Carbamazepine-induced Sinus Node Dysfunction and Atrioventricular Block in Elderly Women

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SUMMARY

We report on four elderly women in whom carbamazepine was suspected of inducing sinus node dysfunction (3 patients) and atrioventricular block (1 patient). Patients were treated with carbamazepine, 200 to 600 mg a day, for trigeminal neuralgia ($n = 3$) or epilepsy ($n = 1$). After 1 to 16 months of carbamazepine therapy, these patients were admitted to our emergency room because of bradyarrhythmia. Their conduction disturbances on electrocardiographic monitoring disappeared immediately after the cessation of carbamazepine intake. Provocation tests were performed on three patients. Because of renal insufficiency, one patient could not undergo the provocation test. Her carbamazepine clearance was markedly decreased. Carbamazepine induced sinus arrest in two patients within 48 hours after intake, but did not induce atrioventricular block in the remaining patient. In two patients, computer simulation of carbamazepine pharmacokinetics was performed and disclosed a clear-cut relationship between the plasma concentration of carbamazepine and the frequency of sinus arrest. During the test, the maximum plasma carbamazepine concentration in these two patients did not exceed the therapeutic range. However, it did exceed the range in the one with a negative test. Our results suggest that careful monitoring of ECG and plasma drug concentration is required with carbamazepine therapy, especially in elderly women. (*Jpn Heart J* 1998; 39: 469–479)

Key words: Carbamazepine, Pharmacokinetics, Sinus node dysfunction, Atrioventricular block

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CARBAMAZEPINE, a tricyclic antidepressant derivative (molecular weight 236.26), is widely prescribed for the treatment of epilepsy and trigeminal neuralgia.¹⁾ It is also known to have antiarrhythmic action.¹⁾ In addition, suppression of sinus nodal automaticity and atrioventricular conduction has been reported in a few subjects.²⁻¹⁸⁾ Using pharmacokinetic analysis, we studied four elderly female patients in whom carbamazepine might have induced sinus node dysfunction or atrioventricular block. In three patients, we observed a strong relationship between plasma carbamazepine concentration and the frequency of sinus arrests or sinus bradyarrhythmia. Some of the clinical data in patient 2 were reported previously.¹⁵⁾

PATIENTS AND METHODS

Patient selection: Four patients suspected of carbamazepine intoxication were studied in our hospital from 1990 to 1997. They were all women, ranging from 70–81 years of age (mean 75.5). Their clinical profiles before and after the emergency admission are shown in the Table. Total carbamazepine dosages administered were estimated as the product of the daily dose times the duration of

Table. Profiles of the Patients

Patients	1	2	3	4
Age/sex	73/F	76/F	81/F	72/F
Weight (Kg)	50.5	51.8	50	41
Height (cm)	149.8	145.6	146.5	157
HR (bpm)/BP (mmHg)	60/98/56	55/110/70	24/148/64	72/132/70
Organic disease	—	breast carcinoma	renal failure	—
Neural disease	trig. neuralgia	trig. neuralgia	trig. neuralgia	epilepsy (?)
Syncope	+	—	+	+
Conduction disturbance	SND-II	SND-III	SND-I	A-V block
Carbamazepine				
Daily dose (mg)	800	600	200	200
Duration (days)	480	90	180	33
Total dose (g)	384	54	36	6.6
Provocation test	+	+	—	+
Total dose (mg)	800	1,000		1,400
Conduction disturbance	+	+		—
T _{max} (hr)	16	31	N.A.	56
C _{max} (μg/ml)	10.7	10.6	(8.7)*	19.2

Patients: F = female; trig. neuralgia = trigeminal neuralgia; HR = heart rate; BP = blood pressure; SND = sinus node dysfunction according to the Rubenstein classification; I: sinus bradycardia, II: sinoatrial block, III: bradycardia-tachycardia syndrome.

Carbamazepine: duration = total duration (days) of the carbamazepine administration; total dose = total dose of carbamazepine administered before the admission (g)

Provocation test: T_{max} = estimated time to achieve maximum plasma concentration following multiple doses of carbamazepine during the provocation test; C_{max} = estimated maximum plasma concentration of carbamazepine during the provocation test; T_{1/2} = biological half-life of carbamazepine (in patient 3, estimated from the time-course of decay).

therapy (6.6 to 384 grams) and are also shown in the Table.

Continuous monitoring of electrocardiogram (ECG) and plasma carbamazepine levels: After hospital admission, the ECG and vital signs were monitored continuously. Once carbamazepine intoxication was suspected, blood was sampled to measure the plasma carbamazepine concentration. Carbamazepine concentration was analyzed by the conventional method (high performance liquid chromatography).¹⁴⁾

Computer simulation of the carbamazepine pharmacokinetics: Pharmacokinetic analysis of multiple doses of carbamazepine (600 mg per day) was performed using a standard single compartment model.¹⁹⁾ In each patient, pharmacokinetic parameters to multiple doses, including time to maximum plasma concentration ($t_{\max}$), maximum plasma concentration achieved ($C_{\max}$) and biological half-life ($t_{1/2}$) were estimated.

Patient profiles: *Patient 1.* A 73-year-old woman was admitted to our emergency room for loss of consciousness on October 24, 1996. Her family found her in a drowsy state that morning. From June 1995, carbamazepine had been prescribed, 200 mg, t.i.d., to treat trigeminal neuralgia. Her ECG 5 months before admission revealed normal sinus rhythm, whereas on admission it demonstrated

Figure 1. *Patient 1.* Upper panel: Carbamazepine provocation test. A total dose of 800 mg was administered. Time course of sinus arrests (> 3 seconds, solid bars) and measured plasma carbamazepine concentrations (solid circles) is shown. Estimated pharmacodynamics of carbamazepine are also expressed by the continuous curve. Lower panel: Typical ECG strips at different plasma levels of carbamazepine. Timing of ECG strips in the lower panel are indicated as A, B and C, respectively in the upper panel. Sinus arrests started to appear in ECG strip B.

Figure 2. Patient 2. Upper panel: Study of sinus node dysfunction and plasma carbamazepine concentration and pharmacodynamics of carbamazepine with a total dose of 1000 mg as indicated by arrows. Time course of sinus arrests (> 3 seconds, solid bars) and measured plasma carbamazepine concentrations (solid circles, $\mu\text{g/ml}$) is shown. The result of the simulation study is depicted with a continuous curve. Lower panel: Typical ECG strips taken during the study. The date of each strip corresponds to A-D of the upper panel. Closed triangles in panels B and C indicate initiation of supraventricular tachycardia by a premature beat (panel B) and short runs (> 5 beats) of atrial premature beats (panel C), respectively.

sinus bradyarrhythmia (25 bpm) and occasional junctional escape beats. The plasma carbamazepine concentration on admission was $3.2 \mu\text{g/ml}$ (therapeutic range: $4\text{--}12 \mu\text{g/ml}$,^{5) $15\text{--}40 \mu\text{gM/L}$ ^{16)). Carbamazepine administration was discontinued on the second day. On the third day, she became alert and her ECG returned to normal sinus rhythm. ECG monitoring did not reveal any sinus node dysfunction or atrioventricular block during the following week.}}

On the 10th hospital day, carbamazepine 200 mg, t.i.d. was administered again, until a total of 800 mg had been given, as shown by the arrows in the upper panel in Figure 1. Continuous ECG monitoring and serial blood sampling were undertaken for the next 3 days. Thirty hours after the initial dose, sinus arrest not exceeding 2 seconds appeared as shown in the ECG in panel B in Figure 1. Sinus arrests became more marked at 36 hours (ECG in panel C) and carbamazepine administration was terminated. The frequency of sinus arrests exceeding 3 seconds per hour (solid bars) and plasma carbamazepine concentra-

tions (solid circles) are illustrated in the upper panel in Figure 1.

After an additional week of observation, the patient was discharged and followed in our outpatient clinic without major complications. Acetylsalicylic acid, instead of carbamazepine, was administered for trigeminal neuralgia.

Patient 2. A 76-year-old woman was hospitalized for complaints of palpitation and dizziness on January 12, 1987. Eleven years earlier, she had undergone a right-side mastectomy for breast carcinoma. In October 1986, carbamazepine was prescribed (200 mg, t.i.d.) to treat severe trigeminal neuralgia. Two months later, she had frequent episodes of dizziness. On January 8, 1987, 24-hour ambulatory ECG monitoring revealed sinus arrest for periods of up to 4 seconds, following brief episodes of supraventricular tachycardia with regular R-R intervals. During the tachycardia, a P wave was overlapped in the QRS complex. The patient was hospitalized on January 12, 1987 for further evaluation.

On admission, the ECG demonstrated sinus bradyarrhythmia and occasional junctional escape beats. Carbamazepine administration was discontinued on the second day, and thereafter she no longer experienced dizziness. Her ECG demonstrated a normal sinus rhythm. An electrophysiological study conducted on the fifth day revealed a maximum sinus node recovery time of 1,740 msec at an atrial pacing rate of 150 bpm when the basic sinus cycle length was 705 msec (corrected sinus node recovery time = 1035 msec). It was not possible to induce tachycardia, and no signs of dual atrioventricular node were evident.

On the tenth hospital day, carbamazepine was administered to the patient, at a daily dose of 600 mg, until a total dose of 1000 mg had been given (arrows in the upper column in Figure 2). The patient did not tolerate a carbamazepine dose exceeding 1000 mg because of frequent episodes of palpitation and dizziness. Sinus arrest started to occur 24 hours after the initial dose was given and gradually increased during the next 18 hours, while the plasma carbamazepine levels remained in the therapeutic range.

The relationship between the frequency of observed sinus arrests, in excess of 3 seconds per hour, and plasma carbamazepine concentration (solid circles) is illustrated in the upper panel in Figure 2. Typical ECG strips obtained during this trial are shown in the lower panel A-D of Figure 2. Sinus arrest of 3 seconds or longer was preceded by 3 to 50 second periods of supraventricular tachycardia at a rate of 120–130 bpm. The plasma concentration after a single 200 mg dose of carbamazepine was sequentially determined on another day and found to reach the maximum value of 4.7 µg/ml 6 hours later.

Carbamazepine was permanently discontinued and the patient was discharged. Three months later, her general medical condition gradually deteriorated and she died of carcinoma in December 1987. An autopsy was not performed.

Patient 3. A 81-year-old woman was admitted to our hospital on February 3, 1997, because of loss of consciousness and marked sinus bradycardia. She had been treated with carbamazepine, 200 mg a day, for trigeminal neuralgia since August 1, 1996. Temporary pacing was started and carbamazepine administration was discontinued. After the cessation of carbamazepine, she became conscious, and her heart rate increased gradually to 60 bpm. The plasma carbamazepine concentration was 1.43 $\mu\text{g}/\text{mL}$ on the fourth day of admission and was reduced to 1.28 $\mu\text{g}/\text{mL}$ and 0.61 $\mu\text{g}/\text{mL}$ on the fifth and sixth days, respectively (Figure 3). On the tenth hospital day, she suddenly lost consciousness with right sided hemiplegia. Computer tomography revealed massive left cerebral bleeding. She died of subsequent respiratory failure on March 10. An autopsy was not performed.

Patient 4. A 72-year-old woman with a history of syncope and convulsion in July 1995 had been treated with carbamazepine, 200 mg, t.i.d., for suspected attacks of epilepsy from July 27, 1997. She was admitted on August 26, 1997 because of loss of consciousness. At first, epileptic seizure was suspected and phenytoin, 250 mg, was administered intravenously. On the ECG monitor, paroxysmal atrioventricular block lasting up to 45 seconds without escape beats was frequently observed together with paroxysmal atrial fibrillation, as shown in the lower panel in Figure 4. Temporary pacing was started and carbamazepine administration was discontinued. After the cessation of carbamazepine, she became conscious and paroxysmal atrioventricular block disappeared quickly. The patient's plasma

Figure 3. Patient 3. Upper panel: Time course of sinus bradycardia (open circles) and plasma carbamazepine concentration (filled circles). Lower panel: Typical ECG strips taken at the time of admission.

Figure 4. Patient 4. Upper panel: Time course of plasma carbamazepine concentration (filled circles) with a total dose of 1400 mg of the drug. The result of the simulation study is depicted with a continuous curve. Lower panel: Paroxysmal atrioventricular block lasting 45 seconds without escape beat observed at the time of admission (parts of continuous ECG).

carbamazepine concentration was less than $1 \mu\text{g/mL}$ on September 1. On the twenty-first hospital day, carbamazepine 200 mg, t.i.d., was re-administered to the patient until a total of 1400 mg was given. Carbamazepine induced frequent episodes of vomiting but no atrioventricular block. A maximum plasma carbamazepine level of $14.0 \mu\text{g/mL}$ was achieved 56 hours after the administration. A permanent pacemaker was implanted and an antiarrhythmic agent was administered to suppress atrial fibrillation. She was followed up without complication in the outpatient clinic until February 1998.

Pharmacological analysis and simulation study: In all patients, we estimated the time course of plasma carbamazepine levels and pharmacological parameters as shown in Figures 1 to 4 and the Table. The simulated time-course of multiple doses of carbamazepine in patient 1 (total 800 mg) is shown as a continuous solid line in the upper panel of Figure 1. The time-course to a total carbamazepine dose of 1000 mg in patient 2 is illustrated in the upper panel of Figure 2. In both patients, apparent sinus node dysfunction (> 30 arrests/hour) appeared 30 to 40 hours after the initial drug intake. The half-life of carbamazepine was within the normal range in both patients.

In patient 3, estimation of $T_{1/2}$ was possible ($T_{1/2} = 39.1$ hours) and showed prolongation from the log-scale graph in Figure 3A. Estimated plasma carbamazepine concentration at the time of her initial syncope attack on the day

of emergency admission ($8.7 \mu\text{g/ml}$) did not exceed the upper therapeutic level. In patient 4, estimation of C_{max} , T_{max} and $T_{1/2}$ also was possible.

DISCUSSION

Maximum carbamazepine concentration and sinus bradyarrhythmia: Sinus bradyarrhythmia is a major complication of carbamazepine, mainly involving individuals with latent sinus node dysfunction.^{2-4,15)} We observed carbamazepine-induced sinus node dysfunction, including all three types of Rubenstein's classification in our three patients. However, we stress that the measured plasma concentrations of carbamazepine during clinically significant sinus bradyarrhythmic periods were in the normal therapeutic range. Plasma concentration simulation study using T_{max} , C_{max} and $T_{1/2}$ also support this idea. Suppression of sinus node function can occur at the normal therapeutic level of carbamazepine. We recommend continuous or intensive ECG monitoring of elderly patients with latent sinus node dysfunction when carbamazepine is prescribed.

Provocation tests in the three patients: Similar time courses of the C_{max} , $T_{1/2}$ and sinus arrests in the provocation tests in the first two patients suggested that the sinus node dysfunction could appear approximately 10 to 20 hours after the maximum plasma level of the drug is reached. This delay might constitute the time required for carbamazepine to affect the sinus node cells and to induce marked sinus bradyarrhythmia. However, in patient 4, a total carbamazepine dose of 1400 mg did not induce atrioventricular block. The maximum carbamazepine concentration exceeded the upper therapeutic level in this patient. We suspect that much longer carbamazepine administration and additional intravenous phenytoin may be required to introduce the marked paroxysmal atrioventricular block observed (45 seconds).

Mechanism of conduction disturbance and underlying structural disease: The mechanism of carbamazepine-induced conduction disturbance has been reported to be due to its composite electrophysiological actions.^{10,17)} Its negative chronotropic and dromotropic effects may induce symptoms in predisposed patients, especially in elderly women.^{10,17)} Our second patient exhibited a moderately prolonged CSNRT, suggesting the presence of underlying structural sinoatrial node disease. Her ECG after the cessation of carbamazepine did not reveal sinus bradyarrhythmia or supraventricular tachycardia. One possible explanation for her sinus node dysfunction is the metastatic spread of the breast carcinoma into the sinoatrial tissue. However, we believe a dropout of the sinus node cells, as described by Sugiura *et al.*,²²⁾ may account for the sinus node dysfunction in our three patients, including patient 2 with prolonged CSNRT.

Supraventricular tachycardia in patient 2 is assumed to be responsible for

the induced sinus node arrest. Although the mechanism of this tachycardia was not clarified, our observations in this case are valuable, since bradycardia-tachycardia types of sinus node dysfunction due to drug intoxication hitherto have not been well-documented in relation to pharmacological kinetics.^{15,17)} An anti-cholinergic action of carbamazepine^{6,10)} may have accelerated the formation of the reentry circuit, or increased the automaticity of the ectopic pacemakers.

In our first two patients, no suppression of atrioventricular conduction or sinus node function was observed during the drug-free ECG monitoring periods after admission. In contrast, Kenneback *et al.* studied 10 similar patients with ECG abnormalities of the conduction system or cardiac symptoms and found sinus arrest exceeding 5 seconds in 2 patients and atrioventricular block with ventricular arrest in 2 patients.¹⁷⁾ Plasma carbamazepine concentration was measured at steady-state in 9 patients and ranged between 18 and 36 $\mu\text{M/L}$ in their study (normal 15–40 $\mu\text{M/L}$). Four patients were given a single bolus dose of carbamazepine and their C_{max} was 25–41 $\mu\text{M/L}$, observed during an invasive electrophysiological study.

In our third patient, plasma clearance of carbamazepine was decreased because of renal insufficiency, possibly due to diabetes mellitus. However, estimated maximum concentration of carbamazepine upon emergency admission did not exceed the upper therapeutic range. Our fourth patient had been suspected of having epileptic attacks, for which carbamazepine was given. They seem to have been due to Adams-Stokes attacks induced by a paroxysmal atrioventricular block. Intravenous phenytoin after emergency admission might have further aggravated the carbamazepine-induced atrioventricular block. Because of her long and frequent episodes of ventricular arrest (45 seconds), phenytoin was not given at the provocation test.

Female dominance of the adverse carbamazepine effect: As for the female dominance observed in our study and other reported cases, Kasarskis *et al.* analyzed 26 patients with carbamazepine-induced conduction disturbances and found that 21 (81%) were women.¹⁰⁾ This ratio is much higher than the female-male ratio of trigeminal neuralgia for which carbamazepine is prescribed (1.08–1.41 to 1). We suspect that the relatively low weight of our four patients (41 to 51.8 kg) might be an independent factor for intoxication. Female dominance was also observed in the occurrence of drug-induced torsades de pointes, especially in elderly pacemaker-implanted patients on disopyramide therapy.²³⁾

Limitations of our study: There are several limitations of our study. First, precise ECG information, including 24-hour ambulatory monitoring before the start of long-term carbamazepine therapy was not available in our patients.²⁰⁾ Second, the provocation tests were not always positive in our patients, partly due to the limited total dose. Third, electrophysiological study was possible in only

one patient.²¹⁾ Finally, the reason for the marked individual differences in the length of carbamazepine therapy before admission, which ranged from 1 to 16 months, remains unexplained. In spite of these issues, we believe that systemic plasma concentration measurements and simulation studies are necessary for the correct diagnosis of bradyarrhythmia in elderly female patients undergoing carbamazepine therapy.

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