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Treatment after Accidental Injection with Epinephrine Autoinjector: A Systematic Review

Michael Wright

London School of Hygiene and Tropical Medicine, London, UK

Corresponding author: Michael Wright, Visiting Research Fellow, London School of Hygiene and Tropical Medicine, 13-15 Tavistock Place, London, WC1H 9SH, UK, Tel: +61 (0) 488916322; Fax +61(0)92804061; E-mail: wrightdrmc@gmail.com

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Abstract

Background: Epinephrine (adrenaline) autoinjectors are increasingly prescribed for the emergency management of severe allergic reactions. There is an increasing incidence of unintentional administration of these devices, typically into a digit. Digital epinephrine has theoretical dangers of ischemia and gangrene and multiple interventions have been advocated in the treatment of these unintentional administrations of epinephrine.

Objective: This systematic literature review examines available evidence about unintentional epinephrine digital injections, in order to advise appropriate treatment.

Methods: Systematic searches were made of electronic databases (Medline, EMBASE, Scopus), reference screening and forward citation searching. Application of inclusion and exclusion criteria: Findings of included articles were summarized and data analyzed.

Results: This literature review found limited published material on the topic. Four observational studies (retrospective cohort studies) and seven case series have been published, along with a number of single case reports. The data described complete recovery of almost all (greater than 99%) patients exposed to a digital epinephrine injection by autoinjector- regardless of treatment. Most patients received no pharmacological treatment. Case reports suggest that recovery may be quicker with use of subcutaneous phentolamine or terbutaline than with observation or conservative treatment. A small number of patients (from one database and one case series) suffered long term or severe effects from the digital epinephrine injection.

Conclusion: There is a growing body of evidence suggesting that accidental injection with epinephrine autoinjector may be managed conservatively in most cases. Evidence to date suggests conservative treatment (observation and/or local heat) will result in full recovery in the vast majority of patients. Treatment with locally injected phentolamine or terbutaline appears to rapidly reverse vasconstriction. There have been a small number of reports of incomplete recovery. This limited evidence needs to be interpreted with caution due to potential selection bias and misclassification. Further observational and randomized experimental research is needed to determine when pharmacological treatment is indicated and if it improves patient outcomes. Patient and carer education about proper use of individual autoinjector devices is the best prevention for these events.

Keywords: Autoinjector; Epinephrine; Adrenaline; Vasconstriction

Introduction

The incidence of drug and food related allergy is increasing in the community. For patients at risk of severe allergic reactions (such as anaphylaxis) emergency treatment with epinephrine (also known as adrenaline in the UK and Australia) is recommended. This treatment has become more readily available with the development of preloaded pen devices- 'epinephrine autoinjectors'- which can be rapidly dispensed into the lateral thigh of an affected patient in a community setting. There are a number of proprietary brands of these devices (Epipen, Twinject, Anapen), with Epipen comprising the majority of the market. With recent approval granted for sublingual immunotherapy in the USA, prescribing of these devices is likely to increase.

With the wider availability of epinephrine autoinjectors there has been an increase in reporting of accidental or inadvertent discharge of these devices by patients, carers and health professionals- typically into a digit [1].

Traditional medical school teaching has suggested that compounds containing epinephrine should not be administered into digits, due to the vasoconstriction caused by this drug, and potential for ischemia and gangrene. Research has questioned this teaching [2,3] and has suggested that adrenaline may be safe to use in digits [4], however medical students are still advised to avoid epinephrine containing compounds when conducting surgical procedures on digits.

With the increase in accidental discharge of epinephrine autoinjectors, there has been debate about the most appropriate post-injection treatment. Product information for these devices advises observation in an emergency setting. Some authors suggest observation, whereas others have advocated treatment with a number of different therapies.

The author is not aware of any prior published systematic reviews specifically examining treatment after unintentional administration of epinephrine autoinjector. One previous review [1] examined incidence of unintentional epinephrine administration and concluded that incidence was increasing. Another (anonymous) review focused on prevention of these injuries [5]. A third review looked for incidence of necrosis after finger injections with adrenaline, and failed to find any published evidence of finger necrosis related to use of adrenaline autoinjectors [6]. These previous reviews did not analyze effectiveness of treatment outcomes after accidental discharge of adrenaline autoinjector.

Methods

The author conducted a Medline, Embase and Scopus search looking for published articles discussing the treatment of digital injection of epinephrine from an autoinjector using a combination of keywords and subject headings. Full search strategy is documented in Appendix One.

Inclusion criteria

Published English language articles with data concerning treatment of (accidental) digital injection by epinephrine autoinjector in humans (adults and children included). Nature of study- experimental or quasi experimental studies, observational studies (cohort studies, cross sectional, case control studies) case reports or case series documenting different treatments of digital epinephrine autoinjection.

Exclusion criteria

Articles discussing intentional injection of epinephrine into digit (such as for plastic surgery procedure) - articles discussing accidental epinephrine injection by other means (such as in other operative procedures where epinephrine can be used to improve anaesthesia).

Reference checking was carried out on the obtained articles and forward citation searching in Medline, Embase and Google Scholar was carried out looking for further evidence. This process was completed until no further new articles were found.

Search Results

There was only a small body of literature on this subject. There were no experimental or quasi-experimental data that compared pharmacological treatment with non-pharmacological treatment after digital epinephrine injection via autoinjector.

Four articles were retrospective cohort studies- examining reporting of accidental autoinjector administration to Poisoning Information Services, all in the USA setting [7-10]. One of these studies also provides analysis of data provided to Adverse Drug Reaction Reporting Department of the Federal Drug Administration (FDA) [9]. These articles are summarized in Table 1. The remaining articles are case series or single case reports- most describing specific treatment and outcomes of accidental autoinjector injection. These papers are summarized in table 2.

Author	Year	Number reported	Outcome reported	Non pharmacological treatment (%)	Pharmacological treatment (specified if available)				% full recovery (with known outcome)	Other notes
					Phentolamine (%)	Nitroglycerin (%)	Terbutaline (%)	Other		
Blume Odon	2010	134	123	94(76)	27 (33)	17(13)	Nil	Nil	100	
Mrvos	2002	28	26	20(77)	1(4)	5(19)	2(8)	Nil	100	
Muck	2010	365	127	98(77)	9(7)	21(16)	1(1)	Nil	100	
Simons (two components)	2010	15190	4101	NA(71%)	29% with any treatment (no specific treatment data)				100%	
	2010	105	105	NA	NA	NA	NA	NA	99%	Note 2 cases of degloving requiring amputation
Cumulative case reports	1999-2013	47	47	6(13)	18(38)	19(40)	3(6)	6(13)	99%	1 case of persisting sensory loss

Table 1: Comparison of retrospective studies (and comparison with combined case report data)

Seven papers report case series with multiple cases and treatments [6,11-16]. The single case reports describe use of a variety of treatments and all have outcomes described [14,17-36].

All of the retrospective series provide (incomplete) data on recovery and treatment of cases. The largest series [9] does not specify type of treatment- only whether treatment was initiated. One article [8] discusses digital ischemia as primary outcome of study.

Review Findings

The largest study [9] reports over 15000 incidents of autoinjector injury, and is much larger than any of the other published series.

Patients have been categorized according to whether they have had pharmacological therapy, or non-pharmacological therapy (hot compresses, massage or ice). The majority of patients did not require

treatment or hospitalization. In the majority of patient in the retrospective studies (average 71%), there was no treatment needed, or conservative treatment was used (defined as heating or warming of affected hand, or hand massage) with full recovery. This treatment has been recommended by some previous authors [37]. Pharmacological therapy was much more likely in the case reports, with 87% of patients having some pharmacological intervention. Further comparison between the retrospective studies and the case study information is found in Table 1.

Author	Year	Study	Cases (n)	Treatment	Recovery	Recovery Time (h)	Notes
Baris	2011	CR	1	Papaverine	Y	3	
Barkhordarian	2000	CR	1	Iloprost	Y	few hours	
Desmukh	1989	CR	1	P	Y	20	
ElMaraghy	1998	S	6	P	Y	NR	
				NG	Sensory loss	NR	
				Nifedipine	N	15.5	persisting sensory loss
				P	Y		
				Nil	Y	10	
				PG	Y		
Fitzcharles	2005	S	2	nil	Y		5 cases reported, but 3 intentional injection with epinephrine
Hardy	1995	CR	1	P	Y		
Hinterberger	1994	CR	1	P	Y	1	
Janssen	2008	CR	1	P	Y	0.33	
Kaspersen	1998	CR	1	NG	Y	NR	
Khairalla	2001	CR	1	CCB/P	Y	NR	
Klemawesch	2009	CR	1	P/02	Y	48	
Lee	1998	S	2	NG	Y	1	
McCauley	1991	CR	1	NG/P	Y	0.3	
Mathez	2009	CR	1	NG + Vasodil	Y	8 (2months)	
Molony	2006	CR	1	P	Y	30	
Murali	1998	CR	1	P	Y	NA	
Nagaraj	2009	S	7	NG (patch)	Y		
Patel	2013	CR	1	NG	Y	NA	
Pyeko	2013	CR	1	NG/T	Y	0.33	
Schintler	2005	CR	1	nil	Y		
Sellens	1999	CR	1	NG/P	Y	0.1	
Sherman	2011	CR	1	NG	Y	48	
Singh	2007	CR	1	W/NG/PGP	Y		
Skorpinski	2006	S	2	NG	Y	2.5	
				Nil	Y	2	
Stier	1999	S	3	T	Y	0.25	
				T	Y	0.5	
				T/NG	Y	1	
Turner	2004	CR	1	NG/P	Y	NA	
Velissariou	2004	S	3	NG	Y	6	
				Nil	Y	NA	
				P	Y	0.1	
Xu	2012	CR	1	P	Y	0.2	
Yousif	2009	CR	1	P + NG	Y	1	

Table 2: Case reports and case series information

Abbreviations: CR: Case Report; S: Series; NR: Not Reported; Treatment (P: Phentolamine; NG: Topical Nitroglycerin; T: Terbutaline; O2: Hyperbaric Oxygen; CCB: Calcium Channel Blocker; W: Warming). "+" indicates both treatments given but timing not statedeg P +NG indicates both treatments given but order not stated; "/"indicates sequential treatment eg NG/P indicates use of phentolamine after failure of reversal with topical nitroglycerin

Nearly all patients (over 99% of patients) made a full recovery after accidental injection with an adrenaline autoinjector. There are a small number of patients who are described to have long term sequelae from accidental autoinjector injection. One study reports a patient having persisting sensory loss after treatment with nifedipine [12], while the larger case series describes two cases of injury reported to the FDA which resulted in degloving injury requiring digital amputation [9]. No details about treatment (if any) are available in these latter two cases.

All remaining patients made a full recovery. This did not vary with individual treatments. Despite a number of different interventions, all individual case reports had a full recovery.

Treatments Used

A number of treatments were used and recommended by different authors. It is unclear what the indication for treatment was in most cases, other than patient discomfort or severity of symptoms (pallor or cold digit). The most commonly used drugs are topically applied nitroglycerin paste or a nitroglycerin patch (which converts to nitric oxide, a powerful vasodilator), locally injected terbutaline (a beta adrenergic receptor agonist which reduces vasoconstriction) and locally injected phentolamine- (a non-selective alpha adrenergic receptor antagonist which also reverses the vasoconstriction brought on by epinephrine).

This latter drug has been reported to provide rapid reversal of epinephrine effect [26,38,39] but not without concern of risk of a local pressure effect [37]. Other agents used have included papaverine (an opium-derived vasodilator), and calcium channel blockers (such as nifedipine). Hyperbaric oxygen has also been reported as a treatment (albeit non-pharmacological).

The case reports provided additional information about treatments, with many patients progressing to pharmacology after a trial of conservative treatment. Information about time to recovery is included where available. This information is included in Table 2. Compiled case study treatment successes and failures are contained in Table 3.

Treatment used	Reported	Success	Failure	Long term sequelae
Phentolamine	16	15	1	
Nitroglycerin	19	13	6	1
Terbutaline	3	3		
Observation	6	6		
Hyperbaric 02	1	1		
CCB	2	2		
Paperevine	1	1		
Iloprost	1	1		
Other vasodilator	1	1		

Table 3: Case report and Case Series Treatments and Outcomes

Failure of Therapy

There are six reports of failure of topical nitroglycerin therapy-usually followed by successful reversal with phentolamine. There has also been a reported case where phentolamine injection failed to fully restore blood flow and hyperbaric oxygen was subsequently used with good effect [33].

Time to recovery appears quicker with phentolamine treatment as many of the phentolamine case reports describe immediate return of perfusion after treatment, while topical nitroglycerin treatment is reported to take hours in some patients. However despite the failure of reversal in the cases above, all case study patients treated with nitroglycerin and phentolamine made a complete recovery.

Discussion

The majority of patients who suffer the accidental administration of epinephrine into a digit from an autoinjector make a complete recovery, usually without pharmacological therapy.

The pharmacology of epinephrine suggests its half-life of action is insufficient to cause tissue ischemia [40]. Recent research has examined the use of digital injection of adrenaline for haemostatic control during surgical procedures and has failed to show evidence of ischemia. However despite this, there are reports of long term damage from these autoinjector incidents, with and without therapy. Caution may still be needed, especially when patients may have other vascular disturbance making ischemia or necrosis more likely [41]. Research is needed to determine which patients require treatment in these situations.

For patients at low risk of complications observation at home may be appropriate, rather than hospitalization. In healthy individuals, observation and warming may be sufficient treatment. The best protection from such accidents is careful and repeated education of patients and care givers.

There are reported failures of acute reversal with nitroglycerin and phentolamine but without long term complications. The only agent with multiple case reports without treatment failure is terbutaline. There are no reports of long term sequelae for patients treated with nitroglycerin, phentolamine or terbutaline.

There is variability in the design of autoinjectors. Some of these devices have a pen-like appearance but mechanism for drug delivery can vary and feel counterintuitive [42]. Patients should be instructed in their particular device, and interchanging of devices may require further instruction or be avoided [43]. This can particularly be an issue for children requiring treatment of parents or themselves in an emergency situation [44]. Recent changes to the design of the Epipen have improved the identification of the needle in the device and will potentially reduce the incidence of accidental injury.

Limitations

Caution is needed in interpreting the published literature because of selection bias with the evidence to date. There is considerable loss to follow up in the larger studies. Although this could imply that patients make a full recovery, caution needs to be taken before this is assumed.

There are other potential confounders that may affect the development of digital ischemia and outcome from digital epinephrine injection. These may include age, previous medical history, epinephrine dosage and exact site of digital injection. This data needs to be collected in order to guide treatment, or randomized controlled trial of treatment options is needed. To date, this has been difficult due to the uncommon occurrence of digital epinephrine injection, but may become feasible with the increasing incidence of this problem [1].

Conclusion

Inadvertent epinephrine injection via an autoinjector is an increasingly common occurrence and may increase as availability of these devices continues to broaden. Evidence to date suggests that these events will resolve without sequelae in nearly all cases. In a small

number of patients, there is the potential for long term complications. It remains unclear who these patients are. Successful reversal of vasoconstriction has been achieved most reliably with phentolamine and terbutaline, although treatment failures have been reported and it is not clear which patients require intervention. Education of patients about the use of their device is the best prevention of these events.

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