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Autoinjector device for rapid administration of drugs and antidotes in emergency situations and in mass casualty management

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Abstract

There are several situations such as medical emergencies and incidents involving mass casualties where drugs and antidotes have to be administered immediately along with other first aid at the site of the event. Self-administration by the affected person or by a companion is required as a life-saving measure. Autoinjector devices (AIDs) are useful for the rapid administration of drugs and antidotes and they can also be used by those who have not been medically trained. This makes them very convenient for emergency and mass casualty management. An AID has a drug cartridge with an embedded needle for subcutaneous or intramuscular injection, which is usually painless. The drugs are delivered slowly by the AID across a large area in the muscle, which increases the absorption and the drug effects are equal to that of intravenous administration. A variety of AIDs are available, such as atropine and pralidoxime for nerve agent poisoning, epinephrine for anaphylactic shock and allergy, diazepam for seizures, sumatriptan for migraine, amikacin for antibacterial treatment, buprenorphine for pain relief and monoclonal antibodies for a variety of diseases. This review describes the published peer-reviewed literature identified by online searches of journal databases.

Keywords

Autoinjector device, nerve agent, anaphylaxis, seizures, migraine, antimicrobial, analgesic, drugs, antidotes, monoclonal antibodies

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Introduction

There are several situations such as medical emergencies and mass casualty incidents when the drugs and antidotes have to be administered immediately together with other first aid at the site of the event.[1] Drugs and antidotes can be administered to humans using several routes, although for some of the routes the rate of absorption is slow or the drugs require a qualified medical person to administer the injection. Self-administration of the drug by the affected individual or by a companion is required as a life-saving measure. Emergency situations like nerve gas exposure, pesticide poisoning, anaphylaxis, seizures, migraine and several other conditions require immediate drug administration. A drug filled autoinjector device (AID) is an ideal choice in situations such as these. The AID has a drug cartridge with an embedded needle for subcutaneous (s.c.) or intramuscular (i.m.) injection. They are convenient for emergency and mass casualty management. The drugs are delivered slowly by the AID across a large area in the muscle, which increases the absorption.[2] Hence, the effect is equal to an intravenous injection.[3] The needle is inside the device and not visible. The injection administered by the AID is painless. A large study was conducted on human participants comparing AIDs and normal injections using a sterile solution.[4] The results showed less pain with the AID and the performance was similar to a syringe.[4] The use of AIDs is a fast-growing area of drug administration. Several antidotes, monoclonal antibodies and life-saving drugs are available for safe and effective delivery through s.c. and i.m. routes. This review describes the published peer-reviewed literature identified by online searches of journal databases.

AID for nerve gas poisoning

The nerve gases (e.g. tabun, sarin, soman and VX) are organophosphorus compounds. They irreversibly inhibit the enzyme acetylcholinesterase (AChE). This results in an accumulation of acetylcholine (ACh), a neurotransmitter, leading to muscarinic and nicotinic receptor stimulation.[5] They are extremely toxic and the symptoms are constriction of the pupil, tightness in the chest with difficulty in breathing, muscular twitching, bradycardia, hypotension, perspiration and involuntary micturition.[5] When the exposure is high there are tremors and convulsions. Death occurs due to respiratory paralysis.[6]

Immediate action is required to prevent continuous exposure, which is usually achieved by decontamination, moving the individual to a clean environment or by donning a 'nuclear biological chemical' (NBC) suit, followed by artificial respiration and drug treatment. The recommended drugs are atropine sulphate and oxime.[5] Atropine sulphate competitively inhibits ACh and blocks the parasympathetic muscarinic effects, but not the nicotinic effects of muscle weakness and respiratory muscle paralysis.[7] The nicotinic effects can be treated by reactivating AChE with an oxime.[7] Hence, atropine sulphate and oxime are essential for nerve gas poisoning. The initial dose of atropine sulphate is 2 mg i.m. or intravenous (i.v.) and it has to be repeated if necessary.[7] The oximes are pralidoxime and bispyridinium oximes (obidoxime, HI 6 and HLö 7).[8] Pralidoxime is used at 600 mg i.m. or i.v.[9] In an emergency situation, it is not possible to administer the drugs manually and an AID is required for the delivery of the drugs i.m. into the thighs or the buttocks. The AID is very sturdy and can penetrate the NBC suit within 5 seconds to deliver the drugs (Figure 1). The dose of obidoxime is 220 mg (also available in an AID),[10] whereas HI 6 and HLö 7 are

Figure 1. Examples of reusable autoinjectors with drug cartridges for emergency situations and mass casualty management. The colour version of this figure is available at: http://imr.sagepub.com.

experimental drugs. Atropine–oxime preparations should be available in an AID for immediate use in the absence of medical personnel as an emergency device. This scenario is possible in the battlefield and also for civilian use as in the case of the Tokyo sarin gas incident, and also for possible organophosphorus insecticide poisoning during agricultural use in remote areas.[11,12]

When an AID is used, the drug absorption is faster due to the large area compared with a manual i.m. injection.[2] The human dose of HI 6 and atropine sulphate were compared using manual injection (i.m. and i.v.) and by AID in pigs.[13] HI 6 and atropine sulphate administered by AID showed equal effectiveness as the i.v. administration and the pigs tolerated the human dose.[13] Dual chamber (binary) AIDs are also available in which atropine is loaded in one chamber and the other chamber contains either pralidoxime chloride, obidoxime or HI 6.[14] In a study with a crossover design, atropine and pralidoxime were administered to humans using a multichambered AID at one i.m. site or by separate AIDs

at two i.m. sites.[15] In the first 30 minutes, atropine absorption was higher with the two separate autoinjectors.[15] However, when atropine and pralidoxime were administered together it did not reduce the overall absorption of atropine.[15] A combination of atropine sulphate and obidoxime also showed that this approach did not hinder the overall absorption.[10,16] When an AID with atropine alone (2 mg) or with HI 6 (500 mg) or HLö 7 (200 mg) was used in beagle dogs, the absorption of atropine was not affected by the oximes.[17] The results of this study demonstrated that instead of using a multichambered AID, the combination of atropine and oxime could be administered from one chamber.[18] HI 6 is not stable in solution.[18] A dry/wet AID is available and the HI 6 is dissolved in the atropine solution prior to injection.[18] A combination of 2 mg atropine sulphate with 500 mg HI 6 or 200 mg HLö 7 was investigated for tolerance, bioavailability and pharmacokinetics in dogs using a dry/wet AID.[19] The dogs tolerated the injections.[19] The effectiveness of a binary AID containing 500 mg HI 6 and 2 mg atropine was evaluated in pigs that had been given a lethal dose of soman by i.v. injection.[20] The symptoms were less and all pigs survived soman toxicity.[20] The administration of atropine alone or atropine with soman did not affect the absorption of HI 6.[20]

In terrorist attacks involving chemical warfare agents both adults and children are likely to be affected. In general, AIDs are for use in adults. An adult atropine dose can be tolerated by young children, but the adult pralidoxime dose cannot be given.[21] Children under 1 year require 0.5 mg of atropine and above 1 year they can be given the full dose.[21] In emergency situations, atropine and pralidoxime from the AID can be transferred into a sterile container and can be withdrawn to facilitate the administration of a lower dose. The solution can also be given by i.v. injection.[22]

AID for seizures

Atropine and oxime are the immediate first-line treatments for nerve agent poisoning. Even after the timely administration of these antidotes there may be seizures, which may cause permanent brain damage in the longer term.[23] To control tremors and seizures, a diazepam injection is also required as an AID.[23] A three-chamber AID with atropine, oxime and diazepam for emergency administration is available.[14] Seizures can also progress to status epilepticus and the recommended treatment by non-medical persons is diazepam rectal gel, but rectal instillation is difficult and undesirable.[24] An AID with diazepam has been developed for i.m. injection. The AID is safe and reliable, and the diazepam absorption is faster compared with a conventional needle and syringe or the gel.[25] Midazolam, another antiepileptic drug, is rapidly absorbed following i.m. administration.[2] The pharmacokinetics of midazolam when administered using an AID was compared with manual i.m. administration in pigs.[2] The study demonstrated a higher concentration of midazolam after 15 min with the AID compared with a manual injection.[2] Midazolam administered using an AID was as effective as i.v. lorazepam in status epilepticus.[3]

AID for anaphylaxis

A severe allergic reaction can cause anaphylaxis with hypotension and breathing difficulties, which can be fatal. Certain food materials are allergic to some individuals causing skin rashes, swelling and sometimes anaphylactic shock. Epinephrine is the recommended drug and must be given immediately. An AID with epinephrine at 0.15 and 0.30 mg doses is available.[26,27] Although epinephrine is a life-saving drug it is not readily available in many countries.[28,29] Among the food allergies, peanut

allergy is the most severe.[30] Delay in the administration of epinephrine may be fatal and there is a need for an AID.[30] Epinephrine administered by i.m. using an AID is more quickly absorbed than following an s.c. injection.[31] The pharmacokinetics of manual injection and AID use for epinephrine are similar.[32] For emergency drug administration, a needle length of approximately 21 mm is adequate.[33] Cold urticaria may cause anaphylaxis that requires an epinephrine AID.[34] Insect venom, latex and some drugs may also cause a systemic reaction leading to anaphylaxis and an epinephrine AID should be available to sensitive people.[35] Anaphylaxis following mild-to-strenuous exercise is a rare disorder characterized by a severe allergic response due to inflammatory mediator generation.[36] An epinephrine AID should be available as a preventive measure for athletic emergencies due to exercise-induced anaphylaxis.[36]

AID for migraine

Migraine is characterized by unilateral, pulsating and moderate-to-severe headache with throbbing pain. Bright light, sound and physical work will aggravate migraine with nausea and vomiting. Some individuals will have an aura with visual, sensory and motor disturbances. Serotonin (5-HT) may be involved in migraine and 5-HT receptor agonists provide relief in migraine.[37] Sumatriptan is a selective 5-HT1D receptor agonist, which can control trigeminal nerve transmission, constrict extracranial blood vessels and reduce inflammation.[38] Orally given sumatriptan has poor bioavailability, so it is administered via an injection.[39] Sumatriptan is also available as an AID and is given subcutaneously for acute migraine attacks to control nausea and visual disturbances.[40] Sumatriptan 3 mg administered using an AID was well tolerated, safe and effective in adults with episodic migraine.[41]

AID with antibacterial and analgesic drugs

There are several emergency situations, such as military operations, road accidents, natural disasters (flooding, landslide, avalanche and earthquake) and terrorist attacks, when injured people will need treatment for severe pain and infection.[42,43] Medical care might not be available immediately, so an AID with an analgesic drug and an antibacterial drug would be useful for on-site administration.[44] The aminoglycoside antibiotic amikacin sulphate is water soluble, long acting, stable and bactericidal.[45] It is effective on aerobic gram-negative bacteria, a few gram-positive microorganisms and gentamycin-resistant organisms.[45] An AID with 500 mg amikacin sulphate has been developed with dual dose adjustment and a dilution facility for child and veterinary use.[46] It can also be used for bio-threat organisms.[47]

Opioids are recommended for severe pain. Buprenorphine hydrochloride, an agonist-antagonist opioid, causes less side-effects and respiratory depression than other opioids.[48] The risk of dependence is also less and it is safer for chronic pain than other opioids.[48] Buprenorphine hydrochloride is preferred for moderate-to-severe pain and it is effective orally as well as by parenteral routes with a long duration of action.[49] It is water soluble and stable, and hence an AID with 0.6 mg buprenorphine was developed.[48] Extensive preclinical studies carried out in animal models showed that an amikacin AID and a buprenorphine AID were tolerated, safe and well suited for mass casualty management.[50] A naloxone AID is very safe and effective for the management of opioid overdose.[51] A combination of buprenorphine and

Table 1. Summary of the available autoinjector devices for subcutaneous (s.c.), intramuscular (i.m.) and intracorporeal (i.c.) administration of a range of drugs.

Serial number	Autoinjector device and route	Clinical condition	Efficacy studies by countries	Preclinical or clinical studies
1	Atropine and an oxime, i.m. (pralidoxime, obidoxime, HI 6 and HLö 7)	Nerve agent poisoning	India, Israel, France, the Netherlands, Germany, Sweden, Czech Republic, UK, USA	Rat, guinea pig, rabbit, pig, dog, monkey, human
2	Diazepam i.m.	Seizures	Italy, USA	Human
3	Midazolam i.m.	Seizures	USA	Pig, human
4	Epinephrine i.m.	Anaphylaxis	Japan, Qatar, Saudi Arabia, Portugal, Spain, Greece, Bulgaria, Austria, France, Italy, Poland, Germany, Switzerland, the Netherlands, Finland, Sweden, UK, Mexico, Brazil, USA, Canada, Australia,	Human
5	Methotrexate s.c.	Rheumatoid arthritis	France, the Netherlands, Germany, USA	Human
6	Etanercept s.c.	Rheumatoid arthritis	France, Germany, Italy, Spain, UK	Human
7	Amikacin i.m.	Antibacterial	India	Rat, rabbit
8	Buprenorphine i.m.	Analgesic	India	Rat, rabbit
9	Naloxone i.m.	Opioid overdose	USA	Human
10	Ezetimibe s.c.	Hypercholesterolaemia	Switzerland, UK, USA	Human
11	Aviptadil and phentolamine i.c.	Erectile dysfunction	the Netherlands, UK	Human
12	Peginterferon β-1a Peginterferon β-1b s.c.	Multiple sclerosis	Germany, the Netherlands, Switzerland, Greece, Spain, Portugal, Italy, Romania, New Zealand, UK, USA, Canada	Human
13	Peginterferon α-2a s.c.	Hepatitis C	USA	Human

(continued)

Table 1. Continued

Serial number	Autoinjector device and route	Clinical condition	Efficacy studies by countries	Preclinical or clinical studies
14	Thrombolytic agents αIIbβ3 and αVβ3 i.m.	Myocardial infarction	USA	Primates
15	Alirocumab s.c.	Hypercholesterolaemia	France, Finland, the Netherlands, UK, USA	Human
16	Evolocumab s.c.	Hypercholesterolaemia	Switzerland, UK, USA	Human
17	Belimumab s.c.	Systemic lupus erythematosus	UK, USA	Human
18	Adalimumab s.c.	Rheumatoid arthritis and joint and bowel disease	Republic of Korea, Poland, Germany, Belgium, the Netherlands, Switzerland, UK, USA, New Zealand	Human
19	Golimumab s.c.	Rheumatoid arthritis and ulcerative colitis	Italy, Poland, Romania, Germany, Belgium, UK, USA, Russia	Human
20	Sarilumab s.c.	Rheumatoid arthritis	France, USA, Russia	Human
21	Tocilizumab s.c.	Rheumatoid arthritis	Spain, Germany, Switzerland, UK, Brazil, Mexico, USA, Canada	Human
22	Sirukumab s.c.	Rheumatoid arthritis	the Netherlands, USA	Human
23	Certolizumab pegol s.c.	Rheumatoid arthritis and psoriasis	Belgium, UK, USA	Human
24	Secukinumab s.c.	Psoriasis	China, Australia, Spain, Estonia, France, Germany, Czech Republic, Switzerland, UK, USA, Canada	Human
25	Ixekizumab s.c.	Psoriasis	Singapore, UK, USA	Human
26	Omalizumab s.c.	Anaphylaxis	Italy, Poland, UK, USA	Human
27	Canakinumab s.c.	Inflammatory diseases	India, Switzerland, USA	Human

naloxone might be better and could be considered.

AID for other drugs and monoclonal antibodies

Rheumatoid arthritis is a debilitating autoimmune disease. Methotrexate is widely used both as an initial therapy and as a long-term therapy.[52] Oral methotrexate at higher doses shows variations in absorption.[53] A prefilled AID is available for subcutaneous self-administration, which shows better bioavailability than oral administration and with fewer gastrointestinal side-effects.[54] The usability and acceptability of this AID was good, even among individuals with hand disability.[54] Multiple sclerosis, an autoimmune disease that affects the brain and spinal cord, is treated using disease-modifying drugs that require parenteral administration, which may cause difficulties for the individual.[55] An AID would be useful instead of a manual injection for these individuals so that they could regularly self-administer their drugs with less anxiety. Interferon beta-1a (IFN-β-1a) is available as an AID for s.c. injection.[56] The AID with IFN-β-1a is safe, convenient, effective and comparable with a prefilled syringe.[57] Hepatitis C is an infectious disease caused by the hepatitis C virus and it primarily affects the liver. Peginterferon alfa-2a is administered in combination with ribavirin using a prefilled syringe.[58] It is also available as a disposable AID, which is convenient and easy to use with no pain and discomfort.[58] Erectile dysfunction is a condition in which erection of the penis cannot be sustained during sexual performance. For this condition, an AID is available with aviptadil, a vasoactive intestinal polypeptide along with phentolamine.[59] It is less painful compared with a normal injection.[59] An AID for growth hormone injection is also available.[60] A variety of monoclonal antibodies in AIDs are being developed for diseases like rheumatoid arthritis, hypercholesterolaemia, multiple sclerosis, myocardial infarction, systemic lupus erythematosus, joint and bowel disease, ulcerative colitis and psoriasis, which are in various clinical stages.[61–65]The details of the range of available AIDs are presented in Table 1.

Conclusion

The administration of drugs using AIDs provides multiple benefits. For example, many parenteral drugs can be delivered using an AID, providing the advantages of safety, efficacy and fast absorption. The drug cartridges can be replaced after the shelf-life has been exceeded and the AID itself has the advantage of being reusable. The AID is also interchangeable. With the provision of being able to adjust the dose, an AID could be used to deliver emergency drugs to children. Since AIDs deliver the drug with a degree of force, they can also be used to deliver antidotes and vaccines for veterinary purposes in farm and pet animals.

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