Three Cases of Sinoatrial Block Induced by Anticonvulsants

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SUMMARY

Diphenylhydantoin (DPH) and Carbamazepine have been widely used as anticonvulsants and known to have antiarrhythmic properties. Previous reports have shown that arrhythmias such as sinus bradycardia and atrioventricular block can be induced by these agents. In this paper, sinoatrial block (SA block) induced by these agents which were used as anticonvulsants in 3 aged patients is reported.

Three patients, 2 women and 1 man, were over 60 years old. In 2 cases, administration of DPH for recurrent epileptic seizures was followed by SA block. After withdrawal of DPH, SA block disappeared, but resumption of DPH resulted in SA block again. In 1 of these 2 patients, overdrive suppression test revealed normal sinus node recovery time. In the third patient, in addition to DPH which was administered for epileptic seizures, Carbamazepine was given for shoulder pain, then SA block occurred. Withdrawal of these agents restored normal sinus rhythm and combined administration of these 2 agents again induced SA block. Autopsy revealed decreased conduction cells in the sinus node.

Additional Indexing Words:
Diphenylhydantoin Carbamazepine Sinus node recovery time Overdrive suppression test

DIPHENYLHYDANTOIN (DPH) and Carbamazepine have been known to have not only anticonvulsive properties but antiarrhythmic properties.1) Adverse effects on the nervous and cardiovascular systems have been reported.11) There have been reports on arrhythmias, such as atrioventricular block (AV block) and sinus bradycardia, induced by DPH3) or Carbamazepine.4) Fatal cases have been reported with the intravenous use of DPH.5) There have been no reports on sinoatrial block (SA block) induced by these agents. The purpose of this report is to present 3 cases of SA block induced by DPH and/or Carbamazepine.

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Case Presentation

Case 1: A 66-year-old female was admitted to our hospital because of gait disturbance on Aug. 21, 1974. Five years previously she had subarachnoid bleeding with resultant right hemiparesis and dysarthria. Three years previously convulsive seizures occurred, since then she had been administered DPH orally in a daily dose of 300 mg. SA block was first noticed on Jan. 9, 1974 (Fig. 1-A), but no special therapy was performed on her SA block. On admission consciousness was alert, the pulse was 62/min and irregular, and blood pressure was 126/60 mmHg. Auscultation of the heart revealed no significant murmurs. There were no signs of congestive heart failure. Neurological examination revealed right hemiparesis and dysarthria. Electrocardiogram on admission showed SA block.

After admission DPH was discontinued, then sinus rhythm was restored (Fig. 1-B). His bundle electrogram, which was taken 10 days after withdrawal of DPH, showed that AH interval was 110 msec and HV interval was 50 msec. Overdrive suppression test (pacing at a rate of 130/min for 3 min) revealed normal sinus node recovery time (1080 msec, 122% of sinus cycle length). Following the oral administration of DPH as the challenge test in a daily dose of 300 mg for 2 days, SA block recurred (Fig. 1-C), and intravenous administration of DPH in a dosage of 200 mg also resulted in SA block. Once SA block had been induced by DPH, it persisted for about 20 days without DPH. She was discharged from the hospital after SA block had disappeared.

Case 2: A 68-year-old male was admitted to our hospital on Sep. 17, 1976 for rehabilitation of hemiplegia following cerebral bleeding which occurred on Jan. 4, 1976. He had had hyperthyroidism and digoxin had been administered to control the heart rate of his atrial fibrillation. On admission the pulse was 66/min and irregular, and blood pressure was 140/80 mmHg. Auscultation of the heart re-

Fig. 1. Electrocardiograms in Case 1 (Lead V1). A) On Jan. 9, 1974, showing SA block during the administration of DPH. B) On Sep. 6, 1974, sinus rhythm was restored after withdrawal of DPH. C) On Nov. 15, 1974, SA block reappeared after resumption of DPH.
revealed splitting of the first heart sound and no significant murmurs. Neurological examination revealed right hemiplegia and aphasia. Electrocardiogram showed atrial flutter with 4:1 atrioventricular conduction, high voltage and ischemic ST depression, but sinus rhythm was restored spontaneously soon after admission (Fig. 2-A). Laboratory data showed that he was in euthyroid state.

Digoxin was continued in a maintenance dose of 0.125 mg every day or every other day. On Jan. 12, 1977 he became unconscious and had convulsive seizures during the physical therapy. At that time, electrocardiogram showed sinus rhythm and frequent atrial premature beats. Oral administration of DPH in a dosage of 150 mg was started. Electrocardiogram on Jan. 31 showed SA block (Fig. 2-B). After withdrawal of DPH, SA block disappeared (Fig. 2-C). Since convulsive seizures recurred on May 22, oral administration of DPH in a daily dose of 200 mg was resumed and continued thereafter. Although SA block has been intermittently noted on electrocardiogram without syncope or dizziness (Fig. 2-D), DPH has been administered for the prevention of epileptic seizure. Plasma concentration of DPH ranged 4.0 to 4.4 µg/ml. He was discharged from the hospital and has been maintained on DPH in a daily dose of 200 mg.

Case 3: A 73-year-old female was admitted to our hospital on Jan. 14, 1969 because of sensory disturbance of the lower limbs and recurrent abdominal pains. At the age of 50 she had chest pains which were suggestive of angina pectoris. On

![Fig. 2. Electrocardiograms in Case 2. A) Lead V1 on Oct. 4, 1976, before the administration of DPH, showing sinus rhythm and an atrial premature beat. B) Lead V4 on Jan. 31, 1977, showing SA block. C) Lead V1 on Feb. 22, 1977, after the cessation of DPH. Sinus rhythm was restored and first degree AV block was noticed. D) Lead V1 on June 6, 1977. DPH had been administered for prevention of epileptic seizures and SA block was intermittently observed.](image)
admission the patient was normotensive and the pulse was 60/min and regular. Neurological examination showed prompt reaction to light and normal deep tendon reflexes in spite of positive serological tests for syphilis in both serum and cerebrospinal fluid. Electrocardiogram on admission showed normal sinus rhythm. Since 1974 DPH had been administered in a dosage of 100 to 300 mg daily for epileptic seizures due to meningovascular syphilis, but SA block had not been noticed (Fig. 3-A). On July 28, 1976 Carbamazepine was given in a daily dose of 600 mg in addition to DPH for the shoulder pain. But 2 days later she suddenly became unconscious and cyanotic, the pulse rate was decreased to approximately 20/min and systolic blood pressure was 50 mmHg. Electrocardiogram showed SA block without any escape beats (Fig. 3-B). With temporary transvenous pacing of the right ventricle she recovered from shock state. After withdrawal of DPH and Carbamazepine sinus rhythm was restored (Fig. 3-C), and overdrive suppression test (pacing at a rate of 130/min for 1 min), which was performed 3 days after withdrawal of these drugs, revealed normal sinus recovery time (1280 msec, 136% of sinus cycle length). DPH was administered intravenously in a dosage of 250 mg, but SA block was not observed. Administration of Carbamazepine in a daily dose of 400 mg (1 day) and 600 mg (2 days) for 3 days in total also failed to induce SA block. But after administration of DPH in a daily dose of 300 mg for 7 days, additional administration of 1200 mg of Carbamazepine was followed by SA

![Image](https://via.placeholder.com/150)

Fig. 3. Electrocardiograms in Case 3. A) Lead V<sub>2</sub> on May 24, 1976. During the administration of only DPH, SA block had not been noticed. B) Lead II on July 30, 1976. After the administration of Carbamazepine in addition to DPH, sinus bradyarrhythmia and SA block appeared. C) Lead II on Aug. 2, 1976. After withdrawal of these 2 drugs, sinus rhythm was restored. D) C<sub>4</sub>-C<sub>5</sub>R on Aug. 20, 1976. After combined administration of these 2 drugs, SA block appeared, which was followed by sinus irregularities.
block on the next day (Fig. 3-D). Two days after the cessation of these agents normal sinus rhythm was restored. On Oct. 2, 1976 she was operated on for ileus. During the operation she became hypotensive, vasopressor agents were administered but ineffective, and she died on that day. Autopsy revealed following findings: The heart was 290 Gm in weight. Coronary sclerosis was moderate and there was small fibrosis in the lateral wall of the left ventricle. The branching portion of the His bundle showed marked fibrosis, but the other parts of A-V conduction system showed, only slight damages. The sinus node artery was patent. Elastic and collagen fibers were increased and the number of the conduction cells was

Fig. 4. The sinus node in Case 3. A) The sinus node artery was patent (Elastica van Gieson, $\times 50$). B) Elastic and collagen fibers were increased, and the number of conduction cells was decreased to approximately 40% (Elastica van Gieson, $\times 250$).
decreased approximately to 40% in the sinus node (Fig. 4). Although the conduction cells were less markedly decreased than those in cases with sick sinus syndrome, they were apparently decreased in number when compared to those in young subjects. There was syphilitic mesoaortitis.

**DISCUSSION**

From an electrophysiologic standpoint DPH is characterized as a membrane depressant, i.e., both automaticity and excitability are depressed. In the animal experiment, Helfant et al showed that sinus rate did not change after the administration of DPH in a dosage of 5 mg/Kg intravenously. Strauss et al showed in the animal experiment with microelectrode technique that high concentration of DPH in Tyrode's solution (10^-4 M) decreased sinus rate, but lower concentration (10^-8 to 10^-6 M) did not decrease sinus rate. In this experiment SA block was not induced and ouabain-induced SA block was returned to sinus rhythm after administration of DPH. But DPH was shown to depress sinus node function in the presence of sinus node damage which was caused by stretching, mechanical trauma and so on. Then it was suspected that sinus node became more susceptible to the negative chronotropic effects of DPH in the presence of sinus node dysfunction.

Untoward effects of DPH on cardiovascular system which have been reported include depression of myocardial contractility, decreased peripheral vascular resistance and disturbances of rate and rhythm. After the first report of a fatal case in 1967, several fatal cases have been reported. These were all over 60 years old and moderately or severely ill because of heart failure or digitalis intoxication, and they had intravenous injection of DPH in a dosage of 100 to 250 mg for the treatment of arrhythmias and died from more lethal arrhythmias such as ventricular fibrillation or cardiac arrest. Clinically, the effect of DPH on sinus cycle length is variable, and a case of sinus arrest has been reported. Factors that have been reported to precipitate side effects of DPH are as follows; old age, severe heart failure, severe anemia, hypotension, hypoxia, and acidosis.

In our Case 1, once SA block had been induced by DPH, SA block persisted without DPH for about 3 weeks. Although the rapid pacing failed to show prolonged sinus node recovery time, persistent SA block suggested that she might have latent sinus node dysfunction which could not be detected by the pacing study. Bigger et al showed that effective plasma level of DPH as an antiarrhythmic agent was 10 to 18 µg/ml and the sinus node activity was not depressed if the plasma level was within this range, but in our Case 2 SA block occurred with lower plasma levels (4.0 to 4.4 µg/ml). In our Case 2, since electrophysiologic evaluation of the sinus node function was
not performed, the mechanism underlying the occurrence of SA block remained unidentified. Although occurrence of SA block in the lower DPH level suggested that latent sinus node dysfunction could be assumed also in this case, maintenance therapy of digoxin and/or thyroid heart disease might play some roles as precipitating factors.

Carbamazepine is characterized electrophysiologically as a membrane depressant as is DPH. The distinct difference between DPH and Carbamazepine lies in the fact that DPH shortens the atrioventricular conduction time while Carbamazepine prolongs it. Sinus rate, intraatrial conduction and intraventricular conduction were not depressed in animal experiment. Prior to the reports of intensive electrophysiologic studies, 3 cases of sinus bradycardia due to Carbamazepine had been reported, who were all over 70 years old and had been maintained on digitalis for atherosclerotic heart disease. And 1 case of complete AV block following oral administration of Carbamazepine was reported. The patient was a 66-year-old female, who had had 2:1 or 3:1 AV block previously and the administration of Carbamazepine for trigeminal neuralgia in a dosage of 1200 mg daily resulted in complete AV block, and defective conduction system might be a necessary prerequisite for induction of AV block.

In our Case 3, clinical state was not deteriorated and pathologic examination revealed neither myocardial derangement nor markedly decreased number of conduction cells of the sinus node, and only DPH or only Carbamazepine failed to produce SA block but combined effect of DPH and Carbamazepine was thought to cause SA block in the presence of moderately defective sinus node.

The sequence of events in our 3 aged cases suggests that anticonvulsants such as DPH and Carbamazepine should be used with caution, even in a small dose, in aged patients who are thought to have more or less defective conduction system, and that serial electrocardiographic examination during the administration of the drug seems to be mandatory.

**References**

16. Mixter CG, Moran JM, Auster WG: Cardiac and peripheral vascular effects of diphenylhydantoin sodium. Am J Cardiol 17: 332, 1966