Electrocardiographic Manifestations of Benzodiazepine Toxicity

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Received: 03.04.2013 *Accepted: 16.04.2013*

ABSTRACT

Background: The aim of this study was to evaluate and compare the clinical and electrocardiographic (ECG) manifestations of benzodiazepines (BZs).

Methods: In this retrospective study, all BZ-poisoned patients hospitalized at Loghman Hakim Hospital between September 2010 and March 2011 were evaluated. Patients' information including age, sex, time elapsed between the ingestion and presentation, and type of the BZ used were extracted from the patients' charts and recorded. ECGs on presentation to the emergency department (ED) were evaluated and parameters such as PR interval, QRS duration, corrected QT, amplitude of S wave in lead I, height of R wave and R/S ratio in the lead aVR were also measured and recorded.

Results: Oxazepam, chlordiazepoxide, lorazepam, alprazolam, diazepam, and clonazepam were ingested by 9 (3%), 13 (4.4%), 29 (9.9%), 105 (35.8%), 65 (22.2%), and 72 (24.6%) patients, respectively. Mean PR interval was reported to be 0.16 ± 0.03 sec and PR interval of greater than 200 msec was detected in 12 (4.5%) patients. Mean QRS duration was 0.07 ± 0.01sec and QRS≥120 msec was observed in 7 (2.6%) cases.

Conclusion: Diazepam is the only BZ that does not cause QRS widening and oxazepam is the only one not causing PR prolongation. It can be concluded that if a patient refers with a decreased level of consciousness and accompanying signs of BZ toxicity, QRS widening in ECG rules out diazepam, whereas PR prolongation rules out oxazepam toxicity.

Keywords: Benzodiazepines, Electrocardiogram, Manifestations, Poisoning.

IJT 2014; 952-955

INTRODUCTION

As a subgroup of sedative-hypnotics, benzodiazepines (BZs) were introduced in the early 1960s and due to their relatively low adverse effects; they became popular and came to be widely used [1]. Ease of access and wide usage of these medications have put them within the fifth common groups of medications causing death due to overdose [1, 2]. In the setting of their toxicity, common signs are respiratory and nervous system depression. Cardiovascular toxicity with BZs alone is not common. Although few changes in cardiovascular or electrocardiogram are seen, the prognosis is considered to be good. However, in physical examination, no specific characteristic is defined to discriminate one from the others [1, 3, 4]. Most of the reported cases of BZ toxicity that cause electrocardiographic (ECG) manifestations are those with alprazolam overdose whose main ECG manifestations are sinus tachycardia and AV block that its relationship with flumazenil administration has not yet been determined [5-9]. Other reported cases are those intoxicated by clonazepam who have experienced first-degree AV block [6]. This study evaluated and compared the clinical and ECG manifestations of BZ medications.

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MATERIALS AND METHODS

In this retrospective study, all BZ-poisoned patients who had referred to and been hospitalized at Loghman Hakim Hospital between September 2010 and March 2011 were evaluated. Those older than 12 with history of BZ ingestion whose first 12-lead ECG had been obtained on presentation and was present in their medical charts were included in the study. Patients with multidrug ingestion (use of different types of BZs), underlying cardiac disease, hypertension, and addiction were excluded. Inclusion and exclusion of the cases were based on history and urine drug screening tests. Patients' information including age, sex, time elapsed between drug ingestion and Emergency Department (ED) presentation, type of the BZ used, vital signs, arterial blood gas analyses, sodium (Na), potassium (K), creatinine (Cr) and blood sugar (BS), were recorded on presentation. The patients' first ECG (on presentation to ED) was evaluated and parameters such as PR interval, QRS duration, corrected QT (QTc), height of R wave, R/S ratio in the lead aVR, amplitude of S wave in the lead I, and R/S ratio in the lead aVR were measured and recorded. Other ECG findings including dysrhythmias, T-wave inversion, J-point elevation, early repolarization, and right bundle branch block (RBBB) were also noted. ECG interpretations were all supervised by a single cardiologist.

The collected data was entered into the standardized forms and analyzed by statistical tests such as Kolmogorov-Smirnov, Mann-Whitney U test, and Pearson's Chi-Square or Fisher's exact test, using SPSS software version 17. A P-value less than 0.05 was considered to be statistically significant. This study was approved by the Regional Ethical Committee.

RESULTS

Of a total of 293 patients enrolled in this study, 189 (64.5%) were female and 104 (35.5%) were male. Mean age was 29±10 years (range: 12 to 86 years). The time elapsed between the ingestion of the BZ and ED presentation was determined in 256 patients. This time was reported to be 5.49± 9.24 hours (range, 0.5 to 96 hours). Oxazepam, chlordiazepoxide, lorazepam, alprazolam, diazepam, and clonazepam were ingested by 9 (3%), 13 (4.4%), 29 (9.9%), 105 (35.8%), 65 (22.2%), and 72 (24.6%) patients, respectively. Vital signs, arterial blood gas analyses, Na, K, Cr, and BS upon presentation are shown in Tables 1 and 2.

Table 1. Mean vital signs, arterial blood gas analyses, Na, K, Cr, and BS on presentation in all patients.

Parameter	Mean
Temperature©	36.9±0.29
Respiratory Rate (/min)	17±3
Pulse Rate (/min)	82±9
Systolic B.P (mmHg)	109±8
Diastolic B.P (mmHg)	71±7
PH (ABG)	7.38±0.05
PCO2 (ABG)	41.62±6.53
Bicarbonate (ABG)	25.18±3.31
Sodium (Na)(mg/dl)	142±4
Potassium (K)(mg/dl)	4±0.5
Creatinine (Cr)(mg/dl)	0.9±0.2
Blood Sugar (BS)(mg/dl)	94±30

Mean PR interval was 0.16±0.03 sec and a PR interval of greater than 200 msec was seen in 12 (4.5%) patients. Mean QRS duration was reported to be 0.07±0.01 sec and QRS duration ≥ 120 msec was detected in 7 (2.6%) cases. Mean QTc was 0.40±0.04 sec and a QTc ≥ 450 and ≥ 460 msec was noticed in 16 men (15.38%) and 21 women (11.1%), respectively (10). Mean height of R wave in the lead aVR was 0.59±0.94 mm and height of R>1mm in this lead was seen in 47 (18%) patients. Mean R/S ratio was 0.12 ± 0.25 and R/S ratio>0 was noted in 112 cases (42.9%). Incomplete RBBB, T-wave inversion, complete RBBB, early repolarization, and J-point elevation were noticed in 7 (2.4%), 3 (1%), 2 (0.7%), 11 (3.8%), and 7 (2.4%) patients, respectively. Mean heart rate (HR) was 81±15 bpm and HR>100 bpm was seen in 22 (8.2%) cases. Dysrhythmia was detected in none of the cases.

Table 2. Mean vital signs, arterial blood gas analyses, Na, K, Cr, and BS on presentation in BZ groups.

	Diazepam	Oxazepam	Chlordiazepoxide	Lorazepam	Alprazolam	Clonazepam
Temperature©	36.8±0.3	36.8±0.2	36.8±0.5	36.9±0.2	36.8±0.2	37±0.2
RespiratoryRate(/min)	16±3	15±3	18±4	16±2	17±3	16±3
Pulse Rate (/min)	81±8	79±7	80±10	83±8	81±9	81±10
Systolic B.P(mmHg)	109±9	107±9	110±12	109±8	110±7	107±7
Diastolic B.P (mmHg)	72±7	68±10	72±7	71±8	71±7	69±6
PH (ABG)	7.38±0.05	7.39±0.06	7.40±0.06	7.39±0.5	7.38±0.4	7.39±0.4
PCO2 (ABG)	41±5	38.6±7	39.7±8	41.6±8	42±6	42±7
Bicarbonate (ABG)	25±3	23.5±3	24.5±4	25±4	25±3	25±4
Sodium (Na)(mg/dl)	142±3	142±4	142±5	141±4	141±4	142±4
Potassium (K)(mg/dl)	4.1±0.5	4.1±0.5	4.1±0.3	4.3±0.8	4±0.5	4.1±0.5
Creatinine(Cr)(mg/dl)	0.9±0.2	0.8±0.07	0.9±0.2	0.9±0.1	0.9±0.1	0.9±0.2
Blood Sugar (BS)(mg/dl)	94±29	91±17	97±20	86±21	94±31	97±35

In the patients poisoned by oxazepam, mean PR interval was 0.14±0.02 sec (range: 0.12 to 0.2 sec) and no case of PR interval greater than 200 msec was detected (P<0.04). In the diazepam group, mean QRS duration was 0.07±0.01 sec (range: 0.04 to 0.12 sec) and a QRS duration≥120 msec was seen in only 2 (3.4%) cases (P<0.04). Moreover, a statistically significant difference was detected between sex and incomplete RBBB (P<0.001). All patients with incomplete RBBB were male. There were not any significant relationships between hyperthermia (T>38.1Ċ), hypothermia (T<35Ċ), tachypnea (RR>20/min), bradypnea (RR<12/min), tachycardia (HR>100/min), bradycardia (HR<60/min), creatinine level, hypernatremia (Na>145meq/l), hyponatremia (Na<135meq/l), hyperkalemia (K>5meq/l), hypokalemia (K<3.5meq/l), hyperglycemia (blood sugar>200mg/dL), hypoglycemia (blood sugar<70mg/dL), ABG disturbance, and ECG disturbances on one side and the type of the BZ used on the other side.

DISCUSSION

According to the obtained results, 15.38% of the male and 11.1% of the female cases had QTc prolongation (10). Previous studies have shown that some ECG changes can be seen in cases of toxicity with BZs, e.g. alprazolam and clonazepam [5-9]. Based on the findings of the present study, oxazepam is different from other BZs in PR interval (P<0.04) while diazepam is different from others in QRS duration (P<0.04). Regarding other ECG parameters, no significant relationship was seen among different BZs. It was also shown that the type of BZ toxicity could not be diagnosed considering ECG parameters. Since ECG findings including early repolarization, RBBB, J-point elevation, and T-wave inversion were seen in few cases, significant relationships between these findings and other parameters could not be detected.

Lack of measurement of plasma level concentration of BZs is certainly a limitation of our study. Moreover, except for Na and K, other electrolyte disturbances that may affect ECG parameters were not considered in this study.

CONCLUSION

Based on the findings of this study, it can be concluded that only diazepam does not cause QRS widening and only oxazepam does not cause PR prolongation. The comparison among these five BZs suggests that in the event of decreased level of consciousness and

the presence of signs of toxicity with BZs, if QRS widening and PR prolongation are detected in ECG, the possibility of toxicity with diazepam and oxazepam can be ruled out, respectively.

ACKNOWLEDGEMENTS

The authors would like to thank the staff of Loghman Hakim Hospital who assisted us in doing this study.

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