Results

The bone mineral mass of the 23 epileptic patients and the 20 normal subjects compared with the values of other normal subjects matched for age and sex are shown in the chart. The initial values of all the 23 epileptic patients were below the corresponding normal mean value. In the group of epileptic patients treated with calcium lactate and vitamin D the mean bone mineral mass rose significantly. In the other three groups the mean bone mineral mass was unchanged (see chart).

Discussion

As previously found, the epileptic patients as a group had subnormal values (Berger and Munde, 1970; Linde *et al.*, 1971; Christiansen *et al.*, 1972), while the values in the normal subjects scatter around the mean.

This finding, and the unchanged values in both groups of normal subjects and in the placebo groups of epileptic patients, underlines that the method used is well reproducible (Christiansen and Rødbro, 1973). Our earlier findings (Christiansen *et al.*, 1972), that bone mineral mass rises in epileptics during treatment with a small dose of vitamin D, are confirmed.

In this study we have found a 3% increase in bone mineral mass, while we previously found an increase of nearly 7% (Christiansen *et al.*, 1972). Two factors might contribute to this disparity. Firstly, the initial values of our nine patients were higher than the initial values of the patients in our earlier report. Secondly, the two studies were not planned in the same way, as the patients in the earlier study were treated with calcium lactate for one month before the treatment with vitamin D.

Assuming that bone mineral mass in the forearm is representative of total body calcium (Christiansen and Rødbro 1973), and that the mean value of normal young men corresponds to 1,000 g of total body calcium (Christiansen *et al.*, 1972), it can be calculated that the mean total body calcium in the epileptic patients on vitamin D rose from 699 to 716 g, corresponding to a mean positive calcium balance of 0·5 g per day during the trial.

The present study confirms that the epileptic patients, as a group, have subnormal values of bone mineral mass. Furthermore it shows that epileptic patients treated with vitamin D respond to this treatment, while normal subjects treated with vitamin D and epileptic patients treated with calcium lactate and placebo do not.

We thank Mrs. Birthe Jørgensen for valuable technical help, and the Danish Epilepsy Association for financial support.

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Effects of Clonidine Withdrawal: Possible Mechanisms and Suggestions for Management

STEPHEN N. HUNYOR, LENNART HANSSON, TIMOTHY S. HARRISON, SIBLEY W. HOOBLER

British Medical Journal, 1973, 2, 209–211

Summary

A severe rebound rise in blood pressure with agitation and insomnia had been noted in five patients when they had previously ceased clonidine (Catapres) This has been shown to be reproducible in these patients and to be associated with a significant increase in urinary catecholamine excretion. The blood pressure can be controlled and the symptoms alleviated promptly by alpha and beta adrenergic receptor blockade using intravenous phentolamine and propranolol.

Repatriation General Hospital, Sydney, N.S.W., Australia
STEPHEN N. HUNYOR, M.B., M.R.A.C.P., Staff Specialist in Hypertension (Recipient of a Travel Grant of the National Heart Foundation of Australia)

Department of Internal Medicine, Sahlgrenska Hospital, Gothenburg, Sweden
LENNART HANSSON, M.D., Physician

University of Michigan Medical Center, Ann Arbor, Michigan, U.S.A.
TIMOTHY S. HARRISON, M.D., Professor of Surgery
SIBLEY W. HOOBLER, M.D., Professor of Internal Medicine, Head, Section of Hypertension

Introduction

Clonidine has found use as an antihypertensive agent in moderate (Smet *et al.*, 1969; Parsons and Morledge, 1970) and severe (Raftos, 1969) hypertension, and when side effects such as orthostatic hypotension make adrenergic blocking agents impractical (Hoobler and Sagastume, 1971). It has a largely central site of action, and in rabbits it has been shown to have a central inhibitory action on adrenal catecholamine release (Shaw *et al.*, 1971). A dose-related depression of urinary catecholamine levels has been shown in man (Hökfelt *et al.*, 1970).

Sudden cessation of clonidine has been seen to result in severe rises in blood pressure (Hökfelt *et al.*, 1969 1970; Hoobler, 1969) and a symptom complex of agitation, insomnia, and palpitations. The cause of the symptoms has been suggested to be a large catecholamine release, and some data after short-term therapy support this view (Hökfelt *et al.*, 1970). Identification and further study of this phenomenon is reported.

Materials and Methods

Five patients were studied who had a previously well-documented blood pressure overshoot when clonidine (Catapres)

had been temporarily stopped. All were admitted to the Clinical Research Unit of University Hospital. Informed consent was obtained for sudden withdrawal of clonidine under controlled conditions and for treatment of any rebound which might arise.

The patients chosen had all been on chronic clonidine treatment (2-4 years) and were taking varying doses (0·3-2·4 mg/day) of the drug.

For three days the treatment regimen was unchanged while baseline blood pressure and heart rate observations were made and urine was collected for estimation of catecholamines during a 12-hour overnight period. Several hours before placebo substitution a control sample was collected for arterial plasma catecholamine estimation. After placebo substitution, successive three-hourly urine specimens were collected and the sample which best reflected the urine secretion during the crisis was sent for analysis. An arterial blood sample for plasma catecholamines was obtained at the peak of blood pressure rebound.

All fractional urinary catecholamines were expressed as μg/24 hr.

In three cases intravenous alpha and beta sympathetic blockade was used in treatment of the crisis and was administered during collection of the urine sample. Propranolol (0·2 mg/kg given intravenously over four minutes) was given in blocking doses (Jose, 1966). Immediately afterwards phentolamine was injected over a period of 30 minutes in 5-10 mg bolus amounts up to a total dose of 20-30 mg.

One patient (case 5) was treated with reserpine 1·0 mg intramuscularly twice daily for three days before clonidine withdrawal. One other patient (case 3) received small oral doses of alpha and beta blockers (phenoxybenzamine 40 mg/day, propranolol 80 mg/day) because she gave a past history of bronchial asthma with wheeze.

Blood pressure was measured in the recumbent position with a standard 14 cm cuff. The diastolic level was taken as phase IV (muffling) of the Korotkoff sounds.

Urine and plasma catecholamines were estimated by the method of von Euler and Lishajko (1961).

Data were statistically analyzed using the t test for paired comparisons.

Results

Four of the five patients studied developed a severe blood pressure overshoot. From an average level of 147/104 mm Hg on clonidine the blood pressure rose within 8-24 hours of withdrawal to 216/161 mm Hg ($P < 0·01$ systolic, $P < 0·01$ diastolic (table I)). However, in one patient (case 5), who had been pretreated with parenteral reserpine, the blood pressure rose by 45/25 mm Hg compared to a mean rise in the others of 69/57.

The overshoot blood pressure level (average 222/170 mm Hg) in three patients (cases 1, 2, and 4) was lowered with the intravenous propranolol and phentolamine regimen to 169/117 mm Hg ($P < 0·01$ systolic, $P < 0·02$ diastolic). The blood pressure was kept under control for up to one and a half hours after stopping phentolamine, but in case 4 the hypotensive response to phentolamine was much more short-lived (10 minutes). This is unexplained, as the urinary catecholamine pattern was no different from the others.

The heart rate response during blood pressure overshoot (table II) bore no relation either to the relative proportion of adrenaline to noradrenaline in urine or plasma or to the degree of blood pressure rise.

TABLE I—*Blood Pressure Data (mm Hg)*

Case No.	B.P. on Clonidine*	Overshoot (Rebound) Level	B.P. after Intravenous Propranolol + Phentolamine	Previous Overshoot Level
1	155/108	220/165	160/105	224/144
2	140/104	195/155	140/115	220/160
3	118/88	200/135	—	250/160
4	175/117	250/190	206/130	254/180
5†	130/95	175/120	—	240/150

*Average of three days before withdrawal of clonidine.
†Reserpine pretreated.

TABLE II—*Heart Rate Response During Rebound*

Case No.	Difference in B.P. (mm Hg) (Overshoot)	Heart Rate (Beats/min)		
		Control	Overshoot	Difference
1	65/57	85	82	−3
2	55/51	75	95	20
3	82/47	75	100	25
4	75/73	65	65	0
5*	45/25	65	75	10

*Reserpine pretreated.

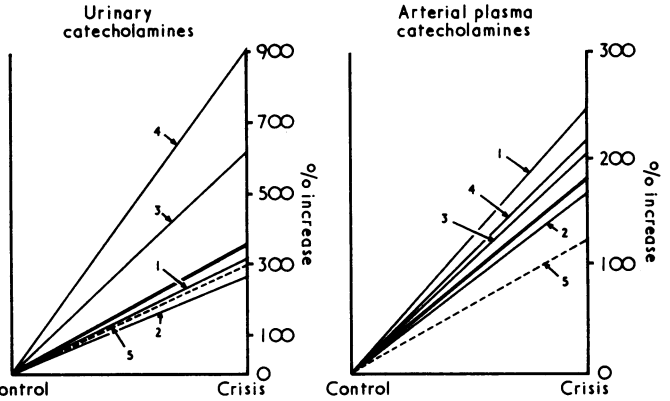
All control urinary total catecholamine levels were in the normal range (average 28 μg/24 hr (table III)). The normal urinary catecholamine excretion in the reserpine-pretreated patient (case 5) corresponds with published data (McDonald and Weise, 1962). During withdrawal of the drug there was a rise in these levels in all patients to an average value of 99 μg/24 hr ($P < 0·05$). However, the absolute increase was lowest and the percentage increase second lowest in the patient (case 5) (table III, graph) pretreated with reserpine

TABLE III—*Urinary Catecholamines (μg/24 hr)*

Case No.	Noradrenaline		Adrenaline		Total Catecholamines	
	Pre	Post	Pre	Post	Pre	Post
1	33	70	3·5	46	36	116
2	54	195	19	5·7	73	200
3	3·8	25	4·4	26	8·2	52
4	3·3	28	5·6	53	8·9	81
5*	8·0	37	6·7	7·8	15	45
Mean, Cases 1–4 ..	23	80	8·2	33	32	112 ($P<0·02$)
Mean, Cases 1–5 ..	20	71 (N.S.)	7·9	28 (N.S.)	28	99 ($P<0·05$)

*Reserpine pretreated.
Pre = Control specimen on clonidine. Post = Postwithdrawal sample, encompassing the rebound period. N.S. = Not significant.

Arterial plasma catecholamines rose in the crisis period in every patient (average 0·56 to 1·03 μg/l (table IV)). The smallest increase occurred in the reserpine-pretreated patient (case 5) (see graph).



Percentage change in urinary and arterial plasma catecholamines from control (on clonidine) to crisis (rebound) period. Numbers on graphs refer to individual patients. Broken line represents the reserpine-pretreated patient. Heavy line is mean of the five estimations.

TABLE IV—*Plasma Catecholamines* (μg/l.)

Case No.	Noradrenaline		Adrenaline		Total Catecholamines	
	Pre	Post	Pre	Post	Pre	Post
1	0·01	0·02	0·11	0·27	0·12	0·29
2	0·01	0·02	0·42	0·74	0·42	0·76
3	0·66	2·30	0·60	0·30	1·26	2·61
4	0·01	0·04	0·25	0·56	0·26	0·60
5	0·44	0·77	0·29	0·12	0·74	0·89
Mean, Cases 1–4 ..	0·17	0·59	0·34	0·47	0·51	1·06 (N.S.)
Mean, Cases 1–5 ..	0·23	0·63	0·33	0·40	0·56	1·03 (N.S.)

Abbreviations as in table III.

Discussion

This report defines a syndrome after abrupt withdrawal of clonidine. The condition bears a close resemblance to crises seen with phaochromocytoma with the associated rise of urinary and arterial plasma catecholamines. There is an equal percentage rise in urinary noradrenaline and adrenaline levels. This is compatible with excessive adrenergic nervous discharge in addition to augmented adrenal catecholamine release. The latter would conceivably occur when the clonidine-induced blockade of reflexly-mediated adrenal catecholamine secretion (Shaw *et al.*, 1971) was removed.

Hökfelt *et al.* (1970) drew attention to increased urinary catecholamines after clonidine withdrawal. While we have confirmed and extended his observations, we were unable to see the clonidine dose-related suppression of urinary catecholamines which he described. In fact, the patient (case 2) taking the largest dose of clonidine (2·4 mg/day) had the highest control urinary catecholamines with levels in the high normal range. This may relate to the fact that our patients were all on chronic therapy (2-4 years), a situation in which some escape from the adrenal suppressant effect of the drug seems to occur. In contrast, the data of Hökfelt *et al.* (1970) showing suppression of adrenal catecholamine secretion on clonidine derive from short-term studies.

No correlation was noted between the clonidine dose (range 0·3-2·4 mg/day) and the severity of blood pressure overshoot. While all patients in this study had been taking the drug for 2-4 years, it seems that short-term treatment (6-30 days) may be associated with similar problems (Hökfelt *et al.*, 1970).

It is hard to establish with certainty that the high crisis blood pressures recorded represent an actual overshoot. However, the readings reached were clearly excessive, were associated with abnormal catecholamine excretion, and far exceeded any previous readings in the patient's clinic chart, including three instances where initial pretreatment figures were available.

Patients studied in this report were selected because of a previously shown severe hypertensive rebound on drug withdrawal. Several other studies have involved cross-over with clonidine (Putzeys and Hoobler, 1972), or conversion from clonidine plus thiazide to a thiazide alone (Parsons and Morledge, 1970). No unusual symptomatology is reported after the clonidine withdrawal although no systematic effort was made to record blood pressure in the immediate clonidine withdrawal period.

The increase in urinary total catecholamines as well as in plasma catecholamines in all patients confirms the finding of Hökfelt *et al.* (1970) that excess catecholamine release was contributing to the syndrome. Plasma catecholamines have not previously been studied in this response and the more clear-cut rise in urinary catecholamines underscores the problems of trying to detect what may be a transient plasma peak. It seems likely that in one patient (case 3), in whom plasma catecholamine levels rose virtually to phaochromocytoma levels, sampling occurred at the peak of catecholamine release.

These observations led to the following plan for clinical management of clonidine withdrawal: either (1) to prevent an overshoot of blood pressure by pretreatment, or (2) if an overshoot had already occurred, to treat the rebound with alpha and beta sympathetic blockers. It was reasoned that pretreatment with reserpine would modify the effects of withdrawal by depleting body catecholamine stores. In the patient who received large doses of parenteral reserpine the blood pressure overshoot was reduced. Theoretically, a longer course of small oral doses of reserpine (Abboud and Eckstein, 1964) should be equally effective in preventing a withdrawal response.

When a rebound is in the making or already established it is proposed that combined alpha and beta adrenergic blockade be undertaken with intravenous propranolol and phentolamine. Alternatively, oral clonidine can be readministered, or for more rapid action intravenous diazoxide or intravenous clonidine preceded by phentolamine offer other forms of management of the rebound phenomenon.

It seems advisable that patients on clonidine treatment should be warned of the possibility of a reaction occurring from 8 to 24 hours after stopping the medication. They should always have a reserve supply of clonidine and should carry instructions which would alert medical personnel in case of accident.

We wish to express our deep appreciation to Mr. John Seeton, of the catecholamine laboratory, for the catecholamine estimations, to the staff of the clinical research unit, and to Miss Judy Mertens for her valuable help with the manuscript.

This work was supported in part from U.S.P.H.S. grant No. 5-MO1-RR-42 to the Clinical Research Unit, University Hospital.

Requests for reprints should be addressed to: Dr. S. Hunyor, Hyertension Research, R 6669 Kresge Medical Research Building, University of Michigan Medical Center, Ann Arbor, Michigan 48104 U.S.A.

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