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REVIEW PAPER

Autoinjector Device for Rapid Administration of Life Saving Drugs in Emergency Situations

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ABSTRACT

A number of emergency situations require immediate drug administration for reducing the morbidity and mortality. Autoinjectors are very useful devices for the rapid administration of the recommended drugs. They are well suited for emergency and mass casualty management, convenient to use and fast in action. A variety of autoinjectors are available viz., for nerve agent poisoning (atropine sulphate and pralidoxime chloride), anaphylactic shock (epinephrine), seizures (diazepam), and migraine (sumatriptan). The advantages of these autoinjectors are reviewed here with a focus on the requirement for autoinjectors for an antibacterial and an analgesic drug.

Keywords: Autoinjector, nerve agent, anaphylaxis, atropine sulphate, pralidoxime chloride, epinephrine, diazepam, sumatriptan, amikacin, buprenorphine

1. INTRODUCTION

A number of emergency situations occur in which the individual has to be attended immediately for possible first aid measures. Along with first aid measures specific drugs have to be administered at the site for reducing the morbidity and mortality. There may be situations and places where a qualified medical person may not be available and the emergency drugs have to be administered by self or any trained individual. Situations like nerve agent exposure in a war scenario or organophosphorus pesticide poisoning require immediate administration of atropine sulphate and pralidoxime chloride to reduce the mortality[1]. A device for self administration of these drugs, the reusable Autoject Injectors were designed for military applications in India[2]. Similarly for other emergency situations like seizures, anaphylaxis, migraine, etc., also require immediate administration of the recommended drugs, preferably by the autoinjectors in which the individual *per se* or the companion can administer the drug. These autoinjectors are different from the insulin pen in which the needle is present inside a cartridge containing the drug for intramuscular administration. Other than convenience these autoinjectors are well suited for emergency and mass casualty management. They can deliver the drugs by deep i.m. injection with a spray effect thereby increasing the area of absorption and the effects are closure to i.v. injection. The needle is not visible in these autoinjectors and the injection will be painless. A variety of autoinjectors are available for emergency and critical situations, mostly in the developed countries. Many of the developed and developing countries possess atropine sulphate and pralidoxime chloride autoinjectors as antidote for nerve gas poisoning only for the military personnel (Table 1).

2. AUTOINJECTOR AS EMERGENCY TREATMENT FOR NERVE AGENT POISONING

The nerve agents are organophosphorus compounds (Tabun, Sarin, Soman, and Vx), and are extremely toxic to mammalian system. They inhibit the enzyme acetylcholinesterase (*AChE*) irreversibly leading to the accumulation of the neurotransmitter, acetylcholine (*ACh*) and the effects are due to the action on the muscarinic and nicotinic receptors. The symptoms are constriction of pupil, perspiration, muscular twitching, decreased heart rate and blood pressure. At high concentrations there will be convulsions and individual will die due to respiratory failure in a very short time of exposure. The emergency measures are to stop further exposure by removing the individual from the contaminated environment, artificial respiration and drug treatment with atropine sulphate and an oxime. Atropine sulphate is a competitive inhibitor of acetylcholine, acts mainly on the parasympathetic muscarinic receptors. The initial dose is 2 mg, i.m or i.v. The oximes are reactivators of the inhibited *AChE*. Atropine sulphate blocks only the muscarinic effects and it has no action on the nicotinic effects of acetylcholine viz., muscular weakness and paralysis of the respiratory muscles. These effects can be relieved by reactivating the inhibited *AChE* by oximes which has to be administered along with atropine sulphate. The commonly used oximes are pralidoxime, obidoxime, *HI-6* and *HLo7* (bispyridinium oximes). The dose of pralidoxime is 600 mg, i.m or i.v. The autoinjectors are handy devices for the immediate administration of these drugs. They contain drug filled cartridges with a needle inside for intramuscular administration either in the thigh or in the buttocks, by a simple actuating mechanism[2,3]. Atropine sulphate and Pralidoxime Chloride are generally used

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Table 1. Autoinjector devices for intra-muscular administration of drugs for emergency and critical situations

Condition or Disease	Drugs	World	India
Carbamate insecticide poisoning	Atropine sulphate (2 mg)	USA, Europe, Russia, Australia and Japan	Not available
Organophosphate insecticide poisoning	Atropine sulphate (2 mg) and Pralidoxime (600 mg) chloride or Obidoxime (220 mg)	USA, Europe, Russia, Australia and Japan	Not available
Nerve gas poisoning	Atropine sulphate (2 mg) and Pralidoxime chloride (600 mg)	Many of the developed and developing countries for the military personnel	Available for the military personnel only
Seizures in adults	Diazepam (10 mg)	USA, Europe and Japan	Not available
Anaphylaxis	Epinephrine or adrenaline (0.15 or 0.30 mg)	USA, Europe and Australia	Not available
Migraine	Sumatriptan (6 mg)	USA, Europe, Australia and Japan	Not available
Autoimmune disease	Disease modifying drugs (varying doses)	USA	Not available
Antibacterial autoinjector	Amikacin (500 mg)	-	Proposed
Analgesic autoinjector	Buprenorphine (0.6 mg)	-	Proposed

in the autoinjectors by many countries. Defence Research and Development Organisation (DRDO) has developed Autoject Injectors that are reusable by replacing the drug cartridges. They are very sturdy and can penetrate the nuclear, biological and chemical (NBC) warfare suit, and deliver the drugs deep intramuscularly, within 5 s as shown in Fig. 1.

Figure 1. The reusable Autoject Injectors of atropine sulphate and pralidoxime chloride in a combo pack. Atropine sulphate Autoject Injector can be taken out first followed by pralidoxime chloride Autoject Injector.

Compared with manual intramuscular injection, autoinjector enhances drug absorption rate. In a crossover experiment healthy volunteers were administered atropine sulphate and pralidoxime chloride in a single intramuscular site by either a multichambered autoinjector or a device which delivers the drugs in two separate intramuscular sites. Atropine absorption was assessed by the appearance of atropine in the serum and by changes in heart rate, salivary secretion, pupil diameter, and near vision accommodation. Atropine absorption was significantly greater in the first 30 min following injection with two separate autoinjectors[4]. In one study commercially available autoinjectors were filled with atropine sulphate either alone (2 mg), or in combination with *HI-6* (500 mg) or HLo7 (200 mg) and injected in beagle dogs. It was found that the atropine absorption half-time (7 min) was not affected by combination with the oximes[5].

The stability of *HI-6* in solution is not good. When atropine sulphate and *HI-6* were mixed and stored for 3 to 14 days at 40 °C, atropine alone showed stability[6]. Hence dry/wet autoinjectors were developed in which the atropine solution dissolve the *HI-6* before injection. The tolerance, bioavailability and pharmacokinetics of 500 mg of *HI-6* or 200 mg of *HLo7* in combination with 2 mg atropine sulphate, delivered by two dry/wet autoinjectors were investigated in dogs. The dogs tolerated all the injections without any symptoms of discomfort[7]. In another study the antidote combination was packed in two plastic compartments separated by a barrier film. One of them contained *HI-6* powder and the other contained atropine and avizafone (prodiazepam) in a liquid mixture. The plastic compartments were mounted in an autoinjector device to study the dissolution of *HI-6* by ejection of the solution. After 6 months of packing the autoinjector mechanism showed complete dissolution of *HI-6* powder in the liquid mixture and the antidote combination was stable[8].

A dual chamber autoinjector containing 500 mg *HI-6* and 2 mg atropine sulphate was tested in anaesthetised pigs. The pharmacokinetics and pharmacodynamics of the drugs were compared with those after conventional syringe administration by i.m. and i.v. The results showed that *HI-6* and atropine sulphate can be given i.m. by the autoinjector with the same effectiveness of i.v. administration. The human dose was tolerated by the pigs and no overt signs of toxicity were observed[9]. The therapeutic effectiveness of the dual chamber

autoinjector containing 500 mg *HI-6* and 2 mg atropine sulphate was tested in anesthetised pigs poisoned by a lethal dose of soman. The symptoms of poisoning were reduced in 15-20 min after the drug therapy and all pigs survived soman intoxication without ventilatory assistance. The administration of either atropine alone or atropine and soman had no significant effect on the pharmacokinetics of *HI-6* in the anesthetised pigs[10]. A three chambered autoinjector consisting of atropine, oxime, and diazepam is an ideal device for emergency treatment[11].

In a terrorist attack involving chemical warfare agents, the civilian population including children will be affected. Autoinjectors may be a readily available source of pralidoxime for potential intramuscular use in small children. The autoinjectors available for self injection are in general meant for adults. Atropine overdose is generally well tolerated in young children. The use of adult formulated atropine and pralidoxime autoinjectors will deliver doses above current recommendations for infants and children. Children under one year of age should be given 0.5 mg of atropine, while children over one year of age should be given a full dose of atropine[12]. If need arises the atropine and pralidoxime can be discharged into small sterile vials to facilitate intramuscular injection on a milligram per kilogram basis for small children. The autoinjector contents can be easily discharged into the vials without need for practice even when investigators were garbed in protective gear. A small core of rubber stopper might be injected into the vial and the vial contents need to be withdrawn carefully before reinjection. In an emergency situation it is also possible to convert the i.m. formulation to the i.v. formulation without losing the stability and sterility[13]. In a three year old boy, accidental injury occurred by pralidoxime chloride autoinjector[14]. In one instance the atropine autoinjector was misused by an individual in a suicidal attempt resulting in anticholinergic toxic effects. The patient was treated successfully[15].

3. AUTOINJECTORS FOR SEIZURES

The treatment of organophosphate poisoning is based mainly on atropine and an oxime. An anticonvulsant is also required to terminate the seizures and to prevent delayed permanent brain damage. In order to control the tremors and convulsions diazepam can be used. Midazolam, a water-soluble benzodiazepine agonist, has the advantage of rapid absorption following intramuscular administration. In mass casualty situations, the availability of an autoinjector, filled with midazolam, might be a further advantage. The plasma pharmacokinetics of midazolam after administration by an autoinjector was compared with conventional intramuscular administration in pigs. During the first 15 min after injection, significantly higher plasma concentration of midazolam was detected following autoinjector administration, compared with the i.m. injection[16]. Acute repetitive seizures can sometimes progress to status epilepticus. Presently the approved treatment which can be administered by non-medical personnel is diazepam rectal gel. Rectal administration can be difficult, inconvenient and objectionable and hence diazepam autoinjector has been developed for intramuscular injection. The diazepam absorption is faster and can be safely and reliably administered using the autoinjector[17].

4. AUTOINJECTOR AS EMERGENCY TREATMENT FOR ANAPHYLAXIS

Anaphylaxis is defined as sudden onset of severe allergic reaction and may also cause death. Certain individuals are allergic to proteins present in some food materials. The symptoms are from mild rashes and swelling to severe anaphylactic shock. Epinephrine is the treatment of choice for anaphylaxis and it must be administered promptly. Delay in administration of epinephrine is a known risk factor for food allergy related mortality. Intramuscular injection of epinephrine into the lateral thigh is the preferred route for therapy in first-aid treatment. Epinephrine autoinjectors are currently available in only 2 fixed doses: 0.15 mg and 0.30 mg[18]. Epinephrine can be life saving in episodes of anaphylaxis, yet it is under prescribed and underused. In general, individuals with food allergy may not have epinephrine readily available. Epinephrine should be prescribed to patients who already experienced at least one food-induced anaphylactic episode. In a study in Italy epinephrine autoinjector is prescribed to 13 per cent patients. Italian allergy specialists prescribe epinephrine autoinjectors on the basis of clinical history of severe reactions[19]. In a community survey of 1885 participants in Canada who reported anaphylaxis, 27 per cent were epinephrine autoinjector users[20]. In another study of 63 food-allergic children in USA, 59 per cent had an epinephrine autoinjector[21]. There is an under prescription of epinephrine autoinjectors in school-going adolescents. In a study in Dutch high schools out of 2284 students interviewed, 23 were considered for the use of epinephrine autoinjectors and only 2 of them had been prescribed the medication[22]. In UK, the risk that a food allergic child will die from a food allergic reaction is about 1 in 8,00,000 per year. The food allergic child with asthma may be at higher risk. The American Academy of Pediatrics and the American Heart Association have published guidelines stressing the need for school leaders to establish emergency-response plans to deal with life-threatening medical emergencies in children. For this, school nurses reported the availability of epinephrine autoinjector one among the medical emergency response plans[23].

Peanut allergy occurs as one of the most severe food-related allergic reactions. Delayed administration of epinephrine and failure to carry epinephrine contribute to fatal outcomes. Epinephrine (adrenaline) autoinjectors are prescribed in Australia for peanut and nut allergy children[24]. Cold urticaria also occurs in children, and may be associated with anaphylaxis with asthma and allergic rhinitis. They should be cautioned regarding the risk of anaphylaxis and provided with an epinephrine autoinjector[25]. Children with history of anaphylaxis to food, hymenoptera venom or substances should be given either subcutaneously or intramuscularly epinephrine autoinjector (0.3 mg). It was observed that epinephrine given by intramuscular route is faster than the subcutaneous route. This delay in absorption may have important clinical implications during an episode of systemic anaphylaxis and hence intramuscular route of injection is preferable[26]. Epinephrine for first aid use by parents and other caregivers and in the form of an autoinjector device is often prescribed for children who have had previous anaphylactic reactions. Recurrent generalised allergic reactions occur more common

in those with food compared with insect venom anaphylaxis. When the epinephrine autoinjector is used appropriately, it appears to reduce subsequent morbidity from anaphylaxis[27]. Patients with insect venom allergy should be able to distinguish a life-threatening systemic reaction from other reactions after an insect sting. Therefore patients with venom allergy should also be well trained in self-administration of epinephrine[28]. Anaphylaxis has a variety of causes including foods, latex, drugs, and hymenoptera venom. Epinephrine given early is the most important intervention. Correct use of epinephrine autoinjector is required and should be available to the sensitised patients at all times[29]. Anaphylaxis from latex products is also known. Immediately after contact with latex the individual will experience urticaria, nasorhinitis, conjunctivitis, asthma, hypotension and shock. Health care workers, children with spina bifida, patients with a history of urogenital procedures, and employees of rubber manufacturing plants have a higher incidence. It is recommended that latex-sensitive patients should be given an epinephrine autoinjector[30]. In the case of a 44-year-old woman who took 20 mg of escitalopram in addition to her usual 10-mg dose showed palpitation, diaphoresis, dyspnea, swelling of the lips and tongue, and fixed upward deviation of the right eye. Partial recovery of all symptoms was observed after epinephrine administration (0.3 mg) by autoinjector[31].

As an athletic emergency preparedness, schools can also equip with epinephrine autoinjectors. Exercise-induced anaphylaxis is a rare disorder characterised by severe allergic response occurring after mild-to-strenuous physical activity. This disorder is especially important due to the recent increase in physical activity and health fitness. The mechanism may be due to mast cell degranulation and inflammatory mediator generation. Clinical manifestations usually occur after 10 minutes of exercise, and follow a specific sequence, starting with pruritis, urticarial lesions, respiratory distress and vascular collapse. Treatment of exercise-induced anaphylaxis consists of epinephrine and anti-histamines. The individual needs to be educated on preventive measures and prescribed with an epinephrine autoinjector in the event of an emergency[32].

In a massive study conducted on 40 human volunteers, a total of 960 injections (480 with autoinjector and 480 with syringe) with a sterile solution of 0.2 mL or 1 mL were given to assess the difference in accuracy, consistency of injected volume, skin reaction and pain associated with the injection. This study indicated that the autoinjector was similar to a syringe in terms of performance and safety in administering the injections. Pain associated with the injection was significantly lower with the autoinjector than with the syringe and all subjects preferred the autoinjector for future treatment[33]. The effectiveness of injection of epinephrine autoinjector was also tested using marbleised beef and it was observed that holding the device in place for 1 s is as effective as 10 s[34]. The injection and functional properties of the autoinjectors under standard conditions, after dynamic and mechanical stresses, and in the presence of denim was also studied. The effective needle length or depth of delivery was found to be 21 mm which is better than the conventional syringe[35]. The epinephrine autoinjector delivers the drug with a needle length of 1.4 cm. The distance from skin to muscle in the anterolateral aspect of the thigh shows that this length is less for the proper delivery of the drug[36]. Majority of physicians do not know how to use epinephrine autoinjectors. After a training, the correct use of epinephrine autoinjector improved from 23 per cent to 74 per cent[37]. Part of the problems related to the use of epinephrine autoinjector may be related to the design of the autoinjector. The design should be simple with colour coding and printed instructions for the correct usage of the device[38].

Accidental parenteral injections of epinephrine by autoinjector do occur. In general the injection sites are digits, palm and rarely thigh. The symptoms include swelling, pallor, pain, and erythema. Simple massage or warm soak is sufficient. Some injection injuries can be treated in an emergency facility and many can be treated at home[39]. Local injection of phentolamine is effective for up to 13 hours after the inadvertent digital instillation of adrenaline[40]. Digital ischemia secondary to accidental injection of epinephrine can be quickly reversed with the use of 0.5 per cent phentolamine mesylate injection at the site. A physician accidentally injected epinephrine into his left thumb. He developed swelling, pallor, and pain in the thumb. Treatment included topical nitroglycerin, oral vasodilators and warming of the thumb[41].

5. AUTOINJECTORS IN THE RELIEF OF MIGRAINE ATTACK

Migraine is a common debilitating headache characterised by throbbing pain. The headache will be severe, unilateral and pulsating which will be aggravated by physical work and will be accompanied by nausea, vomiting and intolerance to light and sound. About 15 per cent to 20 per cent of the patients will have an aura in that case there will be visual, sensory and motor disturbances. At times local edema will also be present. Though, the pathophysiology of migraine is not clearly known, but 5-HT involvement has been established as there is an increase in the urinary excretion of its metabolite 5-HIAA[42].

The drugs for the relief of migraine attack are either 5-HT receptor agonists or antagonists and other agents. They include ergotamine, non-steroidal anti-inflammatory agents with metaclopramide, β-adrenoceptor antagonists, α2 adrenoceptor agonists, selective calcium channel blockers, tricyclic antidepressants, cyproheptadine and sumatriptan and its congeners. Sumatriptan and its congeners are selective 5-HT1D receptor agonists[43]. They block trigeminal nerve transmission, constrict the dilated extracranial blood vessels and suppress inflammation. Sumatriptan is available as an oral formulation which has poor bioavailability and also as an injectable.

Sumatriptan by autoinjector is an alternative to sumatriptan injectable. In general, sumatriptan taken subcutaneously using an autoinjector at home is an effective and well tolerated acute treatment for migraine. In a study of 230 subjects with incidence of migraine, placebo or sumatriptan was given during the first attack and was reversed in the second attack. 62 per cent showed headache relief in 2 hrs following sumatriptan compared to 15 per cent in the placebo group. Nausea and visual disturbances were also reduced in the sumatriptan group[44]. In another study of 169 subjects, preventive oral treatment with sumatriptan, 100 mg three times a day for 7 days did not

produce a significant reduction in the number or severity of cluster headache attacks. However, sumatriptan 6 mg given by autoinjector showed better results[45]. In a multicentre open longitudinal clinical trial, 479 patients suffering from migraine with or without aura were given sumatriptan, 6 mg for self-administration by an autoinjector, subcutaneously. Sumatriptan by autoinjector was found to be well tolerated and was more effective when compared to conventional treatments. The headache response to customary treatment was 30 per cent at 2 hr, while in autoinjector group it was 82 per cent at 2 hr[46].

6. AUTOINJECTORS FOR OTHER ORPHAN DRUGS

Multiple sclerosis is an autoimmune disease of the central nervous system characterised by widespread lesions in the brain and spinal cord. All established disease-modifying drugs for multiple sclerosis require parenteral administration that can cause difficulties for some patients. The ability to self-inject in patients with multiple sclerosis reduces the risk of missed injections and the anxiety due to injection. The use of an autoinjector may improve patients' ability to self-inject. Autoinjectors that allow automatic injection at the press of a button is convenient for injection compared with manual injection. An electronic autoinjector is available for subcutaneous administration of interferon beta-1a (IFN-β-1a)[47]. In a study on multiple sclerosis patients the use of autoinjector, for intramuscular delivery of IFN-β-1a was studied. The autoinjector was found to be safe and effective device for administration of IFN-β-1a and an alternative method for self-injection comparable to the prefilled syringe[48]. Patients with relapsing multiple sclerosis receiving subcutaneous or intramuscular interferon β-1a, interferon β-1b, or glatiramer acetate, preferred the autoinjectors over the prefilled syringes[49]. Hepatitis C is an infectious disease affecting primarily the liver, caused by the hepatitis C virus. Peginterferon α-2a (40 kDa) is administered to Hepatitis C patients along with ribavirin using a prefilled syringe. The peginterferon α-2a disposable autoinjector is also available and in a study patients reported that the autoinjector is more convenient and easier to use compared to the prefilled syringe. No pain or discomfort was experienced using the autoinjector[50]. An electronic injection device for growth hormone is also available and majority expressed a desire to use the device[51]. Erectile dysfunction is characterised by the inability to develop or maintain an erection of the penis during sexual performance. Aviptadil is an injectable formulation of vasoactive intestinal polypeptide (VIP) in combination with an adrenergic antagonist phentolamine. Aviptadil in combination with phentolamine is expected to provide a new and effective alternative for erectile dysfunction. In one study on erectile dysfunction VIP/phentolamine autoinjector was found to cause less pain compared to conventional injection[52].

7. SHELF LIFE EXPIRED AUTOINJECTORS FOR EMERGENCY

Emergency planning for mass casualty situations is very important. Since the drug therapy for nerve agent attack is a rare occasion, large scale production of the autoinjectors is not possible. In one study an attempt was made to estimate atropine beyond its labelled shelf life. Significant amount of atropine was found in all the samples. All samples remained clear and colourless, and no substantial amount of tropine was found[53]. In another study the effect of temperature variation on the stability of atropine was evaluated. It was observed that atropine can be stored at temperatures of up to 29 °C for up to 45 days and tolerate temperature spikes of up to 52 °C for a cumulative time of 13 hr without undergoing degradation[54]. Properly stored lyophilised pralidoxime chloride was found to be chemically stable beyond its expiration date. The pralidoxime chloride stored in the autoinjector was also stable beyond its labelled shelf life, but one of its degradation products, N-methyl pyridinium carboxaldehyde was also detected[55]. In a study autoinjectors containing 300 mg/mL of pralidoxime chloride stored at room temperature for 8-10 years, showed less than 15 µg of cyanide per autoinjector by using an ion-selective electrode. An additional storage for 3-4 years at 5 °C and analysed by HPLC showed more than 90 per cent activity[56]. Shelf life expired epinephrine autoinjectors were evaluated for its bioavailability in rabbits and also by analytical method. The study showed a decrease in the content of epinephrine. The shelf life expired autoinjectors can be used as long as no discoloration or precipitates occur, and the potential benefit of using it is greater than the potential risk of a suboptimal epinephrine dose or of no epinephrine treatment[57].

8. REQUIREMENT FOR AUTOINJECTORS WITH ANTIBACTERIAL AND ANALGESIC DRUG

There are several emergency situations in which the individual may be injured severely and the medical attention may get delayed. For instance in the military service life (army, navy, air force and paramilitary staff) during training and operation, low intensity conflicts, road accidents and also natural disasters such situations may occur in which the individual may be with great pain and there may be chances of infection. In such conditions autoinjectors with an antibacterial drug and an analgesic drug will be very much useful for field administration by an authorised person.

Aminoglycosides are potent bactericidal antibiotics that act by binding to 30s ribosomal subunits. They are particularly active against aerobic, gram-negative bacteria and act synergistically against certain gram-positive organisms. Amikacin is emerging as one of the most effective aminoglycosides on the basis of resistance rates, pharmacokinetics and safety. It is particularly effective against gentamycin resistant organisms[58,59]. Amikacin sulphate is soluble in water and stable, and hence better suited for autoinjector. The adult dose is 500 mg i.m. and can be given every 12 hr.

Opioids are the drugs of choice for the treatment of severe pain. Among the opioids the newer agonist-antagonist opioids cause less dysphoric side effects and the respiratory depression is also comparatively less. The risk of dependence is also less, so that these drugs are safer for the treatment of chronic pain. In this class buprenorphine is preferred as it can be used to control moderate to severe pain, effective parenterally, orally and sublingually, and has a prolonged duration of action of 12 hr after a single dose[60]. Buprenorphine hydrochloride is soluble

in water and stable and hence better suited for autoinjector. The adult dose is 0.6 mg i.m. and can be given every 6 hr.

9. CONCLUSION

Coping for emergency situations is very important that will relatively reduce the morbidity and mortality. Autoinjector devices with the recommended drugs are ideal for such applications.

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