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Electrocardiographic Findings in Mortalities Due to Pure Methadone Toxicity

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Abstract

We aimed to evaluate electrocardiographic (ECG) abnormalities in mortalities due to pure methadone toxicity in ICU patients since methadone-related mortality may be due to cardiac complications even in acute toxicities. In a retrospective single-center study, files of all patients who had died with confirmed diagnosis of pure methadone toxicity between 2011 and 2016 were evaluated. Autopsy was performed in all cases. A cardiologist measured all ECG quantitative and qualitative indices. Fifty-one deaths were recorded. Forty-two dead patients were males. Median [IQR] age of the patients was 44 [30, 60] years. Of them, 38 (69%) were methadone-dependent and were significantly older than methadone-naïve patients ($p=0.008$ and $p=0.001$, respectively). ECG abnormalities were detected in all cases. ST-T abnormalities were found in 33 (64.7%) patients. Except longer PR interval in dependent patients ($p=0.017$) and specific ST elevation in naïve cases ($p=0.008$), other ECG indices were similar in two groups. No correlation was found between ST-T abnormalities and coronary disease in autopsy. ECG abnormalities irrelevant to coronary artery diseases are common in methadone-related mortalities. Methadone toxicity may affect myocardium and play a role in death. Further prospective studies to evaluate other cardiac indices in methadone-poisoned patients are recommended.

Keywords Methadone · Poisoning · Coronary artery disease · Electrocardiography

Introduction and Background

Almost 61% of drug overdose-related deaths are due to an opioid. Frequency of these deaths has tripled between 1999 and 2014 in US [1]. Methadone is an opioid agonist substantially used in the methadone maintenance therapy (MMT) programs with persuading results in the area of drug abstinence [2]. On the other hand, it has been reported to be one of the most dangerous opioids with serious side effects on the central respiratory and nervous systems [3, 4]. Methadone may also be used in intensive care units as a long-acting analgesic. Currently, due to high frequency of methadone prescription, the incidence of mortalities due to this substance has increased in both adults and children [5–9]. Recent data show a significant increasing trend of methadone-associated deaths (7.7 times) contributing 1274 cases from 2009 to 2015 in Iran [6].

With a significant long half-life of 25–52 h, methadone can cause delayed clinical manifestations including cardiac electrophysiological changes particularly QTc prolongation and ventricular arrhythmias [2–6]. In some cases, the patient remains completely well until a sudden death occurs with questionable relationship to the poisoning and cardiac side effects. The question is what are the ECG findings in methadone-related deaths? Management of a methadone-poisoned patient needs careful evaluation of the cardiovascular system for possible ECG abnormalities and proper in-time treatment to avoid mortalities. We aimed to determine electrocardiographic changes in patients who died after admission to a tertiary poisoning center with confirmed diagnosis of pure methadone toxicity. As a secondary aim, we evaluated and

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compared the ECG findings between methadone-dependent and methadone-naïve cases who died due to poisoning, as well.

Materials and Methods

Study Design and Setting, Selection of Participants

This study is based on our previous work on suspected methadone toxicities which had resulted in death [10]. In a retrospective single-center study, files of all non-surviving methadone-poisoned patients who had been admitted to our medical toxicology intensive care unit between 2011 and 2016 were evaluated. They had confirmed diagnosis of pure methadone toxicity and died during the hospital stay. Bodies had been sent for postmortem examination and toxicological analysis to Legal Medicine Organization (LMO). All of them had available on-presentation ECGs. Loghman-Hakim Hospital Poison Center (LHHPC) is the main referral hospital for poisoned patients in Tehran and opioids including methadone are one of the main causes of intoxication in this center [11, 12].

Methadone-poisoned patients who were not sent to LMO for further evaluations and those for whom ECG had not been performed on presentation, were excluded. A self-made questionnaire containing demographic characteristics of the patients, current history of methadone dependency, amount and formulation (syrup versus tablet) of the ingested methadone (if known), and time elapsed between methadone ingestion and hospital presentation was filled for every single patient. A cardiologist measured all ECG quantitative and qualitative indices including rhythm, rate, axis, atrial abnormalities, PR interval, PR deviation, pathologic Q wave, QRS duration, ventricular enlargement, ST abnormalities, J-point elevation, early repolarization, Burgada pattern, T-wave abnormalities, U wave, corrected QT interval (QTc), and Torsade de points. Normal values of each parameter are shown in Table 1 [13, 14].

Autopsy was done by forensic medicine specialists. We only reviewed myocardial and coronary findings of autopsy report including the presence of recent and/or old myocardial infarction confirmed by pathologic examination, coronary thrombus, plaque, and the presence of severe (> 70%) stenosis in coronary arteries.

Diagnosis of methadone toxicity was made based on a positive history of methadone ingestion and confirmed by qualitative urine methadone screening test at hospital and thin layer chromatography test in LMO- only if no other potentially fatal toxicity was detected. Methadone dependency was determined with a positive history of regular use or development of opioid withdrawal syndrome following naloxone administration.

Outcomes

The primary outcome was ECG findings in methadone-poisoned patients. The secondary outcome was determination of quantitative and qualitative ECG parameters in methadone-dependent and methadone-naïve patients.

Analysis

For the description of quantitative variables with normal and non-normal distribution, mean (± SD) and median [IQR interquartile range] were used, respectively. For qualitative variables, percent of frequency was used. Pearson Chi square was applied to analyze distribution of two categorical variables. For comparing continuous variables between two groups, *t* test and Fisher's Exact test were used, respectively. Mann–Whitney *U* test was applied to compare differences between two independent groups when the dependent variable was continuous, but not normally distributed. A *p* value less than 0.05 was considered to be statistically significant. Statistical package for social sciences (SPSS) version 17.0 (SPSS Inc., Chicago, Ill, USA) was used for analysis. Our institutional ethics committee approved this study.

Results

Characteristics of the Study Subjects

Of a total of 6271 patients hospitalized with primary diagnosis of methadone overdose, 128 died and 94 were sent to LMO. Of 57 patients who had confirmed diagnosis of pure methadone toxicity after autopsy, 51 had available on-presentation ECGs and were enrolled into the study.

Main Results

Forty-two patients (82.4%) were male. Their median [IQR] age was 44 [30, 60] years (range 2 months–77 years). The formulation of methadone was tablet in four (7.8%), syrup in 23 (45.1%), and undetermined in 24 (47.1%) patients. Determination of ingested dose of methadone was possible in 12 patients (23.5%) who were awake on presentation with a wide range of 10–1000 mg and a median dose of 100 mg. Other basic characteristics of the patients are shown in Table 2. Table 3 compares the 38 methadone-dependent and 13 methadone-naïve patients in basic demographic characteristics and ECG abnormalities.

ECG abnormalities were detected in all cases. ST abnormalities (elevation, depression, and shortening) and T abnormalities (inversion, other changes) were compared in two

Table 1 Definition of ECG indices used in the study

Terminology/abbreviation	Definition
Tachycardia[a]	Heart rate > 100 per minutes
Bradycardia[a]	Heart rate < 60 per minutes per minutes
LAD (Left axis deviation)	Mean QRS axis more positive than + 90 degrees (usually with rS in lead I)
RAD (Right axis deviation)	Mean QRS axis more negative than − 30 degrees (usually with rS in lead II)
LAHB	QRS axis between − 45 and − 90 degrees and qR pattern in AVL
LPHB	QRS axis between + 90 and + 180 degrees and rS in I and AVL and qR in III and AVF
LA abnormality	P wave duration in lead II > 120 ms or Increased duration and depth of terminal negative portion of p wave in lead V1
RA abnormality	Peaked P wave with amplitudes in lead II > 0.25 mV or Increased area under initial positive part of P wave in lead V1 to > 0.06 mm s
PVC	Premature ventricular contraction
PAC	Premature atrial contraction
PR deviation	Deviation of PR segment from isoelectric line (segment between T and P waves)
First degree AV block	All atrial impulses conducted to the ventricle with prolonged PR (> 200 ms)
PR interval	From the onset of P wave to the onset of QRS
QRS duration	Duration from the onset to the end of QRS
LBBB	QRS duration ≥ 120 ms and absent or small r + deep S in lead V1
RBBB	QRS duration ≥ 120 ms and rsr′, rsR′or rSR′ in leads V1 and V2
Pathologic Q wave	Q-wave duration ≥ 0.03 s and > 0.1 mV deep
LVH	Evaluated by Sokolow–lyon and cornel voltage criteria
RVH	R in V1 ≥ 0.7 mV, QR in V1, R/S in V1 > 1 and R ≥ 0.5 mV, S in V6 > 0.7 mV
Poor r progression	R wave height ≤ 3 mm in V3
ST elevation	ST segment elevation from isoelectric line (segment between T and P waves)
Cup like	ST segment concave up
Dom like	ST segment concave
Specific ST elevation	A ST elevation with characteristics of acute myocardial injury
ST depression	ST segment depression from isoelectric line (segment between T and P waves)
ST abnormality	ST elevation + ST depression
ST shortening	Shortening of ST segment without elevation or depression
J point elevation	Elevation of J point (point of junction between QRS and ST segment)
Early repolarization	Elevation of the QRS-ST junction (J point) often associated with a late QRS slurring or notching (J wave)
Brugada pattern	Coved type ST elevation with at least 2 mm (0.2 mV) J-point elevation and a gradually descending ST segment followed by a negative T-wave
Primary T wave inversion	Primary T-wave abnormalities due to alterations in myocardial cellular electrophysiology not due to LBBB or LVH (secondary)
Other T wave abnormalities	Biphasic T, Tall T, and camel hump T
Pathologic U wave	U wave height > 1–2 mm, U wave height > 25% of T wave height, inverted U wave (different direction from adjacent T wave)
QTc (corrected QT)	QT interval corrected with heart rate by bazett's formula: $QTc = QT/\sqrt{RR}$
QTc prolongation	QTc > 440 ms in men and > 460 ms in women

[a]For children it was calculated based on their age range

groups and found to be similarly common (24 [63.2%] vs. 9 [69.2%], $p = 0.75$) in dependents versus naïve poisoned patients. The analysis showed no change after removing ST shortening (22 [57.9%] vs. 9 [69.2%], $p = 0.529$).

As shown in Table 3, age ($p = 0.008$), gender ($p = 0.001$), PR interval ($p = 0.016$), and specific ST elevation pattern ($p = 0.008$) were significantly different between methadone-dependent and methadone-naïve cases.

We could not detect a significant correlation between ST-T abnormalities and coronary artery disease in autopsy findings (Table 4). Myocardial and coronary artery diseases were not detected in methadone-naïve non-surviving patients.

Of 22 patients with ST depression, in 14 (63%) subjects at least two of the inferior leads (II, III, AVF; Table 3) were involved. A new analysis was done to see if there was any correlation between involvement of inferior leads in methadone-dependent versus methadone-naïve intoxicated patients. Analysis showed a significant difference

Table 2 Basic on-arrival characteristics of confirmed cases of methadone-related deaths ($n=51$)

Variable	Result
Age (year)	44 [30, 60] (0.1–77)
Male sex (%)	42 (82.4)
Mean time [IQR] elapsed from ingestion (*h*) (range)	10 [6, 22] (1–72)
Consciousness level at presentation, *n* (%)	
Awake (1)	12 (23.5)
Verbal stimuli (2)	7 (13.7)
Painful stimuli (3)	23 (45.1)
Unresponsive (4)	9 (17.6)
Arrest no (%)	
No	34 (66.7)
Respiratory	15 (29.4)
Cardiopulmonary	2 (3.9)
Methadone dependence *n* (%)	
Yes	38 (74.5)
No	13 (25.5)
History of use/abuse[a]	
Opium	4 (15.7)
Heroin	6 (11.7)
Tramadol	1 (2)
Hashish	1 (2)
Amphetamine	1 (2)
Methadone	38 (74.9)
None	13 (25.5)
Intent no (%)	
Methadone maintenance	10 (19.6)
Abuse	15 (29.4)
Suicidal	10 (19.6)
Accidental	4 (7.8)
Unknown	11 (21.6)
Pain killer	1 (2)
Mean [IQR] hospital stay (range) (day)	6 [2, 12] (1–36)

[a]Subject to more than 100% due to poly substance abuse

($p=0.05$) in favor of less frequency of ST depression in methadone-naïve group.

Discussion

Previous studies have been conducted on ECG abnormalities in chronic methadone users [15]. Case reports exist which show QT prolongation and Torsades de point in these patients [16–18], but few studies evaluate ECG abnormalities in acute methadone toxicity in detail [19–21]. As far as we know, current study, evaluating detailed ECG abnormalities in pure methadone mortalities, is the only study supported by autopsy findings. We were able to compare ECG abnormalities in methadone-naïve and methadone-dependent poisoned patients simultaneously.

All of our patients were admitted to a specialized medical toxicology ICU and this may be the result of more severe methadone exposures in them as previously defined in Iranian society [6]. We have already shown increasing number of methadone users in Iran [7–9, 22]. Such considerable number of methadone-related mortalities is detected in a small fraction of methadone-poisoned patients who seek for medical care and refer to medical centers since a large number of these patients even do not refer to medical centers after mild poisonings [6–9]. Therefore, reported ECG findings may represent a very severe and lethal toxicity that could not be easily detected in other reports.

A unique finding of the current study is the age of the participants. Methadone-related mortalities may be more prominent in older patients [20, 23], in whom background cardiac electrophysiology may be impaired, while the median age of methadone-naïve non-survivors was only 26 years with no previous history of coronary artery disease. Lack of significant differences in most ECG indices between the two groups and negative autopsy findings in young methadone-naive poisoned patients are strong clues to infer possible effects of methadone on patients' ECGs. Although some studies report bradycardia in methadone- poisoned patients (probably due to sedative effects) [24], tachycardia was observed in the on-presentation ECGs of the patients in the current study. As it has already been stated, this may be a reflection of severity of intoxication in our patients [20, 23].

All subjects had abnormal ECG findings, a finding that was never reported in previous studies on methadone toxicities. Severity of toxicity may also be described by end organ damages which may occur [10, 25, 26]. Eighteen out of 21 patients who revealed left atrial appendage (LAA) and all six patients who showed right atrial appendage (RAA) were methadone-dependent. However, this difference was not statistically significant between methadone-dependent and methadone-naïve patients. This may be due to the relatively small number of the patients in the naïve group and older age in the dependent group.

One patient had prolonged PR interval (> 200 ms) and one had short PR interval (< 120 ms). Although other patients had normal PR intervals, this index was significantly more prolonged in the dependent group. This finding is consistent with the results of the previous studies [27]. Considering calcium channel blocker effect-like properties of methadone [24], PR prolongation was not a surprising finding although older age of methadone-dependent patients might have played a substantial role in this regard.

Pathologic Q wave, ST elevation, ST depression, and T inversion were detected in both groups. These findings are known to be ischemic ECG changes. Two cases had

Table 3 Comparison of chronic methadone users versus naïve methadone-poisoned patients ($n=51$)

Variable	Dependent ($n=38$)	Naïve ($n=13$)	p value*	Total
Median [IQR] age (min, max)	47 [35, 60] (20–77)	26 [6, 40] (0.1–66)	0.008†	44 [30, 60] (0.1–77)
Male gender *n* (%)	36 (94.7)	6 (46.2)	0.001	42 (82.4)
PVC *n* (%)	0	2 (15.4)	0.061	2 (3.9)
PAC *n* (%)	1 (2.6)	0	0.999	1 (2)
Type *n* (%)	0	2 (15.4)		2 (3.9)
Mean rate (±SD) (min, max)	107 ± 23 (57–150)	116 ± 27 (70–160)	0.251‡	109 ± 24 (57–160)
Axis *n* (%)				
Normal	28 (73.7)	10 (76.9)	0.528	38 (74.5)
RAD	3 (7.9)	2 (15.4)		5 (9.8)
LAD	7 (18.4)	1 (7.7)		8 (15.7)
LAHB *n* (%)	5 (13.2)	0	0.311	5 (9.8)
LPHB *n* (%)	2 (5.3)	0	0.999	2 (3.9)
LAA *n* (%)	18 (47.4)	3 (23.1)	0.193	21(41.2)
RAA *n* (%)	6 (15.8)	0	0.318	6 (11.8)
Median PR interval [IQR] (min, max)	140 [140, 160] (120–220)	120 [120, 160] (100–160)	0.016†	140 [120, 160] (100–220)
PR deviation (elevation or depression) *n* (%)	3 (7.9)	0	0.561	3 (5.9)
First degree AV block *n* (%)	1 (2.6)	0	0.999	1 (2)
Median QRS [IQR] duration (ms) (min, max)	80 [80, 90] (70–120)	80 [70, 80] (70–90)	0.218†	80 [80, 90] (70–120)
LBBB *n* (%)	2 (5.3)	0	0.999	2 (3.9)
RBBB *n* (%)	3 (7.9)	0	0.561	3 (5.9)
Pathologic Q wave *n* (%)	4 (10.5)	2 (15.4)	0.638	6 (11.8)
LVH criteria *n* (%)	2 (5.3)	0	0.999	2 (3.9)
RVH criteria *n* (%)	1 (2.6)	1 (7.7)	0.449	2 (3.9)
Poor R progression *n* (%)	12 (31.6)	2 (15.4)	0.472	14 (27.5)
ST elevation *n* (%)	7 (18.4)	5 (38.5)	0.141	12 (23.5)
AVR	1 (2.6)	1 (7.7)	0.269	2 (3.9)
V1	1 (2.6)	0		1 (2)
V2	0	1 (7.7)		1 (2)
High laterals	1 (2.6)	0		1 (2)
V1–V3	3 (7.9)	0		3 (5.9)
V1–V4	1 (2.6)	0		1 (2)
V1, AVR	0	1 (7.7)		1 (2)
V1, V2	0	1 (7.7)		1 (2)
Inferior leads	0	1 (7.7)		1 (2)
ST elevation weight *n* (%)				
1 lead	2 (5.3)	2 (15.4)	0.309	4 (7.8)
2 leads	1 (2.6)	2 (15.4)		3 (5.9)
3 leads	3 (7.9)	1 (7.7)		4 (7.8)
4 leads	1 (2.6)	0		1 (2)
ST elevation height (mm) *n* (%)				
0.5	1 (2.6)	1 (7.7)	0.155	2 (3.9)
1	0	1 (7.7)		1 (2)
Specific ST elevation *n* (%)	0	3 (23.1)	0.008	3 (5.9)
Cup-like *n* (%)	3 (7.9)	0	0.475	3 (5.9)
Dome-like *n* (%)	4 (10.5)	3 (23.1)	0.475	7 (13.7)
ST depression *n* (%)	15 (39.5)	7 (53.8)	0.366	22 (43.1)

Table 3 (continued)

Variable	Dependent ($n=38$)	Naïve ($n=13$)	p value*	Total
Inferior leads	9 (23.7)	1 (7.7)	0.077	10 (19.6)
Lateral leads	1 (2.6)	1 (7.7)		2 (3.9)
I, AVL	1 (2.6)	0		1 (2)
II, III, AVR	1 (2.6)	0		1 (2)
Inferior & lateral	2 (5.3)	0		2 (3.9)
V2–V6	1 (2.6)	0		1 (2)
II, III, AVR, V3–V6	0	1 (7.7)		1 (2)
V2, V3	0	1 (7.7)		1 (2)
Lateral & high lateral	0	2 (15.4)		2 (3.9)
Lateral, III, AVR	0	1 (7.7)		1 (2)
ST depression weight *n* (%)				
2 leads	1 (2.6)	1 (7.7)	0.054	2 (3.9)
3 leads	10 (26.3)	1 (7.7)		11 (21.6)
4 leads	1 (2.6)	1 (7.7)		2 (3.9)
5 leads	1 (2.6)	0		1 (2)
6 leads	0	3 (23.1)		3 (5.9)
7 leads	2 (5.3)	1 (7.7)		3 (5.9)
ST depression height (mm) *n* (%)				
0.5	1 (2.6)	0	0.885	1 (2)
1	2 (5.3)	1 (7.7)		3 (5.9)
2	1 (2.6)	0		1 (2)
5	1 (2.6)	0		1 (2)
Specific ST depression *n* (%)	9 (23.7)	4 (30.8)	0.464	13 (25.5)
Horizontal *n* (%)	8 (21.1)	4 (30.8)	0.474	12 (23.5)
Downward *n* (%)	1 (2.6)	0	0.999	1 (2)
Upward *n* (%)	4 (10.5)	4 (30.8)	0.179	8 (15.7)
ST abnormality *n* (%)	19 (50)	8 (61.5)	0.374	27 (52.9)
ST shortening *n* (%)	4 (10.5)	1 (7.7)	0.999	5 (9.8)
J point elevation *n* (%)	8 (21.1)	3 (23.1)	0.999	11 (21.6)
Early repolarization *n* (%)	1 (2.6)	0	0.999	1 (2)
Burgada pattern *n* (%)	2 (5.3)	0	0.999	2 (3.9)
T wave inversion *n* (%)	6 (15.8)	4 (30.8)	0.253	10 (19.6)
AVL	1 (2.6)	0	0.109	1 (2)
High lateral	3 (7.9)	0		3 (5.9)
V3–V4	1 (2.6)	0		1 (2)
V2–V6	1 (2.6)	0		1 (2)
III	0	2 (15.4)		2 (3.9)
V1–V3	0	2 (15.4)		2 (3.9)
T wave inversion weight *n* (%)				
1 lead	1 (2.6)	1 (7.7)	0.083	2 (3.9)
2 leads	4 (10.5)	0		4 (7.8)
3 leads	0	2 (15.4)		2 (3.9)
5 leads	1 (2.6)	0		1 (2)
Primary T wave inversion	4 (10.5)	2 (15.4)	0.638	6 (11.8)
Other T wave abnormalities	2 (5.3)	1 (7.7)	0.999	3 (5.9)
U wave	9 (23.7)	1 (7.7)	0.419	10 (19.6)
U wave height (mm)				
0.5	3 (7.9)	1 (7.7)	0.307	4 (7.8)
1	6 (15.8)	0		6 (11.8)
Pathologic U wave	3 (7.9)	0	0.561	3 (5.9)

Table 3 (continued)

Variable	Dependent ($n=38$)	Naïve ($n=13$)	p value*	Total
Mean QTC interval (±SD) (ms) (min, max)	437.4 ± 44.0 (371–553)	448.6 ± 44.1 (388–550)	0.432‡	440.3 ± 43.8 (371–553)
QTC prolongation	13 (34.2)	7 (53.8)	0.211	20 (39.2)
Torsade de point *n* (%)	1 (2.6)	0	0.999	1 (2)

PVC premature ventricular contraction, *PAC* premature atrial contraction, *LHAB* left anterior hemi block, *LPHB* left posterior hemi block, *RAD* right axis deviation, *LAD* left axis deviation, *LAA* left atrium abnormality, *RAA* right atrium abnormality, *AV* atrio-ventricular, *LBBB* left bundle branch block, *RBBB* right bundle branch block, *LVH* left ventricular hypertrophy, *RVH* right ventricular hypertrophy

*Using Pearson Chi square/Fisher's exact test unless determined

†Mann–Whitney *U* test

‡*t* test

Table 4 Autopsy findings of coronary arteries in selected ECG abnormalities ($n=51$)

ECG abnormality	Coronary artery disease		p value
	Yes ($n=13$)	No ($n=38$)	
ST depression *n* (%)			
Yes ($n=23$)	5 (38.5)	18 (47.4)	0.557
No ($n=28$)	8 (61.5)	20 (52.6)	
ST elevation *n* (%)			
Yes ($n=12$)	2 (15.4)	10 (26.3)	0.706
No ($n=39$)	11 (84.6)	28 (73.7)	
ST abnormality *n* (%)			
Yes ($n=28$)	7 (53.8)	21 (55.3)	0.929
No ($n=23$)	6 (46.2)	17 (44.7)	
T inversion *n* (%)			
Yes ($n=10$)	3 (23.1)	7 (18.4)	0.701
No ($n=41$)	10 (76.9)	31 (81.6)	
Primary T inversion			
Yes ($n=6$)	1 (7.7)	5 (13.2)	0.999
No ($n=45$)	12 (92.3)	33 (86.8)	

pathologic Q waves. ST-T abnormalities were significant in methadone-dependent patients compared to methadone-naïve poisoned patients with no statistically significant difference (63.2 vs. 69.2%, respectively). ST depression was detected in 22 patients. In 14 cases, at least two of the inferior leads were involved. Postmortem evaluations showed that there was no significant correlation between coronary and/or myocardium findings and ECG abnormalities. Therefore, we believe ECG abnormalities may be due to the toxic effect of methadone on the myocardium.

We could not find any original study that reported ST abnormalities in methadone-poisoned patients. One case report, had shown Brugada pattern in one patient [28]. We also noticed two methadone-dependent patients with Brugada pattern on their on-arrival ECGs. Brugada pattern may be induced by sodium channel blockers [29]. Few human and animal studies have shown methadone interaction with sodium channels [30, 31]. Since the two patients with Brugada pattern in their ECGs died early after admission, we could not follow their serial ECGs to confirm the effect of methadone on this phenomenon (Fig. 1).

Nine patients in the methadone-dependent group and one in the naïve group had U waves in their ECGs ($p=0.419$), of which, three were pathologic. Pathologic U wave has been shown in few case reports [32, 33]. In a case series, 13% of methadone-poisoned patients had U waves in their ECGs although the frequency of pathologic U wave was not reported in that study [19].

We had 20 patients (39.2%) with on-presentation QTc prolongation. This finding is in accordance with the previous studies in both chronic methadone users and acute toxicities [20, 34, 35]. Interestingly, this finding was shown in both groups with no significant difference. A QTc ≥ 443.5 and ≥ 423 ms was previously used as an accurate diagnostic tool for predicting deaths and intubation in methadone-poisoned patients, respectively, which is again in accordance with our results [20].

Finally, the final cause of death was attributed to pure methadone toxicity. Although, central respiratory effect of methadone is usually considered as the main cause of death [2, 21], the current study highlights the importance of ECG abnormalities in deaths due to methadone toxicity, as well.

Limitations

Lack of determination of serum methadone concentration to show the severity of intoxication is a major limitation. The retrospective nature of the study and lack of documentation of some variables were other limitations.

Conclusion

More attention should be given to ECG findings of both dependent and naïve methadone-poisoned patients. Electrocardiographic abnormalities are seen in almost all

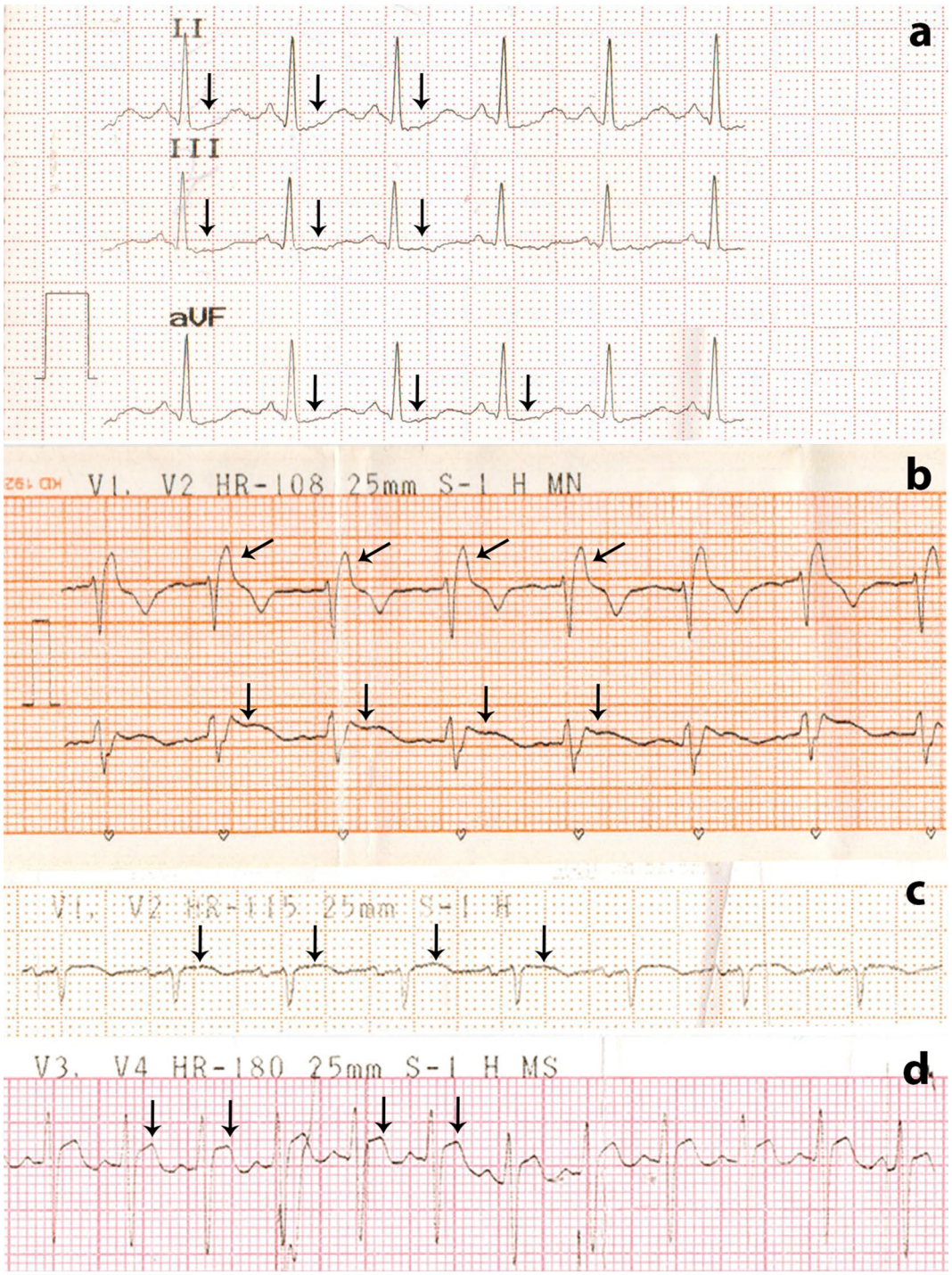

Fig. 1 ECG strips of four methadone-poisoned patients. **a** 24-year-old female. Note ST depression in inferior leads (II, III, AVF). **b** 24-year-old male. Pay attention to the RBBB pattern with coved type ST elevation (Brugada pattern) in V1 & V2. **c** 30-year-old male and **d** 4-year-old male. Note St elevation in leads V1 and V3, respectively

methadone-related deaths with no correlation to coronary artery diseases. Risks accompanied by methadone ingestion are often underestimated by clinicians prescribing the drug. Using methadone for minimizing withdrawal syndrome or control of pain may need prior evaluation for normal ECG [36]. Since QTc prolongation (in both acute and chronic methadone toxicities) and ST abnormalities (especially in the inferior leads) are common findings in lethal cases, we recommend the physicians to pay more attention to ST-T abnormalities, pathologic U wave, and QTc prolongation in

methadone-poisoned patients. ECG abnormalities may show more severe toxicity and predict poorer outcomes.

Close ECG monitoring may help overcome poor outcomes. Further prospective studies to evaluate other cardiac indices in methadone-poisoned patients are warranted.

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Compliance with Ethical Standards

Conflict of interest The authors declare that they have no competing interests.

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