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Recurrent Takotsubo Cardiomyopathy Associated with Opioid Withdrawal During Buprenorphine Induction

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Abstract

This case report describes a 65-year-old female with iatrogenic opioid use disorder for chronic lower back pain, who developed Takotsubo cardiomyopathy on multiple occasions following buprenorphine induction. This patient had three opioid transfers to buprenorphine, over 4 years, two of which were complicated by Takotsubo cardiomyopathy. In the transfer where she did not develop Takotsubo cardiomyopathy, she was treated with high doses of the centrally acting agonist, clonidine (three times a day, total of 600 mcg/day), up to and including the day of her transfer. This case highlights the potential consequences of a precipitated withdrawal with buprenorphine in an opioid transfer and its possible prevention with clonidine. To our knowledge, this is the first description of the recurrent Takotsubo cardiomyopathy in an opioid transfer setting. Given that buprenorphine is a partial agonist, in the presence of a full opioid agonist, it can precipitate withdrawal within minutes to hours of its administration. Opioid withdrawal can result in a sympathetic overdrive. Although complications of opioid withdrawal are extensively documented, cardiotoxicity is uncommon. As the use of buprenorphine and its new injectable formulations rise, it is important for prescribers to be aware of this life threatening complication. The prophylactic administration of clonidine can be considered to reduce the risk of cardiotoxicity, as well as manage opioid withdrawal symptoms.

Keywords Buprenorphine · Opioid withdrawal · Takotsubo cardiomyopathy

Introduction

Takotsubo cardiomyopathy (TCM) is an acquired, reversible cardiomyopathy characterized by a transient left ventricular apical ballooning syndrome [1]. Predominantly affecting post-menopausal women, TCM is frequently trigged by an emotional or physical stressor with catecholamine excess. Sympathetic overstimulation plays a pivotal role in its pathophysiology [2], [3], [4], [5]. At least 57 drugs in 78 case reports have been published describing drugs as a trigger in TCM [6]. Risk of recurrence of TCM is low (5–22%) [7, 8], with drugs implicated in recurrence [6]. Here we report a complex case of a patient with chronic pain who had two episodes of TCM after undergoing opioid transfer to buprenorphine within a 4 year period.

Case Details

A 65-yr-old female with a history of iatrogenic opioid use disorder was electively admitted for transition from methadone to buprenorphine. Her past medical history was that of chronic lower back pain (CLBP), Type 2 Diabetes mellitus, gastroesophageal reflux disease, fibromyalgia, and anxiety disorder.

She had her first uneventful transition from oxycodone to buprenorphine sublingual in March 2014, with a ketamine

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infusion crossover (6 mg/hr) and oral clonidine as required (three times a day (tds), total 300–600 mcg/day). Ketamine was used specifically in this patient to assist with the management of active pain (and to manage her opioid induced hyperalgesia [9]). She discontinued buprenorphine and reverted to oxycodone shortly after discharge. In October 2014, in an external facility, she was readmitted for transition from oxycodone to buprenorphine patch and again managed with a ketamine and clonidine (twice a day, total doses of 100 mcg/day) crossover. This opioid transfer was complicated by TCM based on criteria of transient left ventricular systolic dysfunction on transthoracic echocardiogram (TTE), normal angiography, and new ischemic-type ST-T wave changes and troponin rise (Fig. 1a and Fig. 2). The TTE changes subsequently resolved. Six weeks post transition, she became intolerant of the patch due to skin irritation and methadone was recommenced for management of both her pain and opioid dependence. Escalating doses of methadone and diazepam over the subsequent 3 years resulted in frequent falls and injuries. Due to high levels of anxiety, she was readmitted to our facility in 2017 for transition back to buprenorphine. A timeline of her clinical course for the 2017 admission is shown in Fig. 1b. Due to the high levels of anxiety and increasing levels of pain, diazepam (10 mg tds) was continued and ketamine infusion was initiated at 2 mg/hr and increased up to 24 mg/hr over 2 days. Her last methadone dose (40 mg) was administered prior to admission. A clinical opioid withdrawal scale (COWS) was initiated on admission, but these were not consistently assessed throughout the admission. A single dose of 10 mg oxycodone was administered around 14 h post admission for subjective signs of withdrawal. Thirty hours after admission,

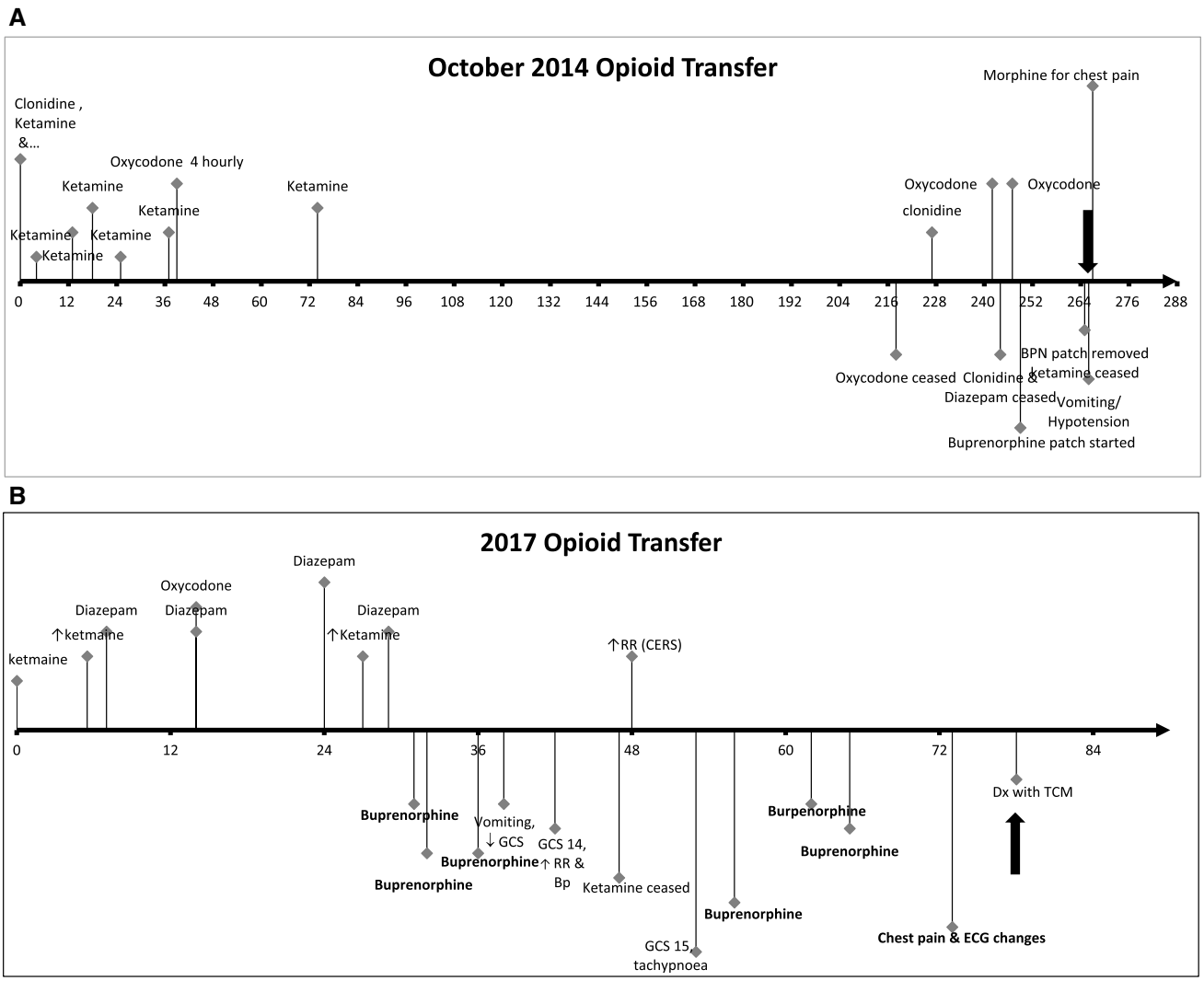

Fig. 1 **a** 2014 Transfer timeline: Takotsubo cardiomyopathy diagnosed 18 h post buprenorphine initiation. Arrow denotes Takotsubo cardiomyopathy diagnosis. **b** 2017 Transfer timeline. GCS = Glasgow Coma Scale, RR = Respiratory rate, BP = Blood Pressures, CERS: Clinical Emergency Response System called for deteriorating patients. Arrow denotes TCM diagnosis

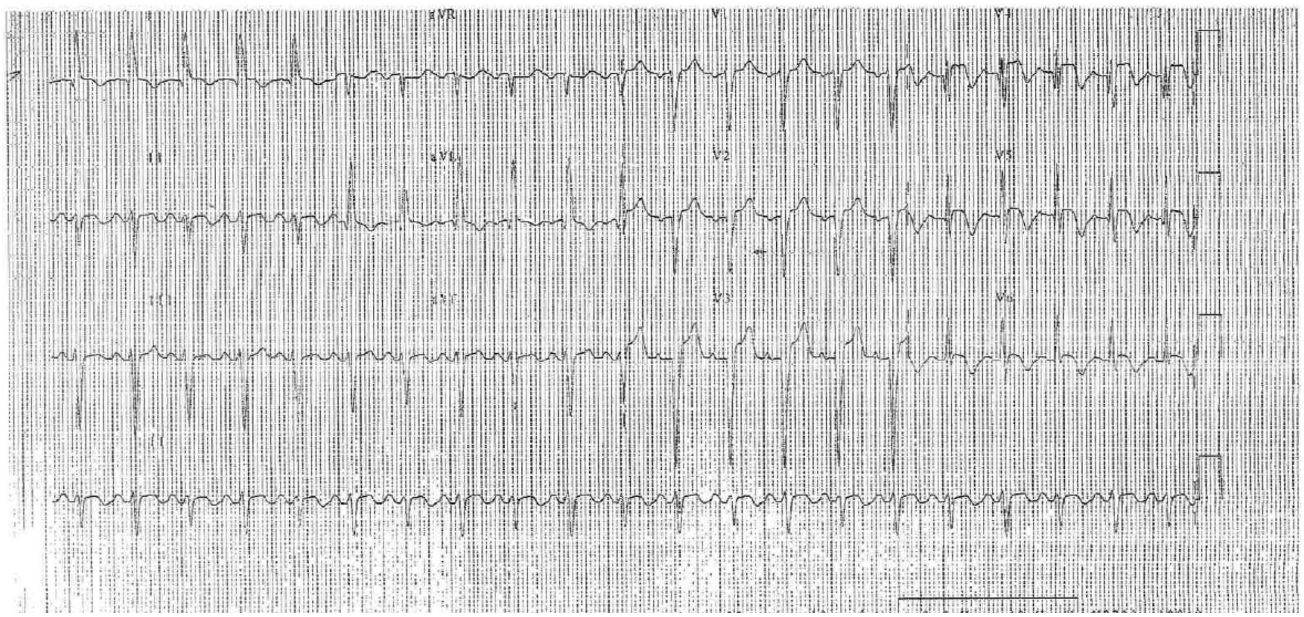

Fig. 2 Electrocardiogram of the patient at the time of second opioid transfer, prior to echocardiogram consistent with Takotsubo cardiomyopathy: Sinus tachycardia, left anterior fascicular block, left ventricular hypertrophy, and ST-t change anterolateral myocardial infarction

4 mg sublingual buprenorphine was initiated and she was given further buprenorphine sublingual 2 mg at 32 and again at 34 h post admission. After the third dose, she started vomiting. Shortly after an urgent medical review was called for reduced consciousness (Glasgow coma score 14) and shortness of breath (SOB) and ongoing vomiting. No COWS score was recorded at this time, pupils were documented to be 5 mm, and the respiratory rate was 30 breaths/minute. Her blood pressure was 170/95 mmHg, heart rate was 98 beats/minute, and oxygen pulse oximetry was 90% on room air. Investigations of chest x-ray, CT brain, venous blood gas, blood glucose, and electroencephalography were unremarkable. No ECG was performed at this point; however, troponin was slightly elevated at 43 ng/L. Her deterioration was considered to be due to over sedation from medications and so the ketamine infusion was weaned and ceased. Diazepam and buprenorphine were also ceased. Her mentation improved; however, she remained SOB with reduced O_2 saturations. Diazepam and subsequently buprenorphine were reintroduced after 12 h. At 74 h post admission, she developed chest pain with anterolateral ST elevation (Fig. 3) on ECG with an associated peak troponin of 238 ng/L. The TTE demonstrated apical left ventricular (LV) akinesis, consistent with TCM (Fig. 4) and the cardiology team decided not to repeat her angiogram. She was treated with a heparin infusion, followed by apixaban and commenced on bisoprolol. Her LV function improved over the subsequent week on repeat TTE. Her buprenorphine dose was increased to 6 mg at 102 h post admission, and slowly to 32 mg over the subsequent week. She was discharged 12 days post admission.

Discussion

The patient described had two episodes of clinically proven TCM, and one where there was no cardiac event, when transferring from opioid agonists to buprenorphine. Takotsubo Cardiomyopathy has been classified into primary or secondary subtypes [7]. Acute stressful events with associated catecholamine surge are implicated in triggering primary TCM [5]. Many drugs have been associated to cause this surge and subsequently result in TCM [6]. Secondary TCM, however, occurs in patients already hospitalized for another medical, surgical, anesthetic, obstetric, or psychiatric condition [7].

Our patient has a number of underlying factors that predisposed her to developing TCM. Her age, post-menopausal status, and underlying anxiety disorder place her in a higher risk category. However, the recurrence of TCM in the setting of opioid transfer warrants further discussion.

Catecholamine surge has been associated with opioid withdrawal [10] and several case reports have been published describing opioid withdrawal induced TCM [11], [12], [13], [14], [15]. Buprenorphine-precipitated withdrawal (PW) when transferring between opioids is also well documented [16] and a recent publication by Surmaitis et al. [15] reported TCM associated with buprenorphine PW.

On the Naranjo Adverse Drug Reaction Probability Scale (Naranjo Scale), our patient scores high, suggesting that the development of TCM was likely a result of an adverse drug reaction. Given the temporal correlation with the initial doses of buprenorphine and development of symptoms in her third presentation, we hypothesize that PW from the use

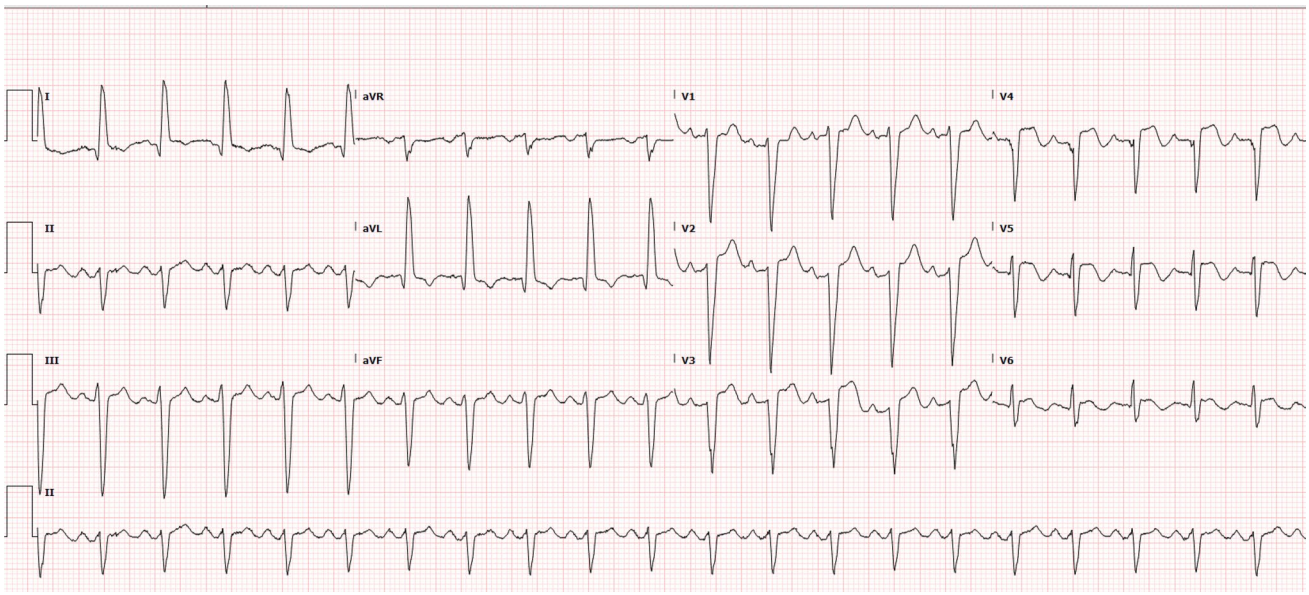

Fig. 3 Electrocardiogram of the patient AG at the time of third opioid transfer, prior to echocardiogram consistent with Takotsubo cardiomyopathy Sinus tachycardia, left anterior fascicular block, left ventricular hypertrophy, and ST-t change anterolateral myocardial infarction

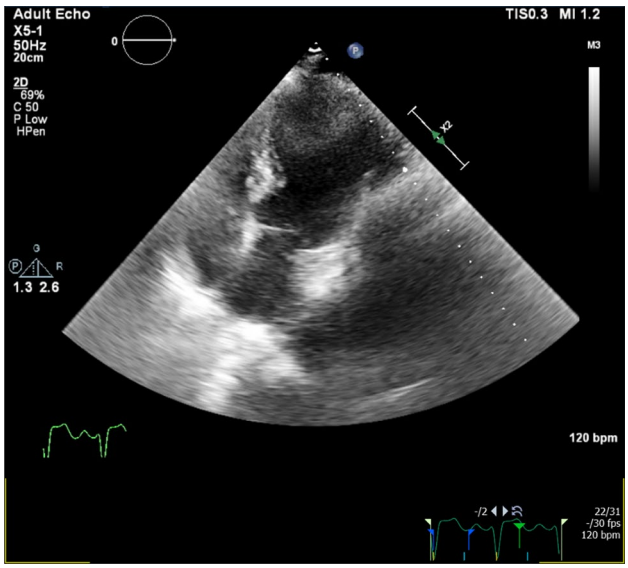

Fig. 4 Transthoracic echocardiogram image from 2017 admission, consistent with Takotsubo cardiomyopathy

of buprenorphine leads to a sympathetic overdrive. Unfortunately, COWS score was not recorded consistently throughout her admissions to clearly implicate PW as the cause of her TCM, and this remains a limitation of this case report. Of note, buprenorphine treatment was continued and the TCM resolved, so the drug itself was not the cause of the cardiac dysfunction.

This patient underwent successful opioid transfer without developing TCM on one occasion which may reflect the higher doses of clonidine that were administered and continued post buprenorphine commencement. Clonidine is an agonist of central presynaptic alpha-2 receptors which decrease sympathetic drive in the locus coeruleus and is effective in reducing opioid-related catecholamine surges [17, 18]. Although clonidine has not been previously recommended in the treatment in TCM [7], this case reports suggest it may play a role in prevention of TCM in the setting of PW.

To date, ketamine has been implicated in the occurrence of TCM in only a single case report during a ketamine procedural sedation in an emergency setting [19]. Animal models of TCM have demonstrated that ketamine enhances the responsiveness to sympathetic stimulation [20] and that ketamine infusions increase plasma noradrenaline concentrations, especially at cardiac sympathetic nerves [21]. Additionally, there has been a recent case report of ketamine-induced TCM [22].While ketamine may not have been the precipitating agent in the development of TCM (given that it was used in all three transfers), these other sympathetic-like effects may have contributed to the presentation, and its use in opioid transfers requires caution. Not in keeping with this is lack of a temporal relationship with the initiation of ketamine and the development of TCM. In addition, the symptoms and signs of TCM worsened after cessation of ketamine.

Identifying buprenorphine-induced precipitated withdrawal as the major cause of TCM in this patient impacts the future management of her opioid dependence. We recommend pre-emptive clonidine dosing prior to

administration of buprenorphine in the future in the acute period to prevent recurrence of TCM.

Conclusion

While multiple triggers may have acted synergistically to cause a recurrence of TCM in this patient, the case highlights that opioid withdrawal in the setting of buprenorphine induction is complex and not without risk and can be associated with significant morbidity. As the use of buprenorphine increases in response to the opioid epidemic, this adverse event may be seen more frequently.

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Author Contributions NJ—Writing of manuscript and takes overall responsibility for the paper. DC—Planning and literature search for manuscript. BM—Oversight, writing, and revision of manuscript.

Compliance with Ethical Standards

Conflict of interest The authors declare no conflicts of interest and do not have any financial disclosures.

Informed Consent Written, informed consent for publication was obtained from the patient.

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