Original Article

Evaluation of serum sodium changes in tricyclic antidepressants toxicity and its correlation with electrocardiography, serum pH, and toxicity severity

Farzad Gheshlaghi, Nastaran Eizadi-Mood, Soodabeh Emamikhah-Abarghooeii[1], Mahdi Arzani-Shamsabadi[1]

Associate Professor, [1]General Physician, Isfahan University of Medical Sciences, Isfahan, Iran

Abstract

Background: Tricyclic antidepressants (TCAs) is a group of drugs used for the depression treatment. One of the effects of these drugs is Na (sodium) channel blocking ability causing cardiac complications such as ventricular tachycardia and Torsades de pointes Arrhythmia. Sodium bicarbonate is used for treatment of these complications which may have some effect on serum sodium levels. Considering no specific research on Na changes on these patients, the serum Na changes and its correlation with ECG changes, serum pH, and TCA toxicity severity were evaluated.

Materials and Methods: A prospective descriptive–analytic cross-sectional study was done on TCA-poisoning patients who were admitted in Noor hospital in Esfahan in last 2 years. Serum sodium levels, ECG changes, and TCA severity toxicity of 92 patients were evaluated five times during first 24 h of admission.

Results: A total of 92 patients were studied. The most common symptoms were conscious level changes (81.52%) and mydriasis (64.1%). Based on toxicity severity by these symptoms the patients were classified into three groups: 12% of the patients had mild toxicity, 50% moderate, and 38% severe toxicity. There were no significant differences in mean serum Na during the time. There was not found any correlation between serum Na level, and serum pH, ECG, and toxicity severity.

Conclusions: Using sodium bicarbonate in TCA-poisoning cases does not change the serum Na levels significantly.

Key words: Overdose, poisoning, tricyclic antidepressant – sodium bicarbonate, toxicity

Address for correspondence:
Dr. Nastaran Eizadi-Mood, Ali-Asghar Hospital, Isfahan University of Medical sciences, Isfahan, Iran. E-mail: izadi@med.mui.ac.ir
Received: 10-03-2012, Accepted: 12-03-2012

INTRODUCTION

Cyclic antidepressants (CAs) include a group of drugs which are used in treatment of depression as well as neurological pains, migraines, urinary incontinence, attention deficit, and hyperactivity disorder. CAs include tricyclic and quadricyclic antidepressants.[1]

TCAs act through inhibition of presynaptic norepinephrine and serotonin reuptake, thus functionally increase these neurotransmitters concentration in central nervous system receptors. Therefore, their therapeutic effect is on autonomic, central nervous, and cardiovascular systems. All the cyclic antidepressant drugs are competitive

Access this article online	
Quick Response Code:	Website: www.advbiores.net
	DOI: 10.4103/2277-9175.102972

How to cite this article: Gheshlaghi F, Eizadi - Mood N, Emamikhah - Abarghooeii S, Arzani - Shamsabadi M. Evaluation of serum sodium changes in tricyclic antidepressants toxicity and its correlation with electrocardiography, serum pH, and toxicity severity. Adv Biomed Res 2012;1:68.

antagonists for acetyl- choline muscarinic receptors.[1]

TCAs have a variety of physiologic effects, including:

- Anti-cholinergic, anti histaminic and anti muscarinic effects
- Alpha adrenergic receptor inhibition
- Amine uptake inhibition
- Sodium channel blockage
- Potassium channel antagonist
- Gamma amino butyric acid (GABA) receptor antagonist[2]

One of contributing factors in TCA overdose mortality is TCA-associated cardiac toxicity.[2]

Cardiac toxicity effects of CAs such as delayed dysrhythmic disorder and hypotension result from changes in vascular tonicity which results from autonomic system function.[1]

Delayed conduction includes prolonged QRS complex and right axis shift in last 40 ms of complex axis (QRS>130 ms). Prolongation of PR, QRS, QTc intervals can occur in therapeutic as well as toxic doses in TCA intoxication. In patients with prolonged QRS time or with hypotension, lethal ventricular tachycardia can occur. Patients with acute intoxication and wide QRS complex usually have changes in their level of consciousness. Hypoxia, acidosis, hyperthermia, convulsion, and beta adrenergic agonists can make patients susceptible to ventricular tachycardia.[2,3] QTc prolongation results from slow depolarization which leads to torsades de pointes. Because this condition usually occurs after bradycardia it is not of acute intoxication findings.[1]

Sodium channel block is resolved after alkalization of serum and increasing serum sodium levels.[2] Therefore, sodium bicarbonate is used for treatment of two conditions discussed above.[4-8] Sodium bicarbonate with its effective alkalization effect is the base of treatment in lethal cardiac toxicity in TCA intoxication.

Although using sodium bicarbonate leads to alkalization and acidosis correction, its effect in serum sodium level with frequent administration and the level of changes with daily sodium bicarbonate administration is not yet clear. One the other hand, hypernatremia can cause convulsion and changes in level of consciousness which is difficult to distinguish from TCA intoxication symptoms. Until this date, there is no specific study on serum sodium changes in patients with TCA intoxication, so the evaluation of serum sodium changes in patients with TCA intoxication and its correlation with ECG changes and serum pH and toxicity severity (in three distinct groups) was performed.

MATERIALS AND METHODS

This was a prospective descriptive–analytic cross-sectional study performed on 92 patients admitted in Noor and Ali Asghar hospital with TCA intoxication between August 2009 and 2011.

Inclusion criteria were TCA intoxication in patients which was established with history (from patient, or other people bringing him/her or referral physician or drug with patient), sign and symptoms, positive urine sample for TCA if suspected. Exclusion criteria were concurrent use of other drugs having cardiovascular effects, including beta blockers, calcium channel blockers, digitals and carbamazepine or past history of cardiovascular disease, as well as symptom-free patients observed 6 h in ER and remained asymptomatic.

Evaluations of serum sodium level, blood PH, and ECG were performed on admission time and every 6 h for 24 h. During the study, patients were divided into three groups; first group included those with anticholinergic symptoms (mild toxicity), second group included those with CNS symptoms (including convulsion and coma, moderate toxicity) as well as anticholinergic symptoms, and third group included those with cardiac symptoms plus anticholinergic and CNS (severe toxicity).

Patients were treated according to the center protocol and obtained data was recorded in checklists.

Serum results were compared with results of ECG changes (QRS complex with, QTc interval time and R wave size in aVR), blood PH changes, and intoxication severity (according to the 3 groups).

Eventually obtained data was processed through statistical software, SPSS 17.0. ANOVA and Pearson correlation tests were used for statistical analysis.

RESULTS

A total of 92 patients were evaluated including 28 males (30.4%) and 64 females (69.4%) with a mean age of 27.5 and in a range of 16–65 during 2 years (2009-2011).

Patients' sodium level on admission and every 6 h was tested; mean sodium level on admission was 137.50 and after 6, 12, 18, 24 h was 136.83, 137.13, 137.76, and 137.86, respectively [Table 1].

Although there was no significant change in sodium level changes during time [Table 1], Pearson correlation coefficient showed there was a reverse relation between number of pills taken and serum sodium levels, especially on admission and the correlation decreases with time (r= –0.47 and *P*-value < 0.001).

Blood PH evaluation showed there was a significant increasing pattern of PH and the most increase was in first 6 h. Mean blood PH on admission was 7.29 which after 6 h reached 7.34 and gradually increased in next hours. [Table 2]

Table 1: Mean serum sodium level over the time in TCA-poisoning patients

Time	Mean + standard deviation (Meq/L)	*P* value
On admission	137.50 ± 3.76	0.19
6 h later	136.83 ± 2.87	
12 h later	137.13 ± 2.28	
18 h later	137.76 ± 1.50	
24 h later	137.86 ± 1.23	

Table 2: Mean blood PH changes in TCA-poisoning patients

Time	Mean + standard deviation	*P* value
On admission	7.29 ± 0.41	0.021
6 h later	7.34 ± 0.03	
12 h later	7.36 ± 0.03	
18 h later	7.36 ± 0.02	
24 h later	7.37 ± 0.02	

Table 3: Mean blood potassium changes in TCA-poisoning patients

Time	Mean + standard deviation (Meq/L)	*P* value
On admission	4.01 ± 0.45	0.01
6 h later	3.90 ± 0.32	
12 h later	3.78 ± 0.27	
18 h later	3.85 ± 0.19	
24 h later	3.94 ± 0.14	

Table 4: Mean ECG changes in TCA-poisoning patients

Cardiac symptoms		Mean + standard deviation	*P* value
QRS complex (ms)	On admission	0.01 ± 0.02	0.03
	6 h later	0.09 ± 0.01	
	12 h later	0.08 ± 0.01	
	18 h later	0.08 ± 0.00	
	24 h later	0.08 ± 0.00	
QTc interval time (ms)	On admission	0.44 ± 0.04	0.011
	6 h later	0.42 ± 0.04	
	12 h later	0.41 ± 0.03	
	18 h later	0.40 ± 0.03	
	24 h later	0.39 ± 0.02	
R wave size in aVR	On admission	1.00 ± 0.97	0.015
	6 h later	0.76 ± 0.95	
	12 h later	0.44 ± 0.69	
	18 h later	0.23 ± 0.45	
	24 h later	0.11 ± 0.26	

Potassium levels showed a decrease after 12 h comparing to admission time and then increased reaching initial number. [Table 3]

Results regarding the mean width of QRS complex, QTc interval time and mean R wave size in aVR on admission has been presented in Table 4.

During the study, patients symptoms was evaluated, which was consistent of three groups: CNS, anti–

Table 5: Clinical symptoms in TCA-poisoning patients

Clinical symptoms			Number of patients	Ratio (%)
Anticholinergic symptoms	Dry mouth		51	55.4
	Blurred vision		14	15.2
	Urinary retention		6	6.5
	Warm and dry skin		59	64.1
	Pupils	Normal	32	34.8
		Miosis	1	1.1
		Mydriasis	59	64.1
Central nervous system symptoms	Conscious		12	13.04
	Decreased level of consciousness (lethargic, obtundation and stupor)		75	81.52
	Coma		5	5.43
	Convulsion		0	0
Cardiovascular symptoms	Without symptom		58	63.04
	Wide QRS complex >0.10 ms		34	36.95
	Prolongation of QTc interval		18	19.56
	R wave size in aVR ≥3mm		7	7.6

Table 6: Relation of different factors with serum sodium level in TCA-poisoning patients

Relation of factors		*P* value	r
Na and PH	On admission	0.315	0.051
	6 h later	0.049	0.174
	12 h later	0.468	0.009
	18 h later	0.102	0.134
	24 h later	0.190	0.093
Na and QRS	On admission	0.112	–0.128
	6 h later	0.008	–0.250
	12 h later	0.072	–0.153
	18 h later	0.327	–0.47
	24 h later	0.117	0.125
Na and QTc	On admission	0.105	–0.132
	6 h later	0.007	–0.258
	12 h later	0.392	–0.029
	18 h later	0.003	–0.285
	24 h later	0.002	–0.293
Na and R wave in aVR	On admission	0.082	–0.146
	6 h later	0.017	–0.221
	12 h later	0.181	–0.096
	18 h later	0.002	–0.297
	24 h later	0.031	0.195

cholinergic, and cardiovascular symptoms [Table 5].

In cardiovascular symptom evaluation, 58 patients had no symptoms (63.04%), while wide QRS complex was observed in 34 patients (36.95%) [Table 5].

There were no significant changes in serum sodium levels over the time. Serum sodium level 6 h after admission had a direct weak relation with blood PH at the same time (r=0.17 and *P*-value < 0.05). Serum sodium level 6 h after admission had reverse weak relation with QRS complex width (r= –0.25 and *P*-value < 0.05) [Table 6].

Based on toxicity severity by these symptoms, patients were classified into three groups: 12% of the patients had mild toxicity, 50% moderate and, and 38% severe toxicity.

DISCUSSION

Antidepressant intoxication is common because these drugs are often available to depressed patients who have a high suicide risk.

Considering that the most important cardiotoxic effect of the CAs is sodium channel blockade and the cardiac sodium channel is responsible for cardiac cell depolarization, its inhibition leads to slowed depolarization of individual cardiac cells. This, in turn, leads to slowing depolarization wave across the myocardium. The ECG manifestation of slowed depolarization is prolongation of the QRS complex, the hallmark of CA overdose. Sodium channel blockade *in vitro* can be partly reversed by increasing the pH or sodium concentration, providing that hypertonic sodium bicarbonate ($NaHCO_3$) has an important role in restoring cardiac arrhythmias.

Given the proven effectiveness of hypertonic sodium bicarbonate and sodium concentration in CAs intoxication, this hypothesis aroused in mind that sodium concentration changes may have correlation with severity of CAs poisoning.

As far as we have searched there is no specific article evaluating serum sodium changes in patients with TCA intoxication.

In our study, 92 patients (28 males, 64 females; mean age 27.5) which got our criteria included in this study entered. In this study, many factors including serum sodium and potassium, blood PH and ECG changes were evaluated which were recorded on admission and every 6 h for 24 h (five times).

Considering sodium concentration, there was no specific study except one published in 2009, in which from 52 children who were studied, hyponatremia was reported in 26.9% of them.[9] In our study, hyponatremia was detected in 25% cases on admission and this not occurred at other times of measurement, however in performed statistical evaluations there was no significant change in mean serum sodium concentration.

There was not found any correlation between serum Na level, and serum pH, ECG, and toxicity severity.

CONCLUSION

Serum sodium concentration changes at different times after admission in patients with TCA intoxication according to statistical evaluations are not generally considerable. It has no correlation with blood PH, ECG changes, and severity of poisoning. However, compared with normal values, 25% of patients had hyponatremia on admission time, which was much more obvious in high doses of drug. If the number of TCA tablets ingested by the patients was considered, serum sodium concentration changes play a significant role and have a correlation with blood PH, ECG changes, and severity of poisoning.

REFERENCES

1. Flomenbaum N, Goldfrank L, Hoffman R, Hawland M, Lewiv H, Nelson L. Goldfrank 's Toxicologic Emergencies. New York: Mcgraw Hill; 2006. p. 1083-97.
2. Tan C, Pillai S, Manning PG. Electrocardiographical case. A man found unconscious. Singapore Med J 2006;47:730-6.
3. Harrigan RA, Brady WJ. ECG Abnormalities in Tricyclie Antidepressant Ingestion. Am J Emerg Med 1997;17:387-97.
4. Bradberry SM, Thanacoody HK, Wat BE, Thomas SH, Vale JA. Management of the cardiovascular complications of tricyclic antidepressant poisoning: Role of sodium bicarbonate. Toxicol Rev 2005;24:195-204.
5. Chan HY, Chan YC, Lau FL. Reversal of Brugada electrocardiographic Pattern.With sodium bicarbonate solution after amitiriptyline overdose. Clin Toxicol 2008;46:892-6.
6. Miller J. Managing antidepression overdose. Emerg Med Serv 2004;33:113-9.
7. Bebarta VS. Waksman JC. Amitriptyline -induced Brugada pattern fails to respond to sodium bicarbonate. Clin Toxicol 2007;45:186-8.
8. Woolf AD, Erdman AR, Nelson LS, Caravati EM, Cobaugh DJ, Booze LL, *et al.* Tricyclic antidepressant poisoning: An evidence - based consensus Guideline for out - of - hospital management . Clin Toxicol 2007;45:203-33.
9. Olgun H, Yildirim ZK, Karacan M, Ceviz N. Clinical, electrocardiographic, and laboratory findings in children with amitriptyline intoxication. Pediatr Emerg Care 2009;25:170-3.

Source of Support: Nil, **Conflict of Interest:** None declared.