

Original Article

A CONCEPT ON THE DEVELOPMENT OF BUPRENORPHINE AUTOINJECTOR FOR SELF AND EMERGENCY ADMINISTRATION

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Received: 06 May 2015 Revised and Accepted: 26 Jun 2015

ABSTRACT

Objective: In natural and man-made disasters, pain and infection would increase morbidity and mortality. In these situations immediate treatment is mandatory and the drug has to be absorbed faster. An auto injector would be useful. The objective of this study was to develop an analgesic auto injector with buprenorphine.

Methods: The auto injector is a reusable device with a disposable drug cartridge, capable of injecting 1 or 2 ml of drug solution. Sterile water filled cartridges were made from a pharmaceutical company. Water was withdrawn from the cartridge under a laminar flow and buprenorphine hydrochloride was injected to make 0.05 mg/ml concentration. Sterility test was carried out before and after injecting buprenorphine in the cartridge by nutrient agar method and aerobic and anaerobic sterility test mediums. Buprenorphine was injected, intraperitoneally in rats through autoinjector and compared with manual injection for its efficacy as an analgesic using Eddy's hot plate.

Results: The water filled cartridge as well as the buprenorphine drug filled cartridge was found to be sterile as no growth was observed in the nutrient agar and no turbidity was observed in the sterility test mediums. The analgesic effect of buprenorphine by autoinjector was found to be significantly (Kruskal Wallis ANOVA) more than manual injection and control group (median analgesic time in seconds, Control-4.0; manual injection-7.0; autoinjector-12.0).

Conclusion: Water filled cartridge could be converted to drug filled cartridge aseptically. Buprenorphine administered through autoinjector was better as an analgesic than manual injection.

Keywords: Autoinjector, Buprenorphine, Analgesic, Sterility test, Eddy's hot plate.

INTRODUCTION

Pain is an unpleasant sensory and emotional feeling experienced by humans and animals, and may be acute or chronic. It is considered as a vital signal of a life threatening problem. Acute pain occurs due to the action on the nociceptors by mechanical, thermal, chemical and inflammatory stimuli, and may be either somatic (outer body) or visceral (internal organs) pain. Chronic pain may be nociceptive (due to tissue damage) or may be neuropathic pain (damage to the central or peripheral neuron system) [1].

Pain, the major reason for about 70 % of the patients visit to the emergency department [2], WHO has rated that road accidents and injuries are one of the leading causes for death [3]. Chronic pain occurs in a wide variety of conditions viz., cancer, arthritis, neurodegenerative diseases and in bacterial and viral infections [4].

To manage acute and chronic pain analgesics and adjuvant treatments are required that should act very quickly. The analgesics preferred are either opioid or nonopioid analgesics. Analgesics commonly used are mostly effective against nociceptive pain but less effective in neuropathic pain. The non-steroidal anti-inflammatory drugs (NSAID) are non opioid analgesics (eg. aspirin, paracetamol, diclofenac, etc) and are used in mild and moderate pain. They do not cause physical dependence but gastric irritation and bleeding problems are the main side effects [5]. Opioid analgesics are strong analgesics and are used in severe acute pain and chronic cancer pain. The most important side effects of opioids are physical dependence when they are taken for longer duration [6]. Some of the commonly used opioids are morphine, hydromorphone, fentanyl, meperidine, methadone, buprenorphine, butorphanol, nalbuphine and are generally given by intravenous route for faster action [7].

In an emergency situation like road accidents, natural calamities (earthquake, tsunami), military operations and low intensity

conflicts, managing pain and treating preventable infection may play a crucial role in reducing morbidity and mortality [8]. To manage this situation, a potent analgesic is required that can reduce somatic and visceral pain. Opioid analgesics are the best choice for these situations. Generally to produce an immediate effect of the drug with a 100 % bioavailability in the emergency situation, the desired route is intravenous. But, it is not practical in the field condition as it requires skilled person to inject the drug. A self administrable device like the auto injector is an appropriate device to overcome these difficulties.

Auto injector is a self inject able device designed to deliver a single dose of a particular drug with reduced needle related injuries. This technique also helps in improved absorption of drug that may be helpful during the emergency situation. Some of the emergency conditions where auto injectors are available are epinephrine for anaphylaxis [9], diazepam for seizures [10], sumatriptan for migraine [11], naloxone for opioid overdose [12], interferon beta-1a, peginterferon-alfa-2a for multiple sclerosis [13], vasoactive intestinal peptide for hepatitis C, pentolamine for erectile dysfunction [8], and atropine and pralidoxime for nerve gas poisoning [14]. Golimumab autoinjector has been approved for the treatment of ankylosing spondylitis and rheumatoid arthritis [15, 16]. Sarilumab autoinjector is presently under clinical trial for the treatment of rheumatoid arthritis [17].

FDA has recently approved methotrexate autoinjector for the treatment of rheumatoid arthritis with very high user preference [18]. Currently an antibiotic autoinjector (amikacin) has been developed and its injection capability and tolerance to laboratory animals have been proved [19]. For an analgesic there is no autoinjector available in the world market. The development of analgesic autoinjector can be helpful in managing the pain during the emergency situation. To develop an analgesic autoinjector, the preferred analgesic is an opioid which can be used in acute or chronic pain. Among the opioids, buprenorphine is a preferred drug for developing as autoinjector [5, 8] (table 1).

Table 1: Analgesic drugs and their actions and side effects

Drug Class	Drugs	Analgesic effect		Effective duration	Side effects
		Somatic	Visceral		
NASAID	Aspirin	+++	-	4-8 hr	Epigastric distress, tinnitus, Reye's syndrome, hypersensitivity.
	Paracetamol	++	-	4-6 hr	Nausea, rashes.
	Diclofenac	+++	+	2 hr	Epigastric pain, nausea, headache, dizziness, heart attack, stroke.
Opioids	Aceclofenac	+++	+	1-3 hr	Epigastric pain, nausea, headache, dizziness, heart attack, stroke.
	Morphine	+++	+++	4-6 hr	Physical dependence, Respiratory depression, Nausea, Vomiting, Dizziness, Mental clouding, Dysphoria, Pruritus, Constipation, Increased Pressure in the biliary tract, Urinary retention and Hypotension.
	Pethidine	+++	+++	2-3 hr	Similar to morphine except Urinary retention and Constipation.
	Methadone	+++	+++	4-6 hr	Less physical dependence, Less sedation, Cardiac arrhythmias.
	Fentanyl	+++	+++	1-2 hr	Respiratory depression, Nausea, Vomiting, Dizziness, Mental clouding, Dysphoria, Pruritus, Constipation, Increased Pressure in the biliary tract, Urinary retention and Hypotension.
	Nalbuphine	+++	+++	3-6 hr	Most common Sedation, Sweating, Headache. At higher doses (70 mg) Psychotomimetic side effects are common.
	Butarphanol	+++	+++	4-6 hr	Common adverse effects are Drowsiness, Weakness, Sweating, Feeling of floating and nausea.
	Buprenorphine	+++	+++	6-8 hr	Lower degree of Physical dependence, Psychological dependence, Respiratory dependence and Constipation.

Buprenorphine was first introduced at low dose as an analgesic for treating cancer and post operative patients. High dose buprenorphine in the doses of 0.4 mg, 2 mg and 8 mg are available for the treatment of opioid addiction. Presently physician can prescribe buprenorphine/naloxone combination for the treatment of opioid addicts [20]. Among the opioid analgesics heroin is the drug used by the abusers. The injectable drugs were found to be one of the reasons for HIV transmission [21, 22]. Buprenorphine has comparatively less drug abusing tendency and shows mild physical dependence because of its unique pharmacological property. Buprenorphine, as an analgesic in the chronic pain management was well established in a number of studies. A transdermal buprenorphine in cancer and non cancer pain showed better safety and efficacy when compared with morphine [23]. The safe usage of buprenorphine has been well established in a number of studies and review articles including treatment of palliative pain in aged people even if they have renal and hepatic problems [24].

Using an analgesic in the management of chronic pain should not produce severe side effects which makes the patient uncomfortable. One of the main side effects produced by the opioid drug is constipation. There are number of studies which support that buprenorphine causes mild constipation [25]. Buprenorphine produces a ceiling effect and hence cause only mild respiratory

depression, unlike morphine which causes serious depression. The use of opioids generally does not affect any further diagnosis and also for surgical intervention which holds very good for buprenorphine.

Buprenorphine can also be given safely in children [26]. Opioids are prone to reduce the immunity in the patients. But usage of buprenorphine in the animal studies and the transdermal buprenorphine used in the opioid addicts to manage the pain and withdrawal symptoms did not show any evidence of reduction in the immunity [27, 28].

Taking all these into consideration in the present study attempt was taken to develop buprenorphine in an autoinjector device.

MATERIALS AND METHODS

Autoinjector device

The auto injector contains a drug cartridge (M/s Neon Laboratories, Mumbai) with a needle inside and is intended for intramuscular injection. It has a safety mechanism to avoid accidental injection and is powerful enough to deliver the drug through the garments (fig. 1). It has an option to select full or partial dose delivery [19]. The auto injectors were obtained from Defence Research and Development Establishment (Gwalior).



Fig. A: Auto injector devices



Fig. B: Drug filled buprenorphine cartridges



Fig. C: Partially and Fully fired buprenorphine drug cartridges

Development of water filled cartridge

Since small quantity of buprenorphine drug cartridge is required for the experiment and also it is a narcotic drug, initially water filled cartridges (2.35 ml/cartridge) were made by M/s Neon Laboratories (Mumbai). The water filled cartridges were subjected to all quality control checks including firing efficiency and sterility test.

Development of buprenorphine drug cartridge

Buprenorphine hydrochloride (0.3 mg/ml, 2 ml/vial) was also procured from M/s Neon Laboratories (Mumbai). After checking for the sterility, the cartridge weight was taken and marked. 0.4 ml of water from the cartridge was removed using a disposable sterile syringe under a laminar flow. The weight of the cartridge was taken

again and 0.4 ml of buprenorphine was injected into the cartridge and reweighed. Each cartridge contained 0.05 mg/ml of buprenorphine. The cartridges were stored at room temperature away from dust and direct light.

Quality control studies

The drug cartridges for the auto injector are expected to function at difficult situations. Various quality control tests viz., drop test, vibration test, low pressure test and firing efficiency test were carried out.

Sterility of buprenorphine drug cartridge

The water filled cartridges and the buprenorphine drug cartridges were subjected to sterility test [29, 30]. The sterility test was carried out by two methods (i) by nutrient agar method and (ii) by aerobic and anaerobic sterility medium (M/s Hi media Pvt Ltd).

Ten cartridges were randomly selected and divided into two groups of 5 each. From 5 drug cartridges 1 ml of the content was withdrawn using a sterile syringe and smeared uniformly on the nutrient agar plate. 48 hr after the application, colony formation in the agar plate was noted. From the remaining 5 cartridges, 2 ml of the content was withdrawn using a sterile syringe and 1 ml each was injected in the aerobic and anaerobic sterility mediums. 48 hr after the injection the medium was observed for any turbidity.

Animal efficacy studies

Randomly bred Wistar male rats (180–250 g) bred and maintained at Biomedical Research Unit and Laboratory Animal Centre (BRULAC) of Saveetha University were used for the study. Three rats each were kept in polypropylene cages with dry and sterilised paddy husk as the bedding material. The animals were fed with commercial laboratory animal feed and purified water *ad libitum*. The care and maintenance of the animals were as per the approved guidelines of the "Committee for the Purpose of Control and Supervision of Experiments on Animals (CPCSEA, India)". The animal procedures were approved by Institutional Animal Ethics Committee of Saveetha University (SU/BRULAC/RD/001/2013, dated 11 July 2013).

The efficacy of the auto injector was determined by comparing with manual injection. The buprenorphine cartridge was loaded in the autoinjector with the plastic clip restrictor. The plastic clip restrictor allowed only partial dose delivery and the needle length was restricted to half the length. The safety mechanism of the autoinjector was unlocked by turning it fully clock-wise. The rats were held firmly on the surgical table with its back on the table. The autoinjector was positioned vertically and securely on the lower abdomen of the animal. The trigger button was pressed and held in position for 10 sec. Then, the autoinjector was removed gently and the needle length was measured which was protruding outside. To determine the quantity of the drug injected the cartridge was weighed before and after injection of the drug. Similar to the dilution made in the cartridge of the autoinjector, dilution was made for the manual injection also. 1 ml of the diluted drug was injected intraperitoneally for each rat.

The animal's response was initially tested by allowing them into the Eddy's hot plate (Inco Analgesimeter). The temperature of the hot plate was regulated to 55 ± 0.5 °C. The responsive animals were randomised and divided into 3 groups of 6 animals each as follows:

a. Control group-saline injection

b. Buprenorphine by autoinjector

c. Buprenorphine by manual injection

After injecting saline or buprenorphine by autoinjector or by manual injection, the reaction time of the animal in the Eddy's hot plate was noted. The end point was taken when the animal licked its forepaws or by jumping out of the hot plate. The responses were noted at 0 hr, 30 min and 2 hr.

Statistical analysis

The data was analysed using one way analysis of variance (ANOVA) on ranks by Kruskal Wallis Test and Student-Newman-Keul's multiple comparisons test (SigmaPlot 12, Systat Software Inc., USA). A probability of 0.05 and less was taken as statistically significant.

RESULTS

Quality control measurements

The buprenorphine drug cartridges passed all the tests of quality control. The cartridges did not show any crack or break when they were dropped by keeping them inside the autoinjector and dropping them horizontally and vertically from a height of 1.5 m. The contents of the cartridge did not leak when they were subjected to low pressure in a vacuum chamber for 24 hr at 200 mm Hg. In the firing efficiency test within 5 s all the contents of the cartridge were delivered without the restrictor (2.0-2.1 ml).

Sterility test

The prepared buprenorphine cartridges passed the sterility test. There was no growth detected in the nutrient agar plates. No turbidity was detected in the aerobic or the anaerobic sterility medium and the solution was clear (table 2).

Table 2: Sterility test of buprenorphine filled drug cartridges

Cartridge No.	Nutrient agar plate	Aerobic medium	Anaerobic medium
1	No growth	No turbidity	No turbidity
2	No growth	No turbidity	No turbidity
3	No growth	No turbidity	No turbidity
4	No growth	No turbidity	No turbidity
5	No growth	No turbidity	No turbidity

1 ml was smeared on the nutrient agar plate, and 1 ml each was injected in the aerobic or the anaerobic medium. The readings were taken 48 hr later.

Animal efficacy studies

Table 3 shows the response of the animals in the Eddy's hot plate following buprenorphine administration through autoinjector and by manual injection. Buprenorphine administration by autoinjector intraperitoneally was successful. The calculated dose of buprenorphine was 0.30 ± 0.03 mg/kg (mean+SD; for manual injection the dose administered was 0.30 mg/kg). The peak response was observed in the autoinjector and the manual group in 30 min. The response was decreased at 2 hr and no effect was observed at 24 hr. The analgesic effect of buprenorphine was significantly higher in autoinjector at 30 min than the manual injection which was better than the control group ($p < 0.05$).

Table 3: Analgesic effect of buprenorphine by autoinjector and by manual injection in rats

Time	Groups			H value	P
	Control	Autoinjector	Manual		
0 hr	4.0 (3.0–4.0)	3.5 (3.0–4.0)	3.0 (3.0–4.0)	2.06	NS
0.5 hr	4.0 (4.0–5.0) ab	12.0 (10.0–17.0) ac	7.0 (6.0–10.0) bc	12.87	<0.01
2 hr	4.0 (4.0–4.0)	9.5 (6.0–14.0)	5.5 (3.0–7.0)	4.74	NS

Values are median (n = 6). Fig. in parentheses are 25 and 75 percentile, Same alphabetical characters are mutually significant ($p < 0.05$).

DISCUSSION

Disasters like earthquakes, cyclones, floods and tsunami occur sometimes with forewarning and occasionally without any indication [31]. The death in these incidences in the last three decades was estimated to be more than 2 million and more than 100 million people would have been seriously injured causing pain and infection. Manmade terrorism also would cause mass disasters equally [32]. In the Gujarat earthquake more than 50 % of the injuries were in the lower extremities [33].

Infections due to wounds and injuries, contaminated food and water, and vector borne diseases coupled with pain would cause increased mortality and morbidity [34]. Immediate medical assistance should be essential in the natural and manmade disasters which would be difficult due to the disturbance in the support systems. Medical treatment by trained personal might be difficult in such type of situations due poor access. If pain and infection were taken care in the field the suffering of the injured people could be reduced. Auto injectors with an analgesic drug and an antibacterial drug with pre-filled drug cartridges would be very useful and they could be used by simple instruction printed on the device [35].

The auto injectors are well suited for emergency and mass casualty management. They deliver the drugs by deep i. m. injection with a spray effect. This increases the area of absorption and the effects are closure to i. v. injection. The needle is not visible in these auto injectors and the injection will be painless. Compared with manual intramuscular injection, auto injector enhances drug absorption rate. Studies are conducted in which it has been proved that drug absorption is faster [36]. Compared to manual injection the auto injector delivery of drugs is painless [37, 38]. Earlier amikacin drug cartridges were made for autoinjectors and they have proved that it is well tolerable for animal models [19].

The auto injectors are developed with dual dose administration so they can be used for adults as well as for children. Other than for mass casualty the buprenorphine autoinjector can be used for cancer pain also [24]. It is also possible to use them for farm and pet animals as the device is very powerful to penetrate the animal skin [39]. The analgesic autoinjector can be considered for further research work.

CONCLUSION

In the present study water filled cartridges were made and they were converted to buprenorphine cartridge. This avoided the bulk production of the scheduled drug. Since the fillings were made under the laminar flow the cartridges were sterile. The buprenorphine administered through the autoinjector was well tolerated by the rats in the present study and the analgesic effect was better than the manual injection.

ACKNOWLEDGEMENT

The authors thank M/s Neon Laboratories (Mumbai) for providing water filled cartridges and Defence Research and Development Establishment (Gwalior) for providing autoinjectors.

CONFLICT OF INTERESTS

Declared None

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