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Novel Medical Countermeasures for Nerve Agent and Pharmaceutical Based Agent Poisoning

Sinir Ajanı ve Farmakolojik Tabanlı Ajan Zehirlenmesine Karşı Geliştirilen Yeni Tıbbi Karşı Tedbirler

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ABSTRACT

Nerve agents are organophosphorus compounds which inhibit acetylcholinesterase (AChE) enzyme. Existing AChE reactivators (Oximes) have several limitations in mean of reactivation potential, broad action spectrum, and penetration rate through blood-brain barrier. Ongoing studies focus on design and synthesis of novel oximes. Pharmaceutical based agents like fentanyl abuse becomes an important public health threat. Naloxone and naltrexone that are centrally acting opioid receptor antagonists, are used for reversing the effects of the opioid overdose.

Key Words

Nerve agents, oxime, fentanyl, naloxone, CBRN.

ÖZ

Sinir ajanları, asetilkolinesteraz (AChE) enzimini inhibe eden organofosforlu bileşikleridir. Mevcut AChE reaktivatörleri (Oksimler), reaktivasyon potansiyeli, geniş etki spektrumu ve kan-beyin bariyerinden penetrasyon hızı açısından çeşitli sınırlamalara sahiptir. Devam eden çalışmalar yeni oksimlerin tasarımı ve sentezi üzerine odaklanmaktadır. Fentanil gibi farmasötik bazlı ajanların suistimali; önemli bir halk sağlığı tehdidi haline geliyor. Merkezi etkili opioid reseptör antagonistleri olan nalokson ve naltrekson; opioid doz aşımının etkilerini tersine çevirmek için kullanılır.

Anahtar Kelimeler

Sinir ajanları, oksim, fentanil, nalokson, KBRN.

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NERVE AGENTS

History of Nerve Agents

Organophosphorus nerve agents (NA) are one of the most toxic synthetic compounds in the world. Despite the story of the NA's started at mid-19th century and first organophosphorus acetylcholinesterase (AChE) inhibitor synthesized at early 1900's, chemists could not realize its toxicity [1]. Then after, in 1936 German chemist G. Schrader, to find a new pesticide, treated an organophosphate with cyanide and experienced a strong toxicity which caused his hospitalization [1]. Therefore, first nerve agent "tabun" was synthesized.

Germans research on NA continued and team of Schrader synthesized "sarin" in 1938. Another German chemist R. Kuhn described the NA mechanism of action in 1943; and synthesized a more potent NA called "soman" in 1944 [2]. Those nerve agents developed by Germans were named as "the G-series" (GA; tabun, GB; sarin, GD; soman). NA were not utilized by Germans during World War II because of some political reservations, but organophosphorus pesticides were keeping their importance for agriculture. In the 1950s, British Scientist R Ghosh with the aim of developing a pesticide, synthesized a new NA called "VX", V stands for venomous [2]. Those new compounds called "V-series" and they were more potent, more persistent, and less volatile than G-series [3]. Between 1971 and 1991, until the fall of the Soviet Union, Russia made research on NA within the scope of the offensive chemical weapons program and synthesized "Novichok"s (newcomer); this new NA series were also named as "A-series" [4].

Since 1980s, there are many examples of NA attacks in the history. The Iraq-Iran war, Gulf war, and the Syrian civil war are some examples of military districts where NA used. There were also examples of NA incidents including terrorist attacks and assassinations. Sarin attacks in Japan in 1994 and 1995 caused 18 people to die and poisoned more than six thousand people [5]. Assassination of Kim Jong-Nam with VX in 2017, in Malaysia and assassination of Sergei Skripal and his daughter with Novichok in 2018, in England were some of the examples of NA use in civil districts [2].

First international legal regulation related to use of chemical warfare agents (CWA) was Geneva Protocol which was signed in 1925 after World War I, that banned to use of CWA in armed conflicts [1]. In 1997, the Organization for the Prohibition of Chemical Weapons (OPCW) which is an intergovernmental organization entered into force and banned not only the use, but also the development, production and stockpiling of chemical weapons and required the destruction of existing ones [2]. Today, OPCW has 193 member states; Egypt, North Korea and South Sudan did not sigbn the convention and Israel singed but not ratified the convention [6]. Although the use of CWA is banned by international regulations, exposure to chemical agents remains a threat for today and for future all over the world.

Nerve Agents' Mechanism of Action

Main mechanism of NA is inhibition of serine esterase; enzymes hydrolyzing esters such as AChE, butyrylcholinesterase (BChE), carboxylesterase, and neuropathy target esterase [7]. AChE and BChE are sister enzymes in mammals and nearly 50% of sequences are homolog [8]. Physiological role of BChE is not known clearly but it's known that BChE is non vital. Using BChE as a bio scavenger at NA intoxication thought as an option; but due to high enzyme production cost, this option was limited [9].

Mechanism responsible of symptoms at NA toxicity is inhibition of AChE. AChE is an enzyme that present in neuromuscular junction, synapses between neurons and erythrocyte membrane [5]. The role of the enzyme is to break down of acetylcholine (Ach) and limiting the post-synaptic stimulation [2]. In case of NA intoxication, Ach accumulates in synapses and causing symptoms which can be remembered with mnemonics: SLUDGE (Salivation, Lacrimation, Urination, Defecation, Gastrointestinal distress, and Emesis) because of muscarinic receptor over stimulation; and MTWTF (days of the week; Miosis, Tachycardia, Weakness, Hypertension, and Fasciculations) as a consequence of nicotinic receptor over stimulation. Inhibition of 50% of AChE might trigger the symptoms and inhibition of more than 90% of the enzyme will result with dead [10].

NA by binding to AChE, causing phosphorylation of the enzyme, that inhibits the hydrolyzing capacity. Inhibitor effect of NA on enzymes is permanent until the generation of new enzymes or usage of oxime like reactivators [5]. However, if the alkyl group bound the phosphorus is lost; that is a non-enzymatic and time dependent reaction, the inhibitor effect of NA on enzyme becomes persistent [11]. This is called "aging reaction" and spontaneous or oxime induced reactivation of the enzyme

becomes impossible after this point. Half-time of aging changes between minutes to hours; aging half-time is 4 min for soman; 3 h for sarin, 19 h for tabun and 36 h for VX [12].

Despite being the most important one, AChE is not the only target of NA. Long term effect of NA exposure are thought to be the results of those non-AChE targets; whose inhibition leads to oxidative stress, neuroinflammation, axonal transport deficits, changes in gene expressions, and autoimmune response [13].

Medical Countermeasures for NA Toxicity

Prophylactic agents

Ideally, pretreatment agents used for NA toxicity should be easily administered, effective against wide range of NA, safe with minimal side-effects at short-term and long-term, have a convenient pharmacokinetic profile to be protective for a sufficient period, and support post-exposure treatment efficacy [14]. However, such an agent does not exist yet. Present prophylactic agents used for NA toxicity aims to decrease the severity of toxicity in case of exposure to NA; but they cannot prevent the toxicity totally nor cannot eliminate the need for post-exposure treatments. Pyridostigmine is the most known molecule used for this aim and approved by Food and Drug Administration (FDA) [2].

Since the main mechanism of toxicity is inhibition of AChE, pyridostigmine by binding to enzyme reversibly, blocks irreversible binding between AChE and NA [15]. Suggested dose of pyridostigmine is 30 mg per oral every 8 hours [16]. Being not able to pass through blood brain barrier (BBB) is a disadvantage of pyridostigmine. There are also studies about the neuromuscular side effects of pyridostigmine for long term use [2,16-17] Physostigmine has also similar mechanism of action. Its superiority against pyridostigmine is being able to penetrate through BBB; that is also the responsible mechanism of cognitive side effects of physostigmine [14]. Galantamine, benactyzine, trihexyphenidyl are examples of other molecules which are searched for pretreatment in animal models; but they all produce behavioral impairment at therapeutic doses [16]. Therefore, with current information, performing limited pretreatment with pyridostigmine, followed by post-exposure therapy seems to be the best option.

Anticholinergics

Most of the symptoms of NA toxicity are consequence of muscarinic receptors over stimulation; therefore, since 1930's atropine has been the first line drug used in NA toxicity [7]. Atropine doesn't have any effects on nicotinic receptors, but it can cross BBB and at high doses and with early administration it can prevent / stop NA induced status epilepticus [18].

The aim of atropinization in NA toxicity is to treat excessive secretions and relief of bronchoconstriction, thus there is no exact dose so titrated dose should be applied [19]. However, there are some protocols in the literature. Balali-Mood recommended 2 mg starting dose of atropine, if possible, administration with autoinjectors, and dose titrated up to symptoms of mild atropinization, which is defined as reduced secretion in airways [20]. Maintenance dose is same with the dose ensures initial atropinization and recommended to given in %5 dextrose solution as a continuous infusion until the mucosal membranes dry [20]. In another study, authors recommended 4 mg initial dose of atropine, continuing with 5mg intravenous atropine 2 minutes later and repeating dose at every five minutes until atropinization signs presented [21].

Atropine can be administered by intramuscular, intravenous, or endotracheal routes. In United States, there is an FDA approved, inhaler form of atropine which is called MANAA (Medical Aerosolized Nerve Agent Antidote) [5]. Side effects of atropine are blurred vision, delirium, hallucinations, decreased sweating, fever, arrythmia and mydriasis. Due to bladder dysfunction, urinary catheterization might be required.

Benactyzine is an anticholinergic drug, which is used as anti-depressant, in meantime searched for use in NA toxicity [7]. Because of higher lipophilic capacity of benactyzine, it can penetrate to central nervous system (CNS) more than atropine and more successful to reverse CNS effects of NAs than atropine [5]. Benactyzine side effects such as sweating inhibition and accommodation impairments, are also less than atropine which made it more suitable using it on casualties in warm environments [5, 22].

Enzyme reactivators (Oximes)

IN NA toxicities, atropine does not have effect on nicotinic receptors and cannot reactivate the inhibited AChE

so research's focused on components which can reactivate AChE. Despite, there are dozens of compounds developed for this purpose, only few of the oxime group reactivators are being used currently.

Mechanism of action

Lead structure for AChE reactivators are pyridine oximes [23]. Oximes mechanism of action is chemical reactivation of the NA inhibited AChE. Nucleophilic oximes attacking the phosphorus atom of the NA-AChE compound at the via the oxygen atom. This reaction results with the formation of NA-oxime compound and release of AChE; and thus, enzyme is reactivated [23]. However, if aging is completed, oximes can then no longer reactivate the enzyme.

Ideal oxime

There are some requirements for an ideal oxime. First, for existence in the physiological pH, preferred range of oxime pKa should be between 7 and 8 [1]. Aliphatic oximes are weak acids with relatively high pKa values and there are some successful strategies, like modification of the structure with halogen atoms, to decrease the oxime pKa [24]. Secondly, for rapid action antidotes are formulated as aqueous solutions, so oximes require to be water soluble [1]. Thirdly, to prevent CNS effects of the NA, oxime penetration from BBB is important. Nevertheless, only about 10% of pralidoxime and 1-3% of bipyridinium oximes can reach to brain [25]. Also, ideal oximes need to have broad spectrum of action, should be efficient against all types of NA, including Novichok's. An oxime that meets all these features has not been developed yet. Commercially available oxime reactivators using today are pralidoxime, trimedoxime, obidoxime, HI-6, and MMB-4.

Main oximes "Great Four"

First oxime reactivator synthesized in USA in 1955 was pralidoxime chloride (2-PAM) [26]. 2-PAM was effective against sarin, cyclosarin, and VX. In 1957, trimedoxime bromide (TMB-4) was synthesized and besides sarin and VX, it was also effective against tabun [27]. But TMB-4 is the most toxic oxime among "Great Four" with 3-8 times less LD_{50} than other oximes [28]. In 1964, obidoxime chloride (LüH-6, Toxogonin) was synthesized in Germany. Like trimedoxime, obidoxime is also effective against tabun, sarin and VX; but, similarly with the others, LüH-6 is not effective against soman [28]. As a side effect, obidoxime has a hepatotoxic potential [29]. In 1966, asoxime chloride (HI-6) was developed, which is the first oxime effective against soman [27]. HI-6 also effective against sarin, cyclosarin, and VX, but it is not effective against tabun. It is the less toxic oxime reactivator [28]. Later in 1986, HLö-7 was synthesized, it has same structure that of HI-6 except an additional ortho oxime group [1]. HLö-7 is effective against all major nerve agents (tabun, sarin, soman, VX, and cyclosarin), but it is difficult to synthetize, and it is chemically unstable [1, 30]. Also, toxicity of HLö-7 was 2.5 times greater than HI-6 [31]. Methoxime chloride (MMB-4) is found to be effective against sarin, cyclosarin, and VX, especially in peripheral tissues in studies done with guinea pigs [32]. Except MMB-4, all the oximes mentioned above approved by FDA [1].

Dosage

Obidoxime and pralidoxime are the main oximes used in clinical practice. Recommended intravenous (IV) dose for obidoxime is 250 mg loading dose and 750 mg/24h continuous infusion. Recommended dose for pralidoxime is 1-2 g loading dose then 500 mg/h continuous infusion [33]. Similar doses can be given intramuscularly (IM) in the field. World Health Organization (WHO) recommended therapeutic schemes for obidoxime and pralidoxime are 8 mg/kg IV initial bolus, followed by 3 mg/kg/h continuous infusion for obidoxime and 30 mg/kg in 5% glucose in 30 min duration as bolus followed by 8 mg/kg/h continuous infusion for pralidoxime [33]. Oxime infusion should be continued until the clinical recovery or 12 h after the reactivation has been achieved. If reactivation of the enzyme has not occurred after 24–48 h oxime infusion, it should be accepted as aging has occurred and enzyme is resistant to oximes, so administration should be stopped [33].

Oxime autoinjectors

There are some autoinjectors developed for the armed forces. First autoinjector developed by USA army in 1980's was MARK I Nerve Agent Antidote kit, which contains 2 mg atropine in an AtroPen (atropine autoinjector) and 600 mg pralidoxime in a MARK I auto injector [1, 34]. Combined injectors appeared in 2000's and Antidote Treatment Nerve Agent Auto-injector (ATNAA) delivers two antidotes in a single injector [34]. In the 2010's pralidoxime replaced by methoxime and atropine replaced by scopolamine. They were combined in a single injector called Improved Nerve Agent Treatment System (INATS) [1]. In United Kingdom (UK) and France, a three component autoinjector is used that contains pralidoxime, atropine, and avifazone with a commer-

cial name of CompoPen® and Ineurope®, respectively [35-36]. Trobigard™ is another autoinjector containing obidoxime and atropine, authorized in 2022 [1]. Turkish Armed Forces is using "Automatic Injector", which contains 2 mg atropine and 220 mg obidoxime.

Novel oximes

As mentioned above, there is no ideal oxime yet and all FDA approved oximes have some limitations. So, research on new oximes with higher reactivation potential, broad spectrum of action, and better penetration through BBB are still going on [37]. There are several oximes in the literature, however only few of the novel oximes could be good candidates for commercial use. Summary of some of the researches are given below.

Numerous pyridinium, imidazolium, and quinuclidinium oximes were synthesized in the former Yugoslavia; some compounds had antidotal effect against sarin and VX comparable with the classic oximes (pralidoxime, obidoxime, trimedoxime), but none of the synthesized oximes were reactivate tabun or soman inhibited AChE [38]. Bispyridinium oximes with C3-9 linkers had promising reactivating capacity; however, they showed toxicity in vitro and in vivo studies [39, 40]. Kuca et al. synthesized many oximes called "K-oximes", among all, KO27 and KO33 showed promising results against cyclosarin that can be comparable to HI-6 [41]. Some of the K-oximes found effective against tabun inhibited AChE such as K048, K203, K127, K074, however further research is required to identify the toxicity and tolerability of these molecules [12]. Laboratory of Hagedorn synthesized thousands of oximes called H-oximes [42]. Among H-oximes, HLö-7 with high reactivation capacity and broad spectrum of action, is the only one which can replace the presently used oximes [43].

Most recent studies focused on uncharged oximes which have higher BBB penetration [44 - 46]. Among sugar-oxime conjugates, sugar-oxime 13c was more active than others and had a similar reactivation potential with PAM, and sugar-oxime 8d had low toxicity [44]. Kalisiak et al. studied on amidine-oximes, which had greater penetration capacity to brain, but their reactivation capacities were lower than PAM [45, 46]. Sit et al. synthesized hydroxyiminoacetamides which had better reactivation potency for VX and cyclosarin inhibited AChE, comparing to PAM [47]. De Konnig et al. worked on new group of non-ionic oxime reactivator, by binding peripheral side ligand to the compound. They tried to increase reactivating potency of the oxime; however, comparing to HI-6, those oximes found less effective against sarin and VX and ineffective against tabun [48].

As a result, among all novel oximes only HLö-7 has a broad spectrum of action, but for a final assessment further study are needed. Also, acute and chronic toxicity potentials of novel oximes are not known well yet. Different experimental protocols in the literature (experiments on different species, using different therapeutic doses and different nerve agents) make the comparison of data very difficult. Most importantly, lack of human in vivo data is a limitation for development and clinical use of those molecules.

Side effects of oximes

Data about toxicity of oximes in non-poisoned humans are very rare. Transient increase in blood pressure, transient tachycardia, numbness of face. and general warmth are reported as side effects of oximes [49].

Non-oxime reactivators

Despite oximes are the main class of reactivators, recent studies are investigating non-oxime molecules. 4-Amino-2-[(diethylamino) methyl] phenol (ADOC) is a non-oxime reactivator which is reported by Katz et al. in 2015, and in vitro studies showed two times better reactivation than PAM for cyclosarin and VX [50]. De Konig et al. made some structural modifications to ADOC molecule and one of them named "31" proved to be the most potent non-oxime reactivator reported so far [7, 51]. Another non-oxime group of compounds selectively targeting the nicotinic receptors. Bispyridinium compound MB327 studied by Seeger et al and in vitro human tissue studies showed a promising nicotinic antagonist activity [52]. Later, Niessen et al. studied on regioisomers of MB327 and found inhibitory effects of the compound at high concentrations in soman-poisoned rat diaphragm model [53]. In 2018, quinone methide precursors (QMPs) are reported by Zhuang et al which have both reactivation and resurrection (recovery from aged to the native state) capacity [54].

Anticonvulsants

Seizures are important clinical feature of NA toxicity, which is a consequence of overstimulation of cholinergic pathways [55]. Seizures cause neuronal inflammation and stimulates astrocytes to produce glial fibrillary acidic protein that results with astrogliosis and glial scarring. Also, by activating microglia, seizure triggers

inflammatory process and releases of reactive oxygen radicals in CNS and so causing oxidative stress [7, 56]. Therefore, for the protection of CNS against long term neurodegenerative effects of NA, medical management of seizures is very important.

Convulsions begin in few seconds after the loss of consciousness in NA toxicity and seizures were not reported after effective antidote therapy with ventilatory support [57]. First line drug for NA induced seizure management is diazepam. Recommended dose for diazepam is 5-10 mg in adults and 0,2-0,5 mg/kg in children [58]. In case of status epilepticus diazepam can be administered in IM route. US army has diazepam containing autoinjectors called "Convulsive Antidote Nerve Agent" (CANA) [59]. Lorazepam and midazolam are other drugs in benzodiazepine group that can be used in seizure management. For being more rapid and more potent than diazepam, midazolam is recommended in some studies as urgent care of NA-induced seizures [60]. Efficacy of benzodiazepines decreases against time and in case of NA exposure, they should be given in 30 minutes to prevent progressive neuronal damage and stop seizures [61]. Other anticonvulsive drugs such as barbiturates and phenytoin are not effective against NA induced seizures [58].

Anticholinergics also have some anticonvulsive effect. In a study with guinea pigs, eight anticholinergics (atropine, benactyzine, aprophen, azaprophen, trihexyphenidyl, procyclidine, biperiden. and scopolamine) were studied and it was showed that except atropine all of the anticholinergics had an anticonvulsive effect on soman induced seizures when given 5 min after seizure onset [62].

For seizure management, inhibition of excitatory neurotransmitter systems or activation of inhibitory pathways are other mechanism used by newly developed drugs [7]. Tezampanel, which antagonizing the excitatory amino acid glutamate's receptors, was showed to be effective to reduce duration of status epilepticus and stopped seizures in soman exposed rats when administered 1 hour after exposure [63]. A NMDA receptor antagonist ketamine, when used together with atropine, stopped seizures at a mouse model and it showed neuroprotective effects by suppressing neutrophil granulocyte infiltration and glial activation [64]. A natural alkaloid Huperzine A has reversible AChE inhibitory effect and antagonize NMDA receptors. It was found to be effective on seizures and status epilepticus prevention in post exposure, in animal models [65]. Another novel anti-NMDA molecule Gancyclidine, which is already approved for human use in neurotraumatology, showed neuroprotective effect in NA toxicity [66].

PHARMACEUTICAL BASED AGENT'S

The Chemical Weapons Convention (CWC) which entered into force on 29 April 1997, prohibits the development, production, stockpiling, transfer, or use of chemical weapons and it is administered by the Organisation for the Prohibition of Chemical Weapons (OPCW). However, the CWC permits the riot control agents (RCA's) that cause temporary incapacitation in humans for domestic riot control purposes [67].

An aerosolized incapacitating agent, probably "a fentanyl derivative" which was effective on the central nervous system (CNS), was used by Russian law enforcement forces against terrorists who took 912 hostages in Moscow Dubrovka Theater on 26 October 2002. 127 hostages and 30 terrorists died due to fetal complications of the inhaled agent [68].

In 2018, OPCW Scientific Advisory Board reported that the CWC does not permit the use of the aerosolized RCA's which cause permanent harm and death on the victims [69]. It is known that some governments and non-state actors have an increasing interest on using incapacitating pharmaceutical based agents (PBA's) as a method of warfare in diverse situations [70]. For this reason, a group of CWC state parties including Australia, Switzerland, and the United States underline the risk of the aerosolized use of CNS–acting agents. It is also stated that the CWC should be adopted for classifying PBA's including fentanyl compounds as chemical warfare agents [71].

Fentanyl

Fentanyl compounds which are synthetic opioid drugs, are solids at ambient temperatures. They are widely used for the induction and maintenance of general anesthesia and analgesia in human and veterinary medicine. Janssen Pharmaceutica synthesized fentanyl in 1963 and then its analogues including carfentanil, sufentanil, and alfentanil were discovered in the 1970's followed by discovery of remifentanil in the 1990's. Fentanyls could be absorbed by inhalation, intramuscular and intravenous injection, intranasal application, di-

rect skin contact, or gastrointestinal system. Fentanyls which are lipophilic, have fast action as they could pass the brain blood barrier (BBB) easily [72]. Fentanyl is a high affinity μ-opioid receptor agonist, and it is 75-100 times more potent analgesic than morphine [73]. While norfentanyl is the major urinary metabolite, hydroxylfentanyl, hydroxynorfentanyl, and despropionylfentanyl are inactive metabolites of fentanyl [74].

As an illicit drug which is less expensive than the heroin, using fentanyl causes euphoria by dopamine releasing and it has potential for abuse and addiction. After a single lethal dose of fentanyl, respiratory depression with apnea, bradycardia, and muscular rigidity occurs in the first 5 to 10 min [72].

Clandestinely produced fentanyl has been abused since 2000's and it significantly increase the incidence of fatal opioid overdoses in the Unites States (US) in recent years [71]. Fentanyl misuse and addiction is an important public health threat in the US because the annual number of fentanyl related deaths exceeds the annual number of deaths from firearms and motor vehicle accidents in recent years. For example, deaths due to fentanyl's increased 10-fold from 2013 to 2017. Besides, the monthly percentage of fentanyl-related overdose deaths increased by over 200% in 21 jurisdictions between 2019 and 2022 due to increased availability of fentanyl and its greater potency relative to heroin [75-76].

Xylazine

Xylazine is a centrally acting agonist of α2 adrenergic receptors, and it inhibits the release of norepinephrine and dopamine from the CNS for the sedation, analgesia, and euphoria. The US Food and Drug Administration (FDA) approved the use of xylazine as a sedative medicine in veterinary practice in 1972. It could be also combined with other narcotic drugs including ketamine. Its use could be fatal in humans due to decreased peripheral vascular resistance, heart rate, and blood pressure. Xylazine could be administered by oral route and intramuscular, intravenous or subcutaneous injections. The abuse of xylazine in humans was first reported in Puerto Rico in 2007. Then, it was used as an additive in the US to enhance the euphoria and analgesia induced by fentanyl and to reduce the frequency of injections. Fentanyl and xylazine combination are mostly known as "tranq dope" in the US [77-78].

The US federal government states that fentanyl-xylazine combination is also another narcotic related significant public health threat. For example, the estimated LD_{50} value of xylazine was 157.2 mg/kg while it is 32.0 mg/kg in the presence of fentanyl. While the number of xylazine-involved overdose deaths in the US was 102 in 2018, it was 3468 in 2021 and 99.1% of these deaths also involved fentanyl [76-79].

Medical countermeasures for PBA intoxication

Naloxone, naltrexone, and nalmefene are centrally acting opioid receptor antagonists which bind to or μ, κ, and δ receptors. They are used for reversing the effects of the opioid overdose.

Naloxone is normally administered by intramuscular or intravenous routes. Oral route is ineffective because of its short half-life (32 min). Intranasal and intramuscular applications of naloxone is preferred for the field management of opioid overdose to treat the fetal respiratory depression because respiratory depression leads to asphyxia, dysrhythmia, bradycardia, cardiac ischemia, and cardiopulmonary collapse. Intranasal spray (Narcan®) and intramuscular auto-injector (Rapid Opioid Countermeasure System (ROCS) are two naloxone products that were approved by FDA [72, 80].
Naltrexone is orally used opioid antagonist which has a longer half-life than naloxone (4 h). Finally, nalmefene which has similar chemical properties with naltrexone, is also used orally and it has much longer half-life than naltrexone (12 h) [72].

Although naloxone is used for suspected opioid overdose cases; it is less effective against fentanyl and fentanyl-xylazine combinations than heroin. Besides, there is no approved antidote for the treatment of xylazine intoxication [76-77, 79-80].

Opioid epidemic becomes more complicated by emerging threats including Nitazenes and Xylazine abuse. For this reason, administration of naloxone antidotes should be a part of first aid training for the public and opioid antidotes containing naloxone like Rapid Opioid Countermeasure System (ROCS) and Narcan® should be available over the counter without a special prescription. Also, these antidotes should be easily accessible by the community law enforcement officers and first responders [81].

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