**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 15 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.

**References**

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**Effects of Clonidine Withdrawal: Possible Mechanisms and Suggestions for Management**

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

*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.

**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 (0-3-24 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 mg intramuscularly twice daily for three days before clonidine withdrawal. One other patient (case 3) received small oral doses of alpha and beta blockers (phenoxymenzamine 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.

Urinary 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.

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.

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

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Total Catecholamines</th>
<th></th>
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<th></th>
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<tr>
<td></td>
<td>Noradrenaline</td>
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<td>Noradrenaline</td>
<td>Adrenaline</td>
<td>Noradrenaline</td>
</tr>
<tr>
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<td>Pre</td>
<td>Post</td>
<td>Pre</td>
<td>Post</td>
<td>Pre</td>
</tr>
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<tr>
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<tr>
<td>Mean, Cases 1–4</td>
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<tr>
<td>Mean, Cases 1–5</td>
<td>0.23</td>
<td>0.63</td>
<td>0.33</td>
<td>0.40</td>
<td>0.56</td>
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</table>

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 phaehromocytoma with the associated rise of urinary and arteria 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 (Putzyes 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 phaehromocytoma 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 pre-treatment with phentolamine would modify the effects of withdrawal by depleting body catecholamine stores. In the patient who received large doses of parenteral phentolamine the blood pressure overshoot was reduced. Theoretically, a longer course of small oral doses of phentolamine (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.

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References