Review

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. 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. Hence, the effect is equal to an intravenous injection. 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. The results showed less pain with the AID and the performance was similar to a syringe. 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. 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. When the exposure is high there are tremors and convulsions. Death occurs due to respiratory paralysis.

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. Atropine sulphate competitively inhibits ACh and blocks the parasympathetic muscarinic effects, but not the nicotinic effects of muscle weakness and respiratory muscle paralysis. The nicotinic effects can be treated by reactivating AChE with an oxime. 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. The oximes are pralidoxime and bispyridinium oximes (obidoxime, HI 6 and HLö 7). Pralidoxime is used at 600 mg i.m. or i.v. 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), whereas HI 6 and HLö 7 are
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.\textsuperscript{11,12}

When an AID is used, the drug absorption is faster due to the large area compared with a manual i.m. injection.\textsuperscript{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.\textsuperscript{13} HI 6 and atropine sulphate administered by AID showed equal effectiveness as the i.v. administration and the pigs tolerated the human dose.\textsuperscript{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.\textsuperscript{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.

\textbf{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.
at two i.m. sites.\textsuperscript{15} In the first 30 minutes, atropine absorption was higher with the two separate autoinjectors.\textsuperscript{15} However, when atropine and pralidoxime were administered together it did not reduce the overall absorption of atropine.\textsuperscript{15} A combination of atropine sulphate and obidoxime also showed that this approach did not hinder the overall absorption.\textsuperscript{10,16} When an AID with atropine alone (2 mg) or with HI 6 (500 mg) or HL\textsubscript{O} 7 (200 mg) was used in beagle dogs, the absorption of atropine was not affected by the oximes.\textsuperscript{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.\textsuperscript{18} HI 6 is not stable in solution.\textsuperscript{18} A dry/wet AID is available and the HI 6 is dissolved in the atropine solution prior to injection.\textsuperscript{18} A combination of 2 mg atropine sulphate with 500 mg HI 6 or 200 mg HL\textsubscript{O} 7 was investigated for tolerance, bioavailability and pharmacokinetics in dogs using a dry/wet AID.\textsuperscript{19} The dogs tolerated the injections.\textsuperscript{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.\textsuperscript{20} The symptoms were less and all pigs survived soman toxicity.\textsuperscript{20} The administration of atropine alone or atropine with soman did not affect the absorption of HI 6.\textsuperscript{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.\textsuperscript{21} Children under 1 year require 0.5 mg of atropine and above 1 year they can be given the full dose.\textsuperscript{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.\textsuperscript{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.\textsuperscript{23} To control tremors and seizures, a diazepam injection is also required as an AID.\textsuperscript{23} A three-chamber AID with atropine, oxime and diazepam for emergency administration is available.\textsuperscript{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.\textsuperscript{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.\textsuperscript{25} Midazolam, another antiepileptic drug, is rapidly absorbed following i.m. administration.\textsuperscript{2} The pharmacokinetics of midazolam when administered using an AID was compared with manual i.m. administration in pigs.\textsuperscript{2} The study demonstrated a higher concentration of midazolam after 15 min with the AID compared with a manual injection.\textsuperscript{2} Midazolam administered using an AID was as effective as i.v. lorazepam in status epilepticus.\textsuperscript{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.\textsuperscript{26,27} Although epinephrine is a life-saving drug it is not readily available in many countries.\textsuperscript{28,29} Among the food allergies, peanut
allergy is the most severe. Delay in the administration of epinephrine may be fatal and there is a need for an AID. Epinephrine administered by i.m. using an AID is more quickly absorbed than following an s.c. injection. The pharmacokinetics of manual injection and AID use for epinephrine are similar. For emergency drug administration, a needle length of approximately 21 mm is adequate. Cold urticaria may cause anaphylaxis that requires an epinephrine AID. 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. Anaphylaxis following mild-to-strenuous exercise is a rare disorder characterized by a severe allergic response due to inflammatory mediator generation. An epinephrine AID should be available as a preventive measure for athletic emergencies due to exercise-induced anaphylaxis.

**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. Sumatriptan is a selective 5-HT1D receptor agonist, which can control trigeminal nerve transmission, constrict extracranial blood vessels and reduce inflammation. Orally given sumatriptan has poor bioavailability, so it is administered via an injection. Sumatriptan is also available as an AID and is given subcutaneously for acute migraine attacks to control nausea and visual disturbances. Sumatriptan 3 mg administered using an AID was well tolerated, safe and effective in adults with episodic migraine.

**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. 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. The aminoglycoside antibiotic amikacin sulphate is water soluble, long acting, stable and bactericidal. It is effective on aerobic gram-negative bacteria, a few gram-positive microorganisms and gentamycin-resistant organisms. An AID with 500 mg amikacin sulphate has been developed with dual dose adjustment and a dilution facility for child and veterinary use. It can also be used for bio-threat organisms.

Opioids are recommended for severe pain. Buprenorphine hydrochloride, an agonist-antagonist opioid, causes less side-effects and respiratory depression than other opioids. The risk of dependence is also less and it is safer for chronic pain than other opioids. 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. It is water soluble and stable, and hence an AID with 0.6 mg buprenorphine was developed. 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. A naloxone AID is very safe and effective for the management of opioid overdose. A combination of buprenorphine and

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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 HL07) | 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            | Multiple sclerosis | Germany, the Netherlands, Switzerland, Greece, Spain, Portugal, Italy, Romania, New Zealand, UK, USA, Canada | Human |
| 13            | Peginterferon β-1b s.c.       |                    | USA                           | Human                        |

(continued)
| Serial number | Autoinjector device and route | Clinical condition | Efficacy studies by countries | Preclinical or clinical studies |
|---------------|-----------------------------|--------------------|------------------------------|-------------------------------|
| 14            | Thrombolytic agents zIIb/3 and zV/3 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. Oral methotrexate at higher doses shows variations in absorption. A prefilled AID is available for subcutaneous self-administration, which shows better bioavailability than oral administration and with fewer gastrointestinal side-effects. The usability and acceptability of this AID was good, even among individuals with hand disability. 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. 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. The AID with IFN-β-1a is safe, convenient, effective and comparable with a prefilled syringe. 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. It is also available as a disposable AID, which is convenient and easy to use with no pain and discomfort. 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. It is less painful compared with a normal injection. An AID for growth hormone injection is also available. 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. 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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**References**

1. Park JO, Shin SD, Song KJ, et al. Epidemiology of emergency medical services-assessed mass casualty incidents
according to causes. J Korean Med Sci 2016; 31: 449–456.
2. Levy A, Kushnir M, Chapman S, et al. Characterization of early plasma concentrations of midazolam in pigs after administration by an autoinjector. Biopharm Drug Dispos 2004; 25: 297–301.
3. Silbergleit R, Lowenstein D, Durkalski V, et al. Lessons from the RAMPART study – and which is the best route of administration of benzodiazepines in status epilepticus. Epilepsia 2013; 54: 74–77.
4. Berteau C, Schwarzenbach F, Donazzolo Y, et al. Evaluation of performance, safety, subject acceptance, and compliance of a disposable autoinjector for subcutaneous injections in healthy volunteers. Patient Prefer Adherence 2010; 5: 379–388.
5. Ganesan K, Raza SK and Vijayaraghavan R. Chemical warfare agents. J Pharm Bioallied Sci 2010; 2: 166–178.
6. Figueiredo TH, Apland JP, Braga MFM, et al. Acute and long-term consequences of exposure to organophosphate nerve agents in humans. Epilepsia 2018; 59: 92–99.
7. Sidell FR and Borak J. Chemical warfare agents: II. Nerve agents. Ann Emerg Med 1992; 21: 865–871.
8. Kuca K, Cabal J, Kassa J, et al. A comparison of the potency of the oxime HLÖ-7 and currently used oximes (HI-6, pralidoxime, obidoxime) to reactivate nerve agent-inhibited rat brain acetylcholinesterase by in vitro methods. Acta Medica (Hradec Kralove) 2005; 48: 81–86.
9. Kobrick JL, Johnson RF and McMenemy DJ. Effects of atropine/2-PAM chloride, heat, and chemical protective clothing on visual performance. Aviat Space Environ Med 1990; 61: 622–630.
10. Ettehadi HA, Ghalandari R, Shafaati A, et al. Development of a combined solution formulation of atropine sulfate and obidoxime chloride for autoinjector and evaluation of its stability. Iran J Pharm Res 2013; 12: 31–36.
11. Tu AT. Aum Shinrikyo’s chemical and biological weapons: more than sarin. Forensic Sci Rev 2014; 26: 115–120.
12. Aodah A, Bafail RS and Rawas-Qalaji M. Formulation and evaluation of fast-disintegrating sublingual tablets of atropine sulfate: the effect of tablet dimensions and drug load on tablet characteristics. AAPS PharmSciTech 2017; 18: 1624–1633.
13. Nyberg AG, Cassel G, Jeneskog T, et al. Pharmacokinetics of HI-6 and atropine in anaesthetized pigs after administration by a new autoinjector. Biopharm Drug Dispos 1995; 16: 635–651.
14. Bajgar J. Optimal choice of acetylcholinesterase reactivators for antidotal treatment of nerve agent intoxication. Acta Medica (Hradec Kralove) 2010; 53: 207–211.
15. Friedl KE, Hannan CJ Jr, Schadler PW, et al. Atropine absorption after intramuscular administration with 2-pralidoxime chloride by two automatic injector devices. J Pharm Sci 1989; 78: 728–731.
16. Sharma R, Gupta PK, Mazumder A, et al. A quantitative NMR protocol for the simultaneous analysis of atropine and obidoxime in parenteral injection devices. J Pharm Biomed Anal 2009; 49: 1092–1096.
17. Thiermann H, Radtke M, Spöhrer U, et al. Pharmacokinetics of atropine in dogs after i.m. injection with newly developed dry/wet combination autoinjectors containing HI 6 or HLÖ-7. Arch Toxicol 1996; 70: 293–299.
18. Schlager JW, Dolzine TW, Stewart JR, et al. Operational evaluation of three commercial configurations of atropine/HI-6 wet/dry autoinjectors. Pharm Res 1991; 8: 1191–1194.
19. Spöhrer U, Thiermann H, Klimmek R, et al. Pharmacokinetics of the oximes HI 6 and HLÖ-7 in dogs after i.m. injection with newly developed dry/wet autoinjectors. Arch Toxicol 1994; 68: 480–489.
20. Göransson-Nyberg A, Cassel G, Jeneskog T, et al. Treatment of organophosphate poisoning in pigs: antidote administration by a new binary autoinjector. Arch Toxicol 1995; 70: 20–27.
21. Baker MD. Antidotes for nerve agent poisoning: should we differentiate children from adults? Curr Opin Pediatr 2007; 19: 211–215.
22. Henretig FM, Mechem C and Jew R. Potential use of autoinjector-packaged antidotes for treatment of pediatric nerve agent toxicity. Ann Emerg Med 2002; 40: 405–408.
23. Lallement G, Clarençon D, Masqueliez C, et al. Nerve agent poisoning in primates: antilethal, anti-epileptic and neuroprotective effects of GK-11. *Arch Toxicol* 1998; 72: 84–92.

24. Lamson MJ, Sitki-Green D, Wannarka GL, et al. Pharmacokinetics of diazepam administered intramuscularly by autoinjector versus rectal gel in healthy subjects: a phase I, randomized, open-label, single-dose, crossover, single-centre study. *Clin Drug Investig* 2011; 31: 585–597.

25. Garnett WR, Barr WH, Edinboro LE, et al. Diazepam autoinjector intramuscular delivery system versus diazepam rectal gel: a pharmacokinetic comparison. *Epilepsy Res* 2011; 93: 11–16.

26. Malling HJ, Hansen KS and Mosbech H. Indication for adrenalin autoinjector after anaphylaxis. *Ugeskr Laeger* 2012; 174: 1741–1743 [Article in Danish, English abstract].

27. Murad HAS and Serry DOA. Pattern of use of epinephrine as anti-anaphylactic at a university hospital, Saudi Arabia. *Biomed Res* 2018; 29: 2637–2639.

28. Flokstra-De Blok BM, Doriene Van Ginkel C, Roerdink EM, et al. Extremely low prevalence of epinephrine autoinjectors in high-risk food-allergic adolescents in Dutch high schools. *Pediatr Allergy Immunol* 2011; 22: 374–377.

29. Simons FE. Lack of worldwide availability of epinephrine autoinjectors for outpatients at risk of anaphylaxis. *Ann Allergy Asthma Immunol* 2005; 94: 534–538.

30. Ben-Shoshan M, Kagan R, Primeau MN, et al. Availability of the epinephrine autoinjector at school in children with peanut allergy. *Ann Allergy Asthma Immunol* 2008; 100: 570–575.

31. Simons FE, Roberts JR, Gu X, et al. Epinephrine absorption in children with a history of anaphylaxis. *J Allergy Clin Immunol* 1998; 101: 33–37.

32. Edwards ES, Gunn R, Simons ER, et al. Bioavailability of epinephrine from Auvi-Q compared with EpiPen. *Ann Allergy Asthma Immunol* 2013; 111: 132–137.

33. Schwitz A and Seeger H. Are adrenaline autoinjectors fit for purpose? A pilot study of the mechanical and injection performance characteristics of a cartridge-versus a syringe-based autoinjector. *J Asthma Allergy* 2010; 25: 159–167.

34. Alangari AA, Twarog FJ, Shih MC, et al. Clinical features and anaphylaxis in children with cold urticaria. *Pediatrics* 2004; 113: e313–e317.

35. Johnson RF and Peebles RS. Anaphylactic shock: pathophysiology, recognition, and treatment. *Semin Respir Crit Care Med* 2004; 25: 695–703.

36. Miller CW, Guha B and Krishnaswamy G. Exercise-induced anaphylaxis: a serious but preventable disorder. *Phys Sportsmed* 2008; 36: 87–94.

37. Negro A, Kovereck A and Martelletti P. Serotonin receptor agonists in the acute treatment of migraine: a review on their therapeutic potential. *J Pain Res* 2018; 11: 515–526.

38. Blumenfeld A, Gennings C and Cady R. Pharmacological synergy: the next frontier on therapeutic advancement for migraine. *Headache* 2012; 52: 636–647.

39. Monstad I, Krabbe A, Micieli G, et al. Preemptive oral treatment with sumatriptan during a cluster period. *Headache* 1995; 35: 607–613.

40. Russell MB, Holm-Thomsen OE, Rishøj Nielsen M, et al. Randomized double-blind placebo-controlled crossover study of subcutaneous sumatriptan in general practice. *Cephalalgia* 1994; 14: 291–296.

41. Landy S, Munjal S, Brand-Schieber E, et al. Efficacy and safety of DFN-11 (sumatriptan injection, 3mg) in adults with episodic migraine: an 8-week open-label extension study. *J Headache Pain* 2018; 19: 70.

42. Kouadio IK, Aljunid S, Kamigaki T, et al. Infectious diseases following natural disasters: prevention and control measures. *Expert Rev Anti Infect Ther* 2012; 10: 95–104.

43. Liu X, Liu YY, Liu SH, et al. Classification tree analysis of the factors influencing injury-related disability caused by the Wenchuan earthquake. *J Int Med Res* 2014; 42: 487–493.

44. Vijayaraghavan R. Autoinjector device for rapid administration of life saving drugs in emergency. *Defence Sci J* 2012; 62: 307–314.
45. Gonzalez LS and Spencer JP. Aminoglycosides: a practical review. Am Fam Physician 1998; 58: 1811–1820.
46. Vijayaraghavan R, Selvaraj R, Krishna Mohan S, et al. Haematological and biochemical changes in response to stress induced by the administration of amikacin injection by autoinjector in animals. Defence Sci J 2014; 64: 99–105.
47. Geetha R, Roy A, Sivanesan S, et al. A concept of a probable autoinjector for biothreat agents. Defence Sci J 2016; 66: 464–470.
48. Sheela D, Geetha RV, Mohan SK, et al. A concept on the development of buprenorphine autoinjector for self and emergency administration. Int J Pharm Pharm Sci 2015; 7: 253–257.
49. Davis MP. Twelve reasons for considering buprenorphine as a frontline analgesic in the management of pain. J Support Oncol 2012; 10: 209–219.
50. Sheela D, Vijayaraghavan R and Sivanesan S. A study on the safety evaluation of buphrenorphine administered through an autoinjector compared with manual injection using haematological and biochemical variables in rats. Hum Exp Toxicol 2016; 36: 901–909.
51. Lewis CR, Vo HT and Fishman M. Intranasal naloxone and related strategies for opioid overdose intervention by non-medical personnel: a review. Subst Abuse Rehabil 2017; 8: 79–95.
52. Schiff M, Jaffe J, Freundlich B, et al. New autoinjector technology for the delivery of subcutaneous methotrexate in the treatment of rheumatoid arthritis. Expert Rev Med Devices 2014; 11: 447–455.
53. Pichlmeier U and Heuer KU. Subcutaneous administration of methotrexate with a prefilled autoinjector pen results in a higher relative bioavailability compared with oral administration of methotrexate. Clin Exp Rheumatol 2014; 32: 563–571.
54. Hudry C, Lebrun A, Moura B, et al. Evaluation of usability and acceptance of a new autoinjector intended for methotrexate subcutaneous self-administration in the management of rheumatoid arthritis. Rheumatol Ther 2017; 4: 183–194.
55. Chiaravalloti ND and DeLuca J. Cognitive impairment in multiple sclerosis. Lancet Neurol 2008; 7: 1139–1151.
56. Burks J. Interferon-beta1b for multiple sclerosis. Expert Rev Neurother 2005; 5: 153–164.
57. Phillips JT, Fox E, Grainger W, et al. An open-label, multicenter study to evaluate the safe and effective use of the single-use autoinjector with an Avonex® prefilled syringe in multiple sclerosis subjects. BMC Neurol 2011; 11: 126.
58. Varunok P, Lawitz E, Beavers KL, et al. Evaluation of pharmacokinetics, user handling, and tolerability of peginterferon alfa-2a (40 kDa) delivered via a disposable autoinjector device. Patient Prefer Adherence 2011; 5: 587–599.
59. Shah PJ, Dinsmore W, Oakes RA, et al. Injection therapy for the treatment of erectile dysfunction: a comparison between alprostadil and a combination of vasoactive intestinal polypeptide and phentolamine mesilate. Curr Med Res Opin 2007; 23: 2577–2583.
60. Tauber M, Payen C, Cartault A, et al. User trial of Easypod, an electronic autoinjector for growth hormone. Ann Endocrinol (Paris) 2008; 69: 511–516.
61. Domańska B, VanLunen B, Peterson L, et al. Comparative usability study for a cetolizumab pegol autoinjection device in patients with rheumatoid arthritis. Expert Opin Drug Deliv 2017; 14: 15–22.
62. Lacour JP, Paul C, Jazayeri S, et al. Secukinumab administration by autoinjector maintains reduction of plaque psoriasis severity over 52 weeks: results of the randomized controlled JUNCTURE trial. J Eur Acad Dermatol Venereol 2017; 31: 847–856.
63. Wang J. Efficacy and safety of adalimumab by intra-articular injection for moderate to severe knee osteoarthritis: an open-label randomized controlled trial. J Int Med Res 2018; 46: 326–334.
64. Kivitz A, Olech E, Borofsky MA, et al. Two-year Efficacy and Safety of Subcutaneous Tocilizumab in Combination with Disease-modifying Antirheumatic Drugs Including Escalation to Weekly Dosing in
Rheumatoid Arthritis. *J Rheumatol* 2018; 45: 456–464.

65. Vermeire S, D’hegyere F, Nakad A, et al. Preference for a prefilled syringe or an auto-injection device for delivering golimumab in patients with moderate-to-severe ulcerative colitis: a randomized cross-over study. *Patient Prefer Adherence* 2018; 12: 1193–1202.