The influence of carbamazepine plasma level on blood pressure and some ECG parameters in patients with acute intoxication

Krzysztof Ciszowski1
Dorota Szpak1
Bartosz Jenner2

Background: Carbamazepine (CBZ) is an antiepileptic drug with tricyclic structure which implies its potential cardiotoxic properties, especially in acute poisoning. Aim: To evaluate some cardiovascular effects connected with CBZ toxicity and to find the relation between them and CBZ plasma level. Material and methods: 34 patients (18 males, 16 females; median age 24.5) hospitalized in our Department in 1996-1997 and 2005-2006 due to acute CBZ poisoning. Analysis included following parameters: systolic (SBP) and diastolic (DBP) blood pressure, ECG parameters: heart rate (HR), duration of QRS complex, PQ interval and corrected QT interval (QTc) calculated with Bazett’s (QTcB) and Hodges’s (QTcH) formulas. These parameters were compared with reference values for general population available in the literature. Relations between above mentioned parameters and CBZ plasma level were studied by means of Generalized Additive Model (GAM). Results: The reference values were exceeded most often for QRS (62%), DBP and QTcB (53%, both) and SBP (50%). The mean number of parameters with exceeded norms was 3.1 per patient (SD=1.71). We failed to find any significant correlation between CBZ plasma level and any of the studied parameters. Positive correlation between SBP and DBP (r=0.68; p<0.001) and negative correlation between QRS and HR (r=-0.50; p=0.003) were found. Conclusion: CBZ could affect different cardiovascular parameters which should be monitored in cases of acute drug poisonings.

Adres do korespondencji:
Krzysztof Ciszowski
Oddział Toksykologii i Chorób Środowiskowych
WSS im. L. Rydygiera
31-826 Kraków, Os. Złotej Jesieni 1
tel./fax: 012 646 89 85
e-mail: wt_poohatek@wp.pl

Introduction
Carbamazepine (CBZ) is a drug commonly used in the treatment of seizures, different neuralgias and certain affective disorders. Chemically, it is an iminostilbene derivative with a structure very similar to tricyclic antidepressants. This structure implies its potential cardiotoxicity especially in cases of acute poisonings. The symptoms of acute CBZ intoxication include cardiovas-
cular effects: tachycardia, hypotension, ECG changes (ventricular extrasystoles, varying degrees of atrioventricular block, QRS interval and corrected QT prolongation) [22,25], as well as coma, hyperirritability, convulsions, respiratory depression [7], nystagmus and ataxia [17]. Some authors consider that cardiac arrhythmias and other cardiovascular complications of CBZ overdose are rare [23,24], but the risk of their occurrence is higher with CBZ plasma level exceeding 40 mg/L [13]. Serum levels below 40 mg/L do not appear to accurately predict the severity of toxicity [24].

The purpose of our study was to evaluate some cardiovascular effects connected with carbamazepine toxicity and to find out the relations between them and drug plasma level.

Materials and methods

Patients

The study group consisted of 34 patients (18 males and 16 females, aged from 15 to 55 with median 24.5). Data were obtained by retrospective analysis of medical records of patients treated in our Department in 1996-1997 and 2005-2006, because of acute CBZ mono-intoxication. Each patient had toxic CBZ plasma level exceeding 12 mg/l. Cases of mixed intoxications with CBZ and other drugs and/or ethanol were excluded from the study.

CBZ determinations

Toxicological determinations of plasma CBZ were performed in blood samples taken at admission. Determinations were done using the fluorescence polarization immunoassay method with apparatus AxSym (Abbott). In the study group CBZ concentration ranged from 16.2 to 70.5 mg/L (mean 32.5 mg/L SD=11.0). The therapeutic concentrations are between 4 and 12 mg/L and all results over 12 mg/L were considered as toxic concentrations.

Cardiovascular and ECG parameters

Systolic (SBP) and diastolic (DBP) blood pressures were obtained from physical examination of each patient at admission. Electrocardiographic parameters were obtained from ECG records of each patient carried out at admission to the hospital. The following parameters were measured manually: heart rate (HR), the duration of QRS complex, PQ and QT intervals. The corrected QT (QTc) was calculated using the Bazett’s formula:

\[ \text{QTc} = \frac{\text{QT}}{\sqrt[4]{\text{RR}}} \] [3]

and Hodges formula:

\[ \text{QTc} = \frac{\text{QT} + 1.75 \times (\text{HR} - 60)}{2} \] [12]

All the parameters were compared with reference values obtained from the literature and collected in table I. Because of lack of generally accepted lower limit of DBP we assumed it as 60 mmHg.

Statistics

To find out if ECG parameters correspond with CBZ plasma level general additive model (GAM) [1] was used. This type of modeling permits to investigate nonlinear dependencies. Relation between level of CBZ and the time of hospitalization was studied by means of the Cox regression model [11].

Results

Figure 1 illustrates percentage of CBZ poisoned patients with abnormal measurements of each of investigated cardiovascular parameters. The data suggest that the reference values were exceeded most often for QRS (62% of studied patients), DBP and QTcB (53%, both) SBP (50%). Least often norms were exceeded for PQ (24%). The majority of parameters exceeded only the upper limit of the range of reference values. In case of PQ, 21% of patients had measurements above the upper limit but there was also one patient with measurement below the lower limit.

Figure 2 presents a histogram of number of patients with exceeded norms for investigated cardiovascular parameters. The distribution seems to be convex and symmetrical around value of 3. That is, 3 is the mode of this distribution - 26% of patients have 3 cardiovascular parameters with exceeded norms. In the set of patients one of them had none of the investigated parameters out of norm limits. Mean number of exceeded norms per patient was 3.1 (SD=1.71), 15% of patients had all 6 parameters exceeded.

Figure 3 is a path diagram summarizing dependencies among studied parameters. Parts of variances of parameters explained...
the correlation between QTcB and QTcH was and HR (r= -0.49; p=0.003). Not surprisingly p<0.001) and a negative one between QRS (p=0.1280). Figure 3 shows how long patients hospitalized due to poisoning with CBZ stay in hospital - the curve is calculated from the Cox regression model. Median time of hospitalization for patients who at admission have an average (32.5 mg/L) concentration of CBZ is about 6 days. Our study suggests that elevated CBZ plasma level is associated with patient’s longer stay in hospital. That is, increase in CBZ plasma level by 1 mg/mL is associated with 3% decrease of the risk of leaving out the hospital (p=0.1280).

Discussion
Carbamazepine, as it was previously mentioned, has tricyclic structure which could be connected with strong cardiotoxicity. Its impact on the blood pressure and cardiac chronotropism is the part of anticholinergic toxidrome explaining the possibility of CBZ to cause hypertension and tachycardia [10,21]. Anticholinergic effects such as tachycardia, mydriasis, confusion, decreased bowel activity, and dry, flushed skin are often seen. However the full constellation of findings of the classic anticholinergic toxidrome does not commonly develop [20]. In the case series of CBZ-poisoned patients tachycardia was seen in less than 50 per cent of patients [13], which is similar to our observations (41%). Hypertension or hypotension has also been documented in patients with either therapeutic or toxic blood levels of CBZ. It is possible that CBZ-induced hypertension in those with therapeutic blood levels is rarely seen because most of the patients who begin treatment are young and do not have baseline hypertension [19]. In the present study the hypertension was seen in 50% of cases, but there was nobody with hypotension induced by CBZ intoxication.

CBZ may affect the cardiac conductance of stimuli causing different electrocardiographically important disturbances. The following abnormalities in ECG were seen after CBZ overdose: sinus tachycardia, atrioventricular block, long PQ segment, long QRS complex, long QT segment, supraventricular tachycardia, bradycardia, wide QRS tachycardia, ventricular fibrillation [20]. The PQ lengthening may occur even at therapeutic CBZ plasma levels. Kenneback G. et al. found that at the highest CBZ dose (800 mg/day), which gave plasma concentrations within the upper therapeutic range, the PQ interval was mildly prolonged (151 ms; p<0.01) [14]. The mechanism responsible for PQ prolongation is the ability of CBZ to block the sodium channels, which is similar to the action of class 1A of antiarrhythmic drugs [14,15]. We observed PQ prolongation in 21% in patients with toxic concentrations of CBZ. There was also one case of shortening of PQ, which was not reported in literature till now.

The QRS widening after CBZ poisoning seems to be relatively common finding (more than 60% in our study). It is also connected with CBZ properties to block the sodium channels, which is the major cardiotoxic effect of TCA poisoning. The ECG changes seen with a TCA overdose predict the risk of an adverse event. A QRS width of >0.16 s indicates a high risk of developing ventricular dysrhythmias [4].

The Qtc interval is a heart rate-corrected value that represents the time between the onset of electrical depolarization of the ventricles and the end of repolarization. CBZ intoxication may contribute to the prolongation of QTc [8], however it was not observed in patients treated with CBZ in therapeutic ranges. The mean QTC of 34 children with carbamazepine/oxcarbazepine

CBZ may affect the cardiac conductance of stimuli causing different electrocardiographically important disturbances. The following abnormalities in ECG were seen after CBZ overdose: sinus tachycardia, atrioventricular block, long PQ segment, long QRS complex, long QT segment, supraventricular tachycardia, bradycardia, wide QRS tachycardia, ventricular fibrillation [20]. The PQ lengthening may occur even at therapeutic CBZ plasma levels. Kenneback G. et al. found that at the highest CBZ dose (800 mg/day), which gave plasma concentrations within the upper therapeutic range, the PQ interval was mildly prolonged (151 ms; p<0.01) [14]. The mechanism responsible for PQ prolongation is the ability of CBZ to block the sodium channels, which is similar to the action of class 1A of antiarrhythmic drugs [14,15]. We observed PQ prolongation in 21% in patients with toxic concentrations of CBZ. There was also one case of shortening of PQ, which was not reported in literature till now.

The QRS widening after CBZ poisoning seems to be relatively common finding (more than 60% in our study). It is also connected with CBZ properties to block the sodium channels, which is the major cardiotoxic effect of TCA poisoning. The ECG changes seen with a TCA overdose predict the risk of an adverse event. A QRS width of >0.16 s indicates a high risk of developing ventricular dysrhythmias [4].

The Qtc interval is a heart rate-corrected value that represents the time between the onset of electrical depolarization of the ventricles and the end of repolarization. CBZ intoxication may contribute to the prolongation of QTc [8], however it was not observed in patients treated with CBZ in therapeutic ranges. The mean QTC of 34 children with carbamazepine/oxcarbazepine

CBZ may affect the cardiac conductance of stimuli causing different electrocardiographically important disturbances. The following abnormalities in ECG were seen after CBZ overdose: sinus tachycardia, atrioventricular block, long PQ segment, long QRS complex, long QT segment, supraventricular tachycardia, bradycardia, wide QRS tachycardia, ventricular fibrillation [20]. The PQ lengthening may occur even at therapeutic CBZ plasma levels. Kenneback G. et al. found that at the highest CBZ dose (800 mg/day), which gave plasma concentrations within the upper therapeutic range, the PQ interval was mildly prolonged (151 ms; p<0.01) [14]. The mechanism responsible for PQ prolongation is the ability of CBZ to block the sodium channels, which is similar to the action of class 1A of antiarrhythmic drugs [14,15]. We observed PQ prolongation in 21% in patients with toxic concentrations of CBZ. There was also one case of shortening of PQ, which was not reported in literature till now.

The QRS widening after CBZ poisoning seems to be relatively common finding (more than 60% in our study). It is also connected with CBZ properties to block the sodium channels, which is the major cardiotoxic effect of TCA poisoning. The ECG changes seen with a TCA overdose predict the risk of an adverse event. A QRS width of >0.16 s indicates a high risk of developing ventricular dysrhythmias [4].

The Qtc interval is a heart rate-corrected value that represents the time between the onset of electrical depolarization of the ventricles and the end of repolarization. CBZ intoxication may contribute to the prolongation of QTc [8], however it was not observed in patients treated with CBZ in therapeutic ranges. The mean QTC of 34 children with carbamazepine/oxcarbazepine
monotherapy was 0.39±0.02 [16]. We found QTc prolongation >500 ms in 12 cases (35%) for QTcF and 1 case (3%) for QTcH. Prolongation of the QTc interval is a surrogate marker for the ability of a drug to cause torsade de points (TdP). In individual patients an absolute QTc interval of >500 ms or an increase of 60 ms from baseline is regarded as indicating an increased risk of TdP. All drugs known to cause TdP block the rapidly activating component of the delayed rectifier potassium current (I_K) [9]. Authors did not find in the literature any cases of TdP induced by CBZ overdose.

Preexisting cardiovascular disease may be a risk factor for CBZ-induced dysrhythmias, though cardiotoxicity can also be seen in patients with no previous cardiac history [20]. Our study confirms that hypothesis only indirectly, because the study group consisted of young patients with median age of 24.5 years, probably without any cardiovascular problems. However, we have not sufficient data about previous cardiac pathologies of the studied patients.

All the investigated cardiovascular parameters did not correlate with the CBZ plasma concentration, which was similar to Apfelbaum J.D. et al. observations [2].

Increased serum levels of CBZ did appear to correlate with increased hospital stay [24]. It was confirmed in our study, because we found that increase in CBZ plasma level by 1 mg/mL is associated with 3% decrease of the risk of leaving out the hospital.

Conclusion
Poisonings with CBZ may cause different cardiovascular complications but assessment of severity of CBZ cardiotoxicity should be based on clinical and ECG features rather than CBZ plasma level.