or thyroid hormones, or both, in patients who prove to be hypothyroid is also being considered.

References


Apparent resistance to hypotensive effect of clonidine

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British Medical Journal, 1977, 1, 136-138

Summary

Clonidine failed to reduce the blood pressures of two patients with essential hypertension. One was given 5-4 mg/day and the other 6 mg/day, and their respective peak plasma clonidine concentrations were 28-2 ng/ml and 14-4 ng/ml. Several months after the end of clonidine treatment a single oral dose of 0-3 mg of clonidine produced maximum falls in blood pressure of 30/22 mm Hg and 88/41 mm Hg with peak plasma clonidine concentrations of 14 ng/ml and 0-9 ng/ml. Resistance to the hypotensive effect of high doses of clonidine may be due to stimulation of peripheral alpha-adrenoceptors causing vasoconstriction, which maintains a raised blood pressure.

Introduction

Clonidine is a hypotensive agent widely used to treat patients with high blood pressure. The reported range of daily doses for optimum blood pressure control is 0-15-4-8 mg. When used in conjunction with a diuretic, however, the maximum effective dose of clonidine may be considerably lower in many patients. In some patients small initial doses of clonidine have lowered blood pressure but when the dose has been increased the blood pressure has risen and become refractory to the drug. We describe here two hypertensive patients whose blood pressures were apparently resistant to high doses of clonidine and the results of studies of both high and low doses of clonidine.

Case 1

A 44-year-old man presented with accelerated hypertension in May 1967, when his blood pressure was 200/140 mm Hg. He had electrocardiographic (ECG) evidence of left ventricular hypertrophy but no cardiac enlargement or impairment of cardiac or renal function. He had a family history of hypertension, but further investigation failed to show any primary cause. For two years he was treated with several antihypertensive drugs, including guanethidine, methyldopa, guanoxan, reserpine, and bendrofluazide. Blood pressure control was unsatisfactory, and side effects, particularly impotence, were unacceptable. In March 1969 clonidine (0-255 mg/day) was introduced. The dose was gradually increased over the next two and a half years to 7 mg/day in an attempt to obtain adequate blood pressure control. His impotence improved but he developed side effects of clonidine, including sedation, dry mouth, and constipation. Control of his blood pressure remained difficult despite the addition of propranolol, debrisoquine, and hydralazine. In October 1975 he was admitted to hospital for further assessment of treatment. His blood pressure was 170/120 mm Hg supine and 122/70 mm Hg erect, and he was receiving clonidine 5-4 mg, bendrofluazide 10 mg, propranolol 960 mg, and hydralazine 600 mg daily. Hydralazine and propranolol were stopped three days before the first (high-dose) clonidine study. After this study clonidine was withdrawn and blood pressure was controlled over the next eight months with labetalol 3-2 g and bendrofluazide 10 mg daily. This treatment was interrupted 16 hours before the second (low-dose) clonidine study.

Case 2

A 51-year-old woman had been hypertensive since her first pregnancy in 1959 (aged 34). There was a family history of hypertension, but investigation had shown no primary cause. Antihypertensive treatment was started with rauwolfia alkaloids in 1962, when her blood pressure was 190/125 mm Hg. This treatment was continued until 1972, when, with a blood pressure of 210/130 mm Hg, treatment was changed to a thiazide diuretic, debrisoquine, and clonidine, the latter in an initial daily dose of 0-2 mg. Blood pressure control remained difficult, however, despite the subsequent use of methyldopa, bendrofluazide, propranolol, and an increased dose of clonidine to a maximum of 6 mg/day by June 1974. She complained of sedation, dry mouth, and constipation on clonidine. In November 1975 she was admitted to hospital for further changes of treatment. At this time blood pressure was 186/122 mm Hg supine and 173/126 mm Hg erect, and she was receiving clonidine 6 mg, propranolol 480 mg, and bendrofluazide 10 mg daily. Propranolol was withdrawn three days before the first clonidine study. After this study clonidine was withdrawn, and her blood pressure was controlled on labetalol 2-4 g and bendrofluazide 10 mg daily. Seven months later the second clonidine study was performed 16 hours after the last dose of labetalol.

Method

Each patient was investigated twice: once during long-term clonidine treatment and again seven to eight months after stopping clonidine. In the first study both patients received their usual morning dose of clonidine—1 8 mg (case 1) and 1 5 mg (case 2) orally. In the second they were given a single 0-3-mg dose of clonidine orally. Both patients gave their informed written consent to the procedures. The investigation was performed in a quiet clinical laboratory, where the
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Patients rested supine throughout each study. They had fasted and received no drugs since the previous evening. An intravenous cannula in a forearm vein was used for blood sampling.

Supine blood pressure was recorded with an Arteriosonde 1217 automatic sphygmomanometer before clonidine and at intervals up to nine hours after dosing. Heparinised blood samples (25 ml) were taken at intervals up to 48 hours after drug administration for measuring plasma clonidine concentrations by selected ion-detection gas chromatography and mass spectrometry.4

Results

In case 1 resting supine blood pressure before the first study was 155/112 mm Hg. After oral clonidine 1.8 mg the blood pressure rose to a maximum of 193/142 mm Hg at three hours and then fell to 176/124 mm Hg at eight hours. The blood pressure never fell below the pre-dose level. In the second study blood pressure was 164/112 mm Hg before dosing and fell to 134/90 mm Hg three hours after oral clonidine 0.3 mg. At nine hours the blood pressure was 178/119 mm Hg (fig 1).

![Blood pressure graph](image1)

**FIG 1—Case 1. Systolic and diastolic blood pressure after oral clonidine 1.5 mg while on long-term high-dose treatment (O—O) and after 0.3 mg clonidine orally seven months after stopping clonidine (●—●).**

In case 2 resting supine blood pressure before the first study was 178/120 mm Hg and did not fall until six hours after an oral dose of 1.5 mg of clonidine. In the second study blood pressure was 200/115 mm Hg before dosing, and it fell rapidly to 112/74 mm Hg at three hours after clonidine 0.3 mg. At nine hours blood pressure was 151/104 mm Hg (fig 2).

The plasma clonidine concentration before dosing and the peak level on each occasion are shown in the table. During long-term high-dose clonidine treatment the peak levels were 26.2 ng/ml and 14.4 ng/ml respectively compared with 1.4 ng/ml and 0.9 ng/ml when a single 0.3 mg dose was given several months after stopping clonidine.

<table>
<thead>
<tr>
<th>Plasma clonidine concentration (ng/ml) in two hypertensive patients before and after clonidine when on chronic high-dose treatment (study 1) and seven to eight months later, after a single oral dose of clonidine 0.3 mg (study 2)</th>
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These plasma concentrations were appropriate for the different oral doses, as the total body plasma clearance of clonidine was similar in these patients to values reported in normotensive1 and hypertensive subjects.6

Discussion

The two hypertensive patients reported in this paper were both resistant to high doses and high plasma concentrations of clonidine. After clonidine had been withdrawn for seven to eight months the administration of a single 0.3-mg dose produced a substantial fall in blood pressure in both patients (30/22 mm Hg in case 1; 88/41 mm Hg in case 2). These reductions in pressure are similar to those observed in normotensive and other hypertensive people after a 0.3-mg dose.6

Resistance to the high doses of clonidine cannot be explained pharmacokinetically because the doses produced appropriately high concentrations of the drug in the patients’ plasma. It is unlikely that treatment with labetalol before the second study could have contributed substantially to the hypotensive effect of clonidine. Labetalol has a short plasma half life, and in both patients the second clonidine administration was performed 16 hours after the last dose of labetalol, when the blood pressure had returned to a high level.

Two pharmacological explanations for the observed resistance to the high dose seem possible: tolerance and peripheral alpha-receptor stimulation.

Clonidine is an alpha-adrenoceptor agonist in both the brain and the periphery.18 Stimulation of alpha-receptors in the central nervous system causes a reduction in sympathetic outflow and a fall in salivary flow.19 Tolerance to the central side effects of sedation and dry mouth seemed to develop during eight days of treatment, but tolerance to the hypotensive effect was not observed during the same period of time.4 In the high-dose study the patients remained awake despite peak plasma concentrations of 26.2 and 14.4 ng/ml, but in the low-dose study the patients were heavily sedated despite peak plasma concentrations of only 1.4 and 0.9 ng/ml. Thus tolerance to the central sedative effects of clonidine did occur, and similar tolerance to the hypotensive effect may also have been present.

The second explanation, which we favour, is that at high concentrations peripheral alpha-receptor stimulation predominated, leading to peripheral vasoconstriction even in the presence of inhibition of central sympathetic outflow. In normotensive1 and hypertensive people4 the hypotensive effect of clonidine is related to the plasma concentration up to 2 ng/ml, but at higher concentrations the hypotensive effect is reduced. Furthermore, clonidine overdose may be associated with a rise in blood pressure.9 The diminishing hypotensive effect of clonidine at plasma concentrations greater than 2 ng/ml may be
Thyrotoxicosis: relations between clinical state and biochemical changes during carbimazole treatment

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British Medical Journal, 1977, 1, 138-141

Summary

The relation between clinical and biochemical changes in thyrotoxicosis were studied in 12 patients with Graves’s disease who were being treated with carbimazole. Clinical assessment (using the Crooks-Wayne index) was combined with the measurement of free thyroxine and triiodothyronine indices (FT4I and FT3I) and the assessment of two tissue markers of thyroid hormone action—sex-hormone-binding globulin (SHBG) levels and the thyrotrophin responses to TRH. In general the FT4I and FT3I fell rapidly once treatment was started, and returned to normal in one to four weeks, followed shortly by SHBG levels. The thyrotrophin response returned at this time in two patients, who still had borderline high levels of FT3I and SHBG. The clinical score fell more slowly and variably and was less closely related to any of the biochemical indices than these were to each other.

During the early phase of treatment with antithyroid drugs the clinical evaluation may be an unreliable indicator of persisting thyroid hormone excess, and when the patient seems clinically but not biochemically thyrotoxic the symptoms should be treated on their own merits with beta-blocking drugs and not with increased doses of antithyroid drugs.

References

5 Davies, D S, et al, Clinical Pharmacology and Therapeutics, in press.

(Accepted 16 November 1976)