International Journal of Cardiology 113 (2006) 276 – 278

International Journal of Cardiology

www.elsevier.com/locate/ijcard

Letter to the Editor

# Clonidine-induced delirium

Jessica Delaney [a,*], Daniel Spevack [b], Sanjay Doddamani [b], Robert Ostfeld [b]

[a] *Albert Einstein College of Medicine/Montefiore Medical Center, Internal Medicine, Bronx, NY, USA*
[b] *Albert Einstein College of Medicine/Montefiore Medical Center, Cardiology, Bronx, NY, USA*

Received 1 September 2005; accepted 20 September 2005
Available online 20 March 2006

**Abstract**

Clonidine-induced delirium has rarely been reported. To the best of our knowledge, there are six related case reports in the literature. We describe one such case here and review the six previously published cases. Clonidine may induce a variety of psychological side effects ranging from depression to acute hallucination and delirium. However, there are no clearly identifiable risk factors for the development of severe psychological side effects, including dose of medication, duration of treatment, and predisposing mental illness. Treatment for clonidine-induced delirium involves cessation of the medication and patient observation. Given the large clinical burden of hypertension and the not uncommon requirement for polypharmacy to achieve blood pressure goals, heightened clinical awareness of this potential side effect appears justified.


*Keywords:* Clonidine; Delirium; Hallucination; Hypertension; Side effect; Polypharmacy

Clonidine hydrochloride is a centrally acting antihypertensive with receptor affinities for alpha adrenoceptors in the nucleus tractus solitarius of the medulla and imidazoline receptors in the rostral ventrolateral medulla [1]. By binding to these receptors, clonidine inhibits sympathetic output resulting in lowered blood pressure [1]. Commonly observed side effects of clonidine include sedation and dry mouth [2]. A less common side effect is depression, primarily seen in patients with a history of stroke or depression [3]. However, there have been a handful of case reports discussing more severe psychological derangement ranging from acute isolated hallucination to delirium [4–7]. In all cases, the symptoms resolved with the cessation of clonidine treatment or eventually subsided over time. We are reporting a case of delirium believed to be secondary to clonidine therapy. We believe this relationship has not been reported since 1981 [7].

A 52-year-old male with a past medical history significant for diabetes mellitus, hypertension, end-stage kidney disease, peripheral vascular disease, stroke, and depression was admitted to the hospital for hypertensive urgency. On initial assessment in the Emergency Room, the patient was alert, oriented, and appropriately answering questions. His blood pressure was 240/110 and his pulse was 89 and regular. He has status post-bilateral lower extremity amputations. Otherwise, the physical exam was within normal limits. His EKG was without ischemic changes (Table 1).

The patient was given lopressor 5 mg IV with no improvement. He was then given clonidine 0.2 mg PO with a slight change in blood pressure to 220/100. Once moved

Table 1
Results of initial diagnostic testing

| | |
|---|---|
| Initial laboratory data | $Na^{1+}$ 141 $K^{1+}$ 4.5 $Cl^{1-}$ 100 HCO3 26 BUN 29 Creat 3.4 $Ca^{2+}$ 9.9 Hbg 13.4 Hct 43.5 WBC 6.5 Platelet 162 CPK 38 Glucose 112 |
| Chest X-ray | No evidence of infiltrate or effusions. Heart size within normal limits |
| Electrocardiogram | Normal sinus rhythm at 87 bpm, no axis deviation, LVH by voltage criteria, flipped T-waves in leads I, AVL, V4–V6, consistent with a strain pattern. |

* Corresponding author.
*E-mail address:* jdelaney@montefiore.org (J. Delaney).

0167-5273/$ - see front matter © 2006 Published by Elsevier Ireland Ltd.
doi:10.1016/j.ijcard.2005.09.032

to the floor, the patient was restarted on his outpatient blood pressure regimen: Imdur 60 mg PO QD, Metoprolol XL 100 mg PO QD, and Lasix 80 mg PO QD. He was also continued on clonidine at 0.2 mg PO TID. His blood pressure decreased to 150/90.

On the second day of the hospitalization the patient was no longer oriented to the place or date, was agitated, and was having visual hallucinations that consisted of people hiding under his bed. The patient also was having delusions that the nursing staff was trying to harm him, and he threatened to cut off their ears. A work-up for acute delirium was initiated (Box 1).

Box 1
Work-up for acute delirium

Laboratory values

$B_{12}$: 1714
Folate: 7.70
TSH: <0.002
Free $T_4$: 2.03
RPR: non-reactive

Imaging

Non-contrast Head CT scan: No mass, shift, or bleed. Small vessel ischemic changes of undetermined age. No evidence of acute change.

The work-up revealed mild hyperthyroidism which endocrinology did not feel was responsible for the patient's current mental status. Without another clear etiology, the clonidine was titrated off. Approximately one day after the drug's cessation, the patient's mental status returned to baseline. The patient was started on Altace and he was discharged with a blood pressure of 120/60.

The etiology for this patient's delirium is believed to be clonidine therapy. This is mainly supported by the temporal relationship between the initiation and cessation of therapy and the onset and resolution of psychiatric symptoms. Furthermore, additional work-up, as above, was unrevealing.

To the best of our knowledge, there are six previously reported cases of clonidine therapy temporally associated with severe psychological side effects. All but one episode resolved with cessation of clonidine therapy [4–7]. In the outstanding case, the symptoms resolved over time even though the clonidine was not stopped.

Upon review of the published cases, it is difficult to predict which patients are more likely to suffer such side effects (Table 2). History of a psychological disorder does not clearly predispose a patient, as only two out of the six cases suffered from mental illness, one with depression and the second with cyclothymic disorder [4,5]. Dose of the drug does not appear to be a risk factor, as one patient developed hallucinations on only 0.1 mg daily [4]. Duration of treatment also does not seem to be a predisposing factor as some patients developed side effects immediately after initiating treatment while others developed side effects when a dose increase was initiated following years of treatment.

Although rarely reported, hallucinations and/or delirium appear to be real side effects of clonidine treatment, which are reversible with cessation of the drug. Given the large clinical burden of hypertension [8] and the not uncommon requirement for polypharmacy to achieve blood pressure goals [9], heightened clinical awareness of this potential side effect appears justified. Future case control studies may help to elucidate risk factors for this potential side effect of clonidine.

Table 2
Demographic and outcome data from previous studies

| Demographics | Past medical history | Previous clonidine use and dose | Dose of clonidine | Symptoms from clonidine intake | Time to return to baseline mental status after cessation of drug |
|---|---|---|---|---|---|
| 68-year-old female [4] | Hypertension depression | 0.2 mg PO QD | 0.3 mg PO QD | Visual hallucinations | Within several days |
| 31-year-old female [4] | Hypertension diabetes mellitus, type 1 | No | 0.2 mg PO QD | Visual hallucinations | Within one week |
| 50-year-old female [4] | Hypertension | No | 0.1 mg PO QD | Auditory hallucinations | Within one week |
| 40-year-old female [5] | Hypertension cyclothymic disorder | No | 0.075 mg PO TID | Acute psychotic episode | 18 days |
| 54-year-old male [6] | Hypertension | No | 0.9 mg (total dose) daily | Acute paranoid reaction with auditory hallucinations | 1 day |
| 34-year-old male [7] | Hypertension | 0.1 mg PO BID | 0.2 mg PO BID | Delirium with visual hallucinations | Within 4 days with reduction of dose to 0.1 mg BID |

## References

[1] Bousquet P, Feldman J, Schwarz J. Central cardiovascular effects of alpha adrenergic drugs: differences between catecholamines and imidazolines. J Pharmacol Exp Ther 1984;230:232–6.
[2] Lowenstein J. Drugs five years later: clonidine. Ann Intern Med 1980;92:74–7.
[3] MacDougal Al, Addis GJ, MacKay N, et al. Treatment of hypertension with clonidine. Br J Med 1970;3:440–2.
[4] Brown MJ, Salmon D, Rendell M. Clonidine hallucination. Ann Intern Med 1980;93:456–7.
[5] Elizur A, Liberson Z. An acute psychotic episode at the beginning of clonidine therapy. Prog Neuro-Psychopharmacol 1980;4(2):211–2.
[6] Enoch MD, Hammad GE. Acute hallucinosis due to clonidine. Curr Med Res Opin 1977;4:670–1.
[7] Hoffman WF, Ladogana L. Delirium secondary to clonidine therapy. N Y State J Med 1981;81:382–3.
[8] American Heart Association. Heart disease and stroke statistics—2003 update. Dallas, Texas: American Heart Association; 2002.
[9] Chobania AV, Bakris GL, Black HR, et al. Seventh report of the joint national committee on prevention, detection, evaluation, and treatment of high blood pressure: the JNC 7 report. JAMA 2003;289:2560–71.