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An Atypical Response to Epinephrine

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Abstract

Introduction: Epinephrine and epinephrine related medications have been widely studied and their side effect profiles have been well documented. Rare reactions can occur due to administration of EpiPen and it is critical to document and explore the cause of such reactions. We present a case report on a patient experiencing a unique reaction to EpiPen administration which we suspect is due to vasospasm.

Case Description: A 38-year-old Caucasian female presented after a bee sting and subsequent EpiPen self-administration. She had no past medical history except for anaphylactic reaction to a bee sting in her childhood, and had undergone desensitization with an allergist. En route to the hospital, she developed: chest pressure, palpitations, facial droop, dysarthria, and decreased strength. The patient's vital signs were within normal range. Blood work was notable for hypokalemia, hyperglycemia and lactic acidosis. CT head with angiography was unremarkable. Neurology was consulted and her MRI brain showed no evidence of acute stroke. Within three hours of hospital admission her symptoms had resolved. The patient was monitored overnight, and subsequently discharged the next day with no residual deficits.

Discussion: The EpiPen is widely used for immediate relief of impending anaphylaxis. We believe this patient's angina and TIA-like symptoms were secondary to non-specific vasospasm given the alpha-adrenergic mechanism of epinephrine. A literature review showed limited information on such reactions after EpiPen injection.

Conclusion: It is imperative that physicians are aware of such potential adverse effects in order to enhance patient care

Introduction

The EpiPen® is a low dose epinephrine self-administered auto-injection that has been commercially available since the 1970's. It is frequently used for relief of allergic reactions in preventing progression of anaphylactic type reactions. As a sympathomimetic, epinephrine acts primarily by stimulating a specific few key receptor targets. Stimulation of the α-1 receptors result in vasoconstriction and increased peripheral vascular resistance, while stimulation the β-2 receptors result in bronchodilation. It additionally functions to decrease the release of chemotactic mediators from basophils and mast cells. As such, epinephrine directly counteracts anaphylactic reactions by promoting organ perfusion and airway protection.

Despite the global distribution and rise in use of epinephrine over the past few decades, not all patients achieve symptomatic relief from the medication. Individual patient response to epinephrine may vary based on genetic predispositions and environmental factors. Furthermore, due to the proposed and understood mechanism of action, a number of side effects have been reported. Some of the more commonly documented adverse effects include palpitations and elevated blood pressure levels. More concerning and rare side effects include fatal ventricular arrhythmias, including ventricular fibrillation, as well as life threatening hemorrhage such as subarachnoid hemorrhage and hemiplegia [1].

One such rare complication, Kounis syndrome, is a unique presentation of an epinephrine induced vasospasm that has been documented only a limited number of times [3]. In this syndrome, the coronary vessels are hypersensitive to epinephrine resulting in symptoms of angina and rarely can cause myocardial infarction [2]. Ultimately, reporting possible rare adverse effects of medications, irrespective of how common or how frequently it is used, should be strongly encouraged in order to promote patient safety and wellness, as well as physician awareness.

Case Description

- A 38-year-old Caucasian female with notable past history for bee-sting related anaphylaxis was stung by a bee while hiking
- EpiPen® was self-administered into the left thigh and EMS was contacted. She had never previously administered EpiPen® in the past. Upon EMS arrival the patient received diphenhydramine 50 mg orally and an albuterol inhaler for wheezing on examination. Examination findings were otherwise benign.
- En route to the hospital, approximately 10 minutes after medication administration, the patient developed new left facial droop, pressure-like chest pain and progressive focal motor weakness
- The patients past medical history is significant for history of bee-sting related anaphylaxis at age 10, requiring hospitalization without need for intubation. Other history includes history of reactive depression following her brothers suicide.
- Following childhood hospitalization, the patient underwent desensitization therapy with an allergist. She was prescribed EpiPen however has never previously had to administer it
- Past surgical history is only notable for a cesarean section 2 years prior to hospitalization due to failure of trial of labor and delivery at home
- The patient does not take any medications, vitamins or supplements. She does not follow with recommended vaccinations, does not follow with a primary care physician and is vegan. She is a stay-at-home mother, with no history of alcohol, tobacco or drug use.
- Family history is notable lupus and type 2 diabetes in her mother, and hypertension in her father.
- On hospital arrival, blood pressure 121/77, pulse 101, temperature 37.5°C, respiratory rate 18 with oxygen saturation at 97% on room air, BMI 24
- On examination, bilateral facial droop was noted, more prominent on the left side. She was unable to raise her left eyebrow and had developed new dysarthria with inability to verbalize her thoughts. Additionally she was unable to actively move her extremities
- Initial blood work (See table 1.) was notable for hypokalemia, and hyperglycemia
- EKG showing normal sinus rhythm, chest x-ray and CT head with angiography without acute abnormalities. Solumedrol and famotidine were administered.
- Over the following three hours of hospitalization, the patient had progressive improvement in her motor strength and ability to verbalize. Cranial nerves II-XII were all intact except for residual inability to lift left the left eyebrow.
- Neurology was consulted and the patient was monitored overnight
- On examination the following day, the patient had regained full motor functionality, including left eyebrow raise. Upper and lower extremity sensory, motor and deep tendon reflexes were all intact.
- MRI brain (See figure 1.) showed no evidence of acute infarct or hemorrhage however an incidental nonspecific punctate hyperintensity on T2 weighted imaging in the left frontal lobe was noted
- Neurology evaluated the patient and determined that the patient may have a stress-related component, however epinephrine induced vasospasm could not be ruled out. The patient was discharged home on the day after admission.

Tables and Figures

	Day 0 14:22	Day 0 23:22	Day 1 05:37
Sodium (mmol/L)	137	139	138
Potassium (mmol/L)	2.4	4.3	4.0
Chloride (mmol/L)	104	111	110
Carbon Dioxide (mmol/L)	19	18	20
Anion Gap	14	10	8
Blood Urea Nitrogen (mg/dL)	19	14	15
Creatinine (mg/dL)	0.64	0.61	0.42
Calcium (mg/dL)	8.8	9.0	8.7
GFR (mL/min)	113	115	>120
Lactic acid, plasma (mmol/L)		3.2	0.9
WBC Count (K/μL)	10.0		11.8
RBC Count (M/μL)	4.53		4.26
Hemoglobin (g/dL)	13.9		13.0
Hematocrit (%)	40.6		38.1
MCV (fl)	89.7		89.6
MCH (pg)	30.7		30.6
MCHC (g/dL)	34.2		34.2
RDW (%)	13.2		13.2
Platelet Count (K/μL)	219		210
Cholesterol (mg/dL)		222	
Triglyceride (mg/dL)		43	
HDL Cholesterol (mg/dL)		68	
LDL Cholesterol (mg/dL)		145	
VLDL (mg/dL)		9	
Glycated hemoglobin (%)		5.1	
Serum glucose (mg/dL)	149	242	112

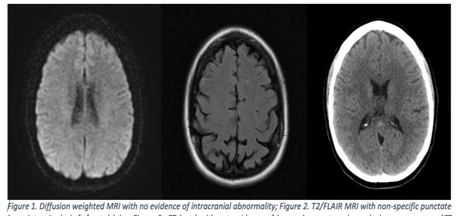

Figure 1. Diffusion weighted MRI with no evidence of intracranial abnormality; Figure 2. T2/FLAIR MRI with non-specific punctate hyperintensity in Left frontal lobe; Figure 3. CT head with out evidence of hemorrhage, stenosis, occlusion or aneurysm (CT angiogram not shown).

Table 1. Blood work values through hospital course. Notable findings include initial presentation with hypokalemia, as well as lactic acidosis 12 hours following admission despite receiving over 2L of normal saline infusion.

Discussion

This case presents a very rare and previously undocumented reaction from the use of an EpiPen. Transient global paralysis has never been previously reported as an adverse reaction . The patient was exposed to a bee sting venom at a young age and was hospitalized due to anaphylactic shock. After this incident she underwent several years of desensitization with an allergist. It is uncertain whether desensitization therapy is able to be maintained without further exposure in the following 28 years of life, or even if the patients immune system developed a new and heighted response to bee venom related antigenic compounds. Bee venom is made up of several toxins and compounds that cause a proinflammatory response. Studies have shown that it can cause a systemic (including possible anaphylactic) or localized response [2].

The patient's presentation is thought to be the first case of global (cerebral and coronary) vasospasm secondary to epinephrine administration. Epinephrine is known to be dose-dependent whereby at lower concentrations, beta-related effects are greater, and at higher concentrations alpha-effects play a greater role. There have been multiple accounts of digital ischemia due to accidental EpiPen injection. This is secondary to localization of high concentration of epinephrine, resulting in vascular constriction from α-1 adrenergic stimulation.

It is uncertain whether certain vasculature beds may be more sensitive to adrenergic receptor stimulation than others. This case presentation suggests is that there was evidence of hypoperfusion to certain areas following epinephrine administration, as far as 12 hours following administration. Relating this to the clinical scenario, it leads us to believe that some individuals are more sensitive to epinephrine stimulation than others. Furthermore, genetics and environmental factors may play a role in sensitivity toward epinephrine and vasospasm.

Based on the history, physical exam and diagnostic studies, the primary care team built a plan of treatment to rule out a concerning diagnosis such as a stroke. After analysis of the results, neurology and the primary team were confident that the patient could be discharged home safely. The patient was recommended to follow-up with her primary care physician within a week of discharge. The history of anaphylaxis in response to bee venom is still concerning. The patient was recommended to continue using her EpiPen in any future incidents as the benefits of the epinephrine outweigh the risks of possible drug induced vasospasm or temporary neurologic deficits.

Conclusion

Despite potentially rare and unusual side effects, patients should be encouraged to continue to use epinephrine in potentially life threatening allergic or anaphylactic reaction settings. Further research should be undertaken to determine whether certain genetic predisposing factors may precipitate epinephrine related side effects. This may additionally include further evaluation of α-1 receptor stimulation testing to determine whether certain environmental triggers play a role in receptor sensitivity. Given the necessity of maintaining a patent airway and circulation, rare side effects from epinephrine should not discourage providers from both educating and prescribing potentially life-saving therapy to patients. Patients should additionally be instructed on how to monitor for concerning signs when being prescribed the medication so as to minimize poor outcomes.

References

1. Coban, Y.K. Mild hemifacial asymmetry cause by a single bee sting. Aesth Plast Surg. 2005; 29: 435. https://doi.org/10.1007/s00266-005-0025-0
2. Jayamali WD, Herath HMMTB, Kulathunga A. Myocardial infarction during anaphylaxis in a young healthy male with normal coronary arteries- is epinephrine the culprit?. *BMC Cardiovasc Disord*. 2017;17(1):237. Published 2017 Sep 4. doi:10.1186/s12872-017-0670-7
3. Kounis, N.G. Soufras, G.D. Lianas, D. Patsouras, N. After administration of intravenous Epinephrine for bee sting-induced anaphylaxis: Kounis syndrome or Epinephrine effect? Chin Med J (Engl). 2016 Feb 20;129(4):500-1. doi: 10.4103/0366-6999.176081
4. Panagariva, A. Sureka ,RK. Sharma, B. Sardana, V. Neurological complications following honey bee sting. J Assoc Physicians India. 1998 Nov;46(11):984.
5. Viswanathan S. J Stroke Cerebrovasc Dis. 2012 Feb;21(2):148-50. doi: 10.1016/j.jstrokecerebrovasdis.2010.06.003.