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Ventricular arrhythmias in patients treated with methadone for opioid dependence

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Abstract
Purpose Over the last decade, there has been a significant rise in reported cases of methadone induced QT prolongation (QTP) and Torsades de Pointes (TdP) in patients treated for opioid dependence. Optimal management of these patients is challenging.
Methods We report a case series of 12 consecutive patients admitted to our institution with methadone-induced QTP and ventricular arrhythmias.
Results All patients survived the presenting arrhythmia. Successful transition to buprenorphine was accomplished in three patients. QT interval normalized and none of these patients had recurrent arrhythmias. Methadone dose was reduced in five patients with improvement of QT interval and resolution of arrhythmia. Four patients, including two with ICDs, refused or did not tolerate a reduction in their methadone dose.
Conclusion Ventricular arrhythmias in patients on methadone are an uncommon but important problem. Buprenorphine, a partial μ-opiate–receptor agonist and a κ-opiate–receptor antagonist does not cause QTP or TdP. Buprenorphine is a useful and effective alternative to methadone in a select group of patients, including those with documented ventricular arrhythmias on methadone. Pacemakers or defibrillators should be reserved for patients who have failed buprenorphine or a reduced methadone dose.

Keywords Methadone · Buprenorphine · Torsades de Pointes · Ventricular arrhythmias

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1 Introduction

Methadone, a long-acting synthetic opioid, is an effective maintenance therapy for opioid addiction [1]. Methadone, like most medications that prolong the QT interval, blocks the cardiac IKr channel and prolongs the action potential [2]. An increasing number of cases of methadone-associated Torsades de Pointes (TdP) have been reported over the last several years [3–11]. We present a retrospective case series of patients on methadone maintenance treatment (MMT) with QT prolongation (QTP) and ventricular arrhythmias.

2 Materials and methods

Beth Israel Medical Center is a tertiary care, urban hospital with the largest MMT program in the United States. It services 6,500 MMT patients in 18 clinics across New York City. All MMT patients with QT prolongation and ventricular arrhythmias admitted to our hospital between July 2007 and April 2009 were included. Follow-up information was obtained for clinical purposes from the MMT programs and via phone interview with the patients.

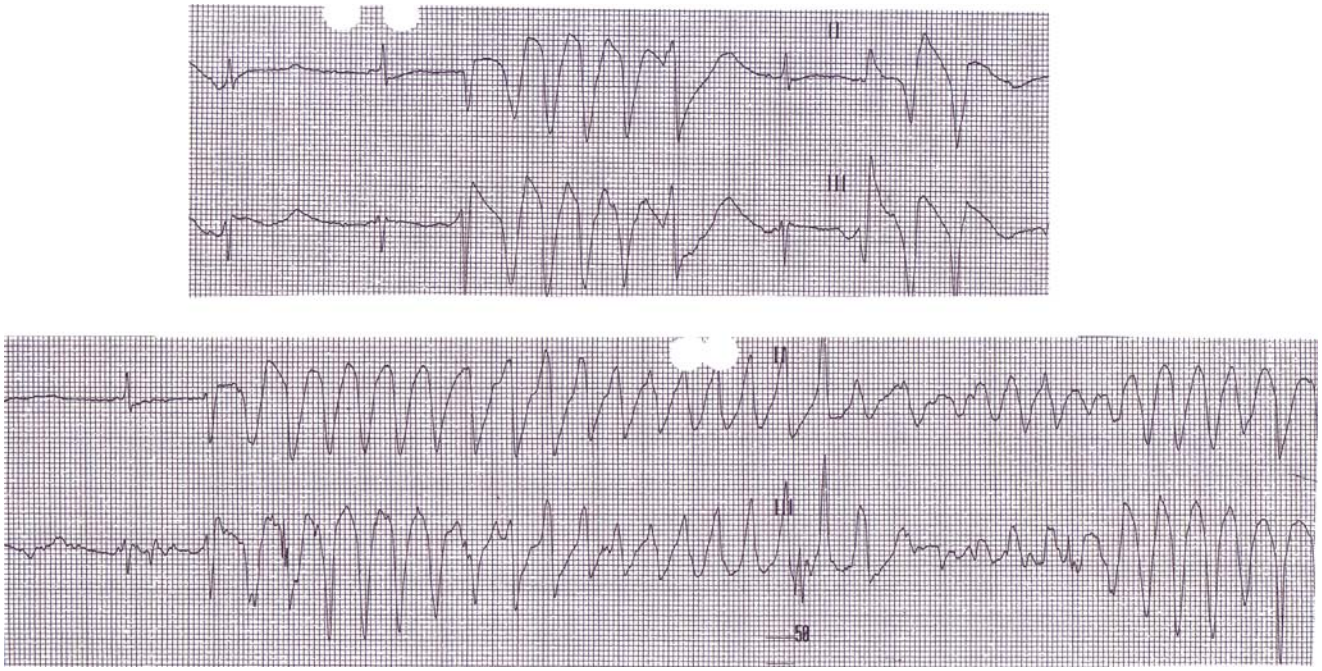

Fig. 1 Syncope and TdP in a 50-year-old man on 35 mg of methadone maintenance therapy

3 Results

Twelve consecutive patients admitted to our Cardiology service at Beth Israel Medical Center (nine men, mean age 53.9±5.4 years) with methadone-associated QTP and ventricular arrhythmias were included (Fig. 1). One of these patients has been previously reported [3]. Clinical characteristics are delineated in Table 1. ECG or telemetry documentation of arrhythmia was available in all patients. Eight patients had an additional predisposing factor for ventricular arrhythmias (four with electrolyte abnormalities, four with other QT prolonging medications). The average methadone dose was 135 mg (range 35–250 mg). All patients had preserved left ventricular ejection fraction

Table 1 Clinical characteristics

	Age (yrs)	Sex	Presentation	Telemetry	QTc interval (ms)	Methadone dose (mg)	Presence of ICD	Complicating factors
Patient 1	56	M	Syncope	TdP	620	100	No	None
Patient 2	60	M	ICD shocks	TdP	V-paced (608)	90	Yes	K-3.3
Patient 3	57	M	VF arrest	VF	574	80	No	None
Patient 4	52	M	VF arrest	TdP	664	80	No	Pneumonia TMP-SMX
Patient 5	54	F	Asymptomatic	Polymorphic NSVT	620	160	No	K-2.9
Patient 6	50	M	Syncope	TdP	560	160	No	Pneumonia K-3.3, Mg-1.0
Patient 7	56	F	Syncope	Frequent polymorphic ventricular ectopy	480	180	No	TMP-SMX
Patient 8	43	M	Presyncope	TdP	480	140	No	Haloperidol
Patient 9	61	M	Presyncope	TdP	530	200	No	None
Patient 10	46	M	Asymptomatic	TdP	620	250	No	Olanzapine
Patient 11	57	F	ICD shocks	TdP	742	160	Yes	K-3.1
Patient 12	50	M	Syncope	TdP	600	35	No	None

VF ventricular fibrillation, *Tdp* Torsades de Pointes, *NSVT* nonsustained ventricular tachycardia, *TMP-SMX* trimethoprim–sulfamethoxazole, *K* serum potassium level, *Mg* serum magnesium level

(60.9%±8.0%) at the time of enrollment. Two patients had implantable defibrillators which were initially placed at other institutions for methadone-associated TdP.

Follow-up is available in 11 patients with a mean follow-up of 7.3 months (range 1–18 months). All patients survived the presenting arrhythmia. Initial treatment included decreased methadone dose and magnesium, isoproterenol and temporary pacing as indicated if TdP was present.

Transition to buprenorphine was accomplished as follows: Methadone was either discontinued completely or rapidly tapered depending on the patient's maintenance dose. Opiate withdrawal was treated with short-acting morphine and benzodiazepines as needed to keep the patient comfortable. Depending on the MMT dose, between 3 and 7 days later, the short-acting opioid was held for 6–12 h. When the patient was in moderate withdrawal as measured by the Clinical Opiate Withdrawal Scale, the observed buprenorphine induction was initiated. Buprenorphine was started at 2 mg s/l and if tolerated, increased by 4 mg s/l every 2–4 h until the patient ceased to report withdrawal symptoms or craving. The maximum daily dose was 32 mg.

Successful transition to buprenorphine was accomplished in three patients. QT interval normalized and none of these patients had recurrent arrhythmias (Fig. 2). Methadone dose was reduced in five patients with improvement of QT interval and resolution of arrhythmia. All continue to follow-up in MMT programs. Four patients, including both with ICDs, refused or did not tolerate a reduction in their methadone dose. Both ICD patients presented to Beth Israel Medical Center with ICD storm secondary to TdP, and one patient had two subsequent hospitalizations for ICD storm.

4 Discussion

QT prolongation due to MMT is well described [4, 5]. However, serious ventricular arrhythmias are reportedly rare [6]. The current series is significant for a large number of cases over a short time and the inclusion of patients on a relatively low dose of methadone. The apparent rise in reports of TdP in MMT patients over the last decade may signal a growing problem [7–11]. As in previous reports, the majority of patients in our series had an additional predisposing factor for TdP [5, 6, 9]. However, the average methadone dose in our population (135 mg), including one patient on 35 mg, is lower than that reported in prior studies [9, 12].

Many studies and decades of clinical experience support methadone's efficacy as a treatment for opioid dependence [1, 13]. Methadone dramatically reduces illicit opioid abuse and prevents a number of major complications including drug overdose, criminal behavior, HIV, and hepatitis C infection [14]. Further, the absence of a suitable alternative in patients requiring high-dose MMT makes management of patients with methadone-associated TdP problematic.

Implantable cardioverter-defibrillators (ICD) have been advocated for patients with TdP on methadone [12]. While ICDs are effective at preventing death in these patients, the ICD option is fraught with difficulty as evidenced by the procedure-related complications and recurrent shocks noted in this group [12]. Indeed, the two ICD patients in our series suffered arrhythmia storms secondary to TdP. Thus, an alternative to MMT that is not associated with ventricular arrhythmias would be preferable.

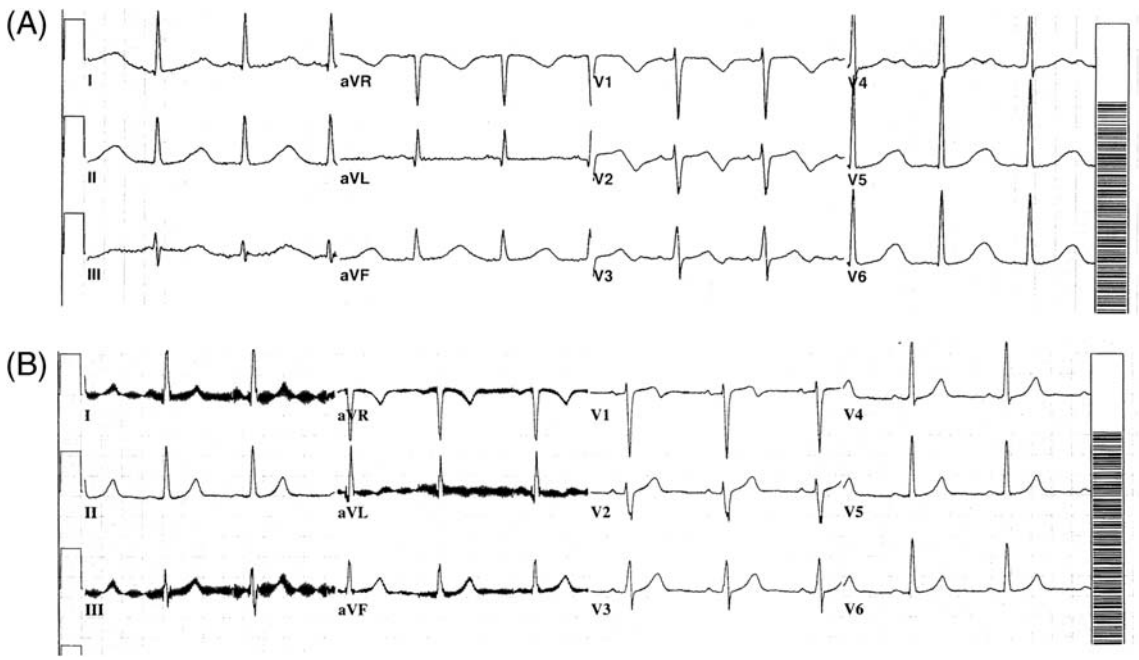

Fig. 2 Admission EKG of a 55-year-old man on 160 mg methadone maintenance therapy (**a**) and following transition to buprenorphine (**b**)

Buprenorphine, a partial μ-opiate–receptor agonist and a κ-opiate–receptor antagonist, is an effective maintenance therapy for a select group of opioid-dependent patients [1, 15–17]. Buprenorphine does not block IKr and does not cause QTP. We previously described conversion from methadone to buprenorphine in a patient with methadone-associated TdP [3]. There are practical limitations to expanded buprenorphine use including restricted access and efficacy not equivalent to MMT, particularly when high doses are required [18]. Despite these limitations, buprenorphine therapy should be attempted in patients who manifest ventricular arrhythmias on MMT.

4.1 Limitations

The main limitation of this case series is the short duration of follow-up. Assessment of long-term risk of either recurrent ventricular arrhythmias or opioid abuse relapse requires extended follow-up. However, our initial patient who presented with TdP and was transitioned to buprenorphine has remained free of recurrent arrhythmia for 18 months. Further, we have not performed a systematic evaluation of MMT patients looking for QT prolongation or ventricular arrhythmias. Thus, we may be identifying a high risk subgroup of MMT patients.

5 Conclusion

We present the largest reported series of patients with methadone-associated QTP and ventricular arrhythmias. This is an increasingly relevant and important question given the recent proliferation of reports of arrhythmias in patients on methadone. Optimal management of these patients is challenging. Risk of ventricular arrhythmias must be weighed against the crucial benefit that opioid agonist pharmacotherapy provides. Avoidance of additional medications that prolong the QT interval and prevention of hypokalemia and hypomagnesemia in those who are at increased risk is vital. In addition, symptoms suggestive of arrhythmia such as syncope or palpitations in patients on MMT should be rigorously investigated.

Buprenorphine is a useful alternative in patients with documented ventricular arrhythmias on MMT. ICDs should be reserved for patients who are not candidates for buprenorphine or a reduced methadone dose. Future research analyzing the risks and benefits of the various strategies would be helpful.

Conflict of interest The authors have no conflict of interest and there was no financial support for this research project.

References

1. Fiellin, D. A., & O'Connor, P. G. (2002). Office-based treatment of opioid-dependent patients. *NEJM, 347*, 817–823.
2. Roden, D. M. (2004). Drug-induced prolongation of the QT interval. *NEJM, 350*, 1013–1022.
3. Esses, J., Rosman, J., Do, L., & Hanon, S. (2008). Successful transition to buprenorphine in a patient with methadone induced Torsades de Pointes. *J Interv Card Electrophysiol, 23*, 117–119.
4. Wedam, E. F., Bigelow, G. E., Johnson, R. E., Nuzzo, P. A., & Haigney, M. C. P. (2007). QT-interval effects of methadone, levomethadyl, and buprenorphine in a randomized trial. *Archives of Internal Medicine, 167*, 2469–2473.
5. Ehret, G. B., Voide, C., Gex-Fabry, M., Chabert, J., Shah, D., Broers, B., et al. (2006). Drug-induced long QT syndrome in injection drug users receiving methadone: high frequency in hospitalized patients and risk factors. *Archives of Internal Medicine, 166*, 1280–1287.
6. Byrne, A., & Stimmel, B. (2007). Methadone and QTc prolongation. *Lancet, 369*, 366.
7. Justo, D., Gal-Oz, A., Paran, Y., Goldin, Y., & Zeltser, D. (2006). Methadone-associated Torsades de Pointes (polymorphic ventricular tachycardia) in opioid-dependent patients. *Addiction, 101*, 1333–1338.
8. Pearson, E. C., & Woosley, R. L. (2005). QT prolongation and Torsades de Pointes among methadone users: reports to the FDA spontaneous reporting system. *Pharmacoepidemiology and Drug Safety, 14*, 747–753.
9. Krantz, M. J., Lewkowiez, L., Hays, H., Woodroffe, M. A., Robertson, A. D., & Mehler, P. S. (2002). Torsade de Pointes associated with very-high-dose methadone. *Annals of Internal Medicine, 137*, 501–504.
10. Fanoe, S., Hvidt, C., Ege, P., & Jensen, G. B. (2007). Syncope and QT prolongation among patients treated with methadone for heroin dependence in the city of Copenhagen. *Heart, 93*, 1051–1055.
11. Chugh, S. S., Socoteanu, C., Reinier, K., Waltz, J., Jui, J., & Gunson, K. (2008). A community-based evaluation of sudden death associated with therapeutic levels of methadone. *American Journal of Medicine, 121*, 66–71.
12. Patel, A. M., Singh, J. P., & Ruskin, J. N. (2008). Role of implantable cardioverter-defibrillators in patients with methadone-induced long QT syndrome. *American Journal of Cardiology, 101*, 209–211.
13. Hubbard, R. L., Craddock, S. G., Flynn, P. M., & Anderson, J. (1997). Etheridge RM overview of 1-year follow-up outcomes in drug abuse treatment outcome study. *Psychology of Addictive Behaviors, 11*, 261–278.
14. Regarding Methadone Treatment. New York State Committee of Methadone Program Administrators (COMPA). 1997, pp 6–10.
15. Johnson, R. E., Jaffe, J. H., & Fudala, P. J. (1992). A controlled trial of buprenorphine treatment for opioid dependence. *JAMA, 267*, 2750–2755.
16. Helm, S., Trescot, A. M., Colson, J., Sehgal, N., & Silverman, S. (2008). Opioid antagonists, partial agonists, and agonists/antagonists: the role of office-based detoxification. *Pain Physician, 11*, 225–235.
17. Ancherson, K., Clausen, T., Gossop, M., Hasnteen, V., & Waal, H. (2009). Prevalence and clinical relevance of corrected QT interval prolongation during methadone and buprenorphine treatment: a mortality assessment study. *Addiction, 104*, 993–999.
18. Mattick, R. P., Ali, R., White, J. M., O'Brien, S., Wolk, S., & Danz, C. (2003). Buprenorphine versus methadone maintenance therapy: a randomized double-blind trial with 405 opioid-dependent patients. *Addiction, 98*, 441–452.