Dark Coronary Toxidrome - "A Case of Methemoglobinemia Presenting as Acute Coronary Syndrome in a Patient with Polysubstance Abuse"

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Received date: November 18, 2015; Accepted date: February 21, 2016; Published date: February 29, 2016

Abstract
Polysubstance abuse is common worldwide, with noticeable tendency of users to mix different types of drugs to reach desirable effects/pleasure. This group of population, present often to ED with acute toxicity with manifestations, that are atypical for the known classic drug abuse syndromes, because of mixing of more than one substance. This case describes a previously healthy young Asian female presented to ED with her boyfriend after she developed sudden severe central chest pain, with SOB and pallor. In ED, patient was found hypotensive, tachycardic and lethargic. EKG showed nonspecific ST changes and troponins were elevated. Emergent referral for cardiac cath center was done, and Cardiac cath showed patent coronaries.

On further questioning of the patient and her boyfriend, patient had taken a lot of alcohol, with Poppers (amyl nitrate), cocaine and Sildenafil, when she was celebrating with her boyfriend. Her methemoglobin (Met Hb) level was 52%. Patient was diagnosed of cocaine induced coronary vasospasm, and Poppers (amylnitrate) and adulterants induced methemoglobinemia. Patient's methomoglobulinemia was treated successfully with one dose of methylene blue (as per poison control center guidelines).

Cocaine itself and its metabolites are not recognized to cause methemoglobinaemia. Adulterants, pharmacologically active substances added to recreational drugs, added to cocaine are associated with methemoglobinaemia. Drug dealers add these substances to increase the weight of the expensive powder (which will increase their profit margin), and to give a false impression of purity to the user. Street cocaine in North America commonly contains both phenacetin and local anaesthetics (benzocaine, prilocaine and cetacaine) as adulterants. Poly-drug use is common in recreational drug users and the use of two or more agents may increase the risk of developing methemoglobinaemia. Clinicians managing patients with acute recreational drug toxicity should be aware of the potential for methemoglobinaemia in these patients.

Keywords: Methemoglobinaemia; Coronary vasospasm; Polysubstance abuse; Cocaine adulterants; Methylene blue

Background
Polysubstance abuse is common worldwide, with noticeable tendency of users to mix different types of drugs to reach a desirable effects or pleasure. This group of population with history of polysubstance abuse often presents to emergency room (ER) with acute toxicity and manifestations, which are sometimes atypical for the known classic drug abuse syndromes, because of mixing of more than one substance [1,2].

As shown here in figure 1, overall deaths from illicit drug overdose have increased with significant increase from 2011 to 2014 and more prominent among males [source: CDC Wonder]. Figure 2 is a bar chart showing the total number of U.S. overdose deaths involving cocaine from 2001 to 2014. The chart is overlaid by a line graph showing the number of deaths by females and males [source: National Institute on Drug Abuse].

Figure 1: The raising trend of the national illicit drug overdose death for the period between 2011 and 2014, with tendency of drug abuse significantly increasing among males. (Y axis represents number of cases, and X axis represents the calendar year).
Case Description

Our case here describes a previously healthy 36 year old Asian female, who presented to ER with her boyfriend after she developed sudden, severe, central chest pain with shortness of breath and pallor. In ER, patient was found hypotensive, tachycardic and lethargic with initial vital signs as mentioned in table 1.

| Blood pressure (BP) | 77/27 mm Hg |
|---------------------|-------------|
| Pulse               | 104/min     |
| Respiratory rate    | 18/min      |
| Temperature (T)     | 36.8°C      |
| SpO₂                | 89% on non-rebreather |

Table 1: Vital signs on initial presentation.

Initial electrocardiogram (EKG) as shown in figure 3 showed ST depressions and T wave inversions in anterolateral leads. Cardiac enzymes were also noted to be elevated as shown in table 2. Findings were suggestive of myocardial ischemia.

| Total CK           | 433 unit/L (Normal: 26-192 units/L) |
|--------------------|-------------------------------------|
| CKMB               | 20.3 ng/ml (Normal: 3.0-4.0 ng/ml)  |
| Troponin T         | 0.494 ng/ml (Normal: 0.009-0.029 ng/ml; Critical high: >0.099) |

Table 2: Cardiac enzymes.

Patient was emergently referred to cardiac catheterization center. Cardiac catheterization was done, and it showed patent coronaries.

On further questioning of the patient and her boyfriend, it was found that patient had taken a lot of alcohol with Poppers (amyl nitrite), Cocaine and Sildenafil, when she was celebrating with her boyfriend. Her initial Methemoglobin (Met Hb) level was 52% on arterial blood gases (ABG) with co-oximetry, as shown in table 3 here. Patient was diagnosed of cocaine-induced coronary vasospasm, and Poppers (amyl nitrite), Sildenafil and adulterants induced methemoglobinemia.

| pH                  | 7.185 (Normal: 7.35-7.45) |
|---------------------|----------------------------|
| pO₂                 | 344 mm Hg (Normal: 80-100 mm Hg) |
| pCO₂                | 32 mm Hg (Normal: 35-45 mm Hg) |
| SaO₂                | 89% (Normal: 95-99%) |
| FiO₂                | 100% |
| Met Hb              | 52% (Normal: 0-2%) |

Table 3: Initial ABG with co-oximetry.

Patient was admitted in Intensive Care Unit (ICU) for close monitoring. She was considered for a treatment with Methylene Blue, as per poison control center guidelines [3]. Patient was not screened for Glucose 6-phosphate dehydrogenase (G6PD) deficiency prior to Methylene Blue dosing, as patient was in a clinically unstable condition, and G6PD results are not available on same day. She was given a dose of Methylene Blue 120 mg, and Met Hb level decreased to 0% in about 6-7 hours, as shown on follow up co-oximetry in table 4.

| O₂ Saturation | 100% (Normal: 95-99%) |
|---------------|----------------------|
| Carboxy Hb    | 1.2% (Normal: 0-1.5%) |
| Met Hb        | 0% (Normal: 0-2%)    |

Table 4: Follow up co-oximetry, arterial.
Methemoglobinemia caused by cocaine adulterants and volatile nitrites commonly contains both phenacetin and local anesthetics (benzocaine, prilocaine and cetacaine) as adulterants [4-6].

The mechanisms of cocaine-associated myocardial ischemia include: 1. Coronary artery spasm, 2. Aprothrombotic state in the coronary circulation, and 3. Increases in heart rate and blood pressure (from the vasospasm and sympathomimetic action of cocaine), which increase myocardial oxygen demand/consumption. Also, toxidromic dissociation curve to the right, which will further compromise the oxidative energy metabolism [6-8].

On the other hand, Alcohol is known to sometimes cause coronary spasm, the mechanism of which is still unknown. Data from a control study of 8 patients with alcohol-induced variant angina and 8 healthy men (as controls), suggested that low levels of PGF1 alpha and the decrease of cGMP levels from alcohol ingestion play important roles in the mechanism of coronary spasm induced by alcohol ingestion [9].

Poly substance use is common in recreational drug users and the use of two or more agents may increase the risk of developing methemoglobinemia. Clinicians managing patients with acute recreational drug toxicity should be aware of the potential for methemoglobinemia in these patients [10,11].

Methemoglobinemia is a life threatening condition that is characterized by inability of hemoglobin to carry oxygen because the ferrous (Fe++) part of the heme molecule has been oxidized to a ferric (Fe+++). Methylene Blue (MB) acts by reacting within RBC to form leukomethylene blue, which is a reducing agent of oxidized hemoglobin converting the ferric (Fe+++ state back to its oxygen carrying ferrous (Fe++). Dose commonly used is 1-2 mg/kg of 1% Methylene Blue solution [12].

For treatment of methemoglobinemia, If the patient is symptomatic or if the methemoglobin level is >20 percent, which is often the case in deliberate or accidental overdoses or toxin ingestion, specific therapy is urgently indicated. The two treatments most often employed are methylene blue (MB) and ascorbic acid (vitamin C). While there have been no randomized trials comparing these two agents, the general experience has been that the action of a single dose of MB in this setting reduces toxic levels of methemoglobin to non-toxic levels (eg, <10 percent) within 10 to 60 minutes, whereas treatment with ascorbic acid requires multiple doses and may take 24 or more hours to reach similarly low levels and is therefore a poor alternative in emergency situations [13]. When MB is not available or when its use is contraindicated as in glucose-6-phosphate dehydrogenase (G6PD) deficiency, ascorbic acid is the only reasonable alternative, although response to this agent is less marked and dramatic than it is to MB.

MB is a potent, reversible inhibitor of monoamine oxidase A, an enzyme responsible for breaking down serotonin in the brain. Its use in patients taking serotonergic psychiatric medications may result in high, occasionally fatal, levels of serotonin the brain (ie, serotonin syndrome). As an example, case reports have described such reactions when MB was used for staining parathyroid glands during surgical resection [14,15].

Ascorbic acid (vitamin C), an agent with reducing potential, may be helpful in a number of settings. 1. As a single agent in moderate doses (300 to 1000 mg/day orally in divided doses) in subjects with symptomatic methemoglobinemia and G6PD deficiency, in whom MB may induce further hemolysis. 2. As a single agent in high doses (10 grams intravenously every six hours) for the treatment of symptomatic methemoglobinemia in patients without renal insufficiency, when MB is not available. 3. Severely affected patients may benefit from adjunctive treatment with blood transfusion, exchange transfusion, and/or hyperbaric oxygen [16].

Pulse oximetry is inaccurate in patients with methemoglobinemia, as the pulse oximeter reading is based on the assumption that the only two varieties of hemoglobin present are Oxy-Hb and Deoxy-Hb. Generally, the pulse oximeter will transmit readings in the region of 85%. Co-oximetry gives accurate concentrations because of the ability to identify the absorptive characteristics of several Hb species at different wavelengths including MetHb [3,5]. In our case, co-oximetry was used to measure the concentration of methemoglobin.

Conclusion

Illicit drug abuse increasing overall and patients often present with presentation atypical for any one substance, as increasing use of multiple illicit drugs simultaneously. Some of the adulterants used in drugs are also linked to potential side effects. It is very important for clinicians to recognize these potentially dangerous adverse presentations and treat them in timely manner.

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