Myocardial infarction following parenteral beta agonists for asthma in two patients with normal coronary arteries- a call for caution

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Abstract

Background. Severe asthma is often treated with parenteral beta agonists. There is however, no solid evidence supporting this treatment and it is no longer recommended in current guidelines.Methods and Results. We have recently treated two patients who developed a myocardial infarction with elevated serum troponin and angiographically-normal coronary arteries following administration of parenteral beta-agonists.Conclusion. Parenteral beta agonist administration in severe asthma may result in myocardial infarction. In addition there is a possibility of Takatsubo or stress-induced cardiomyopathy. We suggest that parenteral beta-agonists should be used, if at all, with extreme caution.

INTRODUCTION

Asthma is characterized by reversible bronchospasm and beta-adrenergic agonists are one of the cornerstones of treatment, being among the most potent and rapidly acting bronchodilators available.

Beta agonists attenuate asthma exacerbations by interacting with beta receptors on the surface of a variety of cells: they relax bronchial smooth muscle, decrease mast cell mediator release, inhibit neutrophil, eosinophil, and lymphocyte functional responses, increase mucociliary transport, and affect vascular tone and edema formation [1].

Due to the presence of beta [1] and beta [2] –adrenoreceptors in the heart even highly selective beta[2] agonists can produce a positive inotropic effect.

Under conditions of hypoxemia, e.g. during a severe asthma attack, beta activation may further impair the myocardial oxygen supply-demand relationship, which may result in myocardial damage.

Although short-acting beta agonists are an important component of the treatment of acute asthma, it appears that inhaled and subcutaneous beta agonists are superior to oral therapy [2,3,4].

Cumulative dose-response curves to inhaled albuterol in asthmatic patients have demonstrated that the dose required to produce 50 percent of maximal bronchodilation is, on average, three to four times the dose needed in nonasthmatic controls. This relative resistance may reflect -receptor down regulation due to the disease itself or to chronic beta agonist overuse [5, 6]. These observations have prompted many clinicians to use larger total doses during acute exacerbation of asthma, both by injection [7] and nebulization [8, 9].

Parenteral beta agonists for treatment of severe asthma attacks appears in published reccomendations [10], although this is not based on good quality medical evidence [11]. There is, however, a paucity of evidence providing a contraindication to the use of subcutaneous epinephrine. We wish to report two cases of myocardial infarction in patients with normal coronary arteries as a result of parenteral beta agonist therapy during a severe asthmatic attack.

METHODS

Case details of 2 patients treated recently in the Department of Internal Medicine C with a myocardial infarction related to parenteral beta-agnoist therapy were obtained from the electronic medical records of Kaplan Medical Center. The medical literature was reviewed by use of the PubMed site using keywords asthma, troponin, myocardial ischemia.

RESULTS

CASE #1

A 38 year old woman with a history of asthma experienced an acute exacerbation. She had suffered from asthma for 10 years and was treated with an inhaler of salmeterol and fluticasone proprionate. The patient had been admitted with status asthmaticus 10 months previously. On that occasion following treatment which included s/c epinephrine, there were ST depressions in the inferior leads and the troponin I increased to 3.7 ng/mL. An echocardiogram revealed normal systolic function with no wall-motion abnormalities. Due to increasing severity of the asthma and lack of response to nebulized bronchodilators, she ordered the Emergency Medicine Service (EMS) to her home. She was treated with methylprednisone intravenously, nebulized salbutamol and ipratropium. The EMS physician administered epinephrine 0.3 mg s/c and transferred her to the Emergency Room. She received an additional 0.3 mg of epinephrine s/c in the Emergency room and was hospitalized. She denied chest pain. On examination her blood pressure was 100/50 mmHg, she had a tachycardia of 100 per minute. She was in respiratory distress with a tachypnea of 28 breaths per minute, there was no central cyanosis, and expiratory wheezes were audible all over the chest. The heart sounds were rapid and normal. The remainder of the physical examination was normal.

The chest x-ray revealed hyperinflation with no evidence of either a lung infiltrate or pneumothorax. The ecg showed a sinus tachycardia. Routine laboratory investigations including a complete blood count and renal function and electrolytes were normal except for arterial blood gases which showed a pH of 7.27 a pCO2 of 41.6 mmHg and a pO2 of 207 mmHg.

A repeat ECG was performed 2 days later showed poor R wave progression in leads V1-V3 and T wave inversion in leads V1-V5. There was no routine for performing daily ecgs on such patients. In light of these changes a serum troponin was tested and found to be elevated to 4.69 ng/mL. Coronary angiography was performed on the next day which showed normal coronary arteries and grade 3 TIMI flow (Figure 1). Echocardiography revealed LV dilatation and depressed LV function (ejection fraction of 45%) with global hypokinesis mostly of anteroapical area. (Figure 2). This finding persisted on follow-up of several months.

CASE #2

A 70-year old asthmatic patient developed a severe asthmatic attack after exposure to acidic vapors while cleaning her house. Due to a rapid deterioration in her condition, the mobile intensive care unit was called. She denied chest pain. On examination she was found to be cyanotic and unconscious, not responding to pain. The respiratory rate was 6 breaths per minute and breath sounds were diminished with widespread wheezing. The patient was intubated and treated with endotracheal salbutamol l5 mg.

Following her arrival to the emergency room she received inhalations of ipatropium. Oxygen saturation was 100% and arterial blood gases results showed respiratory acidosis (number) combined with metabolic acidosis. A chest X-ray was normal. A 12-lead electrocardiogram showed sinus tachycardia with no ischemic changes. One hour later the patient was successfully extubated. At this point physical examination revealed prolonged expiration with diffuse rhonchi.

The next day the patient complained of mild chest pain and electrocardiography revealed ST segment elevation in leads II, III, and aVF. The Troponin I level was 1.54 ng/ml. Echocardiography showed normal systolic and diastolic function and angiography a further day later revealed normal coronary arteries and grade 3 TIMI flow. There were no evolutionary t wave changes on subsequent ecgs.

DISCUSSION

We have described two patients who we believe developed a myocardial infarction following parenteral beta agonist administration, despite having angiographically normal coronary arteries. The patients did not have routine ecgs performed on all hospital days and so the changes were detected more than 24 hours after administration of the catecholamines. It is important to perform daily ecgs on inpatients who have received parenteral epinephrine. An increase in serum troponin is highly suggestive of myocardial damage, although there are other causes including pulmonary embolism, sepsis and myocarditis [12].

In case #1, the focal wall motion abnormalities that were not reversible and ecg changes are consistent with a myocardial infarction. In case #2, the ST elevation is suggestive of myocardial damage. We cannot exclude myocardial necrosis as a result of hypoxia, severe asthma and respiratory failure. However, even if one of the above was the main cause, it would emphasize the need for caution prior to administrating

parenteral epinephrine which could increase the myocardial injury.

Subcutaneous epinephrine has been used in the treatment of asthma since 1910 [13]. It has been shown to be effective in terms of reducing bronchospasm and improving hypoxemia (13). This treatment modality has never been subjected to randomized controlled clinical trials. A systematic review in 2001 of the use of subcutaneous epinephrine in both asthma and anaphylaxis revealed only three case reports (level VII evidence) and several studies (level III and level V) with no adverse effects [11]. However, no controlled trials have been published.

There does not appear to be an advantage to intravenous administration of beta agonists. A meta-analysis on the use of intravenous beta agonist therapy for acute asthma compared the outcomes of 584 patients in 15 trials [14]. Intravenous therapy was not associated with improved outcomes in the study population or any identified subgroup.

Intravenous administration is clearly associated with development of more adverse effects [3, 4]. The common side effects are tremor, increased heart rate and palpitations, and metabolic disturbances, including hyperglycemia and hypokalemia [15, 16, 17]. Despite this the use of beta-agonists parenterally features in the recommendations of many organizations including the Israel Emergency services (personal communication AA) . However, recent guidelines for the treatment of moderate-to-severe asthma in adults from the National Asthma Education and Prevention Program of the National Heart, Lung and Blood Institute have removed the recommendations for subcutaneous epinephrine, after stating that there is no proven benefit for systemic therapy over nebulized [18].

The presumed mechanism for an infarction in such cases is spasm of the coronary arteries related to the intense beta agonist stimulation.

The ability to detect small amounts of myocardial necrosis via the determination of serum troponin, has changed the definition of a myocardial infarction [19]. This test was not available in many of the previous reports of the use of parenteral beta agonists, therefore minor degrees of myocardial necrosis may have been present but not detected.

The endothelium is now no longer considered as an inert barrier to elements contained in the blood, but rather an active biological interface between the blood and other tissues. In some patients there may be a reduced coronary vasodilator or a paradoxical vasoconstrictor response to pharmacologic agents and exercise [20]. This has been termed cardiac syndrome X or microvascular angina. This endothelial dysfunction has been found in atherosclerosis, hypercholesterolemia, diabetes, hypertension, cigarette smoking, ischemia reperfusion, and aging. Consequent to the worldwide epidemic of obesity, there is an increase in many of these parameters. Thus many more people today have endothelial dysfunction and may be at risk of coronary artery vasospasm following parenteral beta agonists. In addition, endothelial dysfunction has been noted to be present in patients with asthma [21].

There are other potential pathophysiologic explanations for these observations. Catecholamine administration can cause myocardial injury through contraction-band necrosis, which has also been described in cocaine-induced myocardial injury. In addition , catecholamine administration has been shown to enhance coagulation through platelet activation and to increase cardiac demand [22].

Furthermore, it has recently become apparent that beta-agonists can have other effects on the myocardium. An entity termed Takatsubo or stress-induced cardiomyopathy has recently been described [23]. This results in transient wall motion abnormalities involving the left ventricular apical and mid-ventricular segments. This entity may present as ST elevation and there may be an increase cardiac enzymes but in the presence of normal coronary arteries. The echocardiographic picture is diagnostic involving left ventricular apical ballooning. We did not encounter evidence for Takatsubo cardiomyopathy in our patients.

Other medications may also cause myocardial infarction by increasing the availability of sympathomimetic amines. The appetite suppressants phentermine and sibutramine have recently been linked to myocardial infarction in obese women with angiographically normal coronary arteries [24].

Other cases in the literature with possible myocardial necrosis related to sympathomimetic treatment are shown in the table.

In the light of ours and others experience with parenteral epinephrine in asthma, the growing evidence for deleterious effects of sympathomimetics on the heart and the lack of any conclusive evidence for efficacy, we suggest that there is no further place for the administration of parenteral epinephrine in the treatment of severe asthma. If there is no response to

intensive therapy with nebulized sympathomimetics then the best option may be mechanical ventilation. Furthermore, patients who do receive parenteral sympathomimetics require close surveillance for ischemia or other effects on the heart.

Figure 1

Reference	Number of patients	Dose of sympathomimetics	Symptoms and Signs	Laboratory results
25	1	Daily doses of oral salbutamol 6 mg, intramuscular orciprenaline1 mg, subcutaneous adrenaline 0.5 mg, chloramphenicol 2g, digoxin 0.8 mg. --- Over 9 hours after admission she was given oxygen, aminophylline 1.7g, salbutamol 1.5mg, digoxin 0.8mg, hydrocortisone 400mg, and erythromycin 0.6mg by slow IV drip through a CVP catheter.	Never had symptoms of coronary heart disease before. --- A confused, cyanotic woman in status asthmaticus,	A two-fold increase in transaminase
26	1	5 doses of nebulised β_2-adrenoceptor agonist given by inhalation.	Had no history of cardiac disease He was cyanosed, tachypnoeic at rest, peak expiratory flow was unrecordable.	Serial cardiac enzymes proved the diagnosis of MI
27	1	A single intravenous bolus injection of salbutamol 200µg	painless	A significant increase in CPK + AST
28	220	Epinephrine infusion IV starting at 0.25 to 1 µg/min The usual dose rate being 2 to 3 µg/min Average epinephrine infusion rate was 1.5 µg/min (range 0.5 to13.3 µg/min)	0.9% felt chest pain without ECG or marker changes	
29	95 (108 episodes)	0.3 ml S.C. epinephrine 1:1000 administered every 20 minutes as indicated by the patient's clinical response (patients were monitored for 60 minutes only)		A significant increase in CPK + ASTI. (highest infusion rate was 2 µg/min

References

1. Gern, JE, Lemanske, RF Jr. Beta-adrenergic agonist therapy. Immunol Allergy Clin North Am 1993; 13:839.
2. Williams, SJ, Senton, A. Intravenous or inhaled salbutamol in severe acute asthma? Thorax 1977; 32:555.
3. Pierce, RJ, Payne, CR, Williams, SJ, et al. Comparison of intravenous and inhaled terbutaline in the treatment of asthma. Chest 1981; 79:506.
4. Salmeron, S, Brochard, L, Mal, H, et al. Nebulized versus intravenous albuterol in hypercapnic acute asthma. A multicenter, double-blind, randomized study. Am J Respir Crit Care Med 1994; 149:466.
5. Lemanske, RF Jr, Kaliner, MA. The assessment of autonomic nervous system function. In: Provocative Challenge Procedures. Background and Methodology, Spector, SL (Ed), Futura Publishing, Mount Kisco, New York, 1989, p. 131.
6. Nelson, HS. Beta-adrenergic agonists. In: Middleton's Allergy: Principles and Practice, 6th Ed, Adkinson, NF, Yunginger, JW, Busse, WW, et al (Eds), Mosby, St Louis, MO 2003. p.803.
7. Tipton, WR, Nelson, HS. Frequent parenteral terbutaline in the treatment of status asthmaticus in children. Ann Allergy 1987; 58:252.
8. Schuh, S, Parkin, P, Rajan, A, et al. High-versus low-dose, frequently administered, nebulized albuterol in children with severe, acute asthma. Pediatrics 1989; 83:513.
9. Wolfe, JD, Yamate, M, Biedermann, AA, Chu, TJ. Comparison of the acute cardiopulmonary effects of oral albuterol, metaproterenol, and terbutaline in asthmatics. JAMA 1985; 253:2068.
10. The Washington Manual of Medical Therapeutics 31st Edition, Editors Green GB, Harris IS, Lin GA, Moylan KC. Lippincot Williams and Wilkins, Piladelphia, PA, 2004 p.243.
11. Safdar B, Cone DC, Pham KT. Subcutaneous epinephrine in the prehospital setting. Prehosp Emerg Care 2001;5:200-7.
12. Blich M, Sebbag A, Attias J, Aronson D, Markiewicz W. Cardiac troponin I elevation in hospitalized patients without acute coronary syndromes. Am J Cardiol 2008;101:1384-1388.
13. Melland B. The treatment of spasmodic asthma by the hypodermic injection of adrenalin. Lancet 1910; 1:1407-11.
14. Travers AH, Rowe BH, Barker S, Jones A, Camargo CA Jr. The effectiveness of iv beta agonists in treating patients with acute asthma in the emergency department: a meta-analysis. Chest. 2002;122:1200-7.
15. Jenne, JW, Valcarenghi, G, Druz, WS, et al. Comparison of tremor responses to orally administered albuterol and terbutaline. Am Rev Respir Dis 1986; 134:708.
16. Leslie, D, Coats, PM. Salbutamol-induced diabetic ketoacidosis. Br Med J 1977; 2:768.
17. Smith, RS, Kendall, MJ. Inhaled bronchodilators and hypokalemia. Lancet 1983; 2:218.
18. Expert Panel Report 3: Guidelines for the diagnosis and management of asthma. National Asthma Education and Prevention Program, National Heart Lung and Blood Institute, Full Report 2007.
19. Saenger AK, Jaffe AS. The use of biomarkers for the evaluation and treatment of patients with acute coronary syndrome. Med Clin North Am. 2007;91:657-81.
20. Mohri M, Koyanagi M, Egashira K, Tagawa H, Ichiki T, Schimokawa H, Takeshita A. Angina pectoris caused by coronary microvascular spasm. Lancet 1988;351:1165-9.
21. Yildiz P, Oflaz H, Cine N, Genchallac H, Erginel-Unaltuna N, Yildiz A, Yilmaz V. Endothelial dysfunction in patients with asthma: the role of polymorphisms of ACE and endothelial NOS genes. J Asthma 2004;41:159-66.
22. Kloner RA, Hale S, Alker K, Rexkalla S. The effects of acute and chronic cocaine use on the heart. Circulation 1992;85:407-19.
23. Bybee KA, Kara T, Prasad A, Lerman A, Barsness GW, Wright RS, Rihal CS. Systematic review: transient left ventricular apical ballooning: a syndrome that mimics ST-segment elevation myocardial infarction. Ann Intern Med 2004;141:858-65.
24. Azarisman SM, Magdi YA, Noorfaizan S, Oteh M. Myocardial infarction induced by appetite suppressants in Malaysia. N Engl J Med 2007;357:1873-4.
25. Szczeklik A, Nizankowski R, Maruk J. Myocardial infarction in status asthmaticus. The Lancet 1977;658-659.
26. Shovlin CL, Tam FWK. Salbutamol nebuliser and precipitation of critical cardiac ischemia. The Lancet 1990;1258.
27. Santo M, Sidi Y, Pinkhas Y. Acute myocardial infarction following intravenous salbutamol. SA Medical Journal 1980;394.

28. Putland M, Kerr D, Kelly AM. Adverse events associated with the use of intravenous epinephrine in emergency department patients presenting with severe asthma. Annals of Emergency Medicine 2006;47:559-563.

29. Cydulka R, Davidson R, Grammer L, Parker M, Mathews J. The use of epinephrine in the treatment of older adult asthmatics. Annals of Emergency Medicine 1988;322:47-51.

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