

CASE REPORT

Myocardial Ischemia as a Result of Severe Benzodiazepine and Opioid Withdrawal

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Long-term infusion of benzodiazepines and opioids is strongly associated with dependence and withdrawal syndromes. We report the first case of severe benzodiazepine and opioid withdrawal resulting in transient myocardial ischemia.

Case Report: A 6-month-old female born at 25 weeks gestation with severe opioid and benzodiazepine dependence resulting from multiple operative procedures and chronic ventilatory support was receiving continuous intravenous infusion of fentanyl and midazolam after trials of enteral methadone and diazepam had been unsuccessful due to gastric intolerance. On postoperative day 5 following Nissen fundoplication and gastrostomy tube placement, she acutely developed tachycardia, hypertension, agitation, loose stools, and yawning. Attempts to provide boluses of benzodiazepines and opioids revealed a very sluggish port in her subclavian central venous catheter. Prompt replacement of the catheter occurred without complication. After resuming infusions and providing additional sedatives and opioids, the loose stools, yawning, and agitation resolved. However, the tachycardia persisted. A 12-lead ECG was notable for significant

ST depression in anterior leads. Laboratory studies revealed significantly elevated cardiac enzymes. The patient was transfused with packed red blood cells to optimize oxygen-carrying capacity. Echocardiography demonstrated a small region of dyskinetic apical endocardium. Cardiac enzymes normalized within 48 h. The ECG and echocardiographic findings fully resolved after approximately 70 h.

Discussion: We believe that the sluggish central venous catheter port limited delivery of the midazolam and fentanyl to our patient. The resultant tachycardia and hypertension limited diastolic filling of the coronary arteries, resulting in myocardial ischemia. As the withdrawal was treated, heart rate and blood pressure returned to baseline, myocardial perfusion normalized, and the ST depression and the cardiac enzyme values normalized. This report underscores the significant morbidity associated with withdrawal syndromes and the need to recognize withdrawal early and to treat it aggressively.

Keywords Myocardial ischemia; Benzodiazepine; Opioid; Withdrawal

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INTRODUCTION

Long-term infusion of benzodiazepines and opioids is commonplace in pediatric intensive care units. These medications are strongly associated with dependence and withdrawal syndromes (1–9). Accordingly, care must be implemented in children with long-term infusions to avoid abrupt cessation of these medications. We report the first case of severe benzodiazepine and opioid withdrawal resulting in transient myocardial ischemia.

CASE REPORT

We present a 6-month-old Caucasian female born at 25 weeks gestation who was transferred to our Pediatric

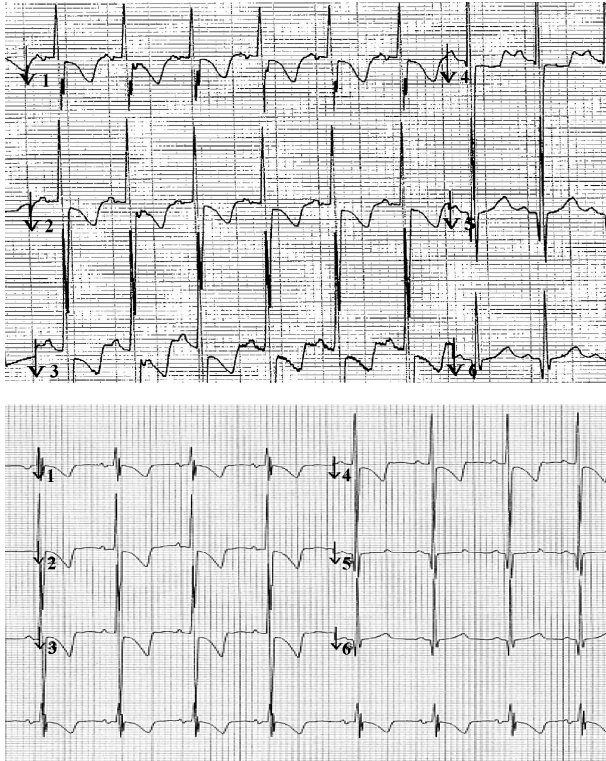


FIG. 1. a) ECG ST depressions on presentation. b) Resolution of ECG ST depressions after therapy.

Intensive Care Unit following tracheostomy tube placement for respiratory support and treatment of multiple chronic complications of prematurity, including severe opioid and benzodiazepine dependence resulting from multiple operative procedures and chronic ventilatory support. This necessitated continuous intravenous infusion of fentanyl and midazolam after trials of enteral methadone and diazepam were unsuccessful due to gastric intolerance. Chronic medications included fluticasone, elemental iron, erythropoietin, ursodiol, calcium carbonate, and dihydrotachysterol.

On postoperative day 5 following Nissen fundoplication and gastrostomy tube placement, she acutely developed

tachycardia with heart rates between 190 and 220 beats/min (baseline 130's) along with hypertension (120–130's systolic/70–80's diastolic), agitation, loose stools, and subjective yawning. Attempts to provide boluses of benzodiazepines and opioids revealed a very sluggish port in her subclavian central venous catheter (CVL). No other medications had been administered through this CVL. Prompt replacement of the catheter via Seldinger technique occurred without complication. After resuming infusions (midazolam 0.2 mg/kg/hr and fentanyl 2 mcg/kg/hr) and providing additional fentanyl (total of 6 mcg/kg) and propofol (2 mg/kg), 2 h after the initial event, the loose stools, yawning, and agitation resolved, however, the tachycardia persisted with heart rates between 180–190s associated with continued hypertension (120s/70s). No hemodynamic change was noted following a subsequent 10 mL/kg bolus of Ringer's Lactate.

Throughout the duration of tachycardia, there were no changes in ventilatory status, and oxygen saturation remained 100% on baseline FiO_2 of 0.3. Urine output was 2–3 mL/kg/hr, pulses were normal, and central capillary refill was slightly prolonged at 3 sec. Chest roentgenogram obtained for confirmation of line placement was unchanged from baseline.

A 12-lead electrocardiogram (ECG) obtained to further evaluate the tachycardia and cardiac function was notable for a sinus tachycardia (rate 185 beats/min) with significant ST depression in anterior leads (Fig. 1a) and prompted evaluation for myocardial ischemia and sepsis with cardiac enzymes (total CK, CK-MB, and troponin-I), electrolyte panel, lactic acid, prothrombin time, partial thromboplastin time, D-dimer, complete blood count (CBC), and blood, urine, spinal fluid, and CVL tip cultures. An additional 20 mL/kg bolus of normal saline was provided to optimize perfusion, and broad spectrum intravenous antibiotics were begun due to concerns for sepsis. Laboratory studies revealed significantly elevated cardiac enzymes (Table 1). Electrolyte panel and lactic acid were normal, and CBC demonstrated an elevated white blood cell count (16.3 k, polys 59%, bands 9%) with mild thrombocytopenia (127 k). Additional analgesia (fentanyl 2 mcg/kg) and sedation (midazolam 0.2 mg/kg) were provided to minimize agitation and cardiac demand. The patient was transfused with packed red blood cells (10 mL/kg) to maximize

TABLE 1
Summary of cardiac enzyme values

	T+4 h	T+8 h	T+16 h	T+24 h	T+48 h
CK (IU/L) (nl = 30–135)	466	413	120	51	<20
CK-MB (ng/mL) (nl = 0.18–4.2)	24.8	18.1	10.2	5.75	3.66
Troponin I (ng/mL) (nl < 0.15)	1.63	1.07	0.62	0.22	<0.15

T = onset of tachycardia.

CK = creatinine kinase.

CK-MB = MB fraction of creatinine kinase.

oxygen-carrying capacity 5 h after the initial event. Beta-blockade was considered but not felt to be clinically necessary as the tachycardia began to respond to the transfusion of packed red blood cells and additional sedation.

Review of cardiac history revealed a history of patent ductus arteriosus which closed spontaneously and mild non-obstructive cardiomyopathy with left ventricular and septal hypertrophy which also resolved spontaneously. She had never received any cardiac nor cardiotoxic medications during her NICU stay. A recent echocardiogram (2 weeks prior) had demonstrated normal structure and function. No prior ECGs were available for comparison. Echocardiography the following morning demonstrated normal structure (including coronary origins) and good cardiac function except for a small region of dyskinetic apical endocardium.

Serial ECGs demonstrated resolving ST depression (Fig. 1b). Cardiac enzymes normalized within 48 h (Table 1). Within 12 h of onset, the patient's heart rate returned to baseline 130s, however, blood pressure remained mildly elevated (110s/60s). Capillary refill time also returned to less than 2 sec. The ECG and echocardiographic findings fully resolved after approximately 70 h. Screening blood, urine, CSF, and CVL tip cultures remained without growth and antibiotics were discontinued after 48 h of therapy. She has since remained hemodynamically stable without any signs of withdrawal and has been transferred to a long-term rehabilitation facility.

Publication of this case report was approved by the Investigational Review Board at the Naval Medical Center Portsmouth.

DISCUSSION

Agitation in the pediatric intensive care unit can be a result of multiple causes. However, in a child who has been receiving long-term infusions of benzodiazepines and opioids, acute withdrawal syndrome must be high on the differential diagnosis. Symptoms of withdrawal include anxiety, tachycardia, insomnia, restlessness, emesis, hypertension, yawning, psychosis, and seizure activity (1,2,5,8). In our review of the literature, transient myocardial ischemia or myocardial infarction have not been reported in conjunction with acute withdrawal. Alcohol and clonidine withdrawal have been associated with hypermetabolic states and acute myocardial infarction (9–11).

The sluggish central venous catheter port limited delivery of the midazolam and fentanyl to our patient. The resultant tachycardia and hypertension limited diastolic filling of the coronary arteries, resulting in myocardial ischemia. As the withdrawal was treated, heart rate and blood pressure returned to baseline, and myocardial perfusion also normalized. This is significant because the myocardium of an infant is not able to increase stroke volume to increase cardiac output, only

increase heart rate. However, if the tachycardia impairs diastolic filling, cardiac output will fall and result in circulatory collapse.

Our hypothesis is supported by a number of pieces of evidence. First, there was clear ST depression on the ECG following the event. Furthermore, there was a marked increase in multiple cardiac enzymes and prolonged capillary refill time. As the withdrawal was treated, the ST depression and the cardiac enzyme values normalized. Additionally the apical myocardial dyskinesis is strongly suggestive of a distal ischemic process. If the ischemia had persisted, global dyskinesis would have been present.

Our ECG analysis is somewhat limited by not having a pre-event ECG. However, an echocardiogram 2 weeks prior demonstrated normal structure and function, so we may extrapolate that the ECG at that time might be normal as well. While she did not have pre-event CK or CK-MB levels, she did have Troponin I levels drawn for sepsis evaluations which were less than 0.15 ng/mL.

This is the first report of transient myocardial ischemia as a result of severe benzodiazepine and opioid withdrawal. This report underscores the significant morbidity associated with withdrawal syndromes and the need to recognize withdrawal early and to treat it aggressively.

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