A comparison of the haemodynamic and behavioural effects of moxonidine and clonidine in normotensive subjects

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- 1 This randomised double-blind placebo controlled crossover study in healthy normotensive males compared the haemodynamic and behavioural responses following single oral doses of moxonidine (200 µg), clonidine (200 µg) and placebo.
- 2 Both active drugs significantly reduced blood pressure as compared with placebo: on average (over the study day) by $-5.6/-0.8$ with moxonidine and by $-13.3/-5.3$ mm Hg with clonidine. The hypotensive effect of clonidine was significantly greater (95% CI 3.2–12.2). Heart rate was unchanged by either drug.
- 3 Psychomotor testing, salivary flow and side effect reporting showed a consistent treatment rank order similar to that of the hypotensive response: clonidine > moxonidine > placebo.
- 4 Although moxonidine produced less adverse effects than clonidine, an equivalent hypotensive response was not demonstrated in normal subjects. Further study at comparable antihypertensive doses is required to clarify the relative side effect profile of these agents.

Keywords clonidine moxonidine haemodynamic responses CNS effects

Introduction

Blood pressure reduction by centrally acting drugs, such as clonidine, is attained principally by stimulation of α_2 -adrenoceptors in the brain stem leading to a reduction of sympathetic nervous system activity (Kobinger & Walland, 1967; Reid *et al.*, 1977). Although these drugs are effective antihypertensive treatments, clonidine and other imidazoline compounds such as tiamenidine (Campbell *et al.*, 1980) and lofexidine (Dollery & Reid, 1982) are limited in clinical utility because of frequent central nervous system side effects such as sedation, drowsiness and dry mouth (Dollery *et al.*, 1976; Reid, 1985). However, it has been suggested that these side effects are mediated via ancillary receptors (Reid *et al.*, 1983) so that a drug with increased selectivity for α_2 -adrenoceptors would be less likely to cause sedation and somnolence. The development of a centrally acting antihypertensive agent possessing truly differential effects on blood pressure and sedation might be of considerable clinical relevance since this class of drug is both effective and without deleterious metabolic effects (Johnson & Danylchuk, 1989; Lardinois & Neumann, 1988).

Moxonidine, 4-chloro-5-(2imidazoline 2 ylamino)-6 methoxy-2methylpyrimidine, is a new centrally acting agent with a different experimental pharmacological profile from clonidine (Armah & Stenzel, 1981; Armah

et al., 1988). Moxonidine appears to mediate blood pressure reduction by stimulation of CNS *pre*-synaptic α_2 -adrenoceptors, as does α -methyldopa (Reid & Elliott, 1988), whereas clonidine acts *post*-synaptically (Armah, 1987; Schlicker *et al.*, 1990). Furthermore, moxonidine is reported to demonstrate a highly specific and selective affinity for central α_2 -adrenoceptors (Armah *et al.*, 1988) and, unlike clonidine, acts as a full agonist at platelet α_2 -adrenoceptors (Bergerhausen, 1985). Early clinical studies in hypertensive patients have reported that moxonidine produces a hypotensive response similar to that of clonidine, at an equivalent dose, but with a significant reduction in adverse effects particularly sedation and xerostomia (Planitz, 1984, 1987).

The principal aim of this study was to compare the haemodynamic and behavioural effects of moxonidine and clonidine.

Methods

Nine healthy normotensive male subjects, aged 18–40 years, weight 45–95 kg (within 20% of ideal body weight) gave written informed consent for their participation in

the study which had been approved by the hospital ethics committee. All subjects were deemed healthy on the basis of clinical history, examination and routine haematology and biochemical screening. No subject ingested any drugs or medication for the 2 weeks prior to study. To preclude any marked learning effect during study all subjects were familiarised with the techniques for visual analogue sedation scores and psychomotor testing at a pre-study visit.

Study design comprised a double-blind comparison of single oral doses of moxonidine 200 µg, clonidine 200 µg, and inactive matched placebo using random treatment order within Latin square design. Subjects attended the Clinical Pharmacology Research Unit at 08.30 h on three occasions, at least 1 week apart, having fasted from 22.00 h the previous night and abstained from nicotine, alcohol and caffeine-containing beverages prior to and during study periods. An indwelling intravenous cannula was inserted into an antecubital vein of the non-dominant arm for blood sampling and, after at least 20 min further rest baseline measurements were made and active drug or placebo was administered with 200 ml water.

Measurements

Blood pressure and heart rate Blood pressure and heart rate were recorded in duplicate using an automated sphygmomanometer (Datascop Acutorr) at baseline (0) and at 0.5, 1, 1.5, 2, 3, 4, 6, 8 and 10 h after dosing. Supine readings were obtained after not less than 10 min recumbent rest and erect readings after 2 and 5 min standing.

Drug concentrations At corresponding times, blood was withdrawn for plasma concentrations of clonidine and moxonidine.

Hormones Blood was withdrawn for measurement of plasma catecholamines, renin aldosterone and angiotensin II at baseline and at 2, 4, 6 and 8 h.

Visual analogue scores Sedation was assessed at baseline and after 1, 2, 4, 6 and 8 h after dosing using a visual analogue scale of 100 mm with 'wide awake' at the left hand extremity and 'nearly asleep' at the right hand extremity. Sedation was expressed as mm from 'wide awake'.

Salivary flow Salivary flow was measured from the change in weight of four pre-weighed dental rolls inserted in the mouth for exactly 1 min using the method described in detail (Dollery *et al.*, 1976).

Psychomotor testing Psychomotor testing (critical flicker fusion threshold and choice reaction time) was performed at 2, 4, 6 and 8 h after dosing using the Leeds psychomotor testing box as described by Hindmarch (1980). Critical flicker fusion threshold is a measure of arousal and choice reaction time of sensori-motor performance. Subjects were tested by a single investigator in a quiet environment with constant illumination (no correction was made for pupil size).

Isometric exercise Isometric exercise was performed at 4 and 8 h after dosing. Subjects were supervised in sustaining 30% of maximum handgrip for 3 min. Baseline recordings of blood pressure and heart rate were recorded and maximum blood pressure and heart rate were determined. Blood sampling for plasma noradrenaline was undertaken before and after 1, 2 and 3 min in the contralateral arm to exercise. Response was assessed by the difference from baseline to maximum increase.

Subjective side effects Subjective side effects were sought at intervals throughout the study day by the question 'how do you feel?'. Subjects were allowed water *ad libitum* throughout the study day and were provided with a standard lunch and snack at 4 and 8 h after dosing respectively.

Plasma clonidine and moxonidine were assayed by GC-MS methods, as described by Kirch *et al.* (1988). Plasma noradrenaline and adrenaline (da Prada *et al.*, 1976) and plasma renin activity (Derks *et al.*, 1979) were performed by radioenzymatic assay. Pharmacokinetic values were derived from the plasma concentration-time profiles using a one compartment model for both drugs. Area under the curve was calculated using the trapezoidal rule.

Statistical analysis was by repeated measures analysis of variance with subsequent determination of the significance of individual time points where appropriate by concentration of Bonferroni confidence intervals. Level of significance was accepted as $P < 0.05$.

Results

Blood pressure and heart rate

Compared with placebo, both moxonidine and clonidine significantly reduced supine systolic blood pressure: respective 95% confidence intervals, -10.1 to -1.07 and -17.8 to -8.8 mm Hg for systolic blood pressure and -6.1 to 4.6 and to -10.0 to 0.07 mm Hg for diastolic blood pressure (Figure 1). The effect of clonidine was significantly greater than that of moxonidine (95% CI, 3.2 to 12.1 for systolic and -0.8 to 9.9 mm Hg for diastolic blood pressure). The time course of hypotensive activity were also different for the two drugs: for supine blood pressure onset for both occurred by about 1 h but the peak effect of moxonidine occurred at 1.5 h with no significant effect at 8 h, whereas maximal hypotensive response for clonidine was observed at 4 h and persisted until the end of study at 10 h.

Erect systolic blood pressure responses were similar to supine measurements. Both treatments reduced erect blood pressure at 2 and 5 min as compared with placebo and the effect of clonidine was significantly greater than that of moxonidine.

There were no significant differences in heart rate, supine or erect.

Plasma concentrations of moxonidine and clonidine

Derived pharmacokinetic parameters for moxonidine and clonidine are shown in Table 1. Mean peak plasma

Figure 1 Mean supine systolic and diastolic blood pressure following single doses of moxonidine (▲), clonidine (■), and placebo (○). * $P < 0.05$ moxonidine/clonidine vs placebo; † $P < 0.05$ moxonidine vs clonidine.

concentrations of moxonidine occurred at 0.9 h whereas that of clonidine was later around 1.9 h ($P = 0.10$). The mean elimination half-life of clonidine was greater for clonidine at 8.4 ± 2.1 h as compared with 2.1 ± 0.2 h for moxonidine ($P < 0.05$). For illustrative purposes the concentration-time profiles for moxonidine and clonidine in a representative subject are compared in Figure 2. The hypotensive response broadly paralleled that of the plasma concentration-time profile for each subject.

Renin, angiotensin II, aldosterone and plasma catecholamines

No significant differences were demonstrated for any circulating hormone.

Sedation scores

Mean sedation scores during the three treatments are shown in Figure 3. Clonidine produced a marked sedative effect, as compared with placebo, maximal at 2 h.

Figure 2 Plasma concentration-time profiles following single doses of moxonidine and clonidine in a representative subject.

Figure 3 Mean (s.e. mean) sedation scores (following single doses of moxonidine (▲), clonidine (■), and placebo (○). * $P < 0.05$ moxonidine/clonidine vs placebo; † $P < 0.05$ moxonidine vs clonidine).

Table 1 Mean (s.d.) derived pharmacokinetic parameters in nine healthy males following single oral doses of clonidine 200 µg and moxonidine 200 µg

Moxonidine				Clonidine			
AUC (1-10) (ng ml ⁻¹ h)	C _{max} (ng ml ⁻¹)	t _{max} (h)	t _{1/2} (h)	AUC (1-10) (ng ml ⁻¹ h)	C _{max} (ng ml ⁻¹)	t _{max} (h)	t _{1/2} (h)
3.42*	1.18*	0.9	2.1*	5.18	0.77	1.9	8.4
±0.51	±0.30	±0.5	±0.2	±1.17	±0.18	±1.0	±2.1

$P < 0.01$ moxonidine vs clonidine (clonidine concentrations converted from pg ml⁻¹).

Figure 4 Mean (s.e. mean) salivary flow (following single doses of moxonidine (▲), clonidine (■), and placebo (○). * $P < 0.05$ moxonidine/clonidine vs placebo; † $P < 0.05$ moxonidine vs clonidine).

Moxonidine was also associated with a sedative effect but this did not achieve statistical significance at any time point. Thus, across the 8 h period of observation there is a consistent rank order of treatment effect with clonidine being significantly more sedative than either moxonidine or placebo. The results were similar to salivary flow with respect to rank order of treatment effect although significant differences between clonidine and both moxonidine and placebo were observed.

Saliva flow

Mean salivary flow during the three treatments is shown in Figure 4 and the pattern of results is similar to that seen with sedation and the same rank order of treatment effects is observed. Clonidine produced a marked decrease in salivary flow which was maximal at 2 h. The fall in salivary flow associated with moxonidine did not achieve statistical significance relative to placebo and was significantly less than the reduction observed with clonidine at 1 and 3 h ($P < 0.05$).

Psychomotor testing

Critical flicker fusion threshold Mean flicker fusion thresholds at 2 to 8 h are shown in Figure 5a. Clonidine reduced the threshold at 2 to 8 h ($P < 0.05$) while moxonidine differed from placebo at 2 h only ($P < 0.05$).

Figure 5 Mean (s.e. mean) results for a) critical flicker fusion threshold (CFFT) and b) choice reaction time (CRT 2) (following single doses of moxonidine (▲), clonidine (■), and placebo (○). * $P < 0.05$ moxonidine/clonidine vs placebo; † $P < 0.05$ moxonidine vs clonidine).

Choice reaction time Clonidine prolonged total choice reaction time (CRT 2) as compared with placebo (95% CI 12.8 to 104.8) with a maximal effect at 2 h (Figure 5b). Although this was the only significant difference for both choice reaction time 1 and 2 the rank order of treatment effect (clonidine > moxonidine > placebo) was similar and consistent with the other tests of psychomotor function and sedation.

Isometric handgrip

The differences between baseline and maximum handgrip responses for blood pressure, heart rate and plasma catecholamines at 4 and 8 h after dosing for each of the three treatments is shown in Table 2. Wide inter-

Table 2 Responses in blood pressure, heart rate and plasma catecholamines measured as difference in baseline maximum values following isometric handgrip for 3 min at 4 and 8 h after dosing

	4 h			8 h		
	Moxonidine	Clonidine	Placebo	Moxonidine	Clonidine	Placebo
BP (mm Hg)	20 ± 12	18 ± 7	12 ± 13	19 ± 7	21 ± 17	17 ± 12
	16 ± 12	18 ± 12	12 ± 9	15 ± 11	20 ± 18	15 ± 10
HR (beats min ⁻¹)	13 ± 9	12 ± 5	7 ± 7	8 ± 7	15 ± 12	15 ± 9
Noradrenaline (nmol l ⁻¹)	0.03 ± 0.1	0.17 ± 0.2	0.29 ± 0.5	0.27 ± 0.4	0.20 ± 0.20	0.09 ± 0.1
Adrenaline (nmol l ⁻¹)	-0.12 ± 1.3	0.26 ± 0.7	0.59 ± 1.0	0.58 ± 0.6	0.14 ± 0.6	0.71 ± 0.8

Table 3 Side effects (reported or observed) in nine subjects receiving moxonidine, clonidine and placebo. Figures refer to total number of subjects experiencing side effects

	Moxonidine	Treatment Clonidine	Placebo
Dizziness	3	4	0
Drowsiness	4	7	1
Tiredness + lethargy	2	1	1
Dry mouth	2	5	0
Headache	0	2	0
Pallor	1	1	0
Total	12	19	2

individual variability was observed and no significant treatment differences were demonstrable.

Subjective side effects

Seven subjects reported side effects on receiving moxonidine. All nine subjects experienced side effects on clonidine treatment. Two subjects complained of side effects on receiving placebo. Twelve adverse events occurred during moxonidine treatment compared with 19 during clonidine and two during placebo treatment. Adverse events are summarised in Table 3.

Drowsiness was the commonest reported side effect which occurred up to 4 h after moxonidine treatment and up to 8 h following clonidine.

Three subjects experienced dizziness following moxonidine treatment within 2 h of dosing. Concurrent blood pressure recording suggested a component of orthostatic hypotension in all subjects with a recorded fall in one subject of 53 mm Hg in systolic pressure. Two of these subjects also experienced dizziness on receiving clonidine, in addition to two subjects who noted dizziness on clonidine alone. A significant fall in systolic blood pressure was observed in three of these subjects.

Discussion

Previous double-blind clinical studies in hypertensive patients comparing clonidine and monoxidine have consistently reported therapeutic equivalence at similar doses (Planitz, 1984, 1987) and this explains the choice of dose in the present study. The results of this study, however, suggest that the hypotensive effect of clonidine is both greater and longer lasting. Further scrutiny of the previous studies reveals that although the mean dosage of both drugs was similar and there was no statistically significant difference after 6 weeks of treatment (Planitz, 1987), the patients treated with clonidine tended to have lower supine systolic pressures, as determined from two recordings obtained during the dosage interval.

A further possible explanation for these apparently discrepant responses for hypertensives and normotensives might be that moxonidine is somehow specifically efficacious in hypertension perhaps because of differences in vascular sensitivity and sympathetic

nervous system activity (Trenk *et al.*, 1987) and that a differential threshold of effect exists between normotensive and hypertensive subjects. For example, moxonidine, in a dose of 0.2 mg (as in the present study) was administered to 12 healthy males in a pharmacokinetic study and negligible haemodynamic effects were reported (Trenk *et al.*, 1987). An alternative and more plausible explanation for all these observations is the recognised direct relationship for most antihypertensive drugs, including placebo, between the height of the initial blood pressure, i.e. higher in hypertensive patients, and the magnitude of the subsequent blood pressure fall (Sumner *et al.*, 1988). Thus, blood pressure reductions in normotensives are invariably relatively small and their accurate detection requires appropriate and careful methodology.

In the earlier, clinical studies, moxonidine treatment was associated with approximately 50% fewer adverse events, for example dry mouth was reported by 20% of the moxonidine patients compared with between 40 and 75% of the clonidine patients. However, in an intra-individual comparison with prazosin (Planitz, 1986), symptoms of dry mouth, albeit mild, were reported in over 50% of patients receiving moxonidine.

In this present study the side effect profiles of both drugs were qualitatively similar with sedation, dry mouth and dizziness the most prominent symptoms. However, with clonidine drowsiness and dry mouth were reported approximately twice as frequently. Furthermore, clonidine apparently exerted more deleterious changes on objective measures of behavioural response; choice reaction time was prolonged and sedation was caused, maximally at 2 h but persisting until 8 h, as measured both by critical flicker fusion threshold and by visual analogue reporting. Salivary flow was also profoundly reduced by clonidine to less than 60% of basal values at 2 to 4 h after dosing. In contrast moxonidine produced significant depression of flicker fusion threshold at 2 h only. Sedation as measured on visual analogue scales did not significantly differ from placebo at any time during the study day but a significant difference from clonidine was detected. Similar relative results were demonstrated for salivary flow where moxonidine was associated with an approximate 30% reduction (not significantly different from placebo) at the time of the peak hypotensive response.

The pharmacokinetic parameters derived in this study are similar to previous investigations in healthy subjects with peak plasma concentrations occurring around 1 and 2 h and terminal half-lives of 2 and 8 h for moxonidine and clonidine respectively (Dollery *et al.*, 1976; Lowenthal *et al.*, 1988; Trenk *et al.*, 1987). The time course of both blood pressure reduction and behavioural effects produced by the two drugs appeared closely related to plasma concentration-time profiles as previously demonstrated for clonidine in normotensive and hypertensive subjects (Davies *et al.*, 1987; Wing *et al.*, 1977a,b). Thus, even within the first 2 h of study when both the plasma concentrations and the blood pressure response were maximal with moxonidine, the hypotensive effect of clonidine was greater. This rank order for hypotensive effect, which was paralleled consistently in the measurements of sedation, salivary flow and to a lesser extent circulatory hormones, suggests

that (at these doses) moxonidine is not pharmacologically equivalent to clonidine. Although the elimination half-life of moxonidine after repeated doses remains less than 2 h, it is suggested that 24 h blood pressure control is achieved after one and two daily doses in hypertensive patients possibly because of longer elimination from the CNS (Planitz, 1986, 1987).

No significant changes in circulating concentrations of catecholamines or hormones of the renin-aldosterone axis were observed in our subjects although there was an apparent trend to lower plasma noradrenaline and adrenaline and higher renin levels following treatment with both agents. These results are consistent with previous studies showing reductions of plasma noradrenaline by moxonidine (Armah *et al.*, 1988) and clonidine (Wing *et al.*, 1977b). Renin release is controlled by complex factors and our results may reflect a balance between reduced sympathetic activity causing depression of secretion and stimulation of release provoked by hypotension via renal baroreceptors (Keeton & Campbell, 1981). While clonidine (Lowenthal *et al.*, 1988) and moxonidine (Armah *et al.*, 1988) are generally reported to suppress renin secretion, significant rises are documented in healthy subjects treated with 0.2 mg clonidine (Wing *et al.*, 1977b). Although cardiovascular and catecholamine responses were unchanged by either agent following isometric exercise this is possibly explained by the time of testing in relationship to peak plasma concentration of drug.

Present evidence in therapeutic studies with clonidine and other centrally acting drugs suggests that CNS depression in some degree is an invariable accompaniment to hypotensive efficacy (Reid, 1986). However, it appears that there are subtle differences in the α_2 -adrenoceptor activities of clonidine and moxonidine

(Armah, 1987) and it has been suggested that non- α_2 imidazoline recognition binding sites in the CNS (Michel & Insel, 1989) may contribute to the hypotensive effect of both agents to a variable degree (Schlicker *et al.*, 1990). Although these binding sites are closely affiliated with α_2 -adrenoceptors (Michel *et al.*, 1989) their physiological role is unknown, although some experimental evidence supports their involvement in blood pressure regulation (Ernsberger *et al.*, 1990). If the hypotensive effect is mediated via a subtype of receptor, which differs from the subtype for sedation, then it is conceivable that agents might be developed to target this preferentially.

The overall results of this investigation comparing moxonidine and clonidine suggest that in normotensive subjects, at least, hypotensive equivalence at similar doses cannot be assumed. Unless the concentration-effect relationship of moxonidine for hypotensive effect and central nervous system depression behaves in a differential and distinct manner from clonidine (Wing *et al.*, 1977a), it appears likely that at comparable hypotensive doses the incidence of side effects with moxonidine will rise. The results of the present study do not preclude the possibility that moxonidine may be better tolerated in clinical practice as compared with clonidine. However, further studies which appraise the relative effects of moxonidine and clonidine on psychomotor function and salivary flow at comparable anti-hypertensive doses are warranted. These should determine whether moxonidine does indeed have a more favourable side effect profile or whether this represents a dose related effect.

We thank Beiersdorf, Hamburg, for supplies of moxonidine and measurements of plasma moxonidine, clonidine and angiotensin II concentrations.

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(Received 26 April 1991,
accepted 10 September 1991)