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Crossover Comparison of Moxonidine and Clonidine in Mild to Moderate Hypertension

V. Plänitz

Clinical Research, Beiersdorf AG, Hamburg, Federal Republic of Germany

Summary. The antihypertensive effect of moxonidine · HCl · H_2O (MOX) was compared with that of clonidine · HCl (CLON) in a randomized double-blind crossover study in 20 hypertensive outpatients (BP range 154–178/96–108 mmHg). After 2 weeks without antihypertensive medication, either MOX 0.2 mg daily or CLON 0.2 mg daily was given and the dose was titrated until the diastolic blood pressure fell below 90 mmHg. The first treatment period was continued for 2 weeks and, after crossover without a wash-out period, it was followed by the second treatment for a further 2 weeks. Within the first 4 days of administration 0.2–0.4 mg of either agent caused a significant decrease in BP ($p < 0.001$) from a mean of 166/100 mmHg to 149/86 mmHg after CLON (approx. −10/−14%), and 163/99 mmHg to 146/84 mmHg after MOX (approx. −10/−15%). No significant difference in the fall in BP or pulse rate was detected between the two drugs. In the mean daily dose of 0.3 mg both drugs showed the same antihypertensive activity, but on CLON a higher incidence of side effects ($p = 0.003$) was noted, and after discontinuation of therapy a more rapid rise in BP (systolic BP $p < 0.01$, diastolic BP $p < 0.02$) was found. 17 patients on CLON complained of side effects, especially tiredness and dry mouth, whilst only 6 patients on MOX were affected ($p = 0.003$).

Key words: moxonidine, clonidine, hypertension; double-blind crossover, side-effects, withdrawal

Moxonidine · HCl · H_2O (BE 5895), 4-chloro-5-(2-imidazoline-2-ylamino)-6-methoxy-2-methylpyrimidine hydrochloride hydrate (Fig. 1) is a new centrally acting antihypertensive agent, which like clonidine, reduces blood pressure by stimulation of central α_2-adrenoceptors. It has been developed to obtain suitable hypotensive properties without marked central nervous system side effects. It reduces blood pressure in mammalian species (Armah et al. 1981) and healthy volunteers (Rüdiger et al. 1982, unpublished results). A first short-term pilot study in patients with mild to moderate hypertension showed, that moxonidine · HCl · H_2O had an antihypertensive effect in the very low daily dose of 0.3 mg (Plänitz et al. 1983).

Clonidine · HCl (Fig. 1), a centrally acting α-adrenoceptor agonist, is a widely used antihypertensive agent (Bock et al. 1966; Grabner et al. 1966; Ng et al. 1967; Davidov et al. 1967; Smet et al. 1969; Garrett et al. 1980). It acts at central α_2-adrenoceptors, resulting in decreased sympathetic outflow to the cardiovascular system (Schmitt 1977; Kobinger 1978). Abrupt cessation of clonidine · HCl treatment has often been reported to provoke a rapid increase in blood pressure and such withdrawal symptoms as anxiety, insomnia, sweating, headache and tachycardia (Hökfelt et al. 1970; Hansson et al. 1973; Reid et

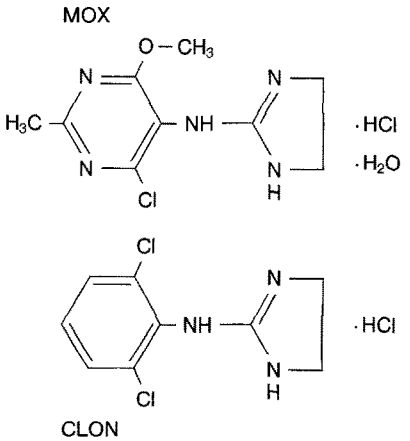

Fig. 1. Structures of moxonidine · HCl · H_2O and clonidine · HCl

al. 1977; Hoefke 1980; Weber 1980). Symptoms suggestive of sympathetic overactivity occurred to a varying degree and were most pronounced in patients who had received doses higher than 1 mg.

The present study in hypertensive patients was undertaken first to investigate the antihypertensive potency and efficacy of moxonidine · HCl · H_2O, as well as its possible withdrawal symptoms and side effects, and second, to compare these actions with those of clonidine · HCl using the double-blind crossover technique.

Patients and Methods

Patient Selection

Twenty outpatients (aged 24 to 54 years) with uncomplicated essential hypertension and without any additional ailments entered the study and all completed it, details of the patients are shown in Table 1. Sixteen of the 20 patients had had some previous antihypertensive therapy, which was interrupted without risk for at least 2 weeks prior to the study. Based on the electrocardiogram, ocular fundus and extent of organ damage the hypertension was graded as WHO I or II; 5 patients had ocular fundal changes of Grade 1 or 2, and 15 had no change.

Table 1. Characteristics of patients in the two treatment groups

	Group 1		Group 2	
	MOX – CLON		CLON – MOX	
Males	7		6	
Females	3		4	
Total	10		10	
Age [years]	41	±5.8	39	± 7.5
Weight [kg]	80	±6.5	79	±10
Height [cm]	178	±8	176	± 9
Classification of hypertension				
WHO I	8		8	
WHO II	2		2	
Duration of hypertension [years]				
≤1	5		7	
>1	5		3	
Systolic BP [mmHg][a]				
supine	166	±6.7	163	± 4.4
standing	163	±6.9	159	± 4.1
Diastolic BP [mmHg][a]				
supine	100	±3.3	99	± 1.6
standing	99	±3.5	98	± 1.9
Pulse rate [beats/min][a]				
supine	71	±2.9	71	± 3.1
standing	72	±2.8	72	± 2.8
Creatinine [mg/dl]	0.97	±0.12	0.98	± 0.17

Mean (± SD) obtained before treatment ($n = 10$).
[a] Mean pretreatment values are averages of 3 measurements taken on 3 different days

Design of the Study

When systolic blood pressure was above 160 mmHg and/or diastolic blood pressure above 95 mmHg after 2 weeks without antihypertensive medication, subjects were put on drug therapy. Patients were randomized in a double-blind manner into 2 treatment groups, to receive either moxonidine · HCl · H_2O (Group 1) or clonidine · HCl (Group 2).

During the first treatment period in both groups, therapy was initiated at a dose of 0.2 mg daily. When diastolic pressure remained above 95 mmHg, the dose was raised to 0.4 mg as a single dose on the following day, thus titrating the dose against the diastolic pressure < 90 mmHg.

Each drug was given for 2 weeks, and then in a crossover design Group 1 was given clonidine · HCl and Group 2 moxonidine · HCl · H_2O in the second treatment period. There was no wash-out between the first and second treatment periods. In the second period both groups again started with the dose of 0.2 mg CLON (Group 1) or MOX (Group 2) and the quantity was increased until diastolic blood pressure was < 90 mmHg. After the second treatment period of 2 weeks, therapy was discontinued and any withdrawal reactions were sought.

After acceptance of this study by an ethical committee, it was carried out in general practice of Dr. Hoffmann.

Procedures

During the first 4 days of each treatment period and after discontinuation of MOX and CLON therapy, blood pressure in the supine and upright positions was measured 3 times daily. Measurements by the physician and self-measurements were taken 4, 8 and 12 h after medication. Three days before therapy and on Days 5–14 of both treatment periods blood pressure was measured once daily. Pulse rate was taken after the blood pressure measurement, by palpation of the wrist for 60 s.

Before and on the last day of each treatment period, routine blood and urine analyses were performed and an electrocardiogram was recorded. Side effects were assessed every day by a symptom check list containing 25 different side effects. Weight was measured on each visit. Patients compliance was assessed by measuring MOX- or CLON-concentration in urine by HPLC.

Statistical Analysis

The effects of both drugs upon all the parameters tested were compared by analysis of variance (repeated measures). Intraindividual comparisons of patients wellbeing were evaluated by the sign test of Dixon and Mood.

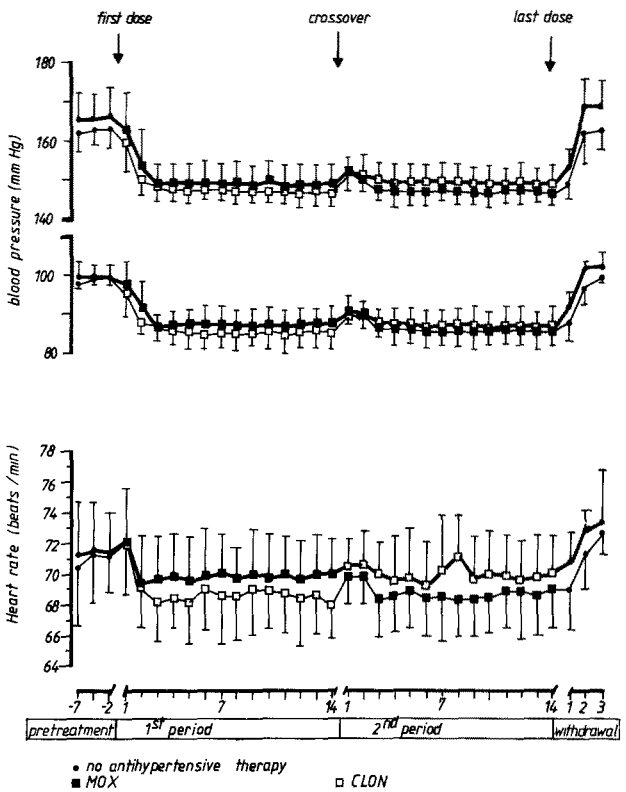

Fig. 2. Supine systolic and diastolic blood pressures and pulse rates in the two treatment groups before treatment, during the first and second treatment periods and after abrupt cessation of therapy. Group 1 started with MOX and Group 2 with CLON. Mean ± SD of 10 patients

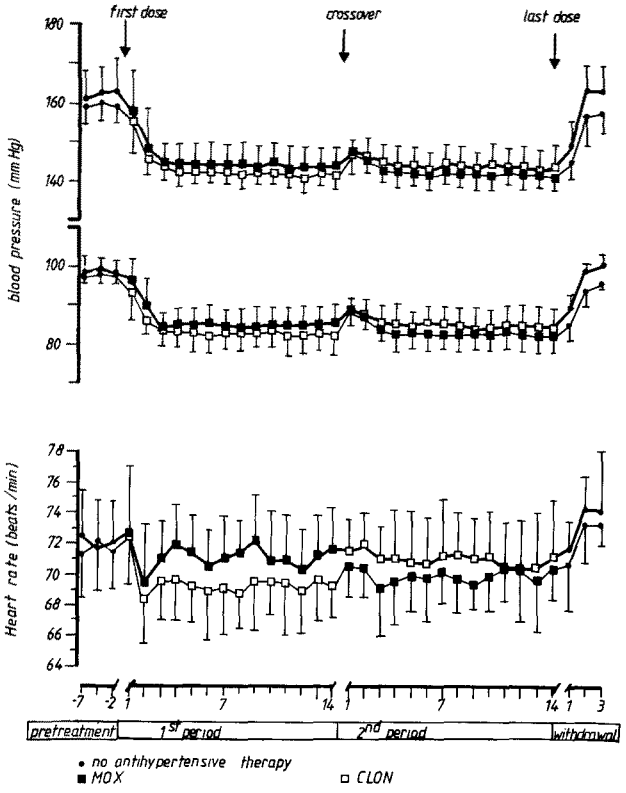

Fig. 3. Standing systolic and diastolic blood pressures and pulse rates in the two treatment groups before treatment, during the first and second treatment periods and after abrupt cessation of therapy. Group 1 started with MOX and Group 2 with CLON. Mean ± SD of 10 patients

Results

Blood Pressure and Pulse Rate

The patient characteristics in treatment Groups 1 and 2 were comparable (Table 1).

The changes in the mean supine systolic and diastolic blood pressures (BP) and pulse rate (PR) in the two treatment groups before therapy (pretreatment values), during the first and second treatment period and after discontinuation of therapy (withdrawal) are shown in Fig. 2; the corresponding changes in the standing values are shown in Fig. 3. On the first day of therapy, in 4 patients of both groups, 0.2 mg of the antihypertensive agents was sufficient to normalize blood pressure, whereas in the other subjects a larger dose was necessary. Within 3 days of medication, a mean dose of 0.3 mg of both agents had caused a significant decrease ($p < 0.01$) in blood pressure (10–15%; Table 2) and pulse rate (1–4%).

These marked responses remained constant throughout the first treatment period. Then, the crossover from MOX to 0.2 mg CLON (Group 1) and from CLON to 0.2 mg MOX (Group 2) was done. The reduction in dose in 5 patients of each group was followed by a an increase in BP and PR immediately after the change (Figs. 2, 3). Subsequently, the dose was again titrated, resulting in a mean daily dose of 0.3 mg. The antihypertensive and pulse rate response in the second treatment period was similar to that in the first period (Figs. 2, 3).

No significant differences in BP and PR were detected between MOX and CLON, either in the first or in the second periods. In both groups (MOX-CLON, CLON-MOX) there was no difference in response before and after the crossover.

The responses in standing blood pressure and pulse rate (Fig. 3) were approximately the same as the corresponding values in the supine position (Fig. 2). The mean difference between the standing and supine values was −4 mmHg systolic BP, −2 mmHg diastolic BP and +1 to 2 beats/min pulse rate.

Withdrawal Reactions

Following the second treatment period, BP and PR were followed for three days at 28, 32, 36, 52, 56, 60, 76, 80 and 84 h after the last doses of CLON and MOX, respectively (Fig. 4).

Table 2. Mean (±SD) supine blood pressure before, during and after discontinuation of MOX and CLON therapy, respectively

	MOX (Group 1)	CLON (Group 2)	*p* value
	Systolic blood pressure [mmHg]		
Before therapy	163±4.4	166±6.7	
14th day of therapy	146±3.1	149±4.6	
1st day after withdrawal	148±3.7	153±4.6	
	151±4.6	162±6.2	0.025
	155±7.7	170±7.6	0.009
2nd day after withdrawal	161±8.2	168±6.7	
	163±7.8	168±4.8	
	162±7.4	170±7.3	
	Diastolic blood pressure [mmHg]		
Before therapy	99±1.6	100±3.3	
14th day of therapy	84±3.8	86±4.8	
1st day after withdrawal	86±4.8	91±3.7	
	89±4.8	97±3.8	0.030
	91±6.4	100±3.2	0.018
2nd day after withdrawal	95±4.0	100±2.0	
	97±3.7	100±1.6	
	97±3.6	101±3.4	

Mean change (%) in blood pressure during and following discontinuation of therapy. $n=10$

During therapy	−10/−15	−10/−14
1st day after withdrawal	−9/−13	−8/−9
	−7/−10	−2/−3
	−5/− 8	+2/−
2nd day after withdrawal	−1/− 4	+1/−
	−/− 2	+1/−
	−1/− 2	+2/+1
3rd day after withdrawal	−1/− 1	+1/+1
	−1/− 1	+2/+1
	−/− 1	+2/−

Blood pressure before therapy is the average of 3 measurements taken at 3 different days

After discontinuation of CLON-therapy, there was a more rapid rise in BP than after MOX-therapy. The difference in the rate of rise of blood pressure after CLON and MOX was statistically significant on Day 1 of withdrawal, i.e. at 32 h (systolic BP $p=0.025$; diastolic BP $p=0.030$), and at 36 h (systolic BP $p=0.009$; diastolic BP $p=0.018$), after the last drug administration. At the 3rd day after discontinuation of MOX, there were still lower blood pressure levels (162/98 mmHg) than 80 h after discontinuation of CLON (169/101 mmHg), but the difference was no longer statistically significant. After abrupt cessation of MOX-therapy, there was a gradual return of BP to the pretreatment level (baseline values) over about 3 to 4 days. There was no indication of an overshoot (Table 2). After abrupt cessation of CLON, pretreatment values were achieved during the first day of withdrawal, i.e. 36 h after the last dose of CLON (Table 2). No subjective withdrawal symptoms, such as anxiety, insomnia, sweating, headache or tachycardia, were observed after abrupt cessation of these low doses of either drug.

Side Effects and Tolerance

Side effects reported by the patients during both treatment periods are listed in Table 3.

In 12 out of 20 patients (60%) CLON caused tiredness, whereas on MOX only 3 patients were affected. Dryness of mouth was reported by 15 patients on CLON and by 4 patients on MOX. 6 patients complained of headache during CLON treatment and only 1 on MOX. The incidence of side effects was significantly higher ($p=0.003$) during CLON- therapy (85%) than MOX-therapy (30%). All side effects had disappeared at latest after 4 days of both treatment periods.

Side effects were more frequent during the first treatment period than the second. 9 patients com-

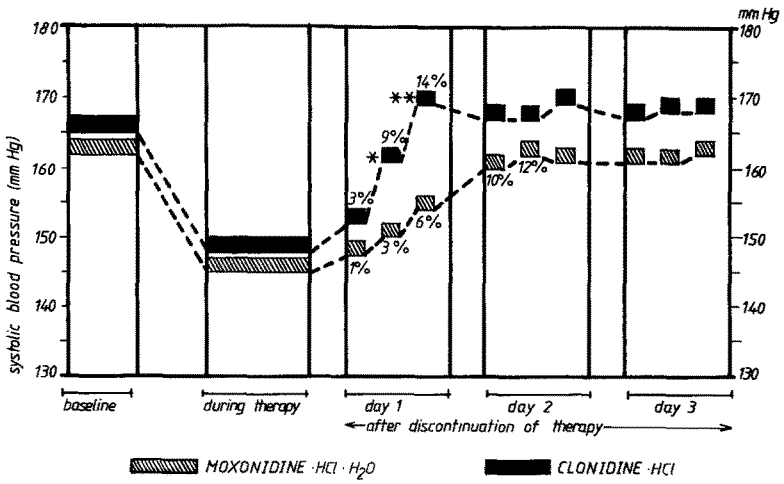

Fig. 4. Supine systolic blood pressure before, during and after discontinuation of therapy (MOX ▨; CLON ■), percentage rise during withdrawal.
* $p=0.025$ } blood pressure rise after MOX
** $p=0.009$ } compared with that after CLON

Table 3. Side-effects reported by all 20 patients

Side-effects	Number of patients on MOX	Number of patients on CLON
Tiredness	(15%)	(60%)
Mild	–	1
Moderate	1	6
Severe	2	5
Dryness of mouth	(20%)	(75%)
Moderate	2	5
Severe	2	10
Headache	1 (5%)	6 (30%)
Limb weakness	–	2 (10%)
Sleep disturbance	1 (5%)	2 (10%)
Vertigo	1 (5%)	–
Total number of patients who complained of any side-effect	6 (30%)	17 (85%)
	$p = 0.003$	

Table 4. Intraindividual comparison of feeling of wellbeing by the patients during MOX- and CLON-therapy

Wellbeing of the patients (MOX/CLON)	($p = 0.01$)
1. better on MOX	$n = 12$
2. no difference between MOX and CLON	$n = 6$
3. better on CLON	$n = 2$

plained of side effects only in the first period, 4 patients only in the second period and 5 patients in both the first and second periods.

Intraindividual comparisons of feelings of wellbeing by the patients are shown in Table 4. Significantly more patients felt better during MOX-therapy than CLON-therapy ($p = 0.01$). In this cross-over study, 12 of 20 patients showed side effects after administration of CLON, but none were reported by these 12 patients after MOX. Only 2 patients showed side effects on MOX and not on CLON. Accordingly, the tolerance reported by the physician was significantly better during MOX- than CLON-therapy ($p = 0.04$).

Laboratory Results, ECG and Body Weight

The serum values did not show any particular trend. There were no clinically relevant changes in ECG or laboratory findings. During the first 4 days both of MOX and CLON treatment, a slight decrease in body weight was observed ($p < 0.001$), accompanied by an increase in 24 h-urine volume ($p = 0.011$). Mean body weight in Group 1 was 79.8 kg before treatment, 78.4 kg after the first treatment period and 77.4 kg after the second period; in Group 2 it was 79.3 kg before, 77.5 kg after the first and 77.2 kg after the second treatment period. Serum Na^+ was not increased; the mean serum level in Group 1 was 144.0 mmol/l before treatment, 144.4 mmol/l after the first treatment period and 146.0 mmol/l after the second period; in Group 2 it was 142.6 mmol/l before, 142.4 mmol/l after the first and 144.8 mmol/l after the second treatment period. There was no significant change in serum K^+; mean concentration in Group 1 was 4.96 mmol/l before treatment, 4.91 mmol/l after the first and 4.72 mmol/l after the second period; in Group 2 it was 4.86 mmol/l before, 4.97 mmol/l after the first and 4.84 mmol/l after the second treatment period.

Discussion

The results of the study suggest that moxonidine is as effective as clonidine in the monotherapy of patients with mild to moderate hypertension. Its antihypertensive action in man was accompanied by a slight decrease in heart rate which is of no clinical relevance. The most prominent side effects were sedation and dry mouth, which were significantly more frequent during clonidine than moxonidine treatment. Both the sedative effect and the centrally mediated fall in blood pressure appear to result from activation of adrenoceptors of the α_2-subtype (Reid et al. 1983). The reason for the different severity and frequency of side effects due to these drugs, which have the same mechanism of action, is not yet known. However, one explanation could be greater α_2-selectivity and specificity of moxonidine. In addition, there may be an additional unknown mechanism of action of moxonidine. It is well known that clonidine causes sedation and dry mouth when administered acutely to hypertensive subjects (Wing et al. 1977) and to normal individuals (Davies et al. 1977). Following clonidine 0.2 mg tid 10 of 16 patients showed dry mouth or drowsiness (Thananopavarn et al. 1982).

Withdrawal symptoms could only be investigated after the second treatment period, i.e. in 10 patients in each group. A significantly more rapid rise in blood pressure was observed after discontinuation of clonidine than moxonidine, though intraindividual comparison of the response to withdrawal was not possible. It is clinically relevant for blood pressure to show a gradual return to its pretreatment level, as shown for moxonidine over 4 days and with no accompanying symptoms. The investigation of withdrawal symptoms in the present study were made after 4 weeks of treatment with centrally acting antihypertensive agents. It will be necessary to verify these results after long-term treatment, but in terms of poor patient compliance the difference in withdrawal effects after short-term administration may be just as important.

Mild or moderate hypertension is mostly accompanied by feelings of wellbeing and therefore by

poor compliance (Holzgreve 1980; Wilber 1980), i.e. a period of therapy is alternated by abrupt cessation and then recommencement of treatment. Thus, the advantages of moxonidine during withdrawal and in terms of side effects after beginning treatment may be clinically important.

For our data neither moxonidine nor clonidine caused sodium or water retention. This is in accordance with results of Yeh et al. (1971), who found that the alleged sodium retaining action of clonidine was transient. Thananopavarn et al. (1982) also found a reduction of blood pressure during monotherapy with clonidine 0.2 mg tid, which was not accompanied by fluid retention or weight gain even after three months.

It should be emphasized that by using a conventional double-blind crossover type of trial an intraindividual comparison of both drugs and the exclusion of interindividual differences of the patients were both possible, and second, that it was an important intention of the present study to employ the lowest dose, necessary to achieve the therapeutic goal. The initial dose of both drugs was 0.2 mg, corresponding to previously employed daily doses of clonidine of 0.25 to 1.05 mg (Garrett et al. 1980). In 20 studies reviewed by Garrett et al. (1980), the mean titrated daily dose was not below 0.2 mg. Recent observations on low dose clonidine therapy have resulted in the use of daily doses of 0.2–0.8 mg (Chrysant et al. 1981), 0.6 mg (Thananopavarn et al. 1982) and 0.2–0.6 mg (Guthrie et al. 1983). These results exclude the possibility that an overdose of clonidine might have been administered.

In conclusion, the study shows that moxonidine and clonidine are of equipotent antihypertensive efficacy. Moxonidine showed fewer side effects and less potential to produce withdrawal symptoms.

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Dr. V. Plänitz
Beiersdorf AG
Unnastr. 48
D-2000 Hamburg 20
Federal Republic of Germany