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The Use of Rectal Clonidine in the Perioperative Period

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Clonidine is an orally administered, centrally acting, antihypertensive drug that is unavailable parenterally in the United States. It is a relatively selective α_2 adrenergic agonist.[1] Stimulation of the presynaptic α_2 receptors by clonidine or norepinephrine mediates inhibition of further norepinephrine release. This serves as a negative feedback loop modulating norepinephrine output. Alpha$_2$ stimulation in the CNS reduces sympathetic outflow, reduces catecholamine levels, and reduces blood pressure.

Rebound hypertension can occur following the abrupt withdrawal of clonidine.[2-4] The onset of this phenomenon usually occurs from 10 h to 7 days after discontinuation of therapy. However, there is no evidence that problems with discontinuation of clonidine therapy are more common than those with other drugs of its type, such as methyldopa.[5] Rebound hypertension also has been reported following the acute withdrawal of guanethidine, diuretics, reserpine, and beta adrenergic blockers.

There are many circumstances in the perioperative period when oral clonidine either cannot be used or is ineffective. The following is a report of a case in which "clonidine rebound" was managed successfully with the rectal administration of clonidine when other drugs, including nitroprusside and oral clonidine, failed. We have used this technique for over 2 yr for maintenance therapy when oral medication is impossible, when withdrawal has been abrupt, or for starting therapy in the postoperative period.

REPORT OF A CASE

A 64-year-old woman, receiving steroid therapy for dermatitis, was admitted to the surgical intensive care unit (SICU) with acute epigastric pain and hematemesis. She had been receiving chronic antihypertensive therapy, which consisted of aldactone, 30 mg bid, and clonidine, 0.2 mg bid. Her arterial blood pressure was 150/80 mmHg. The ECG showed an old inferior wall myocardial infarction with left bundle branch block. The chest roentgenography showed left ventricular hypertrophy. Hemoglobin and hematocrit were 9.6 g/dl and 29%, respectively. The patient was medically managed in the SICU for 3 days, during which time she was without pain following nasogastric intubation. A gradual increase in her arterial blood pressure to 176/102 mmHg occurred despite the continued administration of aldactone and clonidine through the nasogastric tube. Heart rate remained stable, varying between 60 to 80 beats/min during the preoperative period. Gastric *p*H was maintained at 7.0 with antacids and cimetidine. Parenteral steroids were continued for control of exfoliative dermatitis. The patient's condition deteriorated on day 3, and she was prepared for surgery to stop persistent gastric hemorrhage.

An arterial line and pulmonary artery flow-directed catheter were inserted before induction of anesthesia. Preinduction arterial blood pressure was 200/100 mmHg with a heart rate of 130 beats/min. Cardiac output was 3.0 l/min, with a central venous pressure (CVP) of 7 mmHg and pulmonary capillary wedge pressure (PCWP) of 13 mmHg. Pulmonary artery pressure was 24/11 mmHg. Morphine and diazepam were given iv and anesthesia was maintained with enflurane/oxygen. Muscle relaxation was produced with 10 mg metocurine. Blood pressure was controlled with enflurane in the range of 110/60 mmHg, with a heart rate averaging 65 beats/min for the uneventful 4-h procedure. A partial gastrectomy was performed. Muscle relaxation was reversed with 0.5 mg glycopyrrolate and 2.5 mg neostigmine. The patient was awakened and the trachea extubated in the operating room.

Arterial blood pressure gradually increased to 190/110 mmHg in the immediate postoperative period. The ECG showed a normal sinus rhythm with a rate of 70 beats/min. Intravenous morphine was given in 2-mg increments for pain control. The patient expressed comfort at a total dose of 8 mg. A nitroprusside infusion was started at a rate of 1 $\mu g \cdot kg^{-1} \cdot min^{-1}$. A second infusion of nitroglycerine was started at a rate of 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$ after the ECG demonstrated anterior wall ischemia. The postoperative CVP and PCWP were 6 and 10 mmHg, respectively. Arterial blood pressure did not respond to increasing doses of nitroprusside or nitroglycerine infusions over the next 36 h. Therapy included a total of 250 mg nitroprusside, 354 mg phentolamine, 20 mg reserpine, 750 mg alpha methyldopa, 50 mg ethacrynic acid, 12 mg prazosin, and 276 mg of nitroglycerine iv. Clonidine, 5.2 mg, was administered *via* the nasogastric tube without apparent effect. Antacids were continued for gastric *p*H control.

We regarded this refractory hypertension as a clonidine withdrawal syndrome. Clonidine, 0.4 mg, was crushed and mixed in 30 cc of sorbitol. This was given per rectum through a Foley catheter. The 10-cc balloon of the catheter was inflated intrarectally and the clonidine given as a retention enema, allowing a dwell time of 30 min. A response was noted within 45 min, and arterial blood pressure reached an acceptable 140/90 mmHg within 3 h. No ancillary antihypertensives were required within 6 h. Blood pressure was controlled with rectal clonidine alone, using preoperative dose schedule of 0.2 mg bid. This regimen was continued for 3 weeks after surgery until oral medication could be tolerated.

OTHER CASES

Within a period of 2 months, clonidine was used per rectum in five additional patients who required blood pressure control in the ICU

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TABLE 1. Arterial Blood Pressure (BP) Responses (mmHg) in Response to Rectally Administered Clonidine

Patient No.	Procedure	A*		B†‡	C§	
		BP	Dose	BP	BP	Dose (mg)
2	Radical hysterectomy	140/85	0.2 mg bid	220/95	150/70	0.4
3	Hysterectomy	130/80	0.2 mg bid	185/95	145/70	0.2
4	Partial gastrectomy	170/80	0.2 mg qid	210/110	155/90	0.2
5	Radical neck dissection	140/80	0.3 mg qid	190/100	140/80	0.3
6	Vagotomy, pyloroplasty	135/70	0.2 mg qid	185/100	140/80	0.2

Age range, 36–78.
* A = Preoperative blood pressure and oral clonidine dose.
† B = Blood pressure circa 24 h postsurgery and controlled pain.
‡ Heart rates varied considerably, but no patient was tachycardic at 24 h.
§ C = Rectal clonidine dose and blood pressure 2 h after administration.

(table 1). All of the patients had either upper gastrointestinal surgery or postoperative ileus. All of the patients had been taking clonidine before emergency admissions, had nasogastric tubes in place, and were receiving antacid therapy to prevent stress ulceration. Intravenous morphine was used for pain control. We noted that oral clonidine was not effective in these circumstances. Onset of pressure response to rectal clonidine was similar to that observed for oral clonidine in more normal circumstances.

DISCUSSION

The occurrence of rebound hypertension after abrupt cessation of clonidine therapy has received considerable attention. However, the incidence and mechanisms have not been established clearly. Most reported cases of "clonidine withdrawal" represent the abrupt cessation of other antihypertensive drugs as well. Evidence exists that the abrupt withdrawal of certain antihypertensive combinations produces blood pressure increases far more extreme than those expected after withdrawal of a single agent.[5] Most of the cases reported in the anesthesia literature, including ours, represent multiple drug withdrawals.[6–9]

We designated this case as a "clonidine withdrawal syndrome" because the malignant course was arrested only after the rectal administration of clonidine. Rectal clonidine was successful when other powerful antihypertensives, including oral clonidine, were ineffective. Clonidine is completely absorbed after oral administration in man.[1–5] However, we noted that oral or nasogastric administration of clonidine is frequently ineffective or unreliable in the critically ill surgical patient. This may be related to malabsorption due to ileus, loss of gastric or intestinal mucosa, or a physical barrier by the antacid. We have noted, in these circumstances, that the rectal administration of clonidine is an effective alternative. Furthermore, we have noted that the time of onset and duration of action of rectal clonidine is similar to that of the usual oral dose.

This phenomenon may be related to a similar observation by de Leede *et al.*[10] in comparing blood levels of propranolol given orally, iv, or per rectum in humans. Propranolol was more effectively absorbed per rectum compared to oral medication. The absorption/plasma level ratio for the rectal route was midway between that of the iv and oral route. Drugs given per rectum may escape first order hepatic elimination owing to absorption through lower rectal hemorrhoidal drainage. The efficacy of rectal clonidine also may be related to its *p*K of 7. The *p*H of the normal rectal also is, 7 which would enhance its absorption. An alkaline gastric *p*H should enhance absorption, but observation to the contrary points to a physical barrier produced by the administration of the antacids.

Medical literature notes that "clonidine rebound hypertension" is rare unless the total daily dose exceeds 1.2 mg. The usual daily dose ranges from 0.3 to 2.4 mg. This dose range greatly exceeds the total dosage noted in our first six cases and that of other reports of "rebound" in the anesthesia literature.[3,5,6,11] It is difficult to discern from the published reports whether clonidine rebound in the surgical patient is related to actual drug withdrawal or the reemergence of hypertension in the absence of treatment. Increased sympathetic activity related to the pain and stress of surgery may explain the earlier onset and lower doses associated with clonidine rebound in the surgical patient compared to the unstressed medical patient. We excluded, on clinical grounds, pain as a significant source of postoperative hypertension in these patients.

The use of rectal clonidine became widespread throughout our hospital following initial observations. The known danger of withholding clonidine excluded double-blind studies. The actual number of cases managed in this manner over the past 2 yr is unknown, but has become an accepted procedure in our recovery rooms and surgical specialty care units. No case of suspected "clonidine rebound" has been noted since the institution of this regimen. We have further noted that clonidine tablets can be suspended and administered in saline. This is now our choice of suspension because it can be readily prepared at the bedside.

References

1. Hoefke W: Clonidine, Pharmacology of Antihypertensive Drugs. Edited by Scriabine A. New York, Raven Press, 1980, pp 55–78
2. Houston MC: Clonidine hydrochloride: review of pharmacologic and clinical aspects. Prog Cardiovasc Dis 23(5):337–349, 1981
3. Lowenstein J: Clonidine. Ann Intern Med 92:74–77, 1980
4. Reid JL: The clinical pharmacology of clonidine and related central antihypertensive agents. Br J Clin Pharmacol 12:295–302, 1981
5. Weber MA: Discontinuation syndrome following cessation of treatment with clonidine and other antihypertensive agents. J Cardiovasc Pharmacol 2(suppl 1):S73–S89, 1980
6. O'Connor DE: Accelerated acute clonidine withdrawal syndrome during coronary artery bypass surgery. Br J Anaesth 53:431–433, 1981
7. Bruce DL, Croly TF, Lee JS: Preoperative clonidine withdrawal syndrome. ANESTHESIOLOGY 51:90–92, 1979
8. Brodsky JB, Brave JJ: Acute postoperative clonidine withdrawal syndrome. ANESTHESIOLOGY 44:519–520, 1976
9. Stevens JE: Rebound hypertension during anaesthesia. Anaesthesia 35:490–491, 1980
10. de Leede LGH, Hug CC Jr, de Lange S, de Boer AG, Breimer DD: Rectal and intravenous propranolol infusion to steady state: kinetics and β-receptor blockade. Clin Pharmacol Ther 35: 148–155, 1984
11. Geest S, Dijk RB, Donker JM: Clonidine withdrawal in a patient with heart failure. Crit Care Med 3(5):444–445, 1985

Erratum

In the article "Intramuscular Midazolam for Pediatric Preanesthetic Sedation: A Double-blind Controlled Study with Morphine," by L. Rita, F. L. Seleny, A. Mazurek, and S. Rabins (ANESTHESIOLOGY 63:528–530), under Discussion, second line in the fourth paragraph, the correct dose of midazolam should be 0.08 mg/kg, not 0.8 mg/kg.