Torsades de Pointes Therapy With Phenytoin

We present the case of a woman with myocardial infarction complicated by malignant ventricular arrhythmia and torsades de pointes. The torsades de pointes was refractory to conventional therapy but responsive to phenytoin. This case suggests the clinicial usefulness of phenytoin for adjunct therapy of life-threatening ventricular arrhythmias when standard treatment modalities fail. [Vukmir RB, Stein KL: Torsades de pointes therapy with phenytoin. Ann Emerg Med February 1991;20:198-200.]

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INTRODUCTION

Ventricular tachycardia and fibrillation account for 75% to 85% of sudden cardiac death victims.[1] Torsades de pointes, described originally by Dessertenne, is a transitional arrhythmia between ventricular tachycardia and fibrillation.[1,2] The incidence of torsades de pointes has been suggested to be as high as 32% in sudden cardiac death.[3]

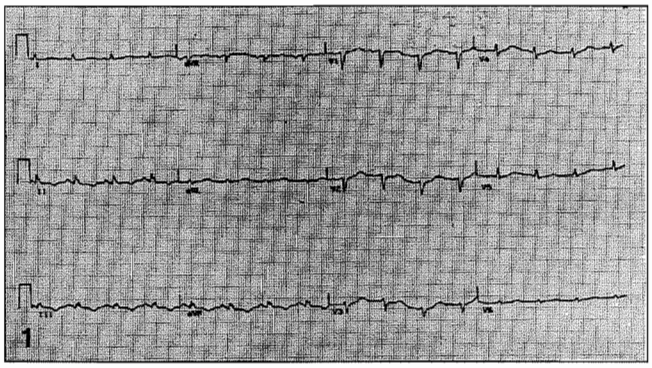
We present the case of a 37-year-old woman who suffered a myocardial infarction complicated by dysrhythmias involving torsades de pointes. Although she died later that day, the torsades de pointes responded promptly to treatment with phenytoin.

CASE REPORT

A 37-year-old woman presented in cardiac arrest after complaints of chest pain. She was found unresponsive by the family and was without resuscitative effort for ten minutes. Emergency medical services personnel found the patient pulseless and apneic. ECG monitoring revealed ventricular fibrillation, asystole, and idioventricular rhythms. Standard advanced cardiac life support intervention included intubation, CPR, defibrillation, and administration of atropine, epinephrine, naloxone, fluids, bicarbonate, calcium, lidocaine, magnesium, and dopamine.

Emergency department assessment found that her medical history included hypertension treated with verapamil, an unknown kidney disorder, and an abortion two weeks before presentation. There was neither history of drug or alcohol abuse nor significant family medical history. Physical examination found the patient to be unresponsive with a systolic blood pressure of 70 mm Hg and heart rate of 130, undergoing assisted ventilation. Neurologic examination revealed dilated pupils with decerebrate posturing. Cardiopulmonary examination found scattered rhonchi, no jugular venous distention, and normal heart tones without murmur or gallop. External examination showed no evidence of trauma.

Laboratory evaluation revealed a hemoglobin of 16.0; hematocrit, 44.3; platelets, 229,000 mm^3; and WBC, 16,200 mm^3. Electrolytes were remarkable for hypokalemia with potassium of 2.9 mEq/L and hyperglycemia with glucose of 447 mg/dL; sodium, 135 mEq/L; chloride, 100 mEq/L; HCO_3, 15 mEq/L; blood urea nitrogen, 15 mg/dL; creatinine, 1.2 mg/dL; calcium, 11.1 mg/dL; P_{O_4}, 2.9 mg/dL; and magnesium, 1.9 mg/dL. Liver function tests showed moderate elevation of parenchymal enzymes with SGPT of 278 and SGOT of 346 IU/L. Urinalysis showed microscopic hematuria and pyuria. Arterial blood gas analysis was remarkable for pH 7.23; P_{CO_2}, 27 mm Hg; HCO_3, 11 mEq/L; base excess, −15; and P_{O_2}, 161 mm Hg on an F_{IO_2} of 100%. ECG was significant for acute changes consistent with inferoposterior myocardial infarction with an intraventricular conduction



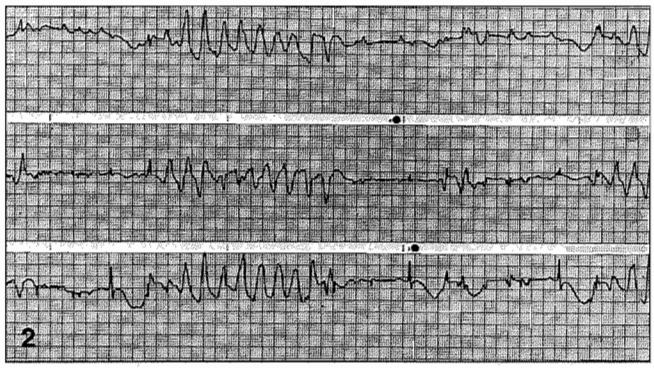


FIGURE 1. *Prolonged QT interval.*

FIGURE 2. *Torsades de pointes.*

delay, QT interval of 488 ms and QTC of 601 ms (Figure 1). Chest radiograph revealed normal cardiac silhouette and a left pneumothorax for which a chest tube thoracostomy was performed.

Assessment in the ICU found a woman in refractory ventricular tachycardia presumably due to a myocardial ischemia. The absence of notable risk factors for cardiovascular disease initiated consideration of other etiologies, including torsades de pointes, myocarditis, toxin ingestion, drug overdose, and pulmonary embolism. Instrumentation included a pacing Swan-Ganz catheter that revealed a central venous pressure of 11 mm Hg; pulmonary arterial systolic pressure, 30 mm Hg; pulmonary arterial diastolic pressure, 16 mm Hg; and pulmonary capillary wedge pressure, 14 mm Hg, with a systemic blood pressure of 90/60 mm Hg. Cardiac profile analysis revealed a temperature of 34.6 C; carbon dioxide, 1.5 L/min; cardiac index, 0.85 L/min/M^2; calculated systolic vascular resistance index, 9,974 dynes · sec/$cm^5 \cdot M^2$; and $C(a-v)O_2$, 10.0 vol %.

Recurrent refractory ventricular tachycardia necessitated subsequent intervention, which included repeated cardioversion and bretylium, lidocaine, sodium bicarbonate, and potassium administration. Torsades de pointes was treated with magnesium, isoproterenol, and a transcutaneous pacemaker followed by transvenous pacing without success (Figure 2). The possible etiologies of drug ingestion or verapamil overdose were addressed with naloxone, gastric lavage, activated charcoal, and calcium supplementation. Inadequate peripheral perfusion was treated with dopamine, epinephrine, and nitroprusside for afterload reduction. After prolonged resuscitative efforts, the patient became hypothermic to 34.1 C with ambient temperature of 80 F. This condition was treated with a warming blanket and heated, humidified ventilation.

Resuscitative efforts continued for four hours with refractory ventricular tachycardia and intermittent torsades de pointes requiring 175 cardioversion attempts. The patient then was administered 1,000 mg phenytoin IV at 50 mg/min. A significant decrease in recurrence of torsades de pointes was noted after 300 mg; aberrant ventricular activity was absent after administration of the total dose. Extrinsic variables in the patient's status were unchanged, including temperature of 34.1 C. Two subsequent episodes of torsades de pointes during the next eight hours responded similarly to phenytoin infusions of 200 mg IV, resulting in normal sinus rhythm. The patient was begun on maintenance phenytoin therapy of 100 mg IV every eight hours, with a serum level of 10.9 mg/dL.

Additional laboratory findings included negative drug and alcohol screens. However, the qualitative verapamil level was 80 ng/mL, which is considered therapeutic. Blood, urine, and sputum cultures were negative, as were acute viral titers. Erythrocyte sedimentation rate was 1 mm/hr, and serum creatine phosphokinase levels ranged from 458 to 25,620 IU/L, with a maximum MB fraction of 9.6%. An echocardiogram revealed left atrial enlargement and biventricular hypokinesis. Although the torsades de pointes resolved, the patient subsequently fulfilled criteria for brain death, and life support therapy was withdrawn at the request of the family. Autopsy was remarkable for a 100% right coronary artery occlusion, and an acute myocardial infarction was considered the cause of death.

DISCUSSION

Phenytoin is thought to restore normal membrane responsiveness, conduction velocity, and automaticity.[4,5] Thus, it acts to depress the action potential of ischemic cells while facilitating the activities of normal cells.[6] This antiarrhythmic action is similar to that of quinidine, with major effects on partially depolarized fibers and reversal of the inactive state of the sodium fast channel.[5,6] However, phenytoin has an opposite effect of that of quinidine, which decreases depolarization of Purkinje fibers and increases the stimulation threshold.[6]

There are several proposed mechanisms for phenytoin's antiarrhythmic action. First, there is a decrease in ventricular automaticity, especially in Purkinje fibers, which results from depression of all phases of repolarization of the transmembrane action potential.[4] Cardiac cells, particularly those with altered automaticity, are affected by phenytoin; they exhibit an increase in rate of the maximum diastolic potential and a decrease in the slope of phase 4, phase 0 (dV/dt) and the effective refractory period.[4] Second, a central antiarrhythmic effect is suggested by a decrease in baseline sympathetic discharge.[6] Finally, phenytoin acts to increase the atrioventricular conduction velocity and membrane responsiveness without decreasing cardiac output.[7] This augmented atrioventricular conduction can be quantified as a decrease in H_1-H_2 interval in patients with documented His-bundle delay or as an increase in depolarization velocity

in Purkinje fibers, particularly those depressed by digitalis.[7,8]

Phenytoin is considered standard therapy for digitalis toxicity, which results in ectopy, conduction defects, and suppression of sinus pacemaking function and is associated with high mortality rates.[9] Phenytoin has been found to be the most effective agent for digitalis toxic arrhythmias in both animals and human beings, with a decrease in mortality rates in the latter from 60% to 5%.[9,10] Similarly, phenytoin is the drug of choice for tricyclic antidepressant overdose.[5,11] In one study of patients with atrioventricular block or intraventricular conduction delay, normalization occurred in 50% by 46 minutes and in the remainder by 14 hours at a mean total dose of 5.7 mg/kg.[4]

The antiarrhythmic activity of phenytoin has been demonstrated in experimental ventricular tachycardia induced by coronary artery ligation, hypothermia, or toxin exposure, as well as in atrial tachyarrhythmia.[6,12] The efficacy of phenytoin for ventricular tachycardia has been described in postoperative pediatric patients with congenital heart disease by reduction of postoperative arrhythmias occurring within 12 hours.[13] A larger study of similar pediatric patients refractory to conventional therapy found complete control in 78.5% or reduction of ectopy in 100% of patients with a 3.4-mg/kg dose resulting in serum levels of 16.8 mg/mL.[14] This correlates with a study suggesting a 10 to 18 mg/mL therapeutic range of phenytoin for control of ventricular arrhythmias.[6] Phenytoin has also proved valuable in the therapy of refractory ventricular tachycardia with response rates of 34% to 92.3% in prospective, placebo-controlled trials.[7,15] In addition, phenytoin has been described as effective therapy for torsades de pointes in two case studies.[16,17]

The suggested dose of phenytoin for antiarrhythmic therapy is 3.5 to 5.0 mg/kg administered at 50 mg/min to a maximum dose of 500 to 1,000 mg.[8,14] Metabolism proceeds by hepatic microsomal enzymes to produce 5-phenyl-5-para hydroxyphenyl-hydantoin, which conjugates with glucuronic acid and is excreted by the kidneys.[18] Duration of action is from five minutes to two hours.[12] Side effects include pain at infusion site (25%), dizziness (18%), and hypotension (5.2%).[7] Sinoatrial arrest in conjunction with lidocaine use has been described and attributed to depressant effect manifested as prolonged sinus node cycle length and recovery time.[7,19] Single-agent therapy has resulted in one reported fatality after administration of 750 mg phenytoin over three minutes for atrial tachyarrhythmias.[7] Contraindications to the use of phenytoin include bradycardia and high-grade atrioventricular block.[7]

Standard therapy for torsades de pointes typically includes magnesium sulfate, isoproterenol, and atrial or ventricular overdrive pacing.[16] Alternative therapeutic modalities include DC cardioversion, lidocaine, mexiletine, verapamil, bretylium, propranolol, calcium gluconate, and atropine.[16,20]

SUMMARY

Although torsades de pointes occurs infrequently, the likelihood of occurrence increases in malignant arrhythmias resistant to routine therapy, as in our patient. This case illustrates the use of routine pharmacologic intervention for abnormal ventricular rhythms, including torsades de pointes, without effect. The case provides additional suport for inclusion of phenytoin into the armamentarium of pharmacologic agents used for refractory ventricular arrhythmias.

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