

ELECTROCARDIOGRAPHIC MANIFESTATIONS IN ACUTE METHANOL POISONING CANNOT PREDICT MORTALITY*

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The aim of this retrospective observational case series was to determine electrocardiographic (ECG) manifestations in patients poisoned with methanol and see whether they could predict mortality. We also wanted to see whether there was an association between ECG changes and time elapsed between ingestion and treatment, age, sex, seizure, coma (Glasgow Coma Scale ≤ 8), arterial blood gas (ABG) parameters, and serum potassium levels on hospital admission. The study included 42 patients aged 31.14 ± 12.5 years. Twenty-five survived and 17 died. Almost all patients had one or more abnormal ECG findings, including heart rate, rhythm, and conduction abnormalities. However, we found no significant difference between survivors and non-survivors. QTc interval did not correlate with time elapsed between ingestion and treatment, age, sex, seizure and coma, HCO_3^- , or serum potassium level. Similarly, T waves showed no correlation with serum potassium. ECG abnormalities did not correlate with coma or seizure. Even though cardiotoxicity in methanol poisoning is high, none of the ECG abnormalities found in our study predicted mortality. This however does not rule out the need to routinely run ECG for cardiotoxicity in every single patient poisoned by methanol.

KEY WORDS: *death, ECG, electrocardiogram, intoxication, methanol*

Formate is a toxic metabolite of methanol that causes acidosis and inhibits cell cytochromes (1-3). The clinical picture of acute methanol poisoning includes gastrointestinal, visual, and nervous system signs and symptoms such as headache, dizziness, nausea, vomiting, abdominal pain, visual disturbances, coma, respiratory arrest, seizure, blindness,

gastrointestinal haemorrhage, putaminal haemorrhage and infarction, and pancreatitis (1, 4-12). Diagnosis is based on these clinical signs and symptoms, acid-base status, direct serum methanol levels and/or serum formate, and anion and osmolal gaps (4). Clinical guidelines for methanol poisoning management recommend using an antidote (ethanol or fomepizole), intravenous (IV) sodium bicarbonate, folic or folinic acid, and often haemodialysis (1, 2, 13). This poisoning can be intentional and unintentional, isolated and epidemic (7, 11, 12, 14-17). In Iran, alcohol

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consumption is banned and methanol poisoning is usually associated with illegal consumption of methanol mixed with other alcohols, including smuggled alcohol, homemade liquor, pharmaceutical ethanol preparations, or industrial alcohol (containing a mixture of varying percentages of ethanol and methanol with colour additives) (12, 18-20). To date, several studies have been performed to identify the prognostic factors of mortality in methanol poisoning (5, 7, 11, 14-16, 18, 20, 21). To the best of our knowledge, no literature has considered electrocardiographic (ECG) abnormalities as potential mortality predictors. Articles that do report ECG changes in patients poisoned with methanol are inconsistent (7, 22-26). In addition, little is known about the relationship between ECG parameters and metabolic/electrolyte disturbances as well as the signs and symptoms of methanol poisoning.

Our aim was therefore to see if patients who had died from methanol poisoning differed in ECG parameters from those who had survived, hoping to identify parameters that might predict mortality. We also wanted to see whether ECG changes were associated with time elapsed between ingestion and treatment, age, sex, seizure, coma, arterial blood gas (ABG) parameters, and serum potassium levels.

METHODS

In this observational retrospective case series we reviewed hospital records of all patients who had been diagnosed and treated for methanol poisoning in three Tehran hospitals [Loghman Hakim, Shohada Yaftabad, and Hazrat Rasoul Akram (p)] from March 2003 to March 2011. The study also included patient data available from two studies published earlier (12, 20).

Methanol poisoning was diagnosed by admitting physicians, based on a history of alcohol consumption (homemade, smuggled, industrial), clinical manifestations, laboratory findings, metabolic acidosis with an elevated anion gap, and computed tomography (CT) of the brain (12, 20). The charts were then re-evaluated by the authors. Inter-rater reliability to determine agreement between evaluators (authors) was tested using *kappa* statistic (27). Any discrepancies between evaluators were resolved by reviewing the original chart. The study included patients with confirmed diagnosis of methanol poisoning whose first 12-lead ECG was performed on hospital admission. Patients with the history of underlying heart or lung disease were excluded from the study.

All included patients had received therapy with ethanol, sodium bicarbonate, folic or folinic acid, and haemodialysis, as indicated (28). None received fomepizole, as it is not available in Iran.

We used patient charts to extract information about age, sex, time between alcohol consumption and hospital admission, coma (Glasgow Coma Scale ≤ 8) and seizure on admission, ABG tests before treatment, and serum potassium levels. This information was recorded in standardised abstraction forms (29).

We proceeded by evaluating the first 12-lead ECG performed on hospital admission and by recording the following ECG parameters: heart rate, PR interval, QRS interval, QRS frontal plane axis, and corrected QT interval (QTc) [based on the Bazett's formula (30)]. Findings such as right or left axis deviation, right or left bundle branch block (RBBB or LBBB), ST-T changes, early repolarisation, premature ventricular contractions, premature atrial contractions, atrial fibrillation, right or left atrial enlargement, right or left ventricular strain pattern, and ventricular dysrhythmias including type were also recorded according to procedures described elsewhere (31, 32). Interpretation of the ECGs was supervised by two cardiologists blind to the topic of the study.

We used the Statistical Package for Social Sciences software (version 17, SPSS Inc., Chicago, IL, USA) for descriptive statistics, Kolmogorov-Smirnov test, Mann-Whitney U test, Student's *t*-test, Pearson chi-square or Fisher's exact test, and Pearson correlation coefficient (*r*). In addition, we ran *kappa* (*K*) statistic (27) to determine the consistency of the evaluation of the ECGs between the cardiologists. A *P* value of less than 0.05 was considered statistically significant. Our study was approved by the regional ethics committee.

RESULTS

After we agreed on the diagnosis of methanol poisoning (*K*=1.00, *P*<0.001), a total of 42 patients met the inclusion criteria. Of them, 36 were men and six women. The mean patient age was (31.14±12.5) years; range: (16 to 75) years. Twenty-five patients survived the poisoning and 17 died.

Table 1 compares the admission data between survivors and non-survivors, including ECG parameters. ECG heart rate above 100 beats per minute was found in 18 patients, PR interval >200 ms in one, QRS interval ≥ 120 ms in one, prolonged QTc interval (≥ 450 ms for men and ≥ 460 ms for women) (33) in 25, atrial

fibrillation in two, flat T waves in leads I and/or II in six, right atrial enlargement in one, right ventricular strain pattern in 10, left atrial enlargement in two, and left ventricular strain pattern in three patients. Three patients had concomitant right and left ventricular strain patterns (Figure 1). In addition, we recorded right axis deviation of more than 110° in one patient, RBBB in two, early repolarisation in four, premature ventricular contractions in three, premature atrial contractions in one, and ST depression in leads II, III, and aVF (pointing to inferior ischaemia) in one patient. None of the patients had ventricular dysrhythmias. The *K* for inter-rater reliability analysis of ECG interpretation between the cardiologists was 0.84 (95 % confidence interval; range: 0.67 to 1.00) at $P < 0.001$.

No significant differences in ECG parameters and ECG abnormalities were found between the survivors and non-survivors. Furthermore, ECG abnormalities did not correlate with coma or seizure. However, we established a weak correlations between QTc interval and pH ($r = -0.353$, $P = 0.023$) or base deficit (BD; $r = 0.387$, $P = 0.016$). QTc interval however did not correlate with time elapsed between methanol consumption and treatment, age, sex, seizure or coma,

HCO_3^- , or serum potassium. The same is true for ECGs with or without flat T waves and serum potassium (Table 1).

DISCUSSION

Our results show that a large majority of patients poisoned with methanol, 35 of them, had ECG abnormalities on admission to hospital. However, none of the abnormalities turned out to be an independent predictor of mortality.

Our findings differ from earlier reports in some of the abnormalities. Hazra et al. (24), for instance, detected right ventricular strain pattern in all 11 methanol-poisoned patients with ECG records. They also found right atrial enlargement in all patients except one. These findings led them to conclude that methanol specifically affected the right heart. We, in turn, observed left ventricular strain in three patients, concomitant right and left ventricular strain in three patients and right ventricular strain in only 10 patients. In other words, our findings suggest that methanol-

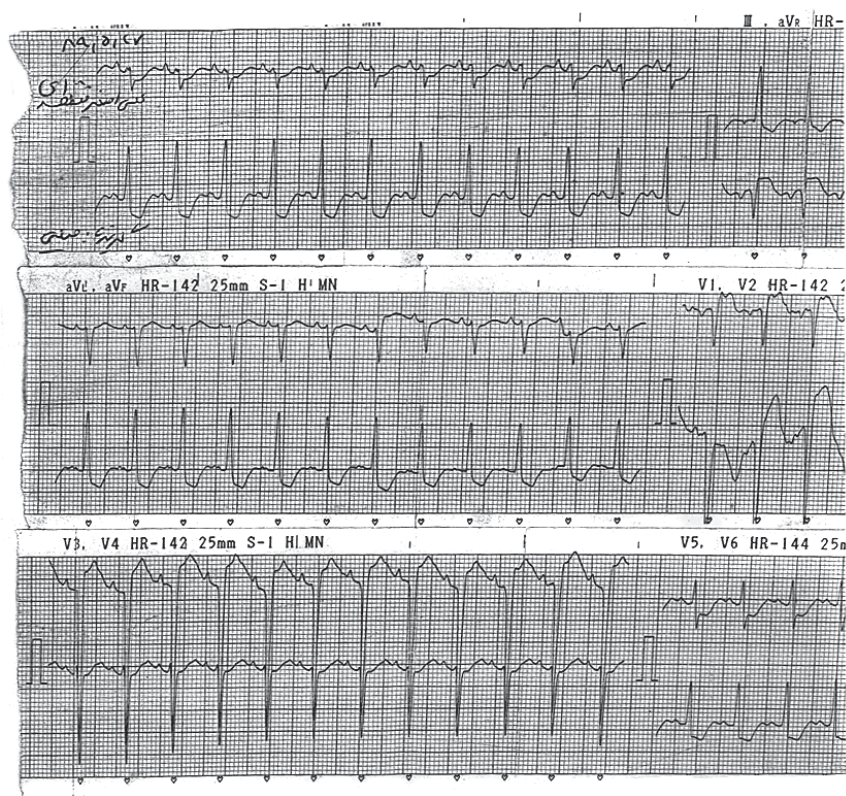


Figure 1 Electrocardiogram of one of the patients with concomitant right and left ventricular strain pattern (31, 32)

Table 1 Electrocardiographic parameters and distribution of age, sex, time between ingestion and treatment, coma, seizure, pH, pCO₂, HCO₃⁻, BD, and serum potassium level on admission to hospital

	All	Survivors	Non-survivors	P-value (applied statistical test)
Patients / number	42	25	17	
Age / years	31.14 (±12.5) ^a	30 (±14)	33 (±11)	0.137 (MWU) ^b
Sex (male/female)	36/6	20/5	16/1	0.374 (Fisher's exact test) ^b
Time interval between ingestion and treatment / h	41.76 (±23.82)	48.63 (±26.67)	32.43 (±15.77)	0.070 (MWU) ^b
Coma (GCS≤8) / number	18	4	14	<0.001 (Fisher's exact test)
Seizure	7	0	7	0.001 (Fisher's exact test)
pH	7.02 (±0.30)	7.16 (±0.25)	6.80 (±0.24)	<0.001 (Student t test)
pCO ₂ / mm Hg	33.23 (±17.57)	26.24 (±10.81)	44.16 (±20.67)	0.001 (Student t test)
HCO ₃ ⁻ / mmol L ⁻¹	8.45 (±5.94)	10.33 (±6.40)	5.33 (±3.40)	0.008 (Student t test)
BD / mmol L ⁻¹	22.35 (±12.27)	17.20 (±11.44)	31.18 (±8.02)	<0.001 (Student t test)
Serum potassium level / mEq L ⁻¹	4.6 (±1.3)	4.5 (±1.1)	4.7 (±1.5)	0.932 (MWU) ^b
Rate / beats per min	95 (±20)	93 (±20)	98 (±19)	0.589 (MWU) ^b
PR interval / ms	168 (±28)	169 (±29)	163 (±28)	0.571 (MWU) ^b
Maximal limb-lead QRS interval / ms	87 (±28)	86 (±31)	88 (±23)	0.686 (MWU) ^b
QTc interval / ms	467 (±49)	465 (±33)	470 (±67)	0.367 (MWU) ^b
QRS frontal plane axis (°)	+50 (±44)	+55 (±39)	+43 (±53)	0.644 (MWU) ^b

MWU: Mann-Whitney U test; BD: base deficit; GCS: Glasgow Coma Scale

^a Data are presented as mean value (±SD).

^b Not significant.

induced cardiotoxicity is not exclusive to the right heart as Hazra et al. seem to suggest.

Weisberger and MacLaughlin (25) reported that the most frequent ECG finding in eight patients poisoned with methanol were low-voltage T waves in leads I and II. They also showed prolonged QTc in four patients. In contrast to Weisberger and MacLaughlin, QTc in our study was prolonged in 25 patients and only 6 had flat T waves in leads I and/or II.

Our study has shown that QTc interval not only bears little relation with pH and BD, but also has no association with HCO₃⁻. Our statistical analysis also shows that QTc prolongation does not correlate with sex and age nor do QTc prolongation and flat T waves correlate with potassium levels.

Koivusalo (34) suggests that cardiac tissue metabolises methanol *in vitro*. Therefore, it is reasonable to assume that in patients with acute methanol poisoning, it is methanol metabolised to formic acid that depresses the myocardium and not acidosis as we did not find a statistically significant relationship between acidosis and ECG abnormalities.

Opherk et al. (35) have shown that some ECG changes may occur in the postictal phase of seizures. All seven of our non-survivors had seizures, but their ECG abnormalities did not correlate with seizures. This suggests that ECG changes are related to methanol poisoning and not to seizure.

There are some limitations to our study; confirmatory methanol and formate levels were not available for all patients, but the diagnosis based on other information and clinical findings ($K=1.00$, $P<0.001$) is reliable.

As we did not look into the relationship between serum calcium and magnesium and ECG abnormalities, future studies will need to address this question.

To conclude, even though cardiotoxicity in methanol poisoning is high, ECG abnormalities can not predict mortality. However, from the clinical point of view, we suggest that ECG should become a routine procedure in methanol poisoning to monitor for cardiotoxicity.

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Conflict of Interest

The authors declare no conflict of interest in this study.

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Sažetak

ELEKTROKARDIOGRAFSKE MANIFESTACIJE KOD AKUTNOG TROVANJA METANOLOM NE MOGU PREDVIDJETI SMRTNOST

Cilj je ovog retrospektivnoga opservacijskog istraživanja bio utvrditi elektrokardiografske (EKG) manifestacije u bolesnika otrovanih metanolom te vidjeti mogu li one poslužiti kao pretkazatelji smrtnosti. Također smo željeli utvrditi postoji li povezanost između promjena na EKG-u i vremena proteklog od unosa metanola do liječenja, zatim dobi, spola, epileptičkog napadaja, kome (≤ 8 prema ljestvici Glasgow), nalaza plinske analize arterijske krvi te razina kalija u serumu u trenutku hospitalizacije. Ispitivanje je obuhvatilo 42 bolesnika u dobi od 31.14 ± 12.5 godine. Dvadeset i petero je preživjelo trovanje, a 17-ero umrlo. Gotovo su svi bolesnici imali jedan abnormalni EKG parametar ili više njih među kojima brzinu otkucaja srca, srčani ritam i provodljivost. Nismo međutim našli značajnih razlika između preživjelih i umrlih. QTc interval nije korelirao s vremenom proteklom od unosa metanola do liječenja, s dobi, spolom, epileptičkim napadajem, komom, HCO_3^- odnosno razinama kalija u serumu. Isto tako, T valovi nisu korelirali s kalijem u serumu. Abnormalni EKG nalazi nisu korelirali s komom i epileptičkim napadajima. Premda je kardiotsičnost značajna kod trovanja metanolom, nijedan abnormalni EKG nalaz nije mogao predvidjeti smrtnost. To međutim ne isključuje potrebu za rutinskim EKG pregledima radi otkrivanja kardiotsičnosti u svih bolesnika otrovanih metanolom.

KLJUČNE RIJEČI: *EKG, elektrokardiogram, metanol, trovanje, smrt*

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