CASE REPORT

Carbamazepine-Induced Sinus Node Dysfunction

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ABSTRACT. Carbamazepine, a drug used for the treatment of epilepsy and neuralgias, may exert hazardous effects on the cardiac conduction system. We report such a case of symptomatic brady-arrhythmia occurring in a 43-years-old male while on therapy with carbamazepine. Additionally, a literature review is made of previous cases of carbamazepine-induced sinus node, AV node and His-Purkinje conduction disturbances. *Key Words: Carbamazepine, Cardiac arrhythmia, Sinus node dysfuction, Epilepsy*

Carbamazepine (Tegretol)* is an anticonvulsant, structurally related to tricyclic antidepressant drugs. It is widely prescribed in neurological and psychiatric disorders, particularly as a first-line drug for various types of epilepsy (complex and generalized seizures) and painful neuralgias, such as trigeminal neuralgia. Recently, it has assumed a role in the treatment of lithium-nonresponding bipolar affective disorders.

Carbamezepine may exert adverse cardiovascular system effects and dysfunction in some patients. The most characteristic of these effects, occurring in certain predisposed individuals, are dizzy spells, syncope, Stokes-Adams attacks, hypertension and hypotension, circulatory collapse, and even death, secondary to its causation of ill effects on the cardiac conduction system, namely sinus node dysfunction and atrioventricular (AV) conduction disturbances. These secondary arrhythmia complications are rare but are well-established from medical literature reports (1-7).

We report a symptomatic bradyarrhythmia occurring in a 43-year old male, with therapeutic and subtherapeutic plasma levels of carbamazepine.

Case Report

A 43 year-old male was admitted to the Centro Cardiovascular de Puerto Rico y del Caribe from a penal institution, because of a four months' history of dizziness, stabbing chest pains, mild dyspnea and cold sweating. He had a history of epilepsy since childhood, for which he had been taking phenytoin (Dilantin)†. Four months prior to his hospital admission phenytoin was discontinued and carbamazepine, 200 mg p.o. twice daily was started. His symptoms dated from this time of the change in medication. Dizziness was most prominent and persistent. There was no history of loss of consciousness and the family history was negative. The patient's blood pressure was 100/70 mm Hg; the radial pulse was 42 bpm, and the heart rhythm was regular at that time. The neurological examination was normal. The hemoglobin and hematocrit were normal, as were cardiac enzymes. A chest x-ray revealed cardiomegaly, the electroencephalogram (EEG) was normal, the HIV test was negative. Blood levels of cocaine, opiates, phencyclidine (PCP) and benzodiazepine were negative.

In the hospital, the patient was continued on carbamazepine 200mg twice daily. Continuous bedside telemetry electocardiographic monitoring was maintained, and a 24 hour Holter ECG was obtained. The electrocardiographic (ECG) tracings as illustrated in figures 1-4 showed continuous marked sinus bradycardias, sinus arrhythmias and sinus pauses. Telemetry ECG monitoring showed bradycardias and sinus pauses, with heart rates of 20-22 bpm while sleeping, with periodic rises in the rates. The longest sinus pause, among many, in the Holter study (performed 5 days after hospital admission) was 3.2 seconds. Eight days after admission, weaning from the carbamazepine was initiated, and

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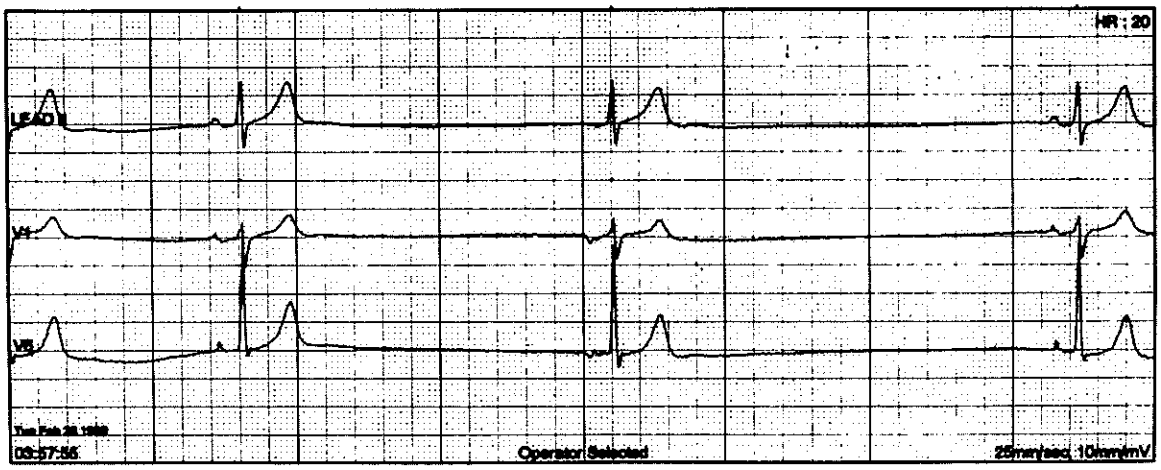

FIGURE 1. Holter ECG. Marked sinus bradycardia, sinus pauses/ arrest. The longest interval is 3.25 sec, reflecting a minimal heart rate of 18.5 bpm. Such a slow sinus rate suggests 2:1 sinoatrial block. The second, center, beat, is a low atrial or high junctional escape beat.

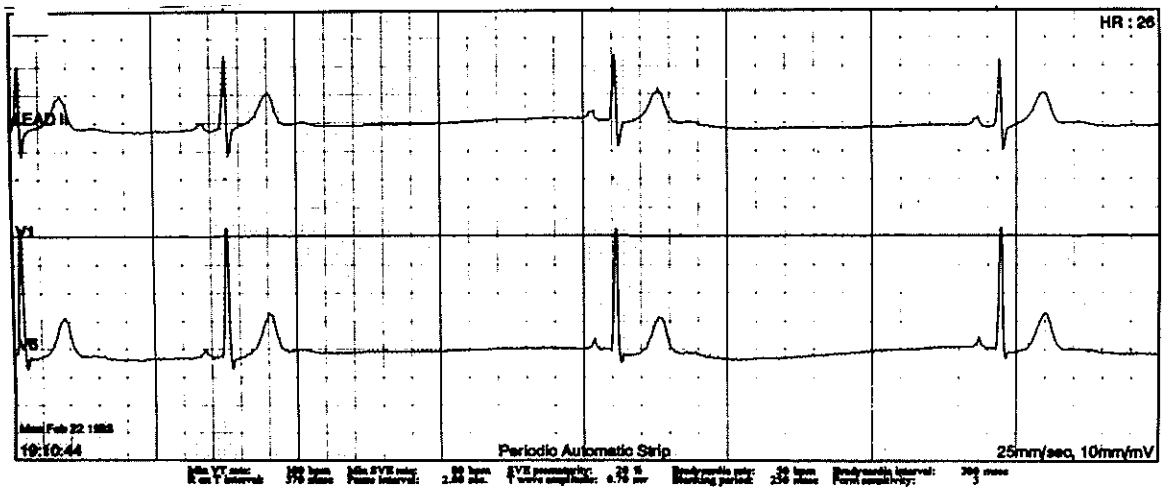

FIGURE 2. Holter ECG. Marked sinus bradycardia, a 2.7 sec. pause =22.2 bpm.

subsequently discontinued. He was then started on divalproex sodium ‡ (Depakote). Two days later, the carbamazepine plasma level was 7.58ug/ml (therapeutic 4-10 ug/ml, toxic>10ug/ml), and four days later it was 3.32 ug/ml. Unfortunately, a carbamazepine plasma level was not done earlier during the hospital course while taking the medication (when the level would most likely have been higher), since adverse effects secondary to the medication were not initially suspected. He had no further dizziness or symptom and during the several days of his hospitalization, he persisted with heart rates in the high 30's, and 40's bpm, with sinus pauses of 2.8 seconds. Subsequently, the heart rates rose to about 50 bpm and to 60-70- bpm when exercising. No seizures occurred, and he remained asymptomatic.

‡ Abbott, Abbott Park, IL, USA

Discussion

Carbamazepine-induced sick sinus syndrome, sinus node dysfunction and AV conduction disturbances have been reported in recent years, but such adverse effects appear to be under-recognized by medical practitioners. These complications have been mainly reversible and occurring in middle-aged and elderly adults, especially older females. The ECG abnormalities which have been linked to carbamazepine are listed in Table I. Kasarskis and

Table 1. Carbamazepine Induced ECG Abnormalities*

Sinus Node	Sinus tachycardia
	Sinus bradycardia
	Sinoatrial block
	Sinus arrest
	Sinus pauses
	Bradycardia-Tachycardia syndrome
	Atrial escape beats
A-V Node	First degree AV block (P-R interval prolongation)
	Second degree AV block - types I, II, high degree
	Complete AV block
	Asystole
	Junctional bradycardia, idionodal escape rhythms
	May unmask a latent sinus nodal or AV nodal defect
Intraventricular	Right bundle branch block
	Left anterior fascicular block
	Bifascicular block
	Suppression of ventricular automaticity
	QRS and QT prolongation
	Cardiac arrest

*References 3-36.

associates (5) in 1992, reported a patient with carbamazepine-induced sinus bradycardia, sinus pauses and AV blocks. They compiled a review and analysis of 25 previously reported cases. These authors mention another 11 cases of elderly patients with bradyarrhythmias reported by the manufacturer since 1972. A few other patients with sinus bradycardia have been observed.

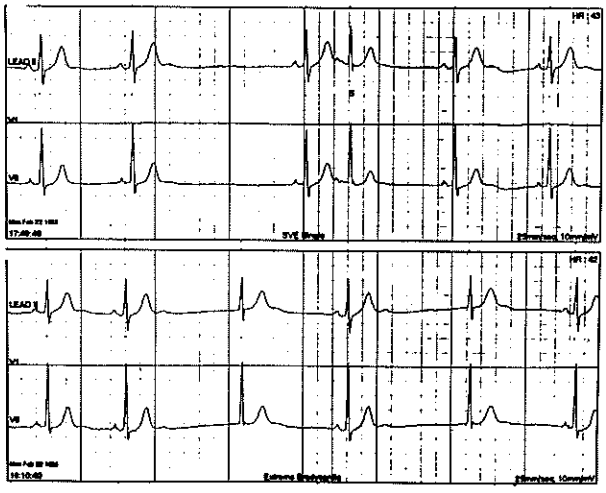

FIGURE 3. Holter ECG. Top panel, a 2.3 sec. pause = 25.9 bpm. The fourth beat is an atrial premature contraction. Bottom panel - Sinus bradycardia and arrhythmia.

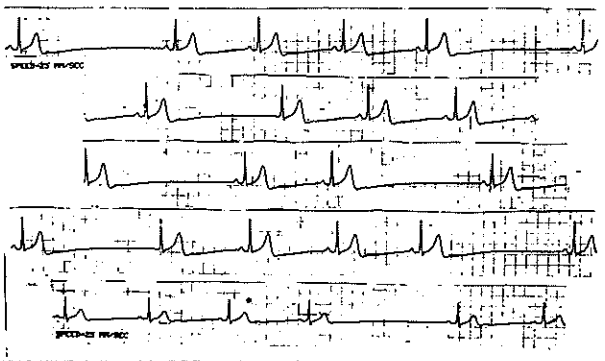

FIGURE 4. Bedside ECG monitor tracing. The upper four strips are continuous. Marked sinus bradycardia and arrhythmia. The longest pause is 2.96 sec. = 20.3 bpm. Two of the pauses are terminated by low atrial/high junctional escape beats. The bottom strip shows sinus bradycardia and arrhythmia, with a sinus arrest of 2.76 sec. = 21.7 bpm.

Other cases not included or noted in their extensive review are those of:

a. Stone and Lange, 1986 (6), who suffered ventricular asystole, syncope and death.
b. Takayanagi et al, 1990 (8), with the bradycardia-tachycardia syndrome, showing sinus bradycardia and junctional escape beats.
c. Kenneback and associates (1991) in individuals with preexistent abnormalities of the cardiac conduction system noted the clinical hazards of the administration of carbamazepine: suppression of sinus node function, AV conduction and intraventricular conduction disorders, and induction of symptoms confusingly similar to the epileptic seizures that the medication was used to prevent (9).
d. Hantson et al, 1993 (10), observed conduction disturbances (asystole, Mobitz type I and II second degree AV block) during carbamazepine therapy for neuralgia following the Guillain-Barré syndrome. They found less than 10 cases of severe cardiac dysrhythmias reported in the medical literature, almost all of which had preexisting conduction abnormalities. They noted that the cardiac effect occurred shortly after oral administration or after several years, and that there was no relation between plasma levels and cardiac toxicity.
e. Weig and Pollack, 1993 (11), documented a young child (the second case of a child) with tuberous sclerosis and cardiac rhabdomyoma who developed reversible AV block after being placed on carbamazepine treatment for complex partial seizures (12).
f. Cardiac conduction disturbances have been observed in younger adults with myotonic dystrophy taking both phenytoin and carbamazepine (13), and in a child

taking both erythromycin and carbamazepine (14).

g. Steckler (1994) recently called attention to a possible role for carbamazepine in lithium-induced sinus node dyfunction. She reported 5 cases of lithium-associated sinus node dysfunction from a large state mental hospital (a 9-year experience); four of the 5 patients had been treated concurrently with carbamazepine (15).

However, Puletti et al's 1991 review of 92 patients on carbamazepine therapy with age range of 7 to 77 years, found no evidence of sinoatrial or AV cardiac conduction disturbances, and they concluded that the overall incidence of cardiac toxicity and conduction disorders was rare and do not occur in younger patients (3).

Electrophysiological Effects of Carbamazepine. Carbamazepine has been shown in normal dogs to prolong A-V conduction and to decrease ventricular automaticity (30). In patients with preexisting AV block, therapeutic levels of the drug markedly suppressed the time it took to initiate an idioventricular rhythm (20). Kenneback and associates (9) carried out standard and long-term ECG monitoring and invasive electrophysiologic testing in 10 patients taking carbamazepine for neurological disorders who had also abnormalities of the cardiac conduction tissues.

Effects observed, at the sinus node, AV node and His-Purkinje system, were:

a. Negative chronotropic effects.
b. Negative dromotropic effects: AV conduction delay; prolongation of the PQ interval Of 16 msec.
c. H-V interval prolongation.
d. Carbamazepine is included in the class IA (Quinidine) group of antiarrhythmic drugs. It has been shown to possess antiarrhythmic action (30).
e. But, at normal heart rates, there was a lack of effects on the QRS, J-T and Q-T intervals, a class IB (Lidocaine group) characteristic.
f. An elevation in the ventricular and atrial myocardial pacing/stimulation thresholds, in accord with the drugs having class I antiarrhythmic properties (plasma level 21 umol/L) (31).

The cardiac conduction disturbances secondary to carbamazepine have transpired both at the initiation of therapy and after long term treatment. Some of the cases resulted from an overdose scenario, but other cases occurred during routine administration of the medication. The adverse conduction disturbances have occurred in the presence of subtherapeutic and therapeutic serum levels of the drug, as well as in the presence of massive overdose levels. However, there may be some, yet poor, correlation between the dose - blood concentrations of the drug and conduction defects. Several reports found a correlation between the serum concentration and the frequency of sinus arrests (8,9,10,13,16,36).

As a result of possible carbamazepine adverse effects, preventive guidelines have been proposed , as shown in Table 2.

Table 2. Preventive Guidelines - Carbamazepine*

Avoid carbamazepine in patients in whom conduction disturbances are likely to occur, like muscular dystrophy, Guillian-Barré, etc.
Perform cardiac evaluation and baseline ECG with ECG monitoring in patients with heart disease, the elderly, those with syncopal episodes and in any patient whose seizure pattern changes.
Progressively increase the daily dose and monitor plasma levels of the drug.
Do continuous rhythm monitoring of any overt overdosage.
Combine carbamazepine with extreme caution with tricyclic depressants or antiarrhythmic agents that slow conduction.
In patients with pacemakers, pay attention to the stimulus amplitude before starting the drug.
If conduction disturbances occur while taking carbamazepine, reduce the dosage or discontinue it.

*References: 3-5, 8-12,, 18, 20-21, 25, 31

The therapeutic measures in carbamazepine-related conduction disturbances (5, 8-36) are withdrawing carbamazepine, or changing to another antiepileptic agent together with supportive care and prompt elimination of the drug from the patient by gastric lavage, vomiting, catharsis, charcoal, forced diuresis, volume and charcoal hemoperfusion. Temporary cardiac transvenous pacing has also been successfully used.

In conclusion, carbamazepine is an anticonvulsant drug widely prescribed in neurological (epilepsies and neuralgias) and psychiatric disorders. However, its adverse effects on the cardiac conduction system (sinus node, AV junction and His-Purkinje system), leading to bradyarrhythmias, appear to be underrcognized by medical practitioners. We report such a case of symptomatic bradyarrhythmia and review other such cases from the medical literature.

Resumen

La carbamacepina, una droga utilizada en el tratamiento de epilepsia y neuralgias, puede tener efectos adversos en

el sistema de conducción cardíaca. A continuación reportaremos el caso de un hombre de 43 años de edad que tuvo una bradiarritmia sintomática secundaria al medicamento previamente mencionado. Además, se hace un repaso de la literatura referente a casos con trastornos de conducción inducidos por carbamacepina a nivel del nodo sinusal, nodo atrioventricular y rama de His-Purkinje.

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