Symptomatic Sick Sinus Syndrome due to Guanethidine

Case Report

JACOB ROWE, M.D., AND MAYER M. BASSAN, M.D.

SUMMARY A patient is described who developed symptomatic sinus bradycardia as low as 20 beats per minute and sinus arrest of up to 4.4 seconds while receiving guanethidine, 75 mg daily. The bradycardia resolved following discontinuation of the drug and reappeared upon challenge with it. Intrinsic disease of the sinoatrial and atrioventricular nodes was evidenced 3 weeks following discontinuation of the guanethidine by a borderline abnormally prolonged sinus node recovery time of 1500 msec and a PR interval of 0.28 seconds. Although sinus bradycardia is a known and not infrequent side effect of guanethidine, such an extreme form as seen in our patient appears to be quite rare, and may be related to the pre-existing disease of the conduction system. (Hypertension 1: 543-546, 1979)

KEY WORDS • guanethidine • sick sinus syndrome • sinus node • bradycardia

SINCE guanethidine was first introduced in 1959 as an antihypertensive agent, there have been numerous reports of its side effects, and it has been recommended that the drug be used only in severe hypertension when treatment with other drugs has failed. More recent reports, however, have called attention to the outstanding absence of significant toxic or allergic effects attributable to guanethidine, and have also challenged the common belief that treatment of moderate hypertension with the drug is accompanied by an intolerably high incidence of side effects.

Mild to moderate sinus bradycardia, not requiring drug discontinuation, has been well documented as a not infrequent side effect of guanethidine. We wish to report the case of a patient receiving guanethidine who developed episodes of dizziness and blurred vision due to severe sinus bradycardia with episodes of prolonged sinus arrest. These phenomena disappeared with discontinuation of guanethidine and reappeared upon challenge with the drug. Sinus node dysfunction, in such an extreme form, has not previously been so conclusively related to guanethidine.

Case Report

A 65-year-old man was admitted to the hospital following an episode of weakness, dizziness, and blurred vision. He had never experienced such symptoms previously. He was known to be hypertensive for at least 8 years, and had suffered a myocardial infarction 4 years prior to admission. His blood pressure had been treated initially with reserpine, then with alpha methyldopa, and finally, for the 12 months preceding admission, with guanethidine, 75 mg once daily, and furosemide, 40 mg twice daily. He was not receiving any other medication.

On examination the patient was quite obese (121 kg) and in no distress. Supine blood pressure was 150/90 with a pulse rate of 35 beats per minute (bpm) and slightly irregular. He was afebrile. The lungs were clear, the heart not palpably enlarged, and there were...
no abnormal heart sounds. There was no abdominal bruit or pedal edema, and all peripheral pulses were palpable.

The ECG showed a sinus bradycardia of 35 bpm with sinus arrhythmia, a PR interval of 0.28 seconds, and an old inferior myocardial infarction. (An ECG taken 4 years earlier was similar except for a heart rate of 70 bpm and a PR interval of 0.20 seconds.) A chest roentgenogram revealed a slightly enlarged cardiac silhouette with some dilatation of the aortic arch. Complete blood count, blood urea nitrogen, serum enzymes, electrolytes and glucose were all within normal limits.

The guanethidine was discontinued upon the patient's admission to the cardiac care unit for observation and electrocardiographic monitoring. During the first week of hospitalization the patient was kept at complete bed rest and was asymptomatic. There was a persistent sinus bradycardia averaging 40-45 bpm (fig. 1) with occasional rates as low as 20 bpm (fig. 2A) and frequent episodes of sinus arrest, the longest of which was 4.4 seconds (fig. 2B). Rare non-conducted P waves were observed in a low-grade Wenckebach type pattern (fig. 2C).

During this first week the blood pressure remained at the upper limit of normal with the patient at bed rest and receiving furosemide, 40 mg three times daily.

Over the next 4 days there was a gradual but marked increase in heart rate to 70 bpm on the 11th hospital day (fig. 1) at which time the patient was discharged. The PR interval remained prolonged at 0.28 seconds.

In order to prove conclusively that the extreme bradycardia was due to guanethidine and thereby save the patient from the unnecessary implantation of a permanent pacemaker, he was readmitted with full consent 9 days later for a challenge with guanethidine. A temporary pacemaker was inserted, and prior to intraventricular positioning, atrial pacing was performed at different rates to determine the sinus node recovery time (SNRT). The basic cycle length was 1000 msec and the longest period of post-pacing arrest was 1500 msec (fig. 2D), yielding a corrected SNRT of 500 msec. The patient was again placed under continuous electrocardiographic monitoring and guanethidine was restarted. The pacemaker was set at a demand rate of 30 bpm.

Over the following 8 days there was a gradual slowing of the average daily heart rate from 62 bpm to 50 bpm, and toward the end of this period, occasional episodes of sinus bradycardia as slow as 32 bpm were observed (fig. 2E). The patient complained of two episodes of dizziness and blurred vision, similar to those which had occasioned his original admission. The guanethidine was stopped at this point.

During the succeeding 2 days there was a further fall in average heart rate to 44 bpm, after which there was a progressive rise to 56 bpm at the time of discharge 6 days later. The pacemaker was removed the day before discharge (7 days after guanethidine was discontinued) at which time a His bundle recording showed an A-H interval of 225 msec and an H-V interval of 35 msec. The maximum SNRT was again 1500 msec. During this second admission occasional non-

**Figure 1.** Fluctuations in the patient's average daily heart rate in relation to guanethidine administration.
conducted P waves were observed before, during, and after guanethidine administration.

A 24-hour ambulatory ECG taken 6 weeks following drug discontinuation showed sinus rhythm varying from 68 to 125 bpm with 15 nonconducted P waves during the 24 hours. The patient was feeling well and denied episodes of dizziness or blurred vision. His blood pressure was controlled on a combination of chlorthalidone and hydralazine.

Discussion

Guanethidine is a potent antihypertensive agent which selectively inhibits peripheral adrenergic neuronal transmission without affecting the parasympathetic system. As with other antihypertensive drugs, clinical use may be limited by the side effects of the drug which in the case of guanethidine are almost always attributable to either excessive sympathetic blockade or a relative increase in parasympathetic activity.

The incidence of bradycardia due to guanethidine is difficult to assess. In one major review of the side effects of the drug, bradycardia was not even mentioned. Blanshard et al. reported bradycardia in only one out of 65 patients, and in an extensive comparison of guanethidine with other antihypertensive agents, Prichard et al. noted a reduction in heart rate to a mean of 65 bpm, but did not mention any cases of severe bradycardia. On the other hand, Dollery et al. refer to bradycardia as one of the “main” side effects of guanethidine, occurring in “many” patients. These authors reported a bradycardia of 35 bpm (rhythm not established) in a woman who was also receiving digoxin. On discontinuation of the digoxin, the heart rate increased to 60 bpm. Similarly, Bauer et al. described a patient who, while on guanethidine, was found to have an irregular pulse of 35 bpm due to sinus bradycardia with nodal escape. The patient was also receiving digoxin. No mention was made of whether the drugs were discontinued and, if so, what happened to the heart rate, but these authors as well as Dollery et al. state that the bradycardic effect of guanethidine is particularly pronounced in digitalized patients. In other reviews, Frolich and Freis reported a bradycardia of 44 bpm in one patient, and Lewis and

FIGURE 2. A. Severe sinus bradycardia on admission. B. Sinus arrest of 4.4 seconds. C. Nonconducted P wave in low-grade Wenckebach type AV block. D. Sinus node recovery time. E. Sinus bradycardia upon rechallenge with guanethidine. (For further explanation see text).
Kavelman found a heart rate "below 50" bpm in nine out of 63 patients, none of whom was symptomatic. Recently, Sheinman et al. described a patient in whom a sinus bradycardia of 33-40 bpm with prolonged sinus pauses developed while he was receiving 25 mg of guanethidine daily. The drug was discontinued following a syncopal episode, and the bradycardia resolved after 8 days. No electrophysiologic studies could be performed, nor was the patient challenged again with guanethidine.

There can be no question that in our patient the extreme bradycardia and periods of sinus arrest were due to guanethidine. The heart rate returned to normal on discontinuation of the drug and upon readministration the heart rate decreased markedly, and the patient became symptomatic.

The pronounced changes in heart rate upon discontinuation as well as re-institution of guanethidine therapy were delayed for 5-7 days. This is in keeping with the known pharmacology of the drug, and is an important factor to be taken into account when attempting to conclude whether or not guanethidine is the cause of bradycardia in an individual patient.

While it has been suggested that bradycardia due to guanethidine causes difficulty especially in patients receiving digitalis, our patient demonstrates that such problems may arise in the absence of digitalis therapy.

We elected to control our patient on hydralazine, rather than with another of the sympatholytic drugs such as alpha-methyldopa or clonidine, which have also been shown capable of producing severe sinus node dysfunction. We have no evidence, however, to indicate that our patient would have responded to these drugs as he did to guanethidine.

It is clear that our patient had intrinsic disease of his cardiac conduction system. The atrioventricular (AV) node was involved as evidenced by the prolonged PR and A-H intervals as well as the occasional episodes of second degree AV block. Sinoatrial node disease was also suspected, indirectly, because of the association with a diseased AV node, and directly, because of the borderline abnormally prolonged SNRT. It is likely that in our patient the severe effects of guanethidine were at least in part related to the pre-existing disease of the conduction system, although the possibility remains that such severe bradycardia might also occur in patients without demonstrable underlying disease.

With the recent increased interest in guanethidine as an agent suitable for widespread use in moderate hypertension, the possibility of precipitating symptomatic sick sinus syndrome needs to be taken into account, especially in patients with evidence of pre-existing disease of the conduction system.

References

Symptomatic sick sinus syndrome due to guanethidine. Case report.
J Rowe and M M Bassan

Hypertension. 1979;1:543-546
doi: 10.1161/01.HYP.1.5.543

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://hyper.ahajournals.org/content/1/5/543

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Hypertension can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Hypertension is online at:
http://hyper.ahajournals.org//subscriptions/