The plasma noradrenaline and growth hormone response to α -methyldopa and clonidine in hypertensive subjects

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1 The mechanism of the antihypertensive effect of α -methyldopa was compared with clonidine by administering equipotent single doses of clonidine (0.2 mg) and α -methyldopa (750 mg) to nine hypertensive patients. Plasma noradrenaline was followed for 8 h thereafter as an index of peripheral sympathetic activity.

2 α -Methyldopa and clonidine produced the same hypotensive response at 6 and 8 h after dosing with a similar fall in plasma noradrenaline levels at these times.

3 Linear regression analysis between the systolic blood pressure fall and the corresponding plasma noradrenaline fall, showed that the slopes of the two regression lines were similar for α -methyldopa as for clonidine.

4 Equipotent doses of α -methyldopa and clonidine produce the same fall in plasma noradrenaline. This supports the current hypothesis that an α -methyldopa metabolite acts centrally, like clonidine, to reduce peripheral sympathetic activity.

Keywords hypertension catecholamines growth hormone α -methyldopa clonidine

Introduction

α -Methyldopa has been used in the treatment of hypertension for over 20 years, but its precise mechanism of action is still uncertain. It is postulated that a metabolite, α -methylnoradrenaline, acts centrally by α_2 -adrenoceptor stimulation in the same way as clonidine. In the case of clonidine, this central action leads to reduction in peripheral sympathetic activity and hence its antihypertensive effect (van Zwieten, 1980). In the case of α -methyldopa, however, the evidence for the above mechanism of action comes from animal studies and there is no direct evidence that α -methyldopa does stimulate central α -adrenoceptors in man or cause a reduction in peripheral sympathetic activity.

We have used plasma growth hormone as an

index of central α -adrenoceptor stimulation (Lovinger *et al.*, 1976) and plasma noradrenaline as an index of peripheral sympathetic nervous activity. Clonidine causes a rise in plasma growth hormone and a fall in plasma noradrenaline concentration (Dollery & Davies, 1980; Gil-Ad *et al.*, 1979). We have now followed these biochemical indices of central α -adrenoceptor stimulation in nine hypertensive patients after single doses of α -methyldopa and clonidine. The doses of the above drugs were chosen to give a similar reduction in blood pressure so that we could determine whether all of the antihypertensive effect of α -methyldopa could be ascribed to a clonidine-like reduction in sympathetic activity.

Methods

Nine patients (aged 28–68 years) with essential hypertension were selected for study because their diastolic blood pressure exceeded 95 mm Hg. They were either untreated or receiving only a thiazide diuretic. The study was approved by the local Research and Ethical Committee.

Each subject attended the Clinical Laboratory at 08.30 h on two separate occasions at least 1 week apart. They were fasted from 22.00 h on the previous evening. An intravenous cannula was inserted and baseline measurements were made 30 min later. They then received either 0.2 mg clonidine or 750 mg α -methyldopa orally in a double-blind randomised fashion. It has been shown previously that in comparison to placebo, clonidine does reduce blood pressure and plasma noradrenaline for at least 8 h and therefore no third placebo study was felt to be necessary to re-establish this (Hossmann *et al.*, 1980; Elliot *et al.*, 1981; Maling *et al.*, 1979). No food was permitted until 3 h after dosing when a light lunch was eaten. Measurements of blood pressure, heart rate, plasma noradrenaline, plasma growth hormone and measurements of sedation on a visual analogue scale were made for 8 h after dosing. Blood pressure was measured by Roche Arteriosonde and heart rate by counting the radial pulse for 1 min. Plasma noradrenaline and α -methylnoradrenaline were measured by a double isotope enzymatic method (Brown & Jenner, 1981) and growth hormone by radioimmunoassay. The subjects also indicated their subjective feeling

of drowsiness by marking a visual analogue scale which was a 10 cm long line with 'wide awake' at one end and 'almost asleep' at the other end.

Results

The haemodynamic changes produced by α -methyldopa and clonidine are shown in Figure 1. As would be expected from previous studies, clonidine had an early antihypertensive effect while that of α -methyldopa occurred later. This was seen for both systolic and diastolic blood pressure. Blood pressure fell significantly by 60 min after clonidine and was maximal at 4 h, whereas α -methyldopa had no significant effect on blood pressure until 4 h after dosing and its maximal effect did not occur until 8 h.

Where both drugs clearly reduced blood pressure, it is interesting to note their different effects on heart rate. Clonidine caused significant bradycardia, as has often been reported, while α -methyldopa had no significant effect on heart rate. Two way analysis of variance confirmed a significant ($P < 0.05$) difference between the heart rate response to the two drugs.

The visual analogue scales (Figure 2) show that sedation was maximal 1.5–2 h after clonidine but not until 6 h after α -methyldopa. There was therefore a close temporal relationship between sedation and the antihypertensive effect. This is the pattern expected for centrally acting drugs.

Figure 3 shows the plasma noradrenaline

Figure 1 The haemodynamic effects of α -methyldopa (●—●) and clonidine (●---●) (mean $\pm$ s.e. mean).

Figure 2 The effect of α -methyldopa (●—●) and clonidine (●---●) on sedation score as measured by visual analogue scale with 0 as 'wide awake' and 100 as 'almost asleep' (mean $\pm$ s.e. mean).

profiles after both drugs. The baseline plasma noradrenaline levels were not significantly different between the two study days. Clonidine reduced plasma noradrenaline levels by 60 min and they remained low for 8 h. This time course agrees with previous studies of clonidine (Dollery & Davies, 1980). There are, however, no previous published data on the effect of a single dose of α -methyldopa on peripheral sympathetic activity. In this study α -methyldopa reduced plasma noradrenaline, although it was only at 8 h that the level was significantly lower than the baseline value. No α -methylnor-

adrenaline was detected in plasma at any time point after either drug. On comparing Figures 1 and 3, it is apparent that the alterations in blood pressure after each drug followed closely the changes in plasma noradrenaline. Table 1 shows that growth hormone levels did not change significantly after either drug.

Because of the different time course of each drug, two way analysis of variance showed a significant ($P < 0.05$) difference between the two drugs with regard to the overall profiles of systolic BP and diastolic BP. We were principally interested in assessing the biochemical response to equipotent antihypertensive doses of each drug and therefore two alternative statistical manoeuvres were used.

Figure 3 The effect of α -methyldopa (●—●) and clonidine (●---●) on plasma noradrenaline (mean $\pm$ s.e. mean).

Table 1 The growth hormone levels (mlu/l) after a single dose of either α -methyldopa (750 mg) or clonidine (0.2 mg) in nine hypertensive subjects (mean $\pm$ s.e. mean).

Time (h)	Drug	
	Clonidine	α -Methyldopa
0	1.9 $\pm$ 0.7	2.1 $\pm$ 0.9
1	1.3 $\pm$ 0.2	4.0 $\pm$ 2.9
1.5	2.9 $\pm$ 1.2	3.5 $\pm$ 1.6
3	1.7 $\pm$ 0.2	2.5 $\pm$ 1.0
4	1.1 $\pm$ 0.1	1.2 $\pm$ 0.2
6	1.7 $\pm$ 0.4	4.0 $\pm$ 1.5
8	1.1 $\pm$ 0.1	2.7 $\pm$ 1.4

Firstly, time points were chosen at which the systolic BP falls were not significantly different (paired *t*-tests) on the two study days. These were 6 h and 8 h when the systolic pressure had fallen by -26 ± 15 mm Hg and -18 ± 15 mm Hg respectively after clonidine (C) and -22 ± 19 mm Hg and -22 ± 22 mm Hg after α -methyldopa (MD). The initial plasma noradrenaline levels were not significantly different between the two study days (C: 0.55 ± 0.12 ; MD: 0.49 ± 0.09 ng/ml). At 6 and 8 h, when the systolic pressure changes were similar, the plasma noradrenaline levels were 0.32 ± 0.13 and 0.45 ± 0.26 ng/ml after clonidine and 0.39 ± 0.18 and 0.31 ± 0.12 ng/ml after α -

Figure 4 Regression analysis between Δ systolic pressure and the prevailing plasma noradrenaline concentration in patient 1.

Figure 5 Regression analysis between Δ systolic pressure and the prevailing plasma noradrenaline concentration in patient 9.

methyldopa. There was therefore no significant difference (paired *t*-tests) between these two noradrenaline levels at these time points. Therefore, at 6 and 8 h, clonidine and α -methyldopa had equipotent antihypertensive activity while also causing plasma noradrenaline levels to fall to the same extent.

Secondly, linear regression was performed in each patient for each drug, correlating the serial changes in systolic pressure from baseline with the simultaneous plasma noradrenaline concentrations. Figure 4 and 5 show the results for patients 1 and 9 as examples and Table 2 shows the slope values found for all patients. There is great interindividual variability, but the res-

Table 2 The slope values for linear regression between Δ systolic BP and the prevailing plasma noradrenaline levels in each patient after single doses of α -methyldopa and clonidine.

Patient number	Drug	
	Clonidine	α -Methyldopa
1	150	90.2
2	6.2	3.6
3	51.4	19.3
4	40.7	42.9
5	57.7	37.2
6	37.8	-7.5
7	17.1	14.8
8	36.8	38.0
9	223	351
	69 $\pm$ 71	66 $\pm$ 111

ponses to both drugs were similar within each individual. Overall the mean slope values were very similar for α -methyldopa as for clonidine. This also is evidence that equipotent antihypertensive doses of α -methyldopa and clonidine cause similar effects on plasma noradrenaline levels.

Discussion

Three main stages can be identified in the understanding of the mode of action of α -methyldopa. α -Methyldopa is known to inhibit aromatic amino acid (a.a.a.) decarboxylase, an enzyme essential for noradrenaline biosynthesis. This was initially thought to be the mechanism underlying its antihypertensive effect until it was shown that more potent a.a.a. decarboxylase inhibitors, such as carbidopa, did not lower blood pressure in man (Kersting *et al.*, 1978).

The second postulated mechanism was that α -methylnoradrenaline, an α -methyldopa metabolite, was concentrated in adrenergic nerves and released instead of noradrenaline. This 'false transmitter' hypothesis required that α -methylnoradrenaline was a less potent α -adrenoceptor agonist than noradrenaline but subsequent studies suggested that α -methylnoradrenaline is equipotent with noradrenaline as an α -receptor agonist (Struyker Boudier *et al.*, 1975). The third and currently accepted hypothesis is that α -methylnoradrenaline acts not as a false transmitter but rather as a potent centrally acting α -adrenoceptor agonist. In accordance with this is the observation that α -methylnoradrenaline is relatively selective for α_2 -adrenoceptors, just like clonidine (Starke *et al.*, 1975).

As mentioned, most of the evidence for this hypothesis comes from animal work. In both the rat and cat, the hypotensive effect of α -methyldopa can be antagonised by the central administration of an α -adrenoceptor blocking drug (Finch & Haeusler, 1973). Also, when α -methylnoradrenaline itself is injected into the cerebral ventricle, it causes a greater pressure fall than α -methyldopa (Heise & Kroneberg, 1972). Furthermore, when administered centrally, only the (-)-isomer of α -methyldopa lowers blood pressure and only the (-)-isomer is decarboxylated to α -methylnoradrenaline (Henning, 1969).

The only pointers towards a central site of action of α -methyldopa in man are indirect and are based on two main observations. Firstly, α -methyldopa has only had a small effect of ejaculatory function in the human male in

comparison to the much greater effect of the peripheral adrenergic neurone blocking drugs like bethanidine or guanethidine (Dollery & Bulpitt, 1975). Also, carbidopa markedly reduces the peripheral conversion of α -methyldopa to α -methylnoradrenaline and yet does not reduce the hypotensive response to α -methyldopa (Kersting *et al.*, 1977).

In this study, we have shown that a single dose of α -methyldopa which is equipotent with clonidine causes the same reduction in peripheral sympathetic activity. This strongly suggests that the antihypertensive effects of α -methyldopa and clonidine are due to the same overall mechanisms. This study does not, however, elucidate the central mechanisms involved. It may well be that as has been suggested, the central mechanisms of both drugs are mediated not only through central noradrenergic neurones but also through 5-hydroxy tryptaminergic neurones (Head *et al.*, 1983).

Most but not all previous reports confirm that α -methyldopa has no significant effect on the resting heart rate (Onesti *et al.*, 1964; Cohen *et al.*, 1967; Chamberlain & Howard, 1964). By contrast, clonidine always produces a bradycardia although its intensity varies depending on the animal species and the route of administration (van Zwieten, 1980). Clonidine induced bradycardia is thought to be due to an enhancement of vagal reflexes as well as to a reduction in peripheral sympathetic activity. There are two possible reasons why α -methyldopa generally has no effect on heart rate. Firstly, in both animals and man, once the vagus is blocked, clonidine blunts reflex changes in heart rate in response to alterations in blood pressure, but α -methyldopa has no such effect (McLean *et al.*, 1983; Badoer *et al.*, 1983). This suggests that clonidine, but not α -methyldopa, influences the sympathetic components of the baroreceptor-heart rate reflex and it may be this which causes the different resting heart rate response to each drug. The alternative explanation is that a metabolite of α -methyldopa, α -methylnoradrenaline, has some β -adrenoceptor agonist activity which offsets any clonidine-like tendency to bradycardia (Wilffert *et al.*, 1983). Indeed, when α -methylnoradrenaline itself is infused into man, a small increase in heart rate is seen. This explanation is, however, unlikely in view of our observation in this study that no circulating α -methylnoradrenaline is detectable in the plasma after α -methyldopa administration, and there is no reason to believe that the synaptic cleft concentrations of α -methylnoradrenaline and noradrenaline are differentially reflected in plasma.

Our observation that neither drug alters growth hormone levels in hypertensive patients is interesting. In normotensive subjects, the stimulation of hypothalamic α_2 -adrenoceptors by clonidine produces a marked increase in growth hormone release. Indeed, oral clonidine has been proposed to replace insulin induced hypoglycaemia as a stimulus to growth hormone release while assessing growth hormone reserve for diagnostic purposes (Gil-Ad *et al.*, 1979). Barbieri *et al.* (1980) have, however, studies the growth hormone response to clonidine in a group of hypertensive subjects and compared this with an age, sex and weight matched group of normotensive subjects. They were able to demonstrate that normotensive subjects had a clonidine induced rise in growth hormone which was not present in hypertensive subjects, suggesting that there is a derangement of

central α -adrenoceptor function in hypertension. Our results are in accord with this intriguing hypothesis although we have no matched normotensive group for comparison. Therefore, although growth hormone release is an accepted index of central α -adrenoceptor stimulation, it is unfortunately of little use as such in hypertensive patients. This topic is complicated further by the observation that although normotensive subjects have a growth hormone response to a single dose of clonidine, they appear to have no such response to the acute administration of α -methyl-dopa (Steiner *et al.*, 1976; Syvalahti *et al.*, 1975). Therefore, the growth hormone response to α -methyl-dopa and clonidine in normotensive subjects appears to represent another as yet unexplained difference between the two drugs.

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