Received: 5 September 2018 | Revised: 1 December 2018 | Accepted: 2 February 2019

DOI: 10.1002/ccr3.2086

CASE REPORT

WILEY Clinical Case Reports Open Access

Is thrombotic event a side effect of oral buprenorphine abuse? Two case reports

Toktam Alirezaei | **Behzad Hajimoradi**

Cardiology Department of Shohaday-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran

Correspondence
Toktam Alirezaei, Cardiology Department of Shohaday-e-Tajrish Hospital, Shahid Beheshti University of Medical Sciences (SBMU), Tehran, Iran.
Email: alirezaei.toktam@sbmu.ac.ir

Key Clinical Message

Buprenorphine is used to treat opioid addiction. The spectrum of complications of oral buprenorphine is not well known. We describe two cases and based on a hypothesis is proposed which suggests that the use of oral buprenorphine could be relevant to the increase of thrombotic risk.

KEYWORDS

myocardial infarction, oral buprenorphine, pulmonary embolism, thrombotic event

1 | INTRODUCTION

Buprenorphine is a potent synthetic opioid that causes morphine-like effects and cross-tolerance to other opioids. Buprenorphine could be used as an alternative to methadone and a maintenance agent in the management of opioid dependence.[1] The effect of buprenorphine on opioid receptors and their ability to make euphoria leads to abuse of this drug.[2]

Oral intake of buprenorphine is safe for most patients. Some users do experience side effects, but most of them are not dangerous.[3] Buprenorphine may cause some adverse side effects that a complete knowledge of them by primary care physicians is needed to provide the best management to prevent complications of buprenorphine.[4]

These cases are presented to highlight the serious complication following oral abuse of buprenorphine and to heighten awareness of its devastating effects.

2 | CASE REPORT 1

A 27-year-old male in the background of prolonged opioid dependence presented to our emergency department with a sudden pleuritic and retrosternal chest pain which has begun from 2 hours ago. Also, he reported to have experienced shortness of breath during the past 4 days before admission.

His vital signs upon arrival to the emergency department showed a blood pressure of 100/70 mm Hg, a heart rate of 125 beats per minute, a respiratory rate of 28 per minute and oxygen saturation of 93% in ambient air.

The cardiac examination showed moderate tachycardia and a right ventricular heave.

Pulmonary examination was normal. The initial electrocardiogram showed sinus tachycardia at a rate of 120 per minute, right axis deviation, S1Q3T3 pattern, ST elevation in V1-V4, and T inversion in V1-V4 and III, AVF (Figure 1).

According to the symptoms and ECG finding, acute ST elevation myocardial infarction (STEMI) and acute pulmonary thromboembolic (PTE) were considered.

Hence, a detailed history was obtained again. He did not have any risk factor for cardiovascular disease and conditions conferring risk for thrombosis. His family history was negative in the first- and second-degree relatives, and he had no history of psychiatric disorders.

The patient had a history of inhaled opioid dependence since 10 years ago and his medication consisted of oral buprenorphine 7.5 mg once daily for treatment of opioid addiction since about 40 days ago with no recent change in the dose and appeared to be dependent on the oral buprenorphine alone and no alcohol or other drugs were used.

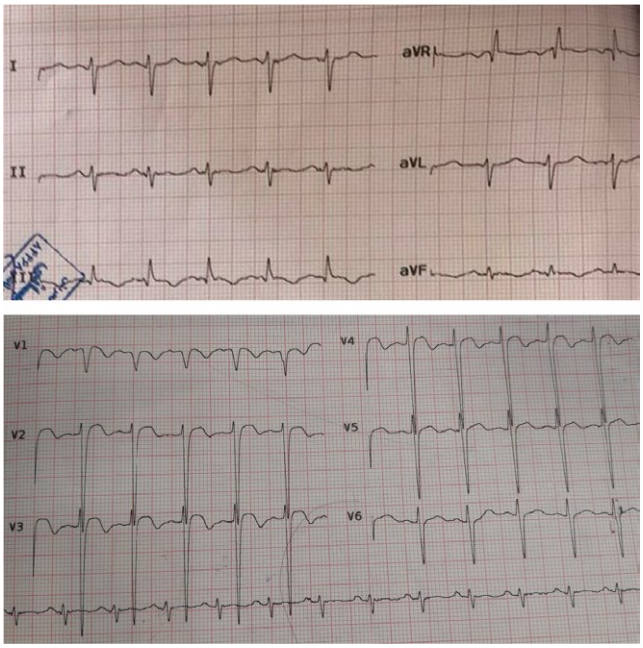

FIGURE 1 ECG shows sinus tachycardia, right axis deviation, S1Q3T3 pattern, ST elevation and T inversion in V1-V4

After 1 hour of admission, blood pressure was decreased to 85/55 mm Hg and despite administration of intravenous normal saline (a 500 cc bolus of 0.9% saline) was not increased and the clinical picture of patient was deteriorated.

The pulmonary CT angiography (CTA) was done and revealed large bilateral pulmonary thromboemboli with evidence of right ventricular strain (Figure 2).

According to hemodynamic compromise resulting from the massive pulmonary embolism, he became candidate for emergent thrombolytic therapy.

Intravenous alteplase was administrated according to approved dosage for massive PTE (100 mg infusion over a 2 hours' period).[5] Approximately at the termination of the infusion, blood pressure returned to 100/70 mm Hg, with a heart rate of 95 beats per minute and a respiratory rate of 18 per minute with an oxygen saturation of 96% in ambient air. Electrocardiogram now shows a rate of 90 per minute and resolved ST elevation, Figure 3.

Transthoracic echocardiography demonstrated mild RV enlargement and pulmonary artery pressure of 35-40 mm Hg. Heparin infusion was initiated, and then, warfarin was prescribed.

Buprenorphine was discontinued. The patient continued to improve clinically and was discharged on warfarin (7.5 mg once daily) and methadone (10 mg once daily) after 7 days.

3 | CASE REPORT 2

A 43-year-old male was hospitalized for pain in the retrosternal, nausea, and cold sweating from 1 hour ago.

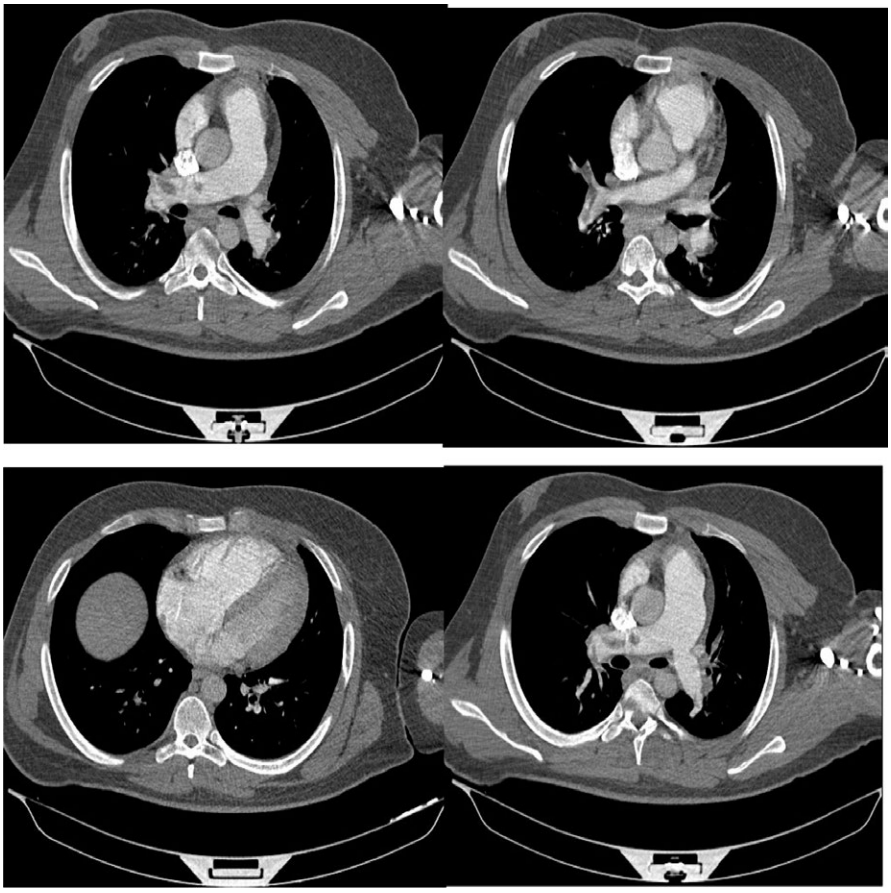

FIGURE 2 Pulmonary CT angiography demonstrates bilateral pulmonary thromboemboli with right ventricular dilatation

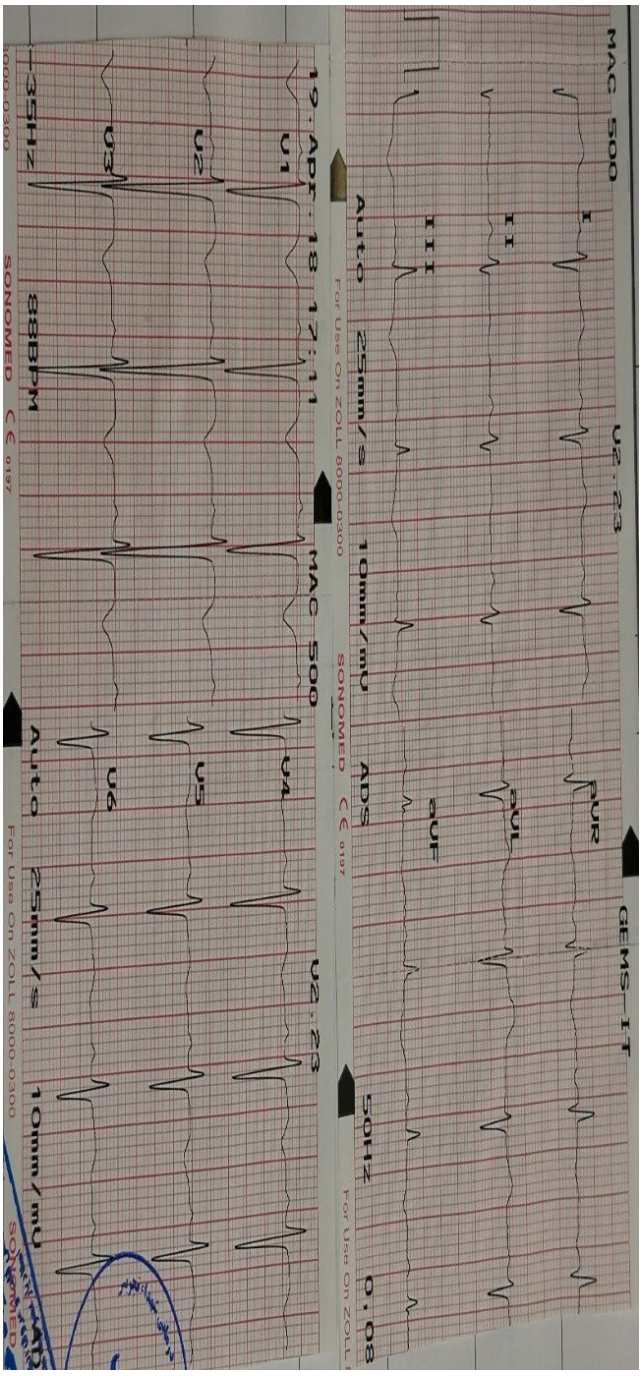

FIGURE 3 ECG shows normal sinus rhythm with resolved ST-segment elevation

He had a history of opioid addiction since 7 years ago. Oral buprenorphine (5 mg once day) was prescribed for him from 40 days ago through health department for treatment of opioid addiction and prevention of withdrawal symptoms. He denied other drug or substance abuse.

The patient did not have any risk factor for coronary artery disease. His family history for cardiovascular diseases and thrombotic events was negative.

Vital signs upon arrival to the emergency department showed a blood pressure of 110/75 mm Hg, a heart rate of

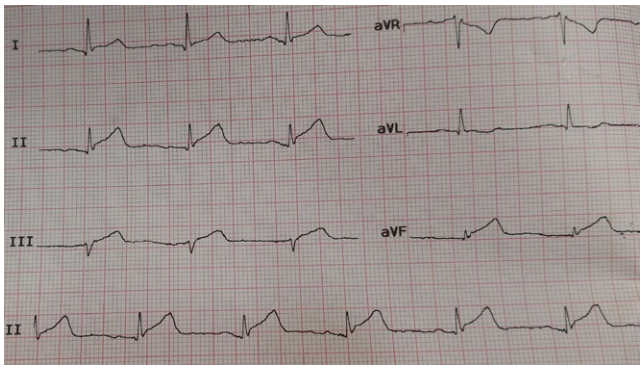

FIGURE 4 ECG shows sinus rhythm and ST elevation in inferior leads (II, III, avf)

56 beats per minute, a respiratory rate of 16 per minute and oxygen saturation of 96% in ambient air.

Electrocardiogram shows sinus rhythm, Normal QRS duration, Normal axis and ST elevation in inferior leads (II, III, aVF) and V3R, V4R, Figure 4.

According to the diagnosis of acute RV& inferior STEMI and no contraindication for thrombolytic therapy, reteplase was selected as a thrombolytic of choice and was prescribed according to approved dosage for STEMI. Within 90 minutes of termination thrombolytic, his chest pain resolved and ST segment elevations returned to isoelectric baseline. Heparin infusion was initiated and after 24 hours it changed to a therapeutic dose of subcutaneous enoxaparin (LMWH 1 mg/kg twice a day) and dual antiplatelet therapy was continued. The patient was referred to another center for cardiac catheterization after 5 days of thrombolytic therapy. The result of cardiac catheterization showed 75% stenosis at mid-part of Right coronary artery (RCA) and PCI on RCA was done.

Oral intake of buprenorphine was discontinued and the patient was discharged on methadone (10 mg once daily).

4 | DISCUSSION

Buprenorphine is a synthetic opioid and a partial agonist that causes weaker opioid effects at receptor sites. This partial agonist effect makes it safer in overdose and causes an easier withdrawal phase. Buprenorphine has been used in the treatment of opioid dependence,[1] although it demonstrated significant improvement as an alternative to methadone in the management of opioid addiction, troublesome symptoms may occur in buprenorphine abuse.[6]

While all drugs are assayed carefully before they are approved for use, they may have potential adverse side effects and some of these complications may become apparent only after use by the general population.[6,7]

These case reports open a possibility that oral abuse of buprenorphine could cause thrombotic events. These reports

suggest a potential side effect that can have serious consequences. It is possible that when buprenorphine is administered as an oral preparation may increase thrombosis rate.

In our patients, oral abuse of buprenorphine had been started since about 40 days ago. One might question if there is a causal relationship between thrombotic event and this drug, buprenorphine may have played a role in the pathogenesis of thrombotic event in our patient.

Several previous studies showed that the users of intravenous opioid drugs such as intravenous buprenorphine had increased risk of thrombosis but similar findings have not been proven in oral intake of buprenorphine.[8-10]

Buprenorphine is widely used as a substitution agent in the treatment of opioid dependence and has become a top-selling new pharmaceutical product.[11] Understanding the spectrum of its complications is very important and buprenorphine administration needs observation and close monitoring amongst opioid-dependent patients. More education and greater awareness of physicians to this current issue is needed and buprenorphine prescription should be by trained physicians.

Identification of complications relating to oral abuse of buprenorphine and demonstration of our proposed theory needs to do more studies.

CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

TA: analyzed data, drafted, did background research, and revised the manuscript. BH: involved in patient management and reviewed results.

ORCID

Toktam Alirezaei https://orcid.org/0000-0002-4473-7093

REFERENCES

1. Mattick RP, Kimber J, Breen C, Davoli M. Buprenorphine maintenance versus placebo or methadone maintenance for opioid dependence. *Cochrane Database Syst Rev*. 2008;2:Cd002207.
2. Yeo AK, Chan CY, Chia KH. Complications relating to intravenous buprenorphine abuse: a single institution case series. *Ann Acad Med Singapore*. 2006;35(7):487-491.
3. Hish GA, Diaz JA, Hawley AE, Myers D, Lester PA. Effects of analgesic use on inflammation and hematology in a murine model of venous thrombosis. *J Am Assoc Lab Anim Sci*. 2014;53(5):485-493.
4. Heel R, Brogden R, Speight T, Avery G Buprenorphine: a review of its pharmacological properties and therapeutic efficacy. *Drugs*. 1979;17(2):81-110.
5. Alirezaei T, Hajimoradi B, Pishgahi M, Nekooghadam SM, Golmohamadi M. Successful systemic thrombolytic therapy for massive pulmonary embolism in a patient with breast cancer, brain metastasis, and thrombocytopenia: a case report. *Clin Case Rep*. 2018;6: 1431-1435.
6. Donaher PA, Welsh C. Managing opioid addiction with buprenorphine. *Am Fam Physician*. 2006;73(9):1573-1578.
7. Renard D, Gaillard N. Brain haemorrhage and cerebral vasospasm associated with chronic use of cannabis and buprenorphine. *Cerebrovasc Dis*. 2008;25(3):282-283.
8. Cornford CS, Mason JM, Inns F. Deep vein thromboses in users of opioid drugs: incidence, prevalence, and risk factors. *Br J Gen Pract*. 2011;61(593):e781-e786.
9. Bouquié R, Wainstein L, Pilet P, et al. Crushed and injected buprenorphine tablets: characteristics of princeps and generic solutions. *PLoS ONE*. 2014;9(12):e113991.
10. Lim C, Lee SH, Wong YC, Hui F. Embolic stroke associated with injection of buprenorphine tablets. *Neurology*. 2009;73(11):876.
11. Seet RC, Oh VM, Lim EC. Complications arising from intravenous buprenorphine abuse. *QJM*. 2007;100(5):312-313.

How to cite this article: Alirezaei T, Hajimoradi B. Is thrombotic event a side effect of oral buprenorphine abuse? Two case reports. *Clin Case Rep*. 2019;7:740–743. https://doi.org/10.1002/ccr3.2086