nidine-Induced Bradycardia

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ine is an alpha-adrenergic agent that is used in atment of hypertension. Bradycardia has been de- as a common effect of clonidine poisoning, but ely been described as a side effect at commonly ed dosages. Bradyarrhythmias, as a side effect, ve several manifestations and may be symptomatic or asymptomatic. This report proposes mechanisms for clonidine-induced bradycardia, describes persons at risk for this effect, and outlines treatments and preventive measures.

Key words. Clonidine, bradycardia, hypertension.
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ine is an alpha-adrenergic agonist with sympathoctivity[1–9] used in the treatment of hyperten-[6,8,10–12] Clonidine has also been used to treat mi-, menopausal complaints, narcotic withdrawal oms,[5] spasticity after spinal cord injury,[9] and attenficit hyperactivity disorder.[6] Bradycardia is a side nly rarely described when clonidine is used at pre- dosages.

e present a case report of clonidine-induced bradyin the treatment of hypertension, followed by a of the mechanisms, risk factors, treatment, and ion of this drug-induced side effect.

Report

tient was a 49-year-old man with a history of hysion. Four months before coming to our office, he d a hemorrhagic stroke with a left hemiparesis. He history of renal insufficiency or cardiac disease. he presented to our office for follow-up of his ension, his medications included amlodipine (Nor-0 mg daily; enalapril maleate (Vasotec) 20 mg aily; clonidine patch (Catapres-TTS-3) delivering per day, applied weekly; paroxetine (Paxil) 20 mg and propoxyphene-acetaminophen (Darvocet-N 100) and naproxen (Naprosyn) as needed. The 0.3 mg clonidine patch had been increased from a 0.2 mg clonidine patch 5 days before coming to our office. His blood pressure at the first visit was 178/92 and his pulse was 62 beats per minute. He was advised to discontinue the enalapril and clonidine patch and was started on enalapril-hydrochlorothiazide (Vaseretic 10–25) twice daily.

Two days later, he returned to the office for a blood pressure check. His blood pressure was 170/96 and pulse was 84 beats per minute. The 0.2 mg clonidine patch was restarted.

Two weeks later, he returned with a blood pressure of 130/84 and pulse of 46 beats per minute. He had stopped taking the amlodipine because of concern regarding a blood pressure of 104/68 measured at home, but had continued taking his other medications. He had no symptoms of chest pain, shortness of breath, dizziness, or orthostasis. He was instructed to monitor his pulse rate and to call should he develop symptoms.

One week later, he returned with a blood pressure of 148/78 and a pulse of 50 beats per minute. An electrocardiogram (ECG) showed sinus bradycardia with borderline first-degree atrioventricular block and voltage criteria for left ventricular hypertrophy. He complained of fatigue, especially during physical therapy, but had no orthostasis, dizziness, or other cardiovascular symptoms. The clonidine patch was discontinued and oral doxazosin mesylate (Cardura) 1-mg by mouth once a day, was added to his regimen.

Six days later, he returned with blood pressure of 160/90 and pulse of 64 beats per minute. He still had

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symptoms of fatigue. His doxazosin was increased to 2 mg by mouth once a day. Subsequently, he elected to have his hypertension managed by another physician. He was contacted by telephone 1 month later and reported that his medications included lisinopril-hydrochlorothiazide (Zestoretic 20–25) daily and doxazosin 8 mg at bedtime. His blood pressure was 120/65 and pulse consistently greater than 60 beats per minute. He had no complaints of fatigue.

Discussion

Clonidine enjoys wide clinical use, mainly as an antihypertensive agent. It is an alpha-2 receptor agonist which acts centrally on postsynaptic alpha-adrenergic receptors in the medulla oblongata.[1,2,4,12] This central effect results in decreased sympathetic outflow and enhanced vagal tone, lowering blood pressure and heart rate.[1–3,7,10,13–15] This may cause side effects of drowsiness, lethargy, dry mouth,[4,10] and parotidynia.[13] Clonidine may also act peripherally within the heart to inhibit norepinephrine release,[7,14,15] contributing to further reductions in heart rate. Intentional overdoses and accidental poisonings have resulted in depressed consciousness and respirations, hypotension, miosis, seizures, hypotonia, hypothermia, hypertension, arrhythmias, and bradycardia.[2,4–6,11,12,16,17] In contrast to the widely reported bradycardiac results of clonidine poisoning, there have been only a few reports of symptomatic bradycardia as a side effect of antihypertensive therapy (<0.3% incidence),[1,3,7–9,11,18–20] and none have been in the family practice literature.

The bradycardias reported have included sinus bradycardia, sinus arrest, nodal and junctional rhythms, sick sinus syndrome, and all degrees of atrioventricular block.[1,3,7,8,11,18–20] Our patient showed only sinus bradycardia and first-degree atrioventricular block. Some patients were asymptomatic, whereas others experienced symptoms of syncope,[3,7,19] weakness and dizziness,[3,19] fatigue with ambulation,[20] and palpitations.[3] Our patient's fatigue during physical therapy resolved after clonidine was discontinued. All patients reported in the literature developed the bradycardia after either starting clonidine or increasing its dosage. There was no consistent dosage, however, above which bradycardia occurred.[19] There were no reported deaths secondary to the bradycardia, and most patients recovered normal cardiac activity after clonidine was discontinued or decreased in dosage. However, a few patients were unable to convert to normal sinus rhythm.[8] Atropine was used successfully in several patients to treat severely symptomatic bradycardia.[6,8,16,19]

The exact mechanism responsible for this clonidine-associated bradycardia is not well understood. The most plausible mechanisms are: (a) reduced sympathetic tone from central mediators,[15] (b) increased vagal activity,[15] (c) stimulation of presynaptic alpha-2 receptors in the heart which have a blocking effect on heart rate,[15] (d) decreased automaticity of the bundles of His,[1,3,9] and (e) atrioventricular nodal block.[1,7,11] It is probable that the mechanisms vary from patient to patient.

Patients at higher risk for clonidine-induced bradycardia seem to be those with an already-diseased conduction system, renal failure, high doses of clonidine, concomitant therapy with medications known to cause bradycardia or heart block, (eg, beta-blockers, verapamil hydrochloride, diltiazem, digoxin, reserpine, guanethidine sulfate, and other antiarrhythmics), and a history of bradycardia or advanced heart block while on these medications.[1,3,7,8,11,19] Our patient had none of these risk factors; however, his renal function was not checked, and records were not available to examine for previous conduction abnormalities.

When treating a patient with clonidine-induced bradycardia, one should obtain an ECG to ascertain the type and severity of the bradycardia. Clonidine should be reduced in dosage or discontinued altogether. For severe, symptomatic bradycardia, atropine can be used.[2,4,6,16,19] Because atropine's half-life is shorter than that of clonidine, repeated doses may be necessary. For refractory symptomatic cases, isoproterenol, epinephrine, dopamine, and pacing can be considered.[4,12]

It is prudent to weigh these risk factors when considering initiating or increasing clonidine therapy,[8] or when using other centrally acting alpha-2 receptor agonists, such as guanabenz and guanfacine, which may cause the same effect.[21,22] This should include taking a thorough cardiac and medication history and possibly obtaining renal function tests and an ECG if the history indicates potential problems.[9] When following a patient on clonidine, the patient's pulse rate and blood pressure should be checked.[9] Clonidine should be used with caution in a patient with known sinus node dysfunction,[19] and patients with renal impairment should be considered for reduced dosages.

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References

1. Kibler, LE, Gazes PC. Effect of clonidine on atrioventricular conduction. JAMA 1977; 238:1930–2.

2. Anderson RJ, Hart GR, Crumpler CP, Lerman MJ. Clonidine overdose: report of six cases and review of the literature. Ann Emerg Med 1981; 10:107–12.
3. Thormann J, Neuss H, Schlepper M, Mitrovic V. Effects of clonidine on sinus node function in man. Chest 1981; 80:201–6.
4. Artman M, Boerth RC. Clonidine poisoning. Am J Dis Child 1983; 137:171–4.
5. Marruecos L, Roglan A, Frati ME, Artigas A. Clonidine overdose. Crit Care Med 1983; 11:959–60.
6. Wiley JF, Wiley CC, Torrey SB, Henretig FM. Clonidine poisoning in young children. J Pediatr 1990; 116:654–8.
7. Schwartz E, Friedman E, Mouallem M, Farfel Z. Sinus arrest associated with clonidine therapy. Clin Cardiol 1987; 11:53–4.
8. Byrd BF III, Collins HW, Primm RK. Risk factors for severe bradycardia during oral clonidine therapy for hypertension. Arch Intern Med 1988; 148:729–33.
9. Rosenblum D. Clonidine-induced bradycardia in patients with spinal cord injury. Arch Phys Med Rehabil 1993; 74:1206–7.
10. Yeh BK, Nantel A, Goldberg LI. Antihypertensive effect of clonidine. Arch Intern Med 1971; 127:233–7.
11. Williams PL, Krafcik JM, Potter BB, Hooper JH, Hearne MJ. Cardiac toxicity of clonidine. Chest 1977; 72:784–5.
12. Mofenson HC, Greensher J, Weiss TE. Clonidine poisoning: is there a single antidote? Clin Toxicol 1979; 14:271–5.
13. van Zwieten PA. Antihypertensive action of clonidine (Catapresan). Contr Nephrol 1977; 8:200–12.
14. De Jonge A, Timmermans PB, van Zwieten PA. Quantitative aspects of alpha adrenergic effects induced by clonidine-like imidazolidines. II. Central and peripheral bradycardia activities. J Pharmacol Exp Therapeut 1982; 222:712–9.
15. Van Zwieten PA, Thoolen MJ, Timmermans PB. The hypotensive activity and side effects of methyldopa, clonidine, and guanfacine. Hypertension 1984; 6(5 pt 2):II28–33.
16. MacFaul R, Miller G. Clonidine poisoning in children. Lancet 1977; 1:1266–7.
17. Neuvonen PJ, Vilska J, Keränen A. Severe poisoning in a child caused by small dose of clonidine. Clin Toxicol 1979; 14:369–74.
18. Abiuso P, Abelow G. Atrioventricular dissociation in a patient receiving clonidine. JAMA 1978; 240:108–9.
19. Scheinman MM, Strauss HC, Evans GT, Ryan C, Massie B, Wallace A. Adverse effects of sympatholytic agents in patients with hypertension and sinus node dysfunction. Am J Med 1978; 64:1013–20.
20. van Etta L, Burchell H. Severe bradycardia with clonidine [letter]. JAMA 1978; 240:2047.
21. Hall AH, Smolinske SC, Kulig KW, Rumack BH. Guanabenz overdose. Ann Intern Med 1985; 102(6):787–8.
22. Burney RG. Bradycardia during epidural anesthesia in a patient receiving guanfacine. Anesthesiology 1992; 77:1228–9.