Haloperidol-Induced Pulseless Electrical Activity: A Case Report

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Background:
Pulseless electrical activity (PEA) is a clinical condition characterized by unresponsiveness and lack of palpable pulse in the presence of organized cardiac electrical activity. It is induced by factors that results in the inability of cardiac muscle to generate sufficient force in response to electrical depolarization. Those factors could be physiological, pathological, or drug-induced. Previous reports have identified haloperidol-induced QT-prolongation, but to the best of our knowledge this is the first case report of a patient with documentation of a normal baseline echocardiogram who experience haloperidol-induced PEA.

Case Report:
A 46-year-old woman was observed who developed a PEA a few minutes after receiving 2 mg of intravenous (IV) haloperidol. Haloperidol was administered to control her agitation and aggressiveness. A few minutes after administering the haloperidol, she experienced PEA and cardiac arrest. She recovered after receiving CPR for six minutes and 1 mg IV epinephrine, then she was intubated for mechanical ventilation and sedated. The drug was discontinue and was not restarted. For the rest of her stay in the hospital, the patient experienced no further cardiac events. Two days later, she became stable and she was extubated. She was discharged after 60 days with an out-patient follow-up appointment. Applying the Naranjo adverse drug reaction probability scale to this case (score of 4) indicated the possible relationship between the patient's adverse cardiac event and haloperidol.

Conclusions:
IV haloperidol is advocated as safe effective therapy for agitated delirium in medical or surgical cardiac patients in the intensive care unit. Thus, it may be overlooked as a cause of pulseless electrical activity. Therefore, practitioners should be instructed about the potential for IV haloperidol to bring about bradycardia prompting pulseless electrical movement despite performing comprehensive cardiac examination before prescribing haloperidol.

MeSH Keywords: Antipsychotic Agents • Echocardiography • Haloperidol

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Background

Pulseless electrical activity (PEA), once considered as electromechanical dissociation, occurs in patients with organized cardiac activity in the absence of profound pulse. Pulseless electrical action is characterized as depolarization of the heart rhythm without synchronous cardiovascular myocyte shortening [1].

The electric mechanisms associated with sudden cardiac arrest (SCA) are comprehensively grouped into tachyarrhythmic and non-tachyarrhythmic classifications, the latter including pulseless electric movement (PEA), asystole, severe bradycardia, and different components regularly connected with noncardiac variables [2].

The four most regular mechanical causes for PEA include cardiovascular tamponade, pressure pneumothorax, mechanical hyperinflation, and respiratory embolism [3]. Clinical scenarios can help to further explore these causes. For example, jugular venous distension and suppressed heart sounds suggest tamponade. Rib fracture, extreme emphysema, positive pressure ventilation, and hyperexpanded chest suggest pneumothorax, mechanical hyperinflation, or auto-PEEP (auto-positive end expiratory pressure) [4].

Several reports have demonstrated the occurrence of PEA in a hospital setting as being between 35% and 40% of cardiac arrest events [5,6]. For out of hospital cardiac arrest, the occurrence of PEA is reported to be between 22% and 30% [7]. Survival to hospital discharge is substantially more likely when the first documented rhythm is shockable rather than nonshockable, and slightly more likely after PEA than asystole. Survival to hospital discharge is less likely following PEA/asystole with subsequent ventricular tachycardia (VT)/ventricular fibrillation (VF) compared to PEA/asystole without subsequent VT/VF [8].

Studies performed in the 1980s reported the initial rhythm to be VF in 61–65% in out-of-hospital cardiac arrest (OHCA), while reports in the most recent ten years found VF initial rhythm in 35–48% of OHCA [9,10]. Correspondingly, the extent of PEA has increased and is currently reported to be between 22–30% in OHCA [7,11]. This demonstrates that PEA happens in 8 to 11 per 100,000 population per year in Europe [7,9,11]. In Finland, studies showed the frequency of PEA to fluctuate from 4 to 20 per 100,000 population per year [12].

It is turning out to be progressively normal for emergency medical services (EMS) suppliers to experience a patient with PEA. It is estimated that PEA may happen in upwards to 35% of prehospital cardiac arrest in the United States [13]. Recent reports likewise suggest that the occurrence of prehospital instances of PEA is increasing [13,14]. According to one review, among more than 3,000 cardiac arrests, PEA was present in more than 35%, while VF represented fewer than 15% [13].

The general prognosis for patients with PEA is poor unless a quickly reversible cause is recognized and adjusted. Evidence suggests that electrocardiogram (ECG) characteristics are identified with patient prognosis. The more abnormal the ECG attributes, the more improbable the patient is to recover from PEA [15].

The ECG can give hints with respect to the cause of the arrest. Cardiac arrest rhythms – mainly pulseless cardiac activity – which is not included in the class of pulseless VT, VF, or heart with no electrical activity, are viewed as pulseless electrical activity. Now and again, the electrocardiogram may suggest a hidden disease, for example, Osborn waves (J waves), which are generally present in PEA, are created by low body temperature [16].

A review by Myerburg et al. [2] described many possible mechanisms for PEA. Up to 33% of patients revived from cardiac arrest brought about by PEA experience a percutaneous mediastial compression for intense coronary obstruction and ST-segment elevation myocardial localized necrosis, suggesting that PEA might be an underlying arrhythmic occasion coming about because of intense ischemia [17].

Standard treatment as indicated by the American Heart Association (AHA) guidelines in 2005 [18,19] stress the requirement to recognize, as well as adjust for, modifiable etiologies along with standard resuscitation (a goal that may not generally be achieved in the early minutes of cardiac resuscitation). Since an extensive assortment of causes can bring about a PEA arrest, it is important to precisely differential potential outcomes of causes so that appropriate treatment can be administered [19]. The ECG is considered an essential investigative tool that may be beneficial combination with history and investigations to conceivably decide the etiology of PEA and the proper strategy to treat the condition. Diagnostic information attained from the ECG, after deciphered in combination with the patient’s past history and detailed investigations can be utilized to recommend treatment and identify the fundamental cause as well as to predict the probability of survival [19].

Studies recommend cause-specific treatment of PEA as more powerful than general treatment offered by advance cardiac life support (ACLS) guidelines such cardiac message, epinephrine, and vasopressin [20].

For patients with a narrow complex PEA from a suspected mechanical etiology, intravenous (IV) fluid administration ought to be started as the cause pf PEA may be liquid responsive. After that, taking into account the likely clinical scenario or results of bedside ultrasonography, pericardiocentesis, needle decompression, adjustment of ventilation, or thrombolytic treatment ought to be considered. For wide-complex PEA
IV calcium chloride and sodium bicarbonate should be administered if the clinical picture shows hyperkalemia. IV sodium bicarbonate boluses ought to be given if the clinical picture suggests sodium channel blocker toxicity. Neither calcium nor bicarbonate has any impact on narrow complex PEA [21].

Epinephrine is currently recommended for the treatment of PEA [18]. Epinephrine increases coronary perfusion pressure (CoP) and myocardial perfusion. Epinephrine-prompted b1 impacts may be relied upon to increase myocardial contractility and rate in PEA, as a result cardiac output increases. However, the use of epinephrine could increase the myocardial oxygen demand, resulting in a supply-demand mismatch in ischemic myocardium [22].

Haloperidol is a butyrophenone neuroleptic drug with an extensive variety of activities. The federal drug administration (FDA) approved haloperidol to treat Gilles de la Tourette’s Syndrome (GTS), hyperactive behavior, (short-term treatment) after the inability to respond to non-antipsychotic solutions and psychotherapy, in addition to psychotic disorder [23]. It is also used to provide rapid control of the symptoms of hostility, aggression, disruptive and violent behavior, confusion, emotional withdrawal, hallucinations, and delusions connected with acute and chronic schizophrenia, mania and hypomania, and organic brain syndrome. Haloperidol has additionally been used for the treatment of nausea and vomiting [24].

The use of IV haloperidol has been associated with the risk factor of QT interval prolongation/torsades de pointes (QTP/TdP). Available data indicates that the total cumulative dosage of IV haloperidol of <2 mg can securely be administered in patients without corresponding risk factors [16]. When drugs altering myocardial contractility were assessed in patients suffering with SCA, the use of antipsychotic drugs was a significant and independent predictor of manifestation of PEA [25].

A limited number of case reports have been published about adults who experienced PEA induced by drugs. An analysis from the Oregon Sudden Unexpected Death Study (Oregon SUDS) showed that the use of antipsychotic agents has been found to be a significant and independent predictor of PEA [33]. Drug overdose (tricyclic antidepressants, digitalis, calcium channel, and beta blockers) or toxins are also rare causes of PEA [26].

Specific classes of medications with either negative or positive cardiac inotropic effects were evaluated for an association with occurrence of PEA versus VF/VT. In multivariate analyses, the use of antipsychotic drugs was a significant and independent risk factor for PEA, possibly related to their negative inotropic effects [2].

To our knowledge, our study is the first reported case of PEA after administration of haloperidol to a patient with chronic renal failure.

Case Report

A female patient, aged 46 years, presented to the National Guard Health Affairs (NGHA) Riyadh, Saudi Arabia. The patient was a nonsmoker, had a known history of hypertension in the previous seven years, had end-stage renal disease, and had been on hemodialysis for the previous three years. On her last admission to King Khalid Hospital in Najran, the patient was diagnosed with rheumatic heart disease with severe mitral regurgitation and tricuspid regurgitation. She was also diagnosed with infective endocarditis on the accessory mitral valve leaflet and aortic valve leaflet. She had been treated with antibiotics for three weeks. Follow-up echocardiogram after three weeks of antibiotic showed that the vegetation on the AMLV was bigger than before so the patient was referred to NGHA hospital for further evaluation and management.

On admission to the hospital, microbiological culture and sensitivity testing were performed on blood samples collected from the patient. The results revealed the presence of Enterococcus faecalis. The patient was treated intravenously with ampicillin (2 g three times a day for seven days), ceftriaxone (2 g once daily for seven days), gentamicin (80 mg once daily on alternate days) and vancomycin 1 gm IV after each course of dialysis every Sunday, Tuesday, and Thursday to treat infective endocarditis and bacteremia.

Upon admission to the NGHA hospital, the patient’s complaints were shortness of breath, night fever, and sweats. On assessment, the patient was determined to have congestive heart failure stage B. The patient had mild levels of physical activity (walked 100 m usually five times a week). The patient was not allergic to any drug or food. Initial physical examination revealed that she was anxious, distressed, with pallor, but vitally stable. Her arterial blood pressure was 88/76 mmHg, her pulse rate was 106 beats per minute, her respiratory rate was 25 breaths per minute, and her body temperature was 37°C. She had grade 2 edema in both legs and ankles, as assessed using the Dent Depth and Rebound Time Grading Method.

Initial laboratory investigations revealed that the patient had serum creatinine levels of 575 µmol/L (normal: 53–106 µmol/L), a mean corpuscular volume of 74 fl (normal: 80–100 fl), an erythrocyte sedimentation rate of 75 mm/hour (normal for women under 50 years old: <20 mm/hour), C-reactive protein levels of 47 mg/dl (normal: 0–10 mg/dl) and blood urea nitrogen levels of 11.8 mg/dl (normal: 7–20 mg/dl). Echocardiographic results showed severe mitral regurgitation and tricuspid regurgitation with large left pleural effusion and pericardial effusion.

On day 2 after admission to the NGHA hospital, the patient became agitated and aggressive, but she was vitally stable with a normal ECG. She was prescribed intravenous STAT therapy with...
haloperidol 2 mg to control her aggressive behavior. After three minutes of haloperidol administration, the patient developed PEA and experienced cardiac arrest. Resuscitation was performed for six minutes, after which the patient recovered. Her heartbeat was 41 beats per minute at the time of arrest; after resuscitation, it became normal, at 89 beats per minute. The patient was given 1 mg epinephrine intravenously, and then was intubated for mechanical ventilation and sedated. Extubated after 2 days, she remained in normal sinus rhythm during the rest of her stay and was discharged after 60 days with an outpatient follow-up appointment.

Discussion

Licensed indications for first generation antipsychotic (AP) drugs constrain their utilization to particular psychiatric issue; however, in general practice these agents are generally recommended for the treatment of a wide range of psychotic symptom and disorders. This reflects the assumption that they are likewise useful in the supposed “established indications” [27], i.e., schizophrenia-related disorders, bipolar affective disorder, delirium, dementia, organic psychoses, and mental retardation. In any case, this off-label use has consequences. In Italy, it has been suggested that specialists assume the full liability for treatment and that patients give informed consent and pay the full price of the drug, as reimbursement is restricted to disorders stated in the label [28].

Delirium is a medical emergency that should be recognized and treated immediately. Antipsychotics – including haloperidol and atypical agents – viably deal with a wide spectrum of delirium symptoms and are a key segment in the standard multimodal approach [29]. Intravenous (IV) haloperidol is advocated as safe, effective therapy for agitated delirium in medical or surgical cardiac patients in the intensive care unit [30].

Haloperidol is an older “typical” or “first-generation” neuroleptic and is non-selective and binds to a broad range of receptors. It can bind to dopamine D1 and D2, 5-HT2, histamine H1 and α2 adrenergic receptors in the brain. Haloperidol inhibits the dopamine and serotonin type 2 receptors on neurons in the brain. As a result, these neurons are not activated by the neurotransmitters released by other neurons. The efficacy of neuroleptics is thought to be due to antagonism of dopamine receptors in the mesolimbic and mesofrontal systems [25,31].

The known side effects of haloperidol include: menstrual infection, myasthenia, lactation, blockage, weight increase, obscured vision, akathisia, rearranging step, dysphagia, cover like face, dysphasia, anxiety, mastalgia, xerostomia, hypertension/hypotension, QT prolongation, heart failure, tachycardia, ventricular arrhythmias, torsade de Points (TdP), extrapyramidal responses, pseudo parkinsonism, jaundice, weakened liver capacity, bronchospasm, and expanded profundity of respiration [32].

In 2007, the FDA educated social insurance experts that the warning section of the prescribing information for haloperidol had been revised to incorporate another cardiovascular subsection with regards to instances of sudden death, QT prolongation, and TdP in patients treated with haloperidol, particularly when given intravenously or at measurements higher than those prescribed. Injectable haloperidol is approved by the FDA just for intramuscular injection, and there is considerable evidence from the medical literature that IV injection of haloperidol is generally used as “off-label” clinical practice, basically for the treatment of serious agitation in intensive care units. Because of various case reports of sudden death, TdP and QT prolongation in patients treated with haloperidol (particularly when the medication is given intravenously or at measurements higher than suggested), the drug sponsor has upgraded the warning labeling for haloperidol. The updated warning takes note that higher dosages and IV administration of haloperidol is associated with a higher risk of QT prolongation and TdP. Because of the risk of TdP and QT prolongation, ECG observing is prescribed if haloperidol is given intravenously [31].

In our patient, the PEA (cardiac arrest) was developed after the administration of haloperidol. However, the most likely causes were hypoxia-related PEA, pulmonary embolism, or stroke as a result of IV administration of haloperidol. Applying the Naranjo adverse drug reaction probability scale to this case (score of 4) indicated the possible relationship between the patient’s adverse cardiac event and haloperidol.

As discussed above, studies have indicated that high doses and IV administration of haloperidol are associated with an increased risk of QT prolongation and TdP. Our patient received the standard dose of haloperidol, but the drug was administered intravenously, which might have increased her risk of adverse cardiovascular outcomes.

Conclusions

Antipsychotic agents are significant and independent determinants of PEA [25] mostly in cases of out-of-hospital sudden cardiac arrest. This association indicates that prescription drugs may affect the pathophysiology of PEA and warrants consideration when designing future clinical and mechanistic studies.

Clinicians need to be educated about the potential for haloperidol to cause bradycardia progressing to PEA, and patients need to be closely monitored. Patients who receive haloperidol and develop a substantial decrease in heart rate may be at high risk for severe bradycardia leading to PEA. Caution is needed when using haloperidol, especially in patients with significant cardiac disease and renal impairment.
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