse to a muscle occurs via the release of acetylcholine from acetylcholine-containing vesicles into the synaptic cleft in response to an incoming axonal signal, and that this very mechanism is blocked by BoNT [34].

Of principal importance is the existence of an energy barrier that prevents the spontaneous fusion of biological membranes—in this case, the membrane of the acetylcholine-containing vesicle and the presynaptic membrane. SNARE proteins (soluble N-ethylmaleimide-sensitive factor attachment protein receptors) [35] constitute the main driving force behind membrane fusion and vesicular transport within eukaryotic cells in general, and neurons in particular. During membrane fusion, complementary SNARE proteins associated with each membrane assemble, generating the force and energy required for fusion (https://fr.wikipedia.org/wiki/SNARE, 2022). This SNARE complex includes proteins responsible for docking ("anchoring") the vesicle to the cytoplasmic side of the presynaptic terminal. They are located in the vesicle membrane (synaptobrevin) and in the acceptor part of the membranes (SNAP-25 and syntaxin), respectively.

The function of this intricate protein complex, embedded in the vesicular and presynaptic membranes, and the subsequent release of neurotransmitters (in this case, acetylcholine) is regulated by membrane ion channels and is closely associated with changes in intracellular Ca^{2+} concentration [2]. Figuratively speaking, in response to a neural impulse, synaptobrevin interacts with SNAP-25 and syntaxin; these three proteins then coil together, drawing the acetylcholine-containing vesicle toward the presynaptic membrane, leading to membrane fusion and the release of acetylcholine into the synaptic cleft [36, 37].

According to the currently accepted view—the four-step mechanism of BoNT action [38–40]—the heavy chain of the neurotoxin selectively binds to ectoreceptors on the nerve terminal. Upon binding to these ectoreceptors, BoNT crosses the plasma membrane through receptor-mediated endocytosis, leading to its uptake into an endosomal structure (internalization). Subsequently, in an ATP-dependent process, the intra-endosomal pH drops to approximately 4.5, causing a conformational change in the toxin molecule and separation of its two chains. Then, the hydrophobic domains of the N-terminal region of the heavy chain integrate into the endosomal membrane, forming a channel that allows translocation of the light chain into the cytosol. The light chain, which functions as a zinc-dependent endopeptidase that cleaves specific cytosolic substrates (certain SNARE proteins), constitutes the final stage—the intracellular action of the toxin [2, 38].

Over the past decade, several important discoveries have clarified the molecular mechanism of BoNT action. Sequence comparison has revealed that the light chains of all BoNT serotypes contain a highly conserved 20-residue segment located in the middle of the peptide, comprising the zinc-binding domain characteristic of zinc-dependent endopeptidases (proteases), with the consensus motif His-Glu-Xaa-Xaa-His [41]. Each of the seven BoNT serotypes, acting as a zinc-dependent protease, cleaves one of three SNARE proteins essential for vesicle fusion and neurotransmitter release: synaptobrevin (vesicle-associated membrane protein, VAMP), SNAP-25 (synaptosomal-associated protein of 25 kDa), and syntaxin [40]. It has now been established that VAMP is the target of BoNT types B [42], D [43], F [44], and G [45]. The specific target for cleavage by BoNT types A and E is SNAP-25 [46, 47]. Syntaxin is the target of BoNT serotype C [48].

The second group of anti-botulism agents mainly consists of compounds still under investigation, which act by facilitating the release of acetylcholine into the synaptic cleft or by interfering with the binding, internalization, translocation, and endopeptidase activity of botulinum neurotoxins [37].

The first drug used in this direction was guanidine hydrochloride, which was administered in 1968 to patients with botulism by Cherington and Ryan [49, 50]. Their rationale was based on guanidine's ability to facilitate acetylcholine release at the myoneural junction, as it had shown beneficial effects in patients with myasthenia. The mechanism of action of guanidine involves its interference with intracellular Ca^{2+} ion binding in nerve terminals, thereby inhibiting Ca^{2+} accumulation by mitochondria. This prolongs and amplifies the effect of calcium entering the nerve terminal during the presynaptic action potential, ultimately increasing the release of acetylcholine [49]. The efficacy of guanidine in botulism intoxication has been studied both by Russian [51, 52] and foreign [53] researchers. The drug was administered intragastrically via a tube in doses ranging from 10 to 20–50 mg/kg per day, with maximum effect observed 30 to 60 minutes after administration [52, 53]. However, in several cases of botulism treatment, guanidine did not produce the expected therapeutic benefit, and its prolonged use was associated with a spectrum of side effects, from isolated muscle fasciculations to intestinal obstruction [51, 52]. A double-blind crossover study [54] in which patients received either placebo or active treatment over different time periods evaluated whether oral guanidine hydrochloride (20 to 35 mg/kg/day) could accelerate recovery in patients with moderate or severe type A botulism. Among the 14 patients who received standard therapy plus guanidine, no improvement in the disease course was observed compared with the group that did not receive guanidine. In other words, adding guanidine to standard therapy did not accelerate the regression of botulism [54]. Ultimately,

by 1994, it was conclusively determined that guanidine, as evaluated in placebo-controlled trials, does not improve the clinical course of botulism [55].

For a long time, the hypothesis circulated in medical society that aminopyridines might also reverse the symptoms of botulism by increasing acetylcholine release [56]. Theoretically, 4-aminopyridine (4-AP) or 3,4-diaminopyridine (3,4-DAP) could be used as antidotes for botulinum intoxication.

Indeed, it has been shown that 3,4-DAP, in a concentration-dependent manner, can temporarily reduce muscle paralysis induced by BoNT [57–60]. 3,4-DAP is a selective potassium channel blocker that prolongs the duration of the neuronal action potential, thereby increasing Ca^{2+} influx through presynaptic voltage-gated Ca^{2+} channels [61–63]. Since vesicle fusion is highly dependent on Ca^{2+} levels, 3,4-DAP increases the probability of acetylcholine release [57, 64–68]. However, aminopyridines have demonstrated variable efficacy in treating botulism signs and symptoms in preclinical and clinical studies, raising concerns regarding their therapeutic potential and mechanism of action.

Ex vivo studies indeed confirm the therapeutic effect of aminopyridines in skeletal muscle paralysis [56, 69–71]. Nevertheless, clinical studies involving a small number of patients exposed to various BoNT serotypes at different doses and stages of disease have yielded highly inconsistent results, leading to uncertainty regarding the therapeutic potential of aminopyridines [72–76]. For example, aminopyridines have been reported as both effective [77, 78] and ineffective [79] in alleviating type C botulism symptoms in rats. Experimental studies have shown that 3,4-DAP prolongs the survival of mice challenged with lethal doses of type A BoNT [24], with treatment restoring muscle tone and mobility for 2–3 hours. Whereas 3,4-DAP is described as effective in treating type A botulism paralysis and prolonging survival in rodent experiments [58, 60, 80], clinical studies often indicate a lack of effect of this drug [73]. Similarly, 3,4-DAP has been reported as ineffective against serotype B in rodents [58, 69, 71]; however, in a clinical case of serotype B with mechanical ventilation, a stable therapeutic effect was demonstrated [74].

Vazquez-Cintron et al. [81] suggest that 3,4-DAP may represent a potentially important adjunct to the FDA-approved heptavalent botulinum antitoxin (HBAT), as the clinical benefit of HBAT is limited to halting disease progression rather than accelerating recovery [4]. The findings of Vazquez-Cintron et al. [81] indicate that 3,4-DAP may be particularly effective in the early stages of botulinum intoxication, when patients experience respiratory depression but not decompensated respiratory failure. It may also help mitigate prolonged muscle weakness observed during the recovery phase of botulism, thereby accelerating overall recovery. From a clinical perspective, this is expected to reduce the risk of life-threatening nosocomial infections, lower treatment costs, and free up scarce healthcare resources for other critically ill patients [16, 82]. The phosphate salt form of 3,4-DAP (Firdapse) is an FDA-approved first-line symptomatic treatment for Lambert-Eaton myasthenic syndrome (LEMS), an autoimmune disease characterized by impaired acetylcholine release and muscle weakness [83]. Since the therapeutic mechanism of action of 3,4-DAP is identical in botulism and LEMS, it may be effective for both diseases at equivalent doses [81]. However, the cost of Firdapse 10 mg oral tablets is approximately USD 29,298 for a package of 120 tablets [84], which significantly limits its widespread use.

There are very limited data on the efficacy of 4-AP in botulism. It is known, for example, that a single administration of 4-AP can transiently counteract neuromuscular paralysis caused by BoNT type A in rats [66]. However, the use of aminopyridines is associated with numerous adverse effects [24, 66]: even at low doses (less than 1 mg/kg body weight), insomnia, anxiety, agitation, paresthesia, and elevated blood pressure have been observed. Moreover, both clinical and experimental studies have demonstrated the efficacy of 4-AP and 3,4-DAP only in diseases caused by BoNT types A and E. Overall, the effects of aminopyridines have proven to be unpredictable, and their adverse effects entirely offset the short-term and questionable positive outcomes [58, 66, 80]. The only clearly noted improvements—in eye movement and limb mobility—were not accompanied by the expected improvement in respiratory muscle function [85]. Taking all of the above into account, it was concluded that the efficacy of 4-AP and 3,4-DAP has not been established [86], and their use in clinical practice for the treatment of botulism is not advisable [74].

The history of studying the plant-derived triterpenoid toosendanin (TSN), an active compound extracted from the bark and fruits of plants of the Melia family [87, 88], is also of considerable interest. In ancient China, TSN was used against gastrointestinal helminths and as an agricultural insecticide [89, 90]. Chinese researchers began exploring the potential of TSN to reduce the severity of BoNT-induced paresis and paralysis as early as the 1980s [91–94], after it was discovered that TSN selectively blocks acetylcholine release from nerve endings [95]. More recent data indicate that TSN is a selective Ca^{2+} channel agonist [96, 97], acting through the inhibition of K^+ channels. The associated increase in Ca^{2+} levels will promote neurotransmitter release and may be related to the botulinum toxin–antagonizing effect of TSN [97].

In 2004, Shi et al. [37] discovered that TSN renders synaptosomes resistant to BoNT type A-mediated cleavage of SNAP-25. This antagonistic effect was not associated with inhibition of the endopeptidase activity of the BoNT type A light chain. It was hypothesized that it is specifically (and solely) the blockade of the approximation of the toxin's light chain (as a proteolytic enzyme) to its substrate (SNAP-25) that is, in a way, responsible for the TSN-induced botulinum toxin–antagonizing effect [97, 98].

There is reason to believe that TSN disrupts the channel-forming activity of BoNT (at least type A) during

the translocation of its light chain from the endosome into the cytosol (see above), thereby protecting SNAP-25 from cleavage [99]. It is possible that TSN-induced disruption of light chain translocation also applies to BoNT type B [100].

In experiments conducted on monkeys, TSN demonstrated a pronounced positive effect [101]. Each rhesus macaque received a subcutaneous injection of one MLD of BoNT type A, and TSN therapy (administered intravenously at a dose of 0.9–1.0 mg/kg) was initiated 24 hours after exposure to BoNT type A. In the TSN-treated group, 10 out of 13 monkeys survived and returned to normal activity, compared with 2 out of 12 survivors in the control group that did not receive TSN. Notably, TSN showed a similar therapeutic effect in mouse models exposed to BoNT types B and E [102].

According to the review by Hu et al. [97], clinical trials conducted by Chinese researchers indicated that oral administration of TSN (1.25–2.25 mg/kg) had a significant therapeutic effect in patients with botulinum toxin poisoning.

TSN is considered a promising botulinum antidote despite its relatively high toxicity and narrow therapeutic index (LD_{50}/ED_{50} = 4.35–5.25) [103]. For example, the maximum clinically effective antibotulinum dose of TSN (2.25 mg/kg orally in humans) is close to the minimum hepatotoxic dose (3.2 mg/kg). This suggests that TSN may cause serious liver injury under such circumstances [97].

According to Chinese experts, further research should focus on identifying and evaluating the therapeutic potential of low-toxicity synthetic derivatives of TSN [97]. However, apart from the previously cited Chinese studies, no new data on such derivatives were found in the available scientific sources. On the other hand, since TSN inhibits insect developmental cycles [90, 104, 105], its use as a safe insecticide is becoming increasingly popular in China [106].

The action of TSN on the end-plate potential is similar to the effect of β-bungarotoxin and the venom of the karakurt spider, which also enhance the potential in the initial phase of their action but are considerably more toxic than TSN [103]. For instance, karakurt spider venom has been shown experimentally to improve neuromuscular transmission by increasing Ca^{2+} concentrations in motor nerve terminals, promoting the exocytosis of acetylcholine-containing vesicles and thereby counteracting BoNT-induced neuromuscular blockade [107–109]. However, due to its high toxicity, this venom is not suitable for clinical use [110].

As previously noted, following receptor binding at the surface of nerve terminals, BoNT undergoes internalization via endocytosis. Subsequently, the toxin—specifically its light chain—is translocated from the endosome into the cytosol through a pH-dependent process. Some agents exert their effects at this stage by interfering with BoNT action. The compounds that are theoretically capable of counteracting translocation are ammonium chloride and methylamine hydrochloride. In 1983, Simpson [111] reported that these agents produced a concentration- and time-dependent antagonism of the onset of BoNT-induced neuromuscular blockade by types A, B, and C. These agents were effective only when administered before or within 10–20 minutes after toxin exposure. At concentrations that antagonized the development of BoNT-induced paralysis, ammonium chloride and methylamine hydrochloride did not inactivate toxin molecules or irreversibly alter tissue function. Furthermore, these agents did not inhibit BoNT receptor binding or reverse established neuromuscular blockade. Research in this direction was not pursued further [37].

The shift of the endosomal lumen pH toward acidity depends on the endosomal H^+-ATPase, which functions as a proton pump, transporting H^+ from the cytoplasm into the endosomal lumen. The use of an H^+-permeable ionophore can disrupt this pH gradient without affecting ATP hydrolysis [112, 113]. In 1996, Sheridan [114] found that two ionophores—nigericin and monensin, which increase membrane permeability to H^+ and K^+ or H^+, Na^+, and K^+, respectively—blocked endosomal acidification by acting as H^+ shunts to neutralize the pH gradient. Nanomolar concentrations of nigericin or monensin delayed the onset of blockade in muscles exposed to BoNT type A or BoNT type B. However, higher concentrations of ionophores directly blocked synapses. Thus, nigericin and monensin can delay the onset of BoNT-associated paralysis only within a narrow concentration range [114].

In 1982, Simpson [115] demonstrated that the well-known antimalarial drug chloroquine is effective in delaying BoNT type A-induced neuromuscular blockade [116]. Subsequent studies revealed that among the tested aminoquinoline compounds, those containing the 7-chloro-4-aminoquinoline configuration—similar to that of chloroquine—or a structurally related 6-chloro-9-aminoquinoline group, as in quinacrine, were effective in prolonging the time required for BoNT type A to block neuromuscular transmission [116, 117]. The presumed mechanism of action of these antimalarial agents lies in their ability to increase endosomal pH levels.

The light chains of BoNTs are zinc-dependent metalloproteases. Accordingly, inhibitors of these enzymes and heavy metal chelators are logically considered potential inhibitors of BoNT.

In 1995, Deshpande et al. [117] investigated the ability of three metalloprotease inhibitors to delay the onset of diaphragmatic paralysis in mice following exposure of the phrenic nerve to botulinum neurotoxins of types A and B. Among the three tested compounds, only phosphoramidon—a clinically used angiotensin-converting enzyme inhibitor—was found to significantly delay the onset of muscle paralysis induced by BoNT type B and to slow its progression by up to 50%. Whereas this effect was not observed in the case of BoNT type A. The other two metalloprotease inhibitors—captopril and a peptide hydroxamate—exhibited no effect in the described experiment [117].

N,N,N′-Tetrakis(2-pyridylmethyl)ethylenediamine (TPEN) is a heavy metal chelator [37]. TPEN has been shown to significantly delay the onset of neuromuscular blockade in

isolated preparations exposed to BoNT, demonstrating efficacy against all BoNT serotypes. The mechanism of action is presumably related to chelation of the catalytically essential zinc ion within the active site of the BoNT light chain [118, 119]. To evaluate the protective efficacy of TPEN against botulinum toxin *in vivo*, mice received TPEN as a single bolus or multiple injections administered 30 minutes before, concurrently with, and 2, 4, and 6 hours after intravenous injection of BoNT serotypes A or B. TPEN treatment did not reduce mortality in mice challenged with BoNT types A or B, it did significantly delay the time to death [37, 118, 119].

To summarize, it must be acknowledged that all efforts to identify compounds capable of reversing the neuromuscular blockade induced by BoNT [120] have, if not failed outright, then certainly fallen short of expectations.

Therapeutic Measures Aimed at Eliminating Pathological Processes and Systemic Effects Induced by Botulinum Neurotoxin

To date, meta-analyses have not found evidence supporting the efficacy of any pharmacological treatment for botulinum intoxication aside from botulinum antitoxin [1].

It is evident that the terminal stage of botulinum intoxication is acute respiratory failure (ARF). However, in the pathogenesis of botulism, intestinal paresis—although not the primary or most apparent manifestation (compared with ARF)—plays a markedly adverse role, being directly associated with the effect of BoNT on the parasympathetic nervous system. As with impaired impulse transmission to striated muscle, modern medicine has no means to bypass this blockade of gastrointestinal smooth muscle innervation or to directly neutralize it.

The intestine, serving as a reservoir for infection and various toxic substances, is among the organs with continuous intensive metabolism, requiring an adequate supply of structural material and energy to maintain normal morphological and functional status [121]. The high sensitivity of intestinal epithelial cells to hypoxia and ischemia leads to early damage to the epithelial barrier separating the enteral environment from the internal milieu in conditions accompanied by impaired microcirculation and hypoxemia [122], which naturally occurs in botulism [7].

Without diminishing the importance of ongoing advancements in intravenous infusion therapy, several authors have explored the potential of supplementing or replacing it with intensive correction of homeostatic disturbances via the administration of specialized fluids directly into the gastrointestinal tract (GIT) [123]. Various formulations and compositions have been proposed for enteral correction (EC) in different pathological conditions [124–126]. According to the scientific data, chyme-like fluids appear to be the most suitable for EC [126]. It is believed that the development of modern saline enteral solutions was informed by the invention patented by Galperin and Baklykova, titled "Method for Determining the Suitability of Nutrient Mixtures for Enteral Feeding" (1980) [127]. Subsequently, in 1988, Galperin et al. proposed a saline enteral solution (SES) with a macroelement composition similar to that of chyme [128]. Currently, the most widely used SES in medical institutions across the Russian Federation is provided in the form of a set of concentrates for the preparation of a specialized dietary medical product (for enteral nutrition) known as SES [129].

In addition to detoxification through GIT cleansing, EC contributes to the normalization of water–electrolyte balance, acid–base status, hemorheology, microcirculation, pro- and antioxidant balance, intestinal microbiota, and GIT motility [130]. In 2020, Matkevich et al. [122] demonstrated that EC using SES, for instance in cases of acute poisoning with psychopharmacological agents, exerts a multifaceted corrective effect on impaired physiological parameters. A key component of this effect is the restoration of water–electrolyte and acid–base balance. This outcome can be explained both by the detoxifying effect of SES—i.e., elimination of the primary cause of the disturbances—and by the direct influence of SES on water–electrolyte exchange across the intestinal wall via autoregulatory mechanisms due to the chyme-like physicochemical properties of the solution. Thus, the therapeutic mechanisms underlying EC are based on two processes: the removal of pathological and excess chemical substances from the body, and the delivery of a balanced amount of electrolytes and water into the bloodstream. The presence of glucose in SES enhances sodium ion absorption from the intestine into the bloodstream, followed by water, which overall increases the absorption rate of the solution [131, 132]. Furthermore, EC using SES is considered one of the most effective methods for restoring intestinal motility [133].

Therefore, there is every reason to consider EC with SES in botulism to be scientifically and practically justified; however, we found no mention of this approach in the available scientific data, either in experimental studies or in clinical practice. We have successfully applied EC in the treatment of several patients with type A botulism during the outbreak in Moscow in June–July 2024, and the corresponding report will form the basis of our forthcoming publication.

CONCLUSION

The above discussion indicates that the treatment of patients with botulism remains an important issue in modern healthcare: at present, there are no radical methods for eliminating BoNT-induced pathological changes, and the possibility of developing fundamentally new therapeutic approaches for this patient population in the foreseeable future raises certain, and entirely justified, doubts. In this context, attempts to optimize existing treatment methods and approaches—from the development of monoclonal antibody–based antitoxins against BoNT to attempts to restore intestinal peristalsis using SES—become relevant.

Research in all these areas is ongoing.

ADDITIONAL INFORMATION

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