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Is there a Correlation between Electrocardiographic Changes and Sodium Valproate Toxicity? An Investigation of 196 Cases

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Abstract

Introduction: Intoxication with Sodium valproate (SVP) is a growing concern owing to its increased use and availability. SVP intoxication may result in cerebral, cardiovascular, respiratory, gastrointestinal, and hematological complications. However, SVP use does not seem to be associated with significant cardiovascular effects and electrocardiographic (ECG) abnormalities. Thus, we aimed to describe SVP intoxication in a series of patients by focusing on ECG findings.

Method: Between February 2011 and February 2012, we enrolled all consecutive patients who referred to Loghman-Hakim Poison Hospital complaining of poisoning and subsequently diagnosed with SVP intoxication. For each patient, we recorded age, sex, and history of SVP use, including indication for use, number of pills ingested, time of ingestion, and total daily dose. We also inquired whether the patient took SVP chronically with or without prescription and whether the ingestion was intentional (suicide attempt).

Result: A total of 194 patients with SVP poisoning at a mean ± SD age of 28.91 ± 11.24 years and a male-to-female ratio of 1:2.8 were admitted. Regarding cardiac presentations, all the subjects were in sinus rhythm, and 1.5% experienced PR prolongation, 16.8% QTc widening, and 0.5% QRS widening. There were no significant correlations between ECG abnormalities and the ingested dose, plasma level of SVP, admission duration, time to reach the hospital, and PH.

Conclusion: The possibility of QT prolongation due to an overdose of the SVP anticonvulsant drug requires particular consideration.

Keywords: Electrocardiographic changes; Valporoic acid; Poisoning

Introduction

Valproate sodium (SVP) was first introduced as an anticonvulsant and has since seen its indications expanding in the treatment of epilepsy, anorexia nervosa, panic attack, anxiety disorder, post-traumatic stress disorder, migraine, bipolar disorder, mood stabilizer, acute episodes of mania, and acute stress reaction [1-3].

Nevertheless, SVP has various side effects such as intoxication, which may occur in therapeutic or high doses. What is now well-established is the cardiovascular toxicity of the older generations of tricyclic antidepressants and neuroleptics, with a delayed intraventricular conduction characterized by prolonged PR, QRS, and QT intervals on standard electrocardiography (ECG) accounting for the side effect most frequently encountered. The delayed conduction may give rise to complete heart block or ventricular reentry arrhythmia. One of these complications, or a combination of both, can be hazardous in overdose and may lead to death [4-6].

Intoxication with SVP is a growing concern on account of its ever increasing use and availability. The American Association of Poison Control Centers in 2000 reported in excess of 5000 calls due to acute SVP poisoning [7]. SVP intoxication may lead to cerebral, cardiovascular, respiratory, gastrointestinal, and hematological complications. Be that as it may, SVP use does not seem to be correlated with significant cardiovascular effects and ECG abnormalities. Accordingly, in the current study, we sought to describe a series of SVP intoxication cases by focusing on ECG findings.

Methods

Between February 2011 and February 2012, this cross-sectional study was conducted at Loghman-Hakim Poison Hospital (LHPH), a referral center for intoxications in Tehran, Iran. All consecutive patients who referred to LHPH complaining of poisoning and subsequently diagnosed with SVP intoxication were enrolled. The study protocol was approved by the Ethics Committee of the Human Research Department, Tehran University of Medical Sciences.

Apart from the patients' age and sex, information was meticulously recorded on each subject's history of SVP use, comprising the indication for use, formulation, total daily use, approximate number of pills ingested, and time of ingestion. Each patient's history also included whether the patient took SVP chronically with or without prescription and whether the ingestion was intentional (suicide attempt). The subjects' clinical symptoms and signs in the immediate post-ingestion hours were recorded at the Emergency Department. Additionally, data were recorded on admission duration, Intensive Care Unit (ICU) admission, and outcome (survival or death). All the patients were monitored for seizure, body temperature, consciousness level, respiratory rate, heart rate, oxygen saturation rate, blood pressure, ECG changes, arterial blood gases, electrolytes, liver function, blood cell count, and levels of blood glucose, BUN, and Cr. Associations between ECG abnormalities and the patients' clinical status and plasma

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Mean ± SD	
28.91 ± 11.24	Age
6.10 ± 7.10	Time to reach the hospital
6080.20 ± 5250.14	Reported dose
140.82 ± 153.93	Plasma level of Sodium Valproate
7.38 ± 0.07	pH
52.52 ± 29.40	PaO_2
24.88 ± 3.97	HCO_3
42.93 ± 8.78	$PaCO_2$
36.98 ± 0.33	Temperature
87.56 ± 15.99	Heart rate
16.39 ± 3.12	Respiratory rate
113.79 ± 15.79	Blood pressure
114.49 ± 50.04	Blood sugar
140.39 ± 3.45	Na
4.01 ± 0.43	K
8.70 ± 0.55	Ca
2.20 ± 0.29	Mg
24.55 ± 11.60	BUN
0.95 ± 0.22	Cr
23.63 ± 54.86	ALT
28.61 ± 46.83	AST
477.11 ± 375.43	LDH
418.62 ± 909.84	CPK
8.98 ± 3.67	WBC
227.87 ± 57.62	PLT

Table 1: The patients' clinical data at presentation.

levels of SVP (recorded in the first 24-hour period post ingestion) were investigated.

Copies of all ECGs were obtained at the Emergency Department and thereafter daily at the Admission Ward. ECG parameters (PR, QRS, and QT intervals) were manually measured. Because variations in the *QT interval* are correlated *with* the heart rate, the QT interval was corrected using the Bazett correction formula (QTc=QT/RR1/2) [8]. In addition, when the QT interval was measured in individual leads, the lead exhibiting the longest QT was employed [9].

A PR interval of 200 ms or longer was considered a prolonged PR; a QRS of 120 ms or longer a widened QRS; a corrected QT of 460 ms or longer in the women and 450 ms or longer in the men a prolonged QT interval; and a QT of 390 ms and shorter a short QT interval.

Statistical Analysis

All the continuous variables are presented as mean and standard deviation (SD). The Pearson correlation analysis was used to analyze the relations between admission duration, time to reach the hospital, reported dose, plasma level of SVP, PH, and electrolytes. Partial Spearman correlation was utilized to analyze the correlation between PR, QRS, and QTc categories with plasma electrolytes and admission duration. In all the analyses, a P value<0.05 was considered statistically significant.

Results

Between March 2011 and March 2012, a total of 194 patients with SVP poisoning were admitted to LHPH. There were 131 (67.52%) females at a mean age ± SD of 28.35 ± 10.90 years and 63 (32.48%) males at a mean age ± SD of 30.08 ± 11.92 years.

SVP was consumed by 23 women and 13 men for the treatment of epilepsy, convulsion, migraine, schizophrenia, autism, post-traumatic stress disorder, bipolarity, or attention deficit hyperactivity disorder. However, there were 188 cases of poisoning due to intentional ingestion.

Concerning the patients' consciousness level on arrival at the Emergency Department, conscious status or some degree of confusion was recorded for107 individuals, disorientation for 57, obtundation for 7, and comatose status for 4. Endotracheal intubation was performed for airway protection and adequate ventilation of the obtunded patients. Severe and moderate acidosis was observed in 2.9% and 12.3% of the study population, respectively.

Regarding ECG findings, the mean ± SD of PR, QRS, and QTc intervals was 148.02 ± 28.37, 64.20 ± 23.71, and 361.81 ± 63.84, correspondingly. All the subjects were in sinus rhythm. Also, 1.8% of the patients experienced PR prolongation, 0.6% QRS widening, 19.9% QTc prolongation, and 68.7% QTc shortening.

The Pearson correlation analysis demonstrated no significant correlations between ECG abnormalities and the reported dose, admission duration, plasma level of SVP, and PH (all P values>0.05). There was a significant correlation between the plasma level of SVP and admission duration (P value=0.015; correlation coefficient=0.237). In addition, admission duration was inversely affected by PH (P value= 0.044; correlation coefficient=-0.155). There were no statistically significant correlations between ECG abnormalities and the ingested dose, plasma level of SVP, admission duration, time to reach the hospital, and PH.

The Spearman correlation analysis, conducted to investigate the correlation between ECG abnormalities and the patients' conscious status, ingested dose, plasma level of SVP, time to reach the hospital, and PH, revealed no statistically significant associations (all P values>0.05).

Analysis via the independent t-test showed a significant association between the ICU admission and admission duration (P value=0.012). In addition, the association between acute ingestion and intubation and outcome constituted statistical significance (P value=0.000). The associations between the ICU admission and the ingested dose, plasma level of SVP, time to reach the hospital, and acute ingestion were not significant.

The principal treatment was symptomatic and supportive, focusing on the central nervous system and respiratory depression. Decontamination with activated charcoal and lavage were conducted for 77.6% and 22% of the patients, respectively. Multiple-dose activated charcoal was used for 2% of the study population with severe toxicity. Hemodialysis and whole bowel irrigation were not required [10].

Discussion

In the present study, the majority of the intoxication cases were in consequence of intentional ingestion. Most of these patients did not have a history of psychological problems and, most probably, had consumed the drug without prescription. Indeed, non-prescribed drug administration is deemed a major health concern in developing countries [11]. The distribution of patients in terms of gender was not equal in our study population: SVP intoxication was more frequent among the females and the most common age group was that between 17 and 39 years of age. Although the male-to-female ratio was 1:2.8, the age distribution was almost similar between the two sexes. However, the range was wider than that in the previous studies having reported that poisoning occurs more commonly among individuals between 21 and 30 years old and that it is more frequent among females [12].

Our findings revealed that severe toxicity did not occur in the majority of overdose cases: most of our patients experienced mild to moderate lethargy and recovered uneventfully. The mortality rate of SVP overdose was 0.51% in our study. The patients' mean plasma SVP concentration level at presentation was 140.82+/- 153.93 mg/L, which is lower than that in previous reports [13]. Nonetheless, the reported dose was much higher and did not correlate with the plasma level of the drug, which suggests that the patients or their companions failed to report the correct dose.

Antiepileptic drugs have been suggested to play a role in sudden unexpected death in epilepsy, which may occur due to the excessive risk of QT prolongation [14]. There is a dearth of data in the existing literature on the effects of SVP on ECG intervals. In patients with underlying cardiac disorders, Walczak et al. [15] did not observe ECG abnormalities during the intravenous administration of valproic acid as a fast infusion. In the current study, 19.9% of our patients experienced a prolonged QTc interval. Even though these results were obtained from the patients who had ingested the drug above the therapeutic dose, there was no correlation between a prolonged QTc and the ingested dose or serum concentration. Notably, the majority of our study population exhibited a shortened length of QTc. To the best of our knowledge, this finding has not been previously reported. Even so, short QTc values do not constitute a rare finding among healthy adults [16], and it has been reported that it is not allied to an increased risk for all-cause or cardiovascular mortality [17].

The effect of drugs on cardiac actions has been attributed to alteration in the different cardiac ionic currents during the action potential, which lengthens the QT interval [18]. Previous studies have reported a relation between electrolyte imbalances, including hypokalemia and hypomagnesemia, and the QTc interval, which decreases after the correction of electrolyte levels [19]. Our findings, however, do not chime in with those studies in as much as we found no correlation between the levels of serum electrolytes, including NA, K, Ca, and Mg, and the QTc length.

The prolongation of the ECG PR interval, when the PR exceeds 200 ms, is usually referred to as first-degree atrioventricular block [20]. In a case report, Nizam et al. reported that the PR interval had doubled 3 months after the initiation of Lacosamide, adjunctive treatment for partial-onset seizures, and that there was also concomitant second-degree atrioventricular block: both of these conditions were resolved after the discontinuation of Lacosamide [21]. Elsewhere, Matsuo *et al.* reported a mean 5-ms rise in the PR interval in their epilepsy patients, randomized to receive retreatment with the anticonvulsant drug, Lamotrigin [22]. In contrast, we did not observe any increase in the mean value of the PR intervals, even in those who had consumed high doses of SVP.

The present study has a major limitation in that its study population was comprised of patients with SVP intoxication without any adjustment for the effect of background factors and consumption of other drugs.

Conclusion

The possibility of QT prolongation secondary to an overdose of the SVP anticonvulsant drug requires particular consideration.

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