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Anesthesiology
59:73-74, 1983

Clonidine Withdrawal Complicated by Amitriptyline Therapy

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Withdrawal from clonidine characterized by rebound hypertension and tachycardia is a recognized, but infrequent, complication of therapy with this drug. The withdrawal syndrome may be exacerbated by other drug therapy, particularly beta adrenergic receptor blockers.¹⁻³ We recently encountered a patient who had a lengthy period of rebound hypertension, tachycardia, and anxiety after sudden cessation of clonidine and amitriptyline therapy.

REPORT OF A CASE

A 73-year-old woman was admitted after a 12-hr illness consisting of nausea, vomiting, and abdominal pain. Her medications included digoxin 0.25 mg and furosemide 40 mg every day, amitriptyline 25 mg four times a day, and clonidine 0.1 mg twice a day. Her arterial blood pressure was 156/80 mmHg and heart rate was 96 beats·min⁻¹. Eight hours after admission, an exploratory laparotomy and resection of 2 feet of necrotic jejunum was performed. Because of insufficient ulnar circulation to both hands, arterial blood pressure was measured indirectly either by blood pressure cuff and stethoscope or an oscillometric monitor (Dinamap®). The patient was given an enflurane and nitrous oxide anesthesia, supplemented by small doses of morphine. Muscle relaxation was induced by pancuronium. At the beginning of the procedure, the arterial blood pressure was 170/90 mmHg and heart rate was 100 beats·min⁻¹ but during the anesthetic, arterial blood pressure was as high as 220/120 mmHg, with a heart rate of 120 beats·min⁻¹; arterial blood pressure was controlled by increasing the concentration of enflurane. Because she had not taken

any of her regular medications for approximately 24 hr, she was given 500 mg of alpha methyl dopa iv during surgery. On the first postoperative day, arterial blood pressure ranged from 170/120-240/150 mmHg, with heart rate of 100-135 beats·min⁻¹. Alpha methyl dopa 250 mg was given iv every 6 hours and nitroprusside for sudden increases in arterial blood pressure. Despite adequate analgesia and diazepam administration, she complained of extreme anxiety. On the second postoperative day, the dose of alpha methyl dopa was increased to 500 mg q 6 hr; nitroprusside was used briefly. Because tachycardia was a prominent part of her syndrome, she also was given propranolol 1 mg IV q 6 hrs. On that day arterial blood pressures were as high as 220/70 mmHg and heart rates 95-105 bpm. On the third postoperative day her arterial blood pressure was 210/90 mmHg at 0800. Alpha methyl dopa and propranolol were continued. Two hours later, arterial blood pressure was 170/90 mmHg and the propranolol was decreased to 0.5 mg q 6 hrs. By that evening, arterial blood pressure was 140/80 mmHg and the propranolol was discontinued. On the following day, arterial blood pressure ranged from 160/70 to 120/70 mmHg and the alpha methyl dopa was decreased to 250 mg q 6 hrs. Her blood pressure has remained well controlled since on 250 mg of alpha methyl dopa four times a day.

DISCUSSION

Clonidine is a central alpha agonist and blocks sympathetic outflow from the central nervous system.⁴ Upon cessation of therapy, catecholamine levels in blood and urine have been found to increase by more than 100%.^{5,6} This increase in catecholamines is felt to be responsible for the symptoms of agitation, anxiety, insomnia, headache, nausea, tremor, and palpitations, and in some patients may lead to a severe "rebound" hypertension. Such a withdrawal can begin as soon as 8 hours or up to 36 hours after the last dose and last 72-96 hours.

Other drug therapy can add to the withdrawal phenomenon. Simultaneous withdrawal of beta adrenergic blocker or withdrawal of clonidine without discontinuance of a beta blocker may result in an unopposed alpha adrenergic crisis.^{1,2} In our case, the therapy with amitriptyline may have contributed to and prolonged

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Key words: Sympathetic nervous system; sympathetic agents, clonidine, alpha methyl dopa, tricyclic antidepressants. Complications: hypertension.

the rebound hypertension and tachycardia. Tricyclic antidepressants in clinical doses have been found to potentiate the pressor effects of norepinephrine.⁷ This can be explained by the blockade of norepinephrine uptake at the adrenergic nerve terminal by the tricyclic drug.⁸ Addition of tricyclic antidepressant therapy to clonidine may interfere with its antihypertensive effect because of the accumulation of norepinephrine outside the nerve terminal.⁹ Although the plasma half-life of amitriptyline is short, less than 30 min, the effects of this drug last for many days.⁸ Thus, the increased amounts of circulating catecholamines that are present after cessation of clonidine may have been slowed in returning to the nerve terminal because of the block of the uptake mechanism by amitriptyline, and rebound hypertension may be more likely in this setting. Tricyclic antidepressant also may block the uptake of methyldopa, because it has been shown experimentally that imipramine given 30 min before methyldopa inhibited the expected decrease in blood pressure.¹⁰

The surgical patient who will not be taking oral medication presents a particular problem because other therapy must be substituted. Perhaps a drug, such as reserpine, which depletes catecholamines might be given for 3 days before withdrawal,^{5,6} or there could be a gradual tapering with substitution of hydralazine.¹ However, for emergency surgery this is not possible. When there is not time to institute a planned withdrawal from clonidine, we have been starting treatment with methyldopa, because its primary antihypertensive effect is by the same mechanism as clonidine, central block of sympathetic outflow.¹¹ Methyldopa should be started as early as possible because it must be biotransformed to methylnorepinephrine, the active compound, before taking effect. It is difficult to evaluate the efficiency of this approach, because not all patients actually will get rebound. Although use of methyldopa may not abolish the need for additional pharmacologic treatment, as seen in our patient, it may decrease the duration and severity of the hypertension. In our patient, the recent amitriptyline therapy may have made methyldopa less effective. When the syndrome of rebound hypertension does develop, treatment with combinations alpha and

beta adrenergic blockers have been recommended,^{5,6} as well as vasodilators, nitroprusside, and hydralazine.¹

With the rapid increase in modalities of antihypertensive therapy and the trend toward shorter-acting drugs, anesthesiologists must be aware of the potential effects caused by discontinuation of medications before operation. In particular, clonidine, alone and in combination with other drugs, has been implicated frequently in a syndrome of sympathetic rebound. In any patient at risk for this syndrome, treatment needs to be aggressive enough to avoid the possible central nervous system and cardiac complications of severe hypertension.

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