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CASE REPORT

Coma with ECG abnormalities: consider tricyclic antidepressant intoxication

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ABSTRACT

Two comatose patients with a psychiatric history were admitted to our hospital. On admission both presented with major cardiovascular instability and needed urgent intensive care treatment. Although initially not suspected, the coma was caused by tricyclic antidepressant intoxication (TCA). Serious neurological, anticholinergic and cardiovascular effects may occur in TCA intoxication. In any comatose patient with ECG changes and a psychiatric history, TCA intoxication should be strongly suspected.

KEYWORDS

Tricyclic antidepressant poisoning, intoxication, coma, ECG abnormalities, cardiogenic shock

INTRODUCTION

In the differential diagnosis of comatose patients with a history of depression and/or suicide attempts intoxications should be considered. Tricyclic antidepressants (TCA), alone or in combination with other drugs, are often used in intentional drug overdosing. Serious neurological (coma, convulsions), anticholinergic and cardiovascular (hypotension and ventricular arrhythmias) effects may occur, and therefore patients are frequently admitted to intensive care units (ICUs).[1,2] However, at initial presentation the aetiology of coma may not be immediately clear, and many other causes can be considered. The following two cases illustrate both the severity of toxic effects and the complexity in diagnosing coma due to TCA poisoning in the clinical setting. ECG abnormalities may provide clues for the final diagnosis.

CASE 1

A 66-year-old female patient was transported to the emergency department in the early morning. The last two days she had been lethargic, and presented influenza-like symptoms. Overnight she became comatose. Her medical history revealed a manic depression, currently treated by a psychiatrist, auto-intoxication, lithium-induced hypothyroidism, gestational hypertension, and cerebral concussion/contusion. No medications were missing. She had been on nortriptyline (for two months), valproic acid (for five years), propranolol, codeine phosphate and calcium.

On arrival to the emergency department, the patient was comatose. Her coma score was E1M1V1. Pupils were moderately dilated (4 mm) and slow reactions to light were noticed. The patient was hyperventilating. Blood pressure was immeasurable. She had cold, white acra. Rectal temperature was 40.5 °C.

Arterial blood gas analysis showed a pH of 7.34 (7.35 to 7.45), pCO_2 4.9 (4.5 to 6.0 kPa), pO_2 8.3 (9.5 to 13 kPa), bicarbonate of 19.2 (22 to 26 mmol/l), base excess −5.5 (−2 to +2), and SaO_2 90% (92 to 99%). Other laboratory results were CRP 11 (0 to 5 mg/l), Hb 8.9 (7.5 to 10.0 mmol/l) and leucocytes 12.5 (4 to 11/nl). The renal tests showed a urea of 20.5 (3.0 to 7.0 mmol/l), creatinine 366 (50 to 90 μmol/l) and were known to have been in the normal range for the last two years. The sodium was 135 (135 to 145 mmol/l) and potassium 5.9 (3.5 to 4.7 mmol/l), with ionised calcium 1.08 (1.15 to 1.29 mmol/l). From the liver tests only the aspartate aminotransferase of 447 (0 to 45 U/l) and alanine aminotransferase of 323 (0 to 45 U/l) were abnormal. Creatine kinase was 6476 (0 to 170 U/l) and troponin-I 0.34 (0 to 0.48 μg/l). Arterial lactate was 2.2 (0.5 to 1.7 mmol/l). Blood glucose level was 20.9 (4.0 to 10.0 mmol/l). Ethanol level was <0.1 °/₀₀, (below detection).

CT scanning of the brain showed no bleeding or cerebral infarction. Cerebrospinal fluid was clear (leucocytes 4 x 10^3/nl, erythrocytes 302 x 10^3/nl, glucose 9.5 mmol/l and total protein 0.53 g/l).

A 12-lead ECG revealed a ventricular escape rhythm of 40 beats/min and widened QRS complexes, 0.24 sec, with right bundle branch block (RBBB) and left anterior fascicular block (LAFB) configurations.

She was endotracheally intubated and mechanical ventilation was started. Chest X-ray showed a pneumonic infiltrate, possibly due to aspiration of gastric contents. The patient was admitted to the ICU. A pulmonary artery catheter was inserted and a pacemaker lead was introduced for ventricular pacing at 80 beats/min. High-dose inotropes (epinephrine, dobutamine and dopamine) and vasoconstrictors (norepinephrine) were commenced. The patient gradually improved over 36 hours, and was eventually transferred to an internal medicine department. She denied taking overdoses. Nortriptyline levels on the day of admission appeared to be 909 µg/l (normal 75 to 250 µg/l), a toxic level. The valproic acid level was 15 mg/l (subtherapeutic, normal 50 to 120 mg/l). The renal tests normalised within a few days. The transient renal dysfunction was probably due to anticholinergic effects of nortriptyline and acute tubular necrosis caused by hypoperfusion of the kidneys during the period of hypotension and bradycardia. After six days patient was readmitted to the ICU with massive gastrointestinal blood loss and shock. On endoscopy, a visible vessel in the pylorus was coagulated. Severe anaemia (Hb 2.8 mmol/l) and acute stress caused an acute anterolateral myocardial infarction. The ECG normalised except for abnormal lateral repolarisation due to the myocardial infarction. Paresis of the right arm resulting from compression of the plexus brachialis during her comatose period at home persisted. After two weeks, the patient was discharged from the hospital, and she was further treated by a psychiatrist and a cardiologist in the outpatient setting.

CASE 2

A 44-year-old woman had been comatose for a few hours and presented to the emergency department. She had a history of hypertension and autointoxication. She had recently been admitted to a psychiatric hospital and was on weekend leave. During this time she became unconscious with involuntary movements. She had not been ill before. It was unknown if she had taken any medication. She was on olanzapine, oxazepam, paroxetine, temazepam, atenolol, irbesartan and hydrochlorothiazide.

She presented comatose, snoring but moving all her limbs. Her EMV score was E1M4V1. Pupil reactions were normal. She demonstrated no lateralisation and reflexes were symmetrical. No meningeal signs were noted.

Blood pressure was 100/ 50 mmHg, pulse 114 beats/min and temperature 37.5 °C. Clinical examination of the thorax and abdomen were normal. An ECG showed a first-degree AV block and RBBB (*figure 2*), a PQ interval of 0.24 seconds, with a QRS width of 0.14 seconds. Arterial blood gases were normal. Other laboratory results were glucose 7.8 (4.0 to 10.0 mmol/l) and normal liver and kidney functions.

Figure 1. *Ventricular escape rhythm of 40 beats/min, and widened QRS complexes, 0.24 sec, with right bundle branch block and left anterior fascicular block configurations*

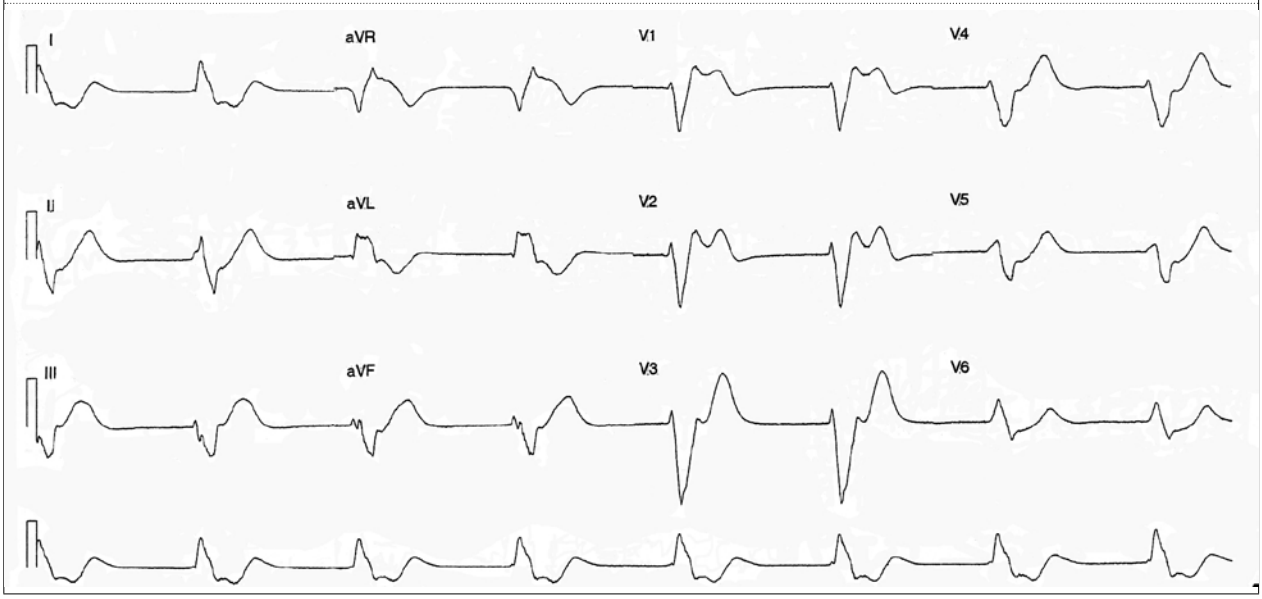
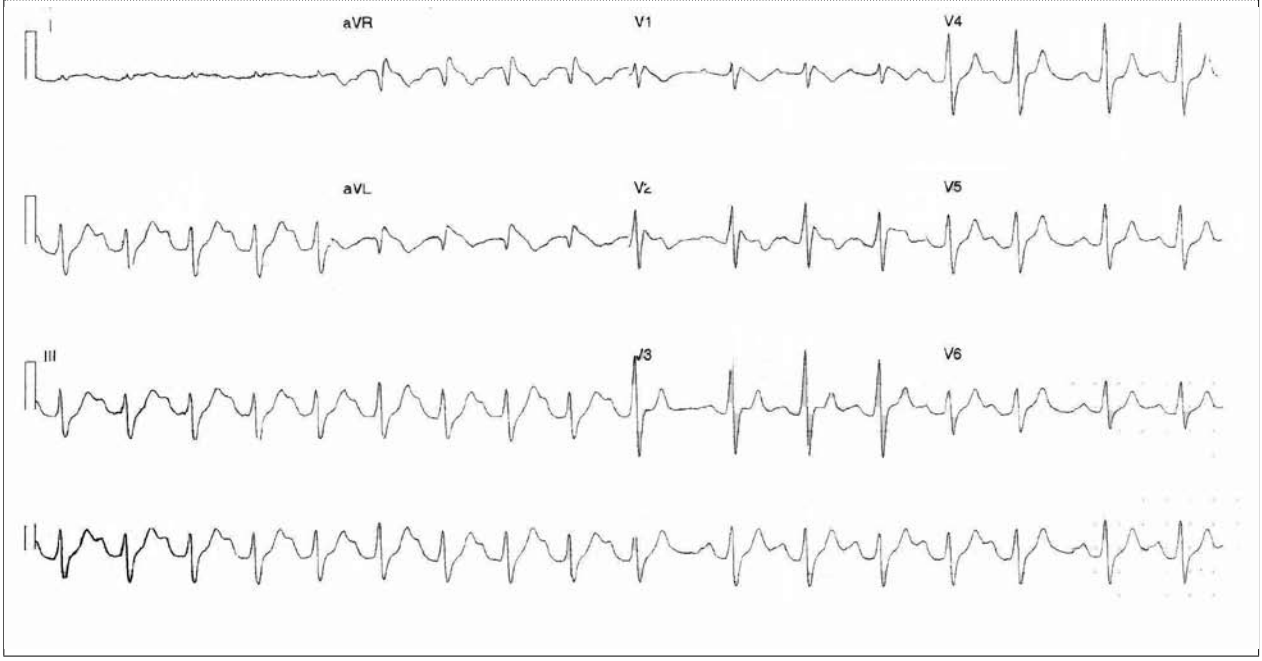


Figure 2. *Sinus tachycardia (110 beats/min), first-degree AV block (0.24 sec) and RBBB (0.14 sec)*



She was admitted to the ICU for observation. Intoxication with benzodiazepines was assumed because her medication list revealed these medications. However, there was no response after the administration of anexate.

In the evening she developed tonic-clonic seizures for which clonazepam 6 mg/24 hours was started. Serum lithium <0.1 (0.4 to 1.2 mmol/l) and ethanol <0.1 °/$_{oo}$, were below detection limits. On the second day she still did not wake up. CT brain, cerebrospinal fluid and EEG were normal. The patient developed respiratory failure after *i.v.* midazolam (used for lumbar puncture) in combination with a pneumonia. She was intubated, ventilated and needed inotropic support. After four days, the patient was extubated and was transferred to the internal medical ward. Nortriptyline levels were 1149 µg/l (therapeutic range 75 to 250, toxic) and the paroxetine level was 167 µg/l (therapeutic range 10 to 75, maximal 250, this level can be attributed to a daily dose of 40 mg, not being a trough level), both taken during the day of admission. Five days later the nortriptyline level was to 352 µg/l. So, she had unexpectedly taken nortriptyline, which had been prescribed earlier, way beyond its therapeutic level.

DISCUSSION

Of all the antidepressants, TCAs are the most toxic drugs often used for suicide attempts.[3-5] Diagnosis of TCA intoxication can be very difficult. The clinical signs, however severe, are nonspecific. The mechanism of toxicity of TCAs is probably related to four pharmacological actions: anticholinergic, vascular α_1-antiadrenergic action, adrenergic reuptake inhibition at nerve terminals and fast sodium channel blockade, a quinidine-like effect in the heart.[6] Serious anticholinergic effects include decreased bowel movements resulting in ileus, hyperthermia causing rhabdomyolysis, urinary retention, renal failure, and confusion.[7]

Cardiovascular and neurological effects are most common (*table 1*). By inhibiting sodium channels, TCAs can delay the propagation of the depolarisation and repolarisation in the myocardium. This can lead to prolongation of the PR, QRS and QT intervals. AV blocks and bundle branch blocks can be seen. Severe ventricular tachycardia and sinus tachycardia may occur.[8,9] Our two patients both presented with RBBB and one of them also had LAFB and first-degree atrioventricular block, which fully recovered.

Hypotension may be the result of a combination of diminished myocardial contractility (inhibition of fast sodium channels), vascular dilatation (blockade of α_1-adrenergic neurotransmitters) and norepinephrine (NA) reuptake inhibition (can lead to NA depletion).[9,10] Case one had a cardiogenic shock caused by the TCA intoxication.

Table 1. *ECG changes in TCA overdosing*

Primary dysrhythmia	Primary conduction delays
Sinus tachycardia	QRS >100 msec
Supraventricular arrhythmias	PR/QT prolongation
Ventricular tachycardia	Terminal R wave extension in
Ventricular ectopy	QRS in lead aVR
Asystole	First-degree AV block
	Bundle branch blocks

Severe neurological symptoms include drowsiness, ataxia, hypertonia and hyperreflexia with extensor plantar responses. Agitation and delirium are known presentations. Respiratory depression may occur with the coma.

Convulsions occur in more than 5% of patients and often in combination with QRS prolongation.[11] In the second case, anexate was administered because we initially suspected benzodiazepine intoxication to be more likely than TCA intoxication. However, when TCA intoxication is suspected, especially in combination with benzodiazepine intoxication, anexate should not be used. If anexate is used in this situation, there is an increased risk that treatment of convulsions is more difficult since TCA and benzodiazepines can act as competitive antagonists.

Another possible symptom, although rare, is lung injury. Pulmonary oedema and ARDS-like symptoms can occur, in combination with nonspecific changes on the chest X-ray.[12,13]

The manifestations of acute toxicity can vary greatly between patients. It is hard to predict which patients will have more serious symptoms, such as seizures or arrhythmias. Individual variation in absorption, protein binding and metabolism might give a variation in plasma TCA levels, making plasma levels an unreliable predictor of toxicity.[4,14] Toxicity has been suggested to be more likely if plasma concentrations are >100 μg/l, but has also been seen at lower levels.[4] TCAs have a long half-life, due to the high protein binding and large volume of distribution. These drugs are rapidly absorbed in the gastrointestinal tract. After metabolism by hepatic enzymes the metabolites are conjugated and excreted by the kidneys.[14] Hypoalbuminaemia and acidaemia increases the amount of free drug.[9]

Plasma TCA levels are difficult to determine, and are not readily available. The plasma level of TCA (no distinction can be made between the different kinds of TCA) can only be measured within 30 minutes with the fluorescence polarisation immunoassay.[4] This technique was not available in our hospital. The value of levels of TCA metabolites in red blood cells is under investigation and seems to have a better correlation with QRS duration.[15]

TCA are extensively metabolised by several cytochrome P450 enzymes. Therefore, drug levels can be influenced by comedication with hepatic clearance. Valproic acid is a CYP 2C9 inhibitor; although the main metabolic pathway of nortriptyline is CYP2D6, the interaction between valproic acid and nortriptyline has been previously described and hesitantly attributed to CYP2C9 or CYP2C19.[16,17]

The intoxication is likely due to the fact that the patient had been on valproic acid for five years at low drug levels and nortriptyline was added recently. The patient denied having taken an overdose. This drug interaction may have reduced nortriptyline elimination.

The second patient was on paroxetine, which is known to be a potent inhibitor of CYP 2D6. Since she had a high level of paroxetine, it is most likely that this interaction took place, especially since the long half-life of nortriptyline after the initial (due to treatment with activated charcoal) sharp decline of levels (1148 day 0, 437 day 3, 416 day 4, 352 day 5), had a terminal half-life of about 100 hours.

An ECG is an essential diagnostic tool in assessing the clinical severity of overdose, because impaired conduction can progress into arrhythmias with cardiovascular collapse. However, it can never be used as the sole method of risk determination.[18,19] The accuracy of the ECG is influenced by the time of drug ingestion. Directly after intake the ECG is usually still normal, with abnormalities developing after several hours. Repeat ECGs are necessary when TCA intoxication is suspected.

A QRS >100 to 120 msec, QTc >500 ms and R/S ratio in aVR >0.7 (R wave >0.3mm), with right-axis deviation, increase the risk of arrhythmias.[4,8,10,20] Heart rate analysis and variation can be useful, but is still controversial.[21] When the QRS is >100 msec, there is a greater risk of seizures.[4,6,8-10,14] Both our patients had a QRS >100 msec, but only one (patient two) demonstrated seizures. It might be that the R/S ratio in aVR may be a better predictor of complications. In some studies the R/S ratio in aVR was a better predictor than the QRS interval for association with arrhythmias or seizures.[8,22] Niemann and coworkers suggested that the right bundle may be more susceptible to TCA-induced conduction block, which could explain why both patients had RBBB.[23]

The time of resolution of ECG abnormalities varies widely, possibly related to the severity of the toxicity.[20] Specific treatment to prevent arrhythmias could be justified for patients with QRS >100 msec or R/S ratio >0.7. Patients with hypoxia, acidosis, seizures or other significant noncardiac complications should receive specific treatment.

The moment a TCA overdose is suspected, rapid gastrointestinal decontamination should be initiated to prevent further absorption of TCA. Since TCA slows down gastrointestinal movement, activated charcoal is still useable several hours after ingestion.

In case of nortriptyline intoxication associated with severe acidosis, sodium bicarbonate administration may be considered to diminish direct cardiac toxicity.[24] However, it is likely that not the correction of the acidosis, but the administration of sodium causes this beneficial effect. Experimental data suggest that hypertonic saline is even more effective than sodium bicarbonate.[25] Although administration of sodium bicarbonate may have immediate effects on cardiac toxicity in critical situations it can decrease renal excretion. In fact acidification of urine promotes elimination.[26] Bicarbonate administration and hyperventilation have been associated with (near) fatal

alkalosis if not properly monitored.[27] Therefore we advise that sodium bicarbonate is used with caution in TCA intoxication and suggest considering hypertonic saline as an alternative.

CONCLUSIONS

We have presented two comatose patients with a TCA intoxication. On admission to the ICU, a TCA intoxication was not immediately diagnosed or even considered. ECG clues could have led to earlier diagnosis and specific toxicological analysis. So, in any comatose patient with ECG changes and a psychiatric history, TCA intoxication should be strongly suspected.

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