Waveforms and Deflections in Toxicology

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ABSTRACT

Introduced as pieces of wires in the early 18th century, the electrocardiograph (ECG) machine has become an important clinical bedside tool. This easily available, user friendly, noninvasive, inexpensive investigation has spread its wings not only in the field of cardiology, but in almost all other medical fields. Herewith we present a synopsis of few case reports of drug overdose (digoxin, β-blockers, diazepam and tricyclic antidepressants) either accidental or by deliberate harmful intention who presented to our hospital, to highlight the importance of electrocardiogram (ECG) in toxicology field. One of the leading causes of mortality and morbidity is drug overdose and poisoning, more commonly in rural areas where sophisticated investigations like serum levels of toxins and treatment modalities may not be available. The cardiotoxic poisons bring changes in the ECG wave forms due to multiple effects, the most common being effects on ion channels. In such situations, ECG will help in early detection of life-threatening events, paving way for targeted and timely intervention.

Keywords: Waveforms, ion channels, cardiotoxic poisons, drug overdose

Electrocardiogram (ECG) is an important diagnostic tool in the field of cardiology as a patient with drug overdose and drug poisoning can present with typical ECG changes. Serial ECG is mandatory in patients with suspected exposure to cardiotoxic overdose.

Ionic current flow from cell to cell through the heart as a result of the activity of selectively permeable ion channels which, when activated transiently, open, allowing the movement of charged ions (Na^+, K^+, Cl^- and Ca^{2+}) across a muscle membrane that is otherwise impermeable. A sound knowledge of ECG interpretation and specific characteristics of cardiotoxic drugs is very much necessary to establish a good foundation for an early diagnosis and prompt management. Few case reports are presented here to highlight this fact.

CASE REPORT 1: BENZODIAZEPINE AND POTASSIUM CHANNEL

A 59-year-old female was brought to the emergency room (ER) with history of consumption of 10 mg diazepam tablets (unknown quantity). The patient was not a known case of hypertension, diabetes mellitus or coronary artery disease, had no other significant comorbid conditions and was not on any medications. There was no preceding history suggestive of any gastrointestinal disorders or underlying psychiatric disorders, trauma or similar weakness in the past. There was no significant family history.

At the time of presentation, the patient was slightly drowsy but was responding to oral commands. On examination, patient was afebrile, not anemic and not cyanosed and had no clubbing or pedal edema. She had a pulse rate of 90/min and blood pressure of 90/60 mmHg. Examination of cardiovascular system was normal. Bilateral air entry was present with no added sounds. Abdomen was not distended. Bowel sounds were present. Neurological examination revealed weakness of all four limbs with muscle power of Grade 3 with diminished deep tendon reflexes. There was no neck muscle weakness or ptosis. Pupils were equal and reacting to light. Fundus was normal. Bilateral plantars were flexors. Other modalities of neurological examination could not be elicited. Investigations revealed normal hemogram and renal parameters. Electrolyte analysis revealed sodium of 134 mEq/L, potassium of 2.5 mEq/L and chloride of 109 mEq/L. Arterial blood gas (ABG) analyses showed no evidence of acidosis or alkalosis.

ECG showed heart rate of 68 bpm, with normal sinus rhythm and no evidence of atrial enlargement or

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ventricular hypertrophy. There were no ST changes. However, prominent "U" waves were present in the precordial leads (V1-V3) (Fig. 1).

Following gastric decontamination, correction of potassium was done with potassium chloride. Figure 2 shows ECG after potassium chloride correction. Patient improved and was discharged on 7th day post-admission.

Diazepam

Diazepam, a prototype benzodiazepine, is the most commonly used drug for various effects acts on gamma-aminobutyric acid type A ($GABA_A$) receptor, as a positive allosteric modulator. It amplifies the inhibitory signal by opening the chloride ion channel, and thereby inhibits the neurons. With no risk of addiction and milder withdrawal symptoms, overdose is common and essentially never fatal. However, in a retrospective analysis of 53,931 people of diazepam poisoning, among the various side effects reported like hypotension, drowsiness, etc., 0.64% were found to have hypokalemia. Hypokalemia is more common in elderly females in the age group of 50-60 years. Several studies have found that the incidence of hypokalemia with diazepam overdose is maximum during the first few weeks and it steadily decreases with increasing duration of drug intake. The mechanism attributed to this includes the exhaustion of the $GABA_A$ receptors and resistance to diazepam on repeated exposures. If left unnoticed or untreated, diazepam can lead to major fatal outcomes such as impaired vision, ataxia, apnea, hypotension, respiratory depression, AV blocks and coma. Hypokalemia induced by diazepam is a rare yet a serious adverse effect, which is a completely reversible condition. Diazepam is the only benzodiazepine that does not cause QRS widening and oxazepam is the only one not causing prolongation of PR interval.

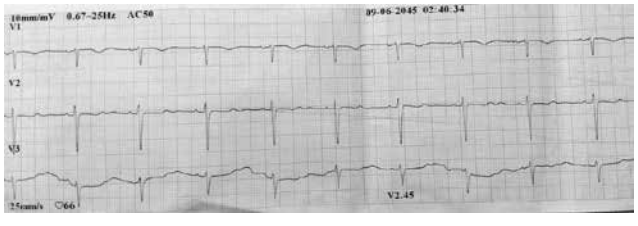

Figure 1. "U" waves.

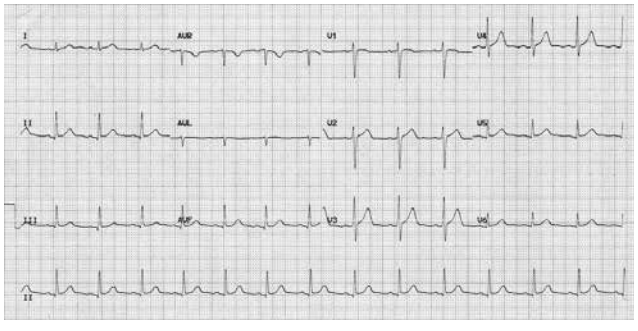

Figure 2. ECG taken after potassium chloride correction.

The use of flumazenil as an antidote for benzodiazepine poisoning is very less as the risks outweigh the benefits as it also acts as an inverse agonist. Hence, in the absence of a safe antidote, identifying the electrolyte imbalance by ECG and correcting them will be more relevant in diazepam poisoning.

CASE REPORT 2: TRICYCLIC-ANTIDEPRESSANT AND SODIUM CHANNEL

A 32-year-old female patient presented to ER after 3 hours of history of consumption of 10 tablets of amitriptyline (10 mg) and 10 tablets of clonazepam (0.5 mg). There was no preceding history of chest pain, palpitation, breathlessness, convulsions and loss of sensorium. She was a known case of psychogenic nonepileptic seizure for the past 1 year and was on regular treatment with amitriptyline 10 mg, clonazepam 0.5 mg and sodium valproate 600 mg. On examination, patient was drowsy, responding to deep painful stimuli and febrile. She had a pulse rate of 140/min and blood pressure of 100/60 mmHg. Pupils were equal and reacting to light. Fundus was normal. Plantar reflexes were flexors. Other modalities of neurological examination could not be elicited. Examination of cardiovascular system/respiratory system/abdomen was normal.

Investigations revealed a normal hemogram, renal parameters and metabolic acidosis (pH - 7.24, HCO_3^- - 11 mEq/L, pCO_2 - 35 mmHg). ECG was taken at the time of admission (Fig. 3 a-c).

Patient was treated with activated charcoal 1 g/kg and acidosis was corrected by sodium bicarbonate infusion.

Tricyclic Antidepressant Poisoning

Poisoning with tricyclic antidepressants (TCAs) is an important cause of drug-related poisoning with mortality of 1.3%. Neurological and cardiovascular toxicity, resulting in reduced levels of consciousness, reduced blood pressure and arrhythmias, are mainly responsible for mortality attributed to TCA overdose. It causes mild symptoms such as agitation, due to slow absorption in overdose, reduced by the cholinergic antagonist effects of TCA, which may worsen over time, leading to convulsions, coma and death.

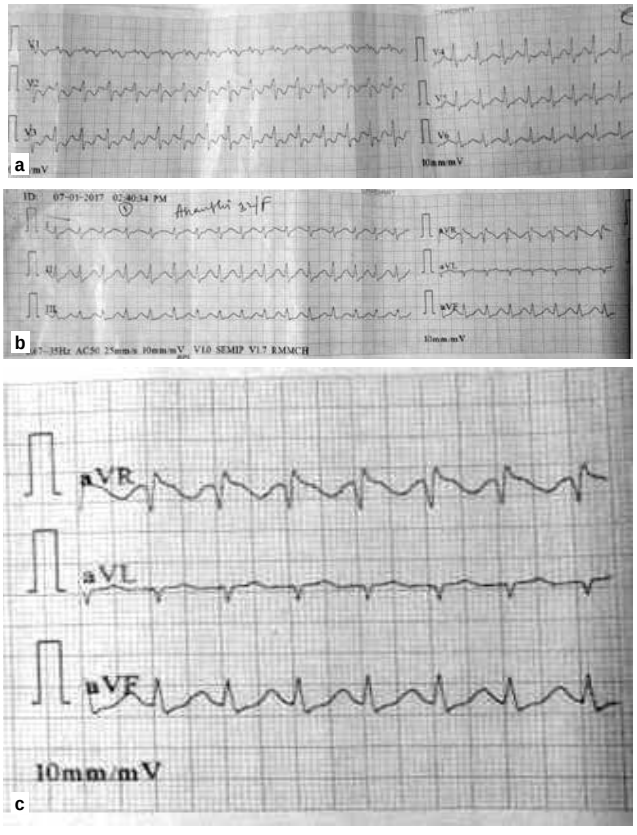

Figure 3 a-c. ECG figures reveal sinus tachycardia, right axis deviation, prolonged PR interval, QRS width prolongation with QTc interval of 0.506 sec, aVR was positive with deep S-wave.

Cholinergic antagonist effects of TCAs include delirium, widened pupils, reduced gut motility and retention of urine. Cardiovascular effects include α receptor blockage in vasodilatation, blockage of sodium channel resulting in increased depolarization time and the inhibition of potassium channels causing increased repolarization time and dysrhythmias. Neurological symptoms can include lowered levels of consciousness, due to antihistaminic effects and seizures due to TCA antagonist effects on the $GABA_A$ receptor.

ECG findings are used for:

- Risk stratification
- To guide subsequent therapy.

The typical ECG changes that can be found in a TCA overdose are QRS width >100 ms, QTc prolongation >430 ms and R/S ratio 0.7 in lead aVR, R in aVR of >3 mm and right axis deviation of 130-270° in the terminal 40 ms of the QRS. These ECG findings are identified as the most important risk stratification, more important than serum drug levels for the prediction of complications (seizure, dysrhythmias such as torsade de pointes) following a TCA overdose and thereby resolve by the administration of 1-2 units/kg of sodium bicarbonate. Sodium bicarbonate acts at three levels. It raises the sodium gradient across the affected sodium channel counteracting the drug-induced side effect of sodium channel blocking action, increases the pH, which promotes dissociation of TCA from cardiac sodium channels and finally TCAs bind more easily to protein in the higher pH range resulting in a lower pharmacologically active TCA concentration. Alkalinization to a pH of 7.45-7.55 is advised until normalization of the QRS interval, even in the absence of initial acidosis. When the PH becomes >7.6, the risk of dysrhythmias increases.

Similar ECG changes can occur in cocaine toxicity and class IA, IC antiarrhythmic drugs. Hence, these drugs should be avoided because of their ability to block cardiac sodium channels.

CASE REPORT 3: DIGITALIS AND CALCIUM CHANNEL

A 28-year-old male patient presented to ER with complaints of palpitation and giddiness of 2 hours duration. There was no history of chest pain, breathlessness, convulsions and loss of sensorium. He was a known case of rheumatic heart disease with atrial fibrillation for the past 2 years and was on regular treatment with digoxin 0.25. Inadvertently, he took 4 tablets of digoxin.

ECG was taken at ER which showed an irregular RR interval with controlled ventricular rate, absent P waves and inverse tick sign (Fig. 4).

Digoxin

A positive inotropic drug, digoxin inhibits the Na^+ K^+ ATPase, increases calcium concentration in the cell and thus, the effects of digoxin act through all 3 ions. Digoxin toxicity is most common in elderly patients with kidney injury and electrolyte imbalance like hypokalemia, hyperkalemia, hypercalcemia, calcium channel blockers and diuretics. Digoxin has very narrow therapeutic index (0.5-2 ng/mL).

Thus ECG helps us:

- *To find out toxicity versus effect*: Classical digoxin effect (Fig. 5): It appears as a down sloping of ST segment, also known as "Reverse tick"/"Reverse check sign."
- Digoxin toxicity (Fig. 6): The most common dysrhythmia associated with toxicity induced by

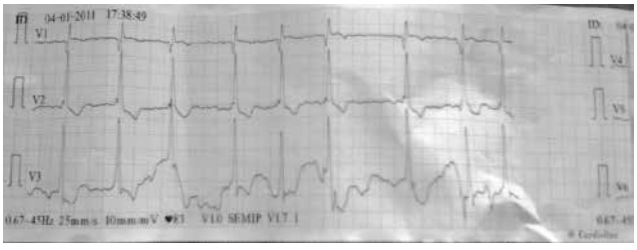

Figure 4. ECG showing irregular RR interval with controlled ventricular rate, absent P waves and inverse tick sign.

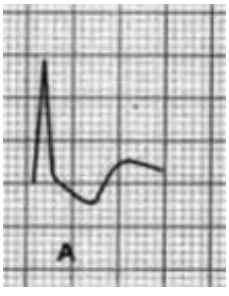

Figure 5. Digoxin effect - T wave rises above the baseline.

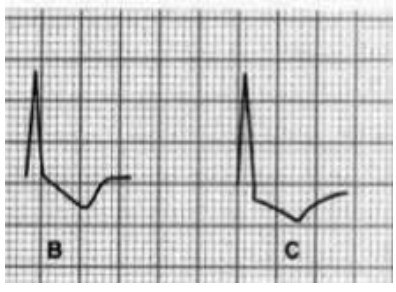

Figure 6. Digoxin toxicity - T wave does not rise above the baseline.

these agents is frequent premature ventricular beats, paroxysmal atrial tachycardia with variable block or accelerated junctional rhythm is highly suggestive of digitalis toxicity.

- *Help us to identify electrolyte disturbances*: Hyperkalemia is one of the indicator for Fab fragment treatment in digoxin toxicity, when estimation of serum digoxin level is not available or amount of ingested digoxin not known.

CASE REPORT 4: β BLOCKERS AND SODIUM, POTASSIUM CHANNELS

A 60-year-old female, known hypertensive, diabetic and dyslipidemic, on regular treatment, was brought to ER with history of giddiness since 2 hours duration. She had a dispute with her family members and consumed 10 tablets of antihypertensive drugs (bisoprolol). On examination, patient was conscious, responding to oral commands. She had a pulse rate of 45/min and blood pressure of 90/60 mmHg. Pupils were equal and reacting to light. Fundus was normal. Plantar reflexes were flexors. Other modalities of neurological examination could not be elicited. Examination of cardiovascular system/respiratory system/abdomen was normal.

ECG taken at ER showed heart rate of 42/min, NSR, no ST, T-wave changes (Fig. 7).

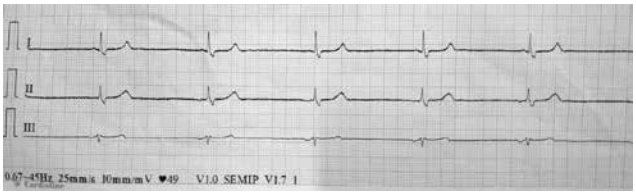

Figure 7. ECG showing no ST, T-wave changes.

β-blocker Toxicity

β blockers act mainly on cardiac β_1 receptors and produce decreased automaticity, negative chronotropic and inotropic effect. Hence, these drugs not only have a direct effect on the myocardium, but also exert an indirect effect by blocking the sodium and the potassium channels, thereby depressing sinoatrial and atrioventricular nodal activity.

The hallmark of β-blocker poisoning is myocardial depression and decreased contractility leading to bradycardia, hypotension and in large dose, cardiogenic shock. Highly lipophilic β blockers like propranolol readily cross the blood-brain barrier and can produce central nervous system (CNS) effects such as seizures and coma. β blockers with membrane stabilizing property, such as propranolol or acebutolol, may prolong the QRS interval (>0.10 sec) and predispose to dysrhythmias. These inhibitory effects of propranolol on the fast inward sodium current producing prolongation of QRS may be used as predictors of propranolol-induced seizures. Prolonged PR can be an early sign of β-blocker overdose. Propranolol overdose has been associated with a higher mortality rate compared with other β blockers. Sotalol is a unique β-blocker in that it possesses the ability to block delayed rectifier potassium channels in a dose-dependent fashion.

General goals of therapy are aimed at improving the inotropic and chronotropic effect. Potential intervention utilized to manage severe toxicity includes intravenous fluid, atropine, glucagon, calcium and vasopressors.

CONCLUSION

To summarize, the myocardial resting and action potential depends mainly on sodium, potassium and calcium ion channels. Many cardiotoxic poisons have well-known effect on these channels producing varied ECG findings. Hence, toxidrome approach, in the management of poisoning, should also include ECG interpretation for guided, targeted, interventions.

Toxidrome approach: In patients with normal sinus rhythm (like TCA toxicity), subtle changes like prolonged QTC, etc. should be looked for. Bradycardia

in poisoned patients can be assessed with the toxidrome approach to search for signs of toxicity of drugs like digoxin overdose (PVC), β-blocker poisoning (AV block). ECG of tachycardia patients should be assessed for wide complexes (TCA poisoning, Na^+ channel blockade drugs) - R-wave in aVR, S in lead 1, aVL; QTc prolongation and ischemia.

Reasonable period of observation in patients with normal ECG without other signs of cardiotoxicity is usually 6-8 hours, but in patients exposed to sustained release preparations or drugs (like citalopram) with delayed toxicity may be beyond 24 hours. Serial ECGs should be performed in patients with suspected cardiotoxicity.

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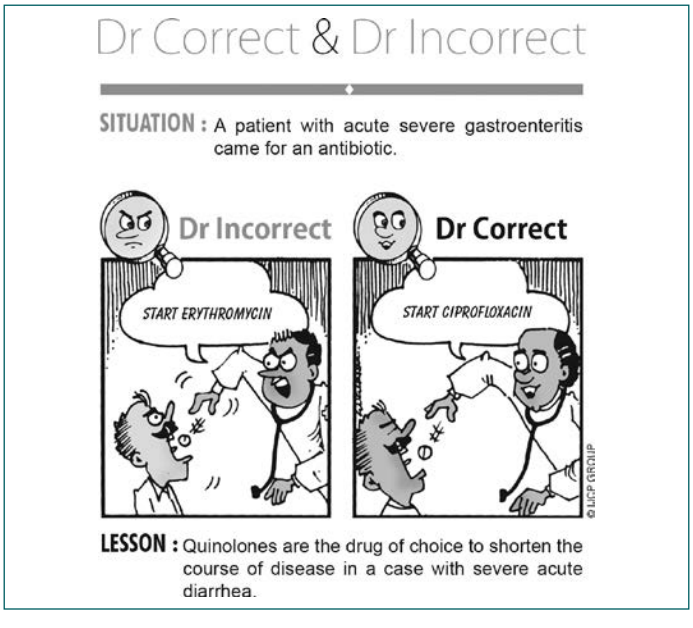

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