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Clinical Experience with Moxonidine

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Summary. **Moxonidine is an imidazoline receptor modulator, specific for the I_1-imidazoline receptor. The stimulation of imidazoline receptors represents a new mode of antihypertensive action to inhibit peripheral alpha-adrenergic tone by a central mechanism. Acute hemodynamic studies reveal moxonidine produces an acute fall of blood pressure and systemic vascular resistance. Heart rate, cardiac output, stroke volume, and pulmonary artery pressures are not affected. Left ventricular end-systolic and diastolic volumes are reduced. Ejection fraction is not significantly affected but 6-month studies showed a regression of left ventricular hypertrophy. After oral administration the maximum concentration of moxonidine is reached in about 1 hour, and elimination half-life is 2.5 hours, prolonged by renal insufficiency. The antihypertensive effect lasts longer than would be expected from the half-life. Open studies with moxonidine have revealed falls between 20 and 29 mmHg systolic, and between 10 and 19 mmHg diastolic blood pressure. In the largest study, over 12 months in 141 patients, most patients were controlled by 0.2mg daily (58%) or 0.2 mg b.i.d. (38%). Moxonidine has been compared with representatives from each important class of antihypertensive drugs. In a crossover trial of clonidine in 20 patients, blood pressure control was similar, but the incidence of tiredness and dry mouth was less on moxonidine, as was the total number of patients experiencing side effects, 85% versus 30% ($p < 0.01$). In a larger parallel group study of moxonidine ($n = 122$) and clonidine ($n = 30$), blood pressure control was similar, but the overall incidence of side effects was less on moxonidine. In comparative studies of moxonidine with atenolol, ACE inhibitors, dihydropyridine calcium antagonists, hydrochlorothiazide, and α_1 blockade, the blood pressure control with representatives of these various classes of drugs was similar to moxonidine.**

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Key Words. **moxonidine, hemodynamics, pharmacokinetics, comparative antihypertensive studies**

Moxonidine is an imidazoline receptor agonist [1]. It is highly selective for the I_1-imidazoline receptor with minimal effect at central α_2 receptors [2]. Stimulation of imidazoline receptors represents a new mode of antihypertensive action to inhibit peripheral alpha-adrenergic tone by a central mechanism of action, which is in contrast to established centrally acting drugs, such as clonidine, which lower blood pressure by the stimulation of central α_2 receptors [3].

There is evidence that it is the central α_2 stimulation that is responsible for the sedative effect of clonidine, and thus an agent having weak action at this site might be expected to have less sedative effect [2].

Experimental Studies

Hemodynamics

The hemodynamic effect of moxonidine can be summarized as a fall in blood pressure due to a reduction in peripheral resistance due, in turn, to inhibition of peripheral adrenergic tone. The cardiac hemodynamics are essentially unchanged. The changes have been demonstrated in single oral doses studies in both normotensives [4] and in hypertensive subjects [5,6] (Table 1, Figure 1).

Hüting et al. [7] compared moxonidine and nifedipine in a double-blind parallel-group, 4-week study in hypertensive patients, and the hemodynamic findings were very similar (Figure 2). Hüting et al. [7] also observed a fall in left ventricular end systolic volume (from 75 to 64 ml) and end-diastolic volume (from 164 to 151 ml), while LV ejection fraction was unchanged. Single doses of moxonidine had no effect [6], but pulmonary artery resistance, like systemic resistance, was reduced after 4 weeks administration of moxonidine while pulmonary artery pressure was unchanged [7]. The administration of moxonidine for 6 months is associated with a decline in left ventricular hypertrophy [8] (Figure 3).

Other pharmacodynamic effects

In accord with a central reduction in adrenergic tone, studies in man have demonstrated a reduction in renin and catecholamine levels. Confirming animal studies which have shown a decline in sympathetic nerve activity and catecholamine levels [9,10]. Studies in hypertensive patients with a single oral dose have dem-

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Table 1. Effect of 0.4 mg oral moxonidine on hemodynamics in an open study in patients with hypertension

	HR (min^{-1})	BP (mmHg)	CO ($l\ min^{-1}$)	SV (ml)	SVR ($dyne.sec.cm^{-3}$)
Control	69	176/105	6.1	93	1695
3 hour	72	156/96	6.6	92	1446

$p < 0.01$.

HR = heart rate; BP = blood pressure; CO = cardiac output; SV = stroke volume; SVR = systemic vascular resistance.
n = 10.
After Mitrovic et al. [6], with permission.

onstrated a fall in noradrenaline levels [5,6] (Figure 4). While the fall in adrenaline levels did not reach significance in the studies of Mitrovic et al. [6], Kirch et al. [5] did note a significant fall in resting adrenaline levels (Figure 4). Mitrovic et al. [6] also reported a decline in exercising noradrenaline levels with single doses of 0.4 mg moxonidine from 541 to 407 pg/ml ($p < 0.01$), but again the decline in adrenaline was not significant (110 and 81 pg/ml).

Renin levels fall at rest with single doses of moxonidine [5,6] (Figure 4). There is also a fall in renin on exercise [6]. Resting angiotensin II and aldosterone levels also declined, but not significantly [6], while ANF was not altered at rest but fell by 23% on exercise [6].

Single doses of 0.2 mg moxonidine in normal volunteers reduce salivary secretion, but less than the same dose of clonidine [4], while single doses of 0.25 mg moxonidine in hypertensive patients were without effect [5]. Sensitive laboratory tests have revealed slight degrees of sedation from moxonidine, but less than seen with clonidine in normal volunteers [4]. No sedative effect was seen after single doses in hypertensive patients [5], nor did moxonidine have any effect on various driving skills [11].

Pharmacokinetics

Moxonidine is well absorbed, and its t max is about 1 hour. Mitrovic et al. [6], in their study of single 0.4 mg doses, observed a maximum concentration of 2319 pg/ml at 1 hour, after which the concentration declined. Weimann and Rudolph [12] reviewed the pharmacokinetics of moxonidine (Table 2). Kirch et al. [5] studied three groups of patients (n = 8) with varying renal function. Those with normal function (GFR > 90 ml/min) had a $t_{1/2}$ of 2.6 hours, patients with a GFR of 30–60 ml/min had a $t_{1/2}$ of 3.5 hours, while those with a GFR of <30 ml/min had a $t_{1/2}$ of 6.9 hours.

The maximum effect of moxonidine on the blood pressure lags about 2–4 hours behind its maximum concentration in the blood [5].

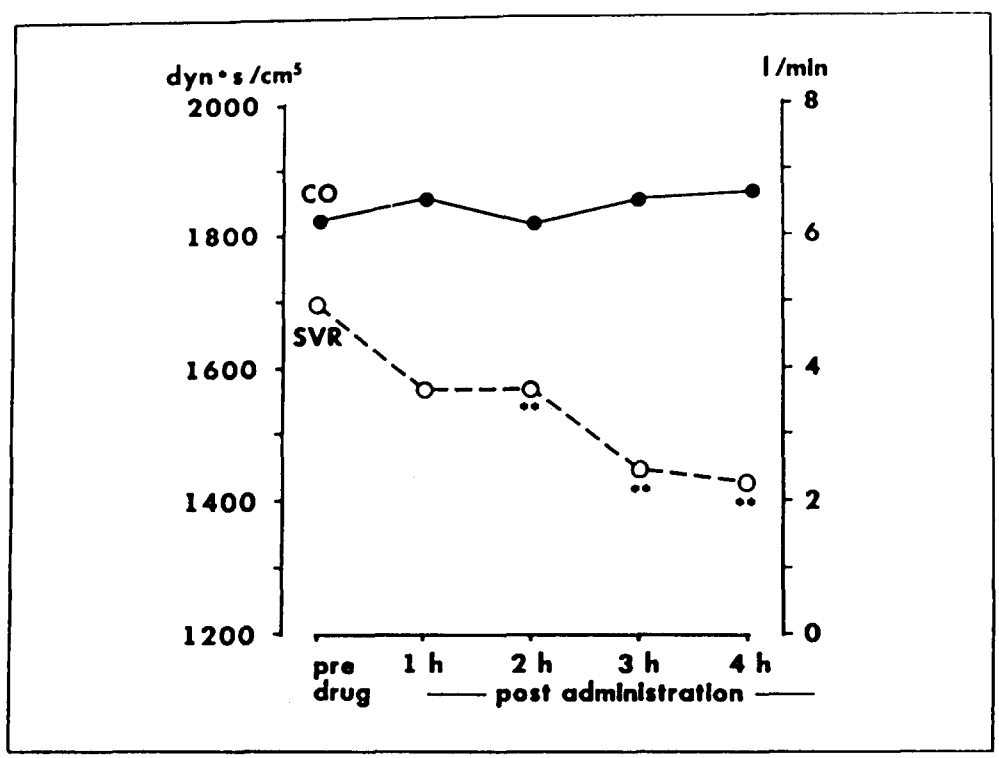

*Fig. 1. Effect of oral moxonidine (0.4 mg) on cardiac output (CO) and systemic vascular resistance (SVR) at rest **$p \leq 0.01$. From Mitrovic et al. [6], with permission.*

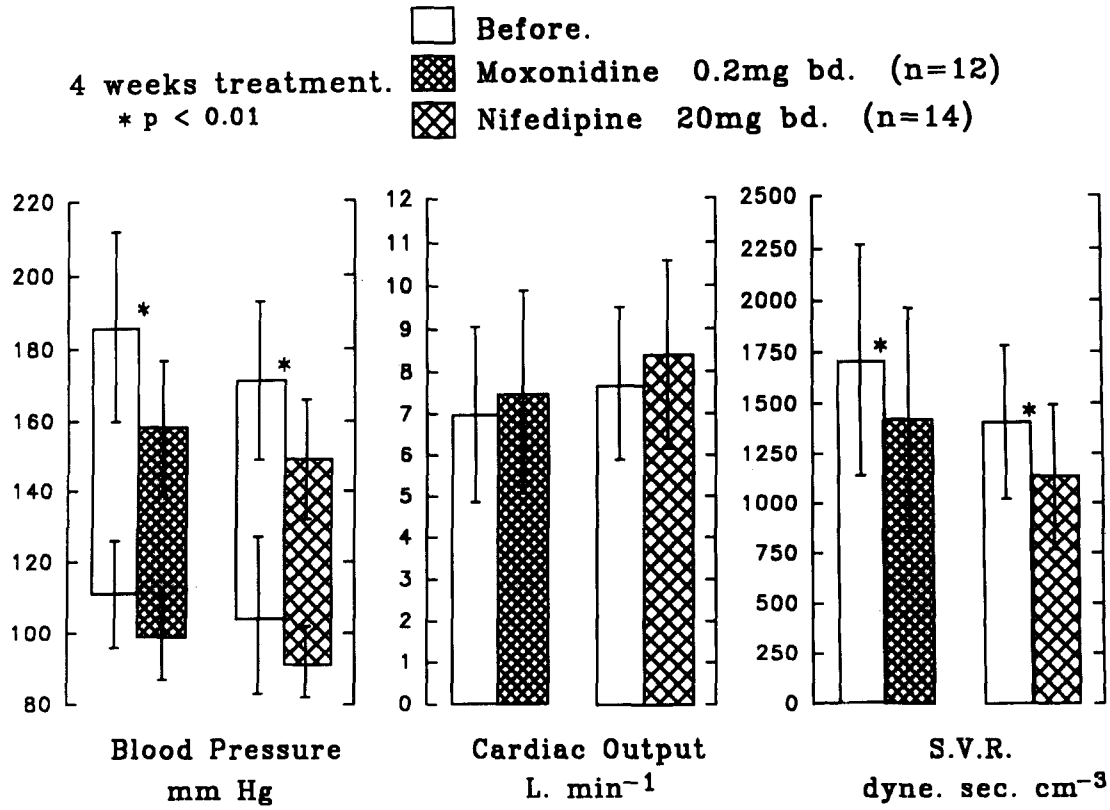

Fig. 2. *Hemodynamic double-blind comparative study of 4-weeks oral moxonidine or nifedipine treatment in patients with hypertension. Pulmonary artery pressure was unchanged but pulmonary resistance was reduced by moxonidine (from 76 ± 24 mmHg to 61 ± 36 mmHg; p < 0.01) and by nifedipine (from 81 ± 70 mmHg to 68 ± 30 mmHg; p < 0.01). After Hüting et al. [7], with permission.*

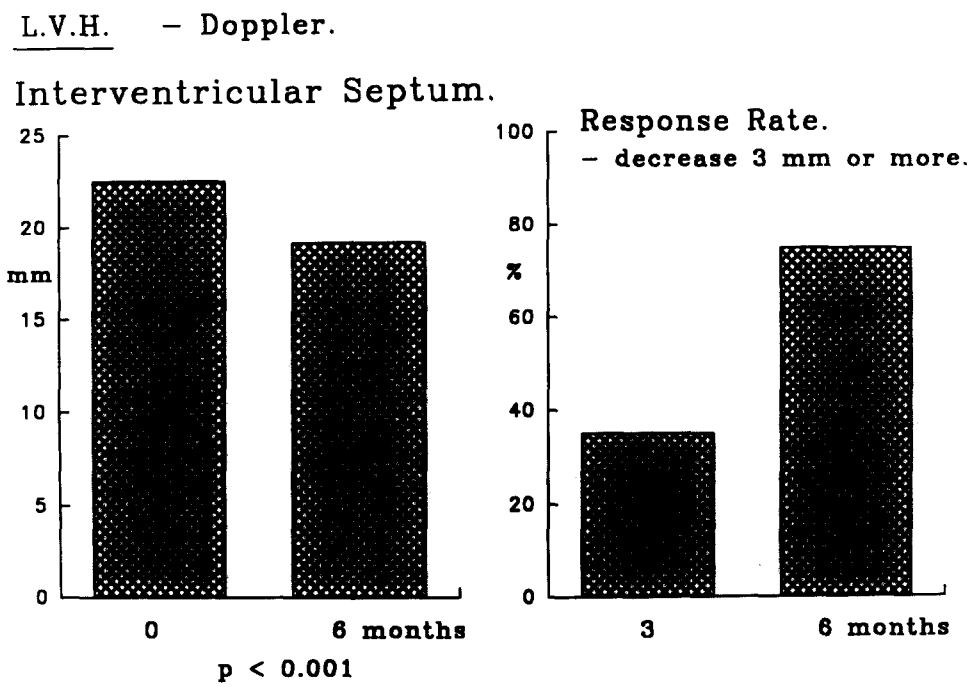

Fig. 3. *Effect of moxonidine (0.2 mg, n = 6; 0.2 mg b.i.d., n = 14) for 6 months on left ventricular hypertrophy (assessed by Doppler) in hypertensive patients. After Eichstädt et al. [8], with permission.*

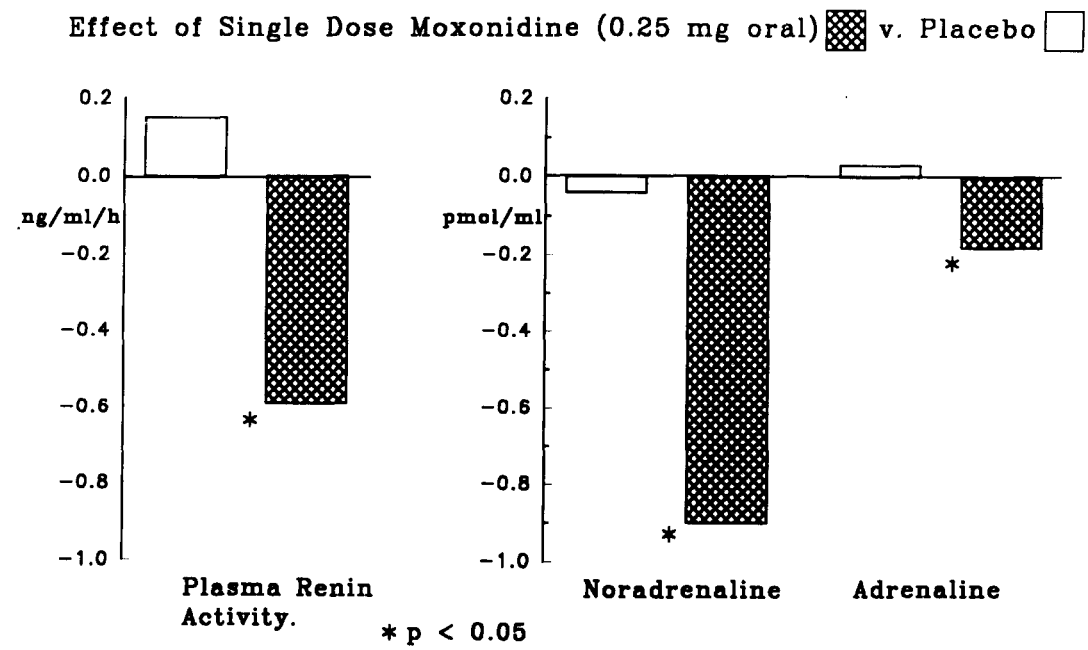

Fig. 4. Effect of moxonidine (0.25 mg oral) and placebo in a single-blind crossover study in eight patients with hypertension, 6 hours postdose compared to baseline. After Kirch et al. [5], with permission.

Table 2. *Summary of the pharmacokinetics of moxonidine*

1. Rapidly, almost completely absorbed
2. Absolute bioavailability 88%
3. Mostly excreted unchanged—biotransformation unimportant
4. $t_{1/2}$ 2 hours—? retained in CNS
5. Chronic treatment—no accumulation
6. Not affected by food; age has little effect
7. Renal impairment, C_{max} $t_{1/2}$ increased
8. No interactions with digoxin, hydrochlorothiazide, glibenclamide

After Weimann and Rudolph [12], with permission.

Table 3. *Trial outline and dose profile in an open, single-drug study of moxonidine*

Open multicenter study: n = 161, n = 141 at 12 months	
Placebo washout: DBP ≥ 95	
Moxonidine 0.2 mg if BP not < 90 mmHg	
Dose increased up to 0.8 mg	
Dose at 12 months (n = 141)	
0.1 mg	0.7%
0.2 mg	58.2%
0.4 mg	37.6%
0.6 mg	2.8%
0.8 mg	0.7%

After Schwartz and Kandziora [15], with permission.

Initial Studies in Hypertension

Several preliminary open studies have been performed with moxonidine in hypertension [13,14]. The largest published study was reported by Schwartz and Kandziora [15]. In a multicenter study 161 patients were entered, and 141 patients were present for the 12-month follow-up. After placebo washout, if diastolic blood pressure was ≥95 mmHg, 0.2 mg moxonidine was commenced and the dosage was increased to control blood pressure to <90 mmHg, with most patients being controlled by 0.2 or 0.4 mg daily (Table 3). The standing blood pressure was reduced from 170 ± 13.6/103.2 ± 6.3 mmHg on placebo to 147.5 ± 12.1/88.4 ± 5.9 mmHg on moxonidine (Figure 5). Similar results were reported in a study with 185 patients of an original 223 patients completing an open 1-year follow-up. The sitting blood pressure was reduced from 176.1/103.5 to 148.0/87.0 mmHg at 52 weeks. There was an 84.2% response rate (a fall of 10 mmHg or a diastolic blood pressure <90 mmHg) in those who completed the protocol. There were no adverse effects on laboratory measurements [16].

Comparative Studies in Hypertension

The place of moxonidine in the treatment of hypertension has been demonstrated by studies with representatives from each class of antihypertenisve drugs in current use. Studies have been performed against the various classes of vasodilators; calcium antagonists,

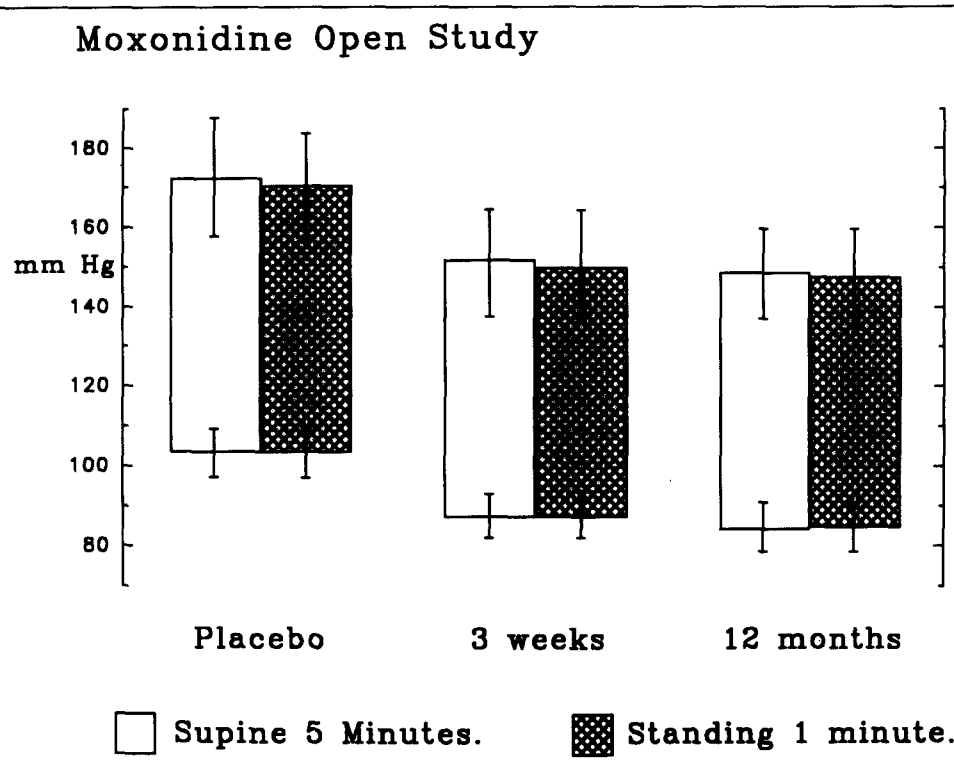

Fig. 5. *Open study with moxonidine in hypertension (n = 141). Effect on supine and standing blood pressures. See Table 3 for the dose profile. After Schwarz and Kandziora [15], with permission.*

angiotensin-converting enzyme inhibitors, α_1-receptor blocking drugs, beta-blockade, diuretics, and pharmacologically the most comparable agent, the centrally acting clonidine.

Comparison with calcium antagonists

Wolf [17] reported a large multicenter, parallel-group, double-blind study in which 0.2mg moxonidine (57.3% of patients) and 0.2 mg moxonidine b.i.d. (42.7% of patients; n = 116) was compared with 20 mg sustained-release nifedipine (52.7% of patients) and 20 mg nifedipine b.i.d. (47.3% of patients; n = 113). The fall in blood pressure was similar in the moxonidine group, from 168.4/102.3 to 144.6/86.0 mmHg after 26 weeks, to that in the nifedipine group, from 167.2/102.1 to 139.8/83.1 mmHg after 26 weeks of treatment.

Comparison with angiotensin-converting enzyme inhibitors

Chrisp and Faulds [1] referred to a hitherto unpublished study of Lotti and Gianrossi [18], who performed a double-blind comparative study of 25 mg captopril daily or b.i.d. against 0.2 mg moxonidine daily or b.i.d. Response rates, i.e., diastolic blood pressure less than 90 mmHg, on moxonidine (72%) and captopril (68%) were similar (Figure 6). In a larger study involving 100 patients, moxonidine was again found to produce similar blood pressure control as captopril. Average blood pressure fell from 176/101

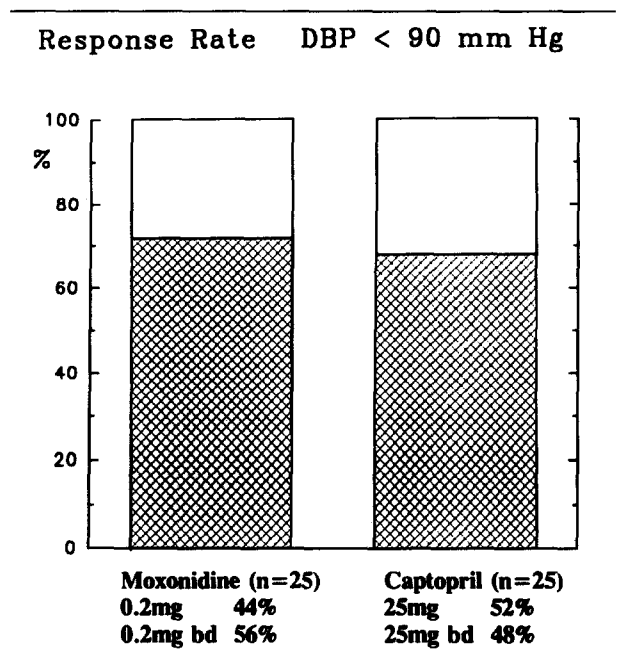

Fig. 6. *Response rate in a double-blind study on moxonidine (0.2 mg, n = 11; 0.2 mg b.i.d., n = 14) and captopril (25 mg, n = 13; 25 mg b.i.d., n = 12) in hypertension. After Lotti and Gianrossi [18], with permission.*

to 155/91 mmHg with moxonidine, and from 170/99 to 150/89 mmHg with captopril [19].

Kraft and Vetter [20] described a double-blind comparison of 0.2 mg moxonidine b.i.d. and 25 mg captopril b.i.d. utilizing ambulatory blood pressures employing a Spacelabs 90207 device. The 24 hour blood pressures after 4-weeks single-blind placebo fell from 144.6 ± 15.8/91.4 ± 5.3 mmHg to 139.7 ± 18.4/86.8 ± 9.7 mmHg after 28 days on moxonidine (n = 13 completed patients). The fall with captopril (n = 10 completed patients), from 146.7 ± 10.6/91.5 ± 4.1 mmHg to 141.0 ± 13.7/87.1 ± 7.1 mmHg, was similar, for both day and night blood pressures. In addition to the 23 patients who completed the study, three others were withdrawn, two because of adverse events. The incidence of side effects was similar in the two groups.

Comparison with alpha$_1$-adrenoceptor blocking drugs

Plänitz [21] reported a crossover study in 30 patients. After a placebo washout, patients received moxonidine for 4 weeks, and subsequently after a further washout prazosin was administered for 4 weeks. Supine blood pressure fell from 184/100 mmHg on placebo to 149/89 mmHg on moxonidine, and from 180/100 to 150/87 mmHg on prazosin, although three patients could not tolerate prazosin. The sense of well-being was better on moxonidine in 15 of 30 patients, only one felt better on prazosin ($p < 0.001$), although conclusions must be very tentative, as the study was not randomized nor double blind.

Comparison with beta-adrenoceptor blocking drugs

We have reported a parallel-group, double-blind trial of moxonidine versus atenolol. After a single-blind washout, patients received a titrated dose of either moxonidine (0.2 or 0.2 mg b.i.d.) or atenolol (50 or 100 mg o.d.) for 8 weeks. There were 25 patients who were treated according to the protocol on moxonidine; a dose of 0.2 mg b.i.d. was taken by 28% and the remainder took a 0.2 mg dose o.d. The dose of atenolol was 100 mg o.d. in 21% in 28 patients who were treated according to the protocol, and the remainder received 50 mg daily in the atenolol group. The placebo blood pressures (sitting) in the moxonidine group were 167 ± 8/101 ± 3 mmHg, decreasing after 8 weeks of treatment to 148 ± 22/89 ± 10 mmHg, and in the atenolol group from 169 ± 12/102 ± 4 mmHg on placebo to 145 ± 17/87 ± 8 mmHg on atenolol. There were five patients in the atenolol group who were withdrawn; two because of side effects, one because of cold extremities, i.e., most probably drug related, and one because of leg pain, also possibly a drug effect [22].

Comparison with diuretics

In a double-blind parallel group study, 35 patients were treated with moxonidine and 38 patients with hydrochlorothiazide. There were 28 patients who completed 8 weeks on moxonidine: 11 received 0.2mg/day and 17 received 0.4mg/day; 34 patients took hydrochlorothiazide for 8 weeks, 16 patients at 25 mg/day and 18 at 50 mg/day. The blood pressure control was very similar in the two groups [23] (Figure 7). Supine blood pressure fell from 160.1/103 mmHg on placebo to 147.6/91.9 mmHg with moxonidine, and from 167.3/103.3 mmHg to 151.4/92.1 mmHg with hydrochlorothiazide.

Küppers [24] has performed a double-blind, parallel-group comparison of placebo (n = 37), moxonidine (n = 35), hydrochlorothiazide (n = 37), and the combination (n = 38). The fall in blood pressure on 8 weeks of moxonidine (0.4 mg) compared to a 4-week placebo baseline was 21.2/12.4 mmHg, significantly greater than the fall on placebo of 14.2/9.7 mmHg, but similar to the hydrochlorothiazide (25 mg) decline of 23.7/12.8 mmHg. The side effect profile was comparable in both groups. The combination of moxonidine and hydrochlorothiazide for 8 weeks resulted in a fall of blood pressure of 28.6/16.5 mmHg. The response rate, defined as a 10 mmHg reduction or a fall to <90 mmHg, was 71.4% with moxonidine 67.6% with hydrochlorothiazide, and 86.8% with the combined treatment.

Comparison with other centrally acting drugs

Plänitz [25] reported a large double-blind, parallel-group study that compared moxonidine (n = 122) and clonidine (n = 30) over a 6-week drug administration period following an initial washout period. The dosage in each case was titrated during the first week to give a diastolic blood pressure <90 mmHg. The dose profile (Table 4) was very similar to that used in the study of Schwartz and Kandziora [15]. Moxonidine reduced blood pressure from 177/100 to 151/87 mmHg in the 115 patients who completed the treatment with moxonidine (Figure 8). Two patients were withdrawn because of dry mouth, and the remaining five were excluded for reasons unrelated to the drug. Clonidine produced a fall in blood pressure from 176/99 to 147/87 mmHg in 27 patients who completed treatment, and three patients were withdrawn because of side effects.

Adverse Effects

Assessment of adverse events from a drug requires placebo comparison to obtain evidence of the absolute incidence, or a double-blind comparative study to assess the comparative incidence of side effects. None of the various studies have found a greater incidence of adverse events on moxonidine versus the comparator agent.

Two large double-blind, parallel-group studies provide the most interesting evidence relating to side ef-

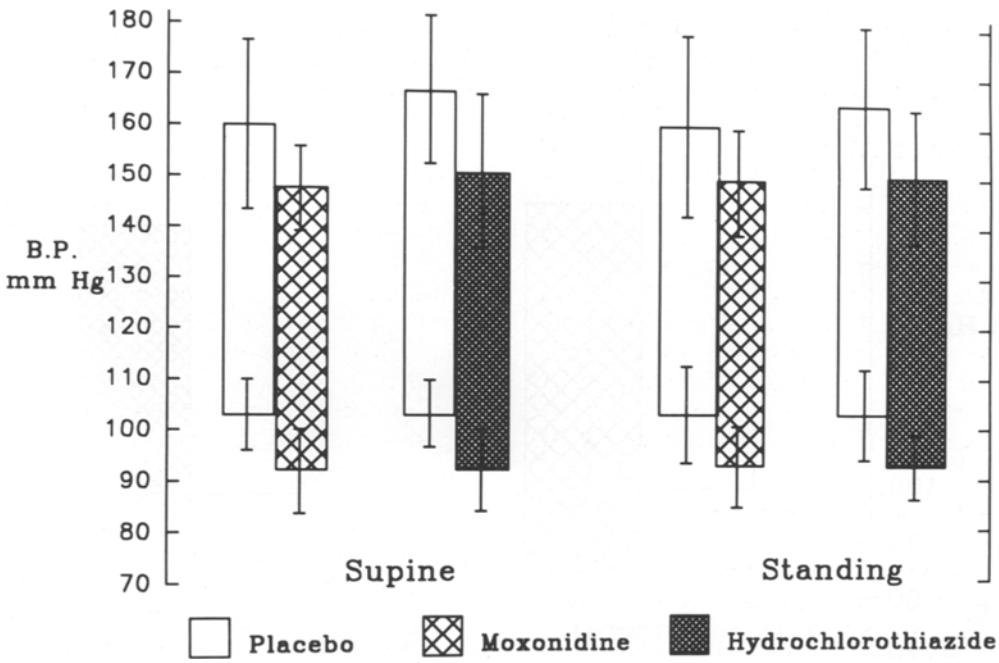

Fig. 7. *Effect of moxonidine (0.2 mg o.d., n = 11; 0.4 mg o.d., n = 17) or hydrochlorothiazide (25 mg o.d., n = 16; 50 mg, n = 18) in double-blind study in hypertension. After Larrat [23], with permission.*

Table 4. *Trial outline and dose profile in a double-blind comparative study of moxonidine and clonidine*

Washout
2–3 weeks off treatment
SBP > 160 mmHg or DBP > 95 mmHg
Double-blind parallel-group, 6 weeks
Dosage to give DBP <90 mmHg
Adjusted over first week

Dose (mg/day)	*Moxonidine* (n = 122)	*Clonidine* (n = 30)
0.2	42.6%	40.0%
0.3–0.4	41.0%	46.7%
0.6	10.7%	6.7%
0.8–1.0	5.7%	6.7%
Aver. dose	0.366 mg/day	0.363 mg/day

After Plänitz [25], with permission.

fects. Plänitz [25] found that the incidence of dry mouth of 20% and 47%, and an overall incidence of side effects of 30% and 53%, were significantly less with moxonidine than with clonidine (Figure 9). Wolf [17] in a comparison with nifedipine, observed an overall incidence of 28% adverse events with moxonidine and 37.2% with nifedipine, although the nature of the side effects observed differed with the drug (Figure 10).

Plänitz [26] reported a cross-over double-blind study of clonidine and moxonidine in 20 patients. Tiredness occurred in 15% versus 60%, and dry mouth in 20% versus 75% of the patients treated with moxonidine and clonidine, respectively. The overall incidence of patients complaining of any side effects was 30% on moxonidine, which was significantly less than the 85% incidence on clonidine ($p = 0.003$). An overall assessment of well-being was also carried out, 12 patients felt better on moxonidine, two on clonidine, and six did not express a preference ($p = 0.01$).

Schmidt and colleagues [11], in an open controlled study, assessed the effect of 0.2–0.4 mg/day moxonidine on various driving skills in hypertensive patients compared to a group of normotensive patients. Moxonidine was not found to adversely affect any of the parameters tested.

Finally withdrawal of clonidine was reported to be associated with an overshoot of blood pressure if treatment was stopped abruptly. Plänitz [26] investigated this phenomenon and reported the rate of rise of blood pressure in the 3 days after moxonidine and clonidine were stopped. The blood pressures climbed over 2 days after moxonidine was stopped, whereas with clonidine blood pressures rose over the first day, but in neither case was an overshoot observed. The 14% rise of systolic blood pressure at the end of the first day following clonidine withdrawal was significantly greater than the 6% increase seen with cessation of moxonidine treatment ($p < 0.01$).

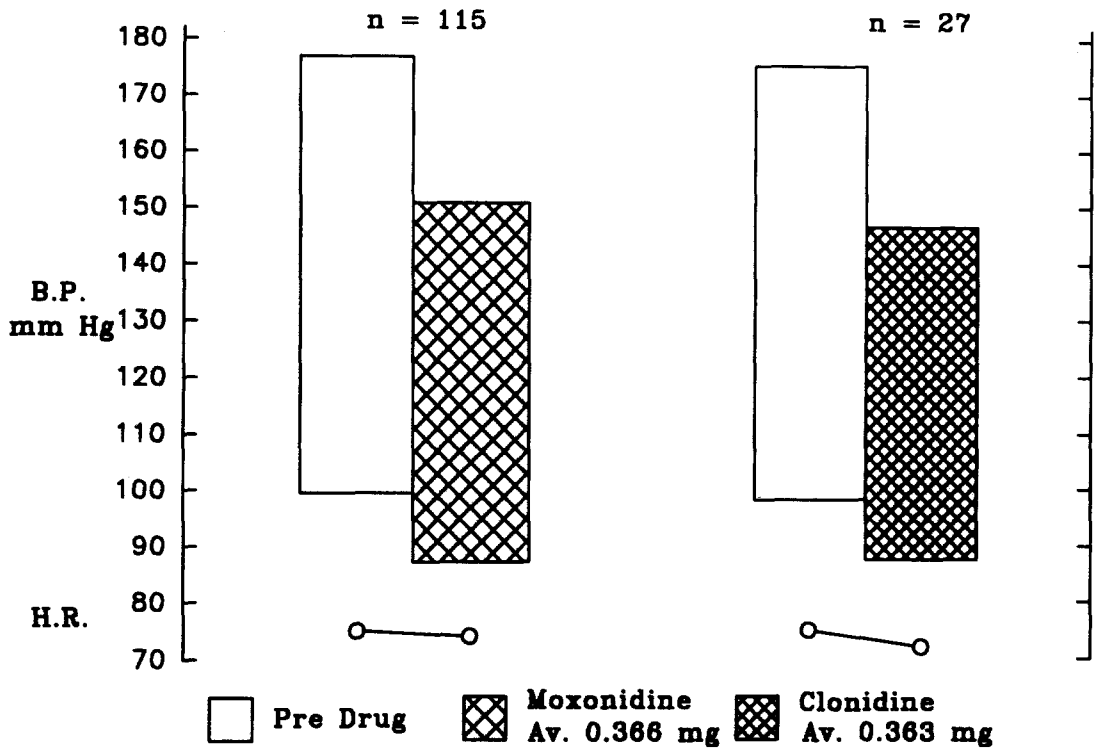

Fig. 8. Effect of 6-week treatment with moxonidine (n = 115) or clonidine (n = 27) in a double-blind study in patients with hypertension. Details of dosage are given in Table 4. After Plänitz [25], with permission.

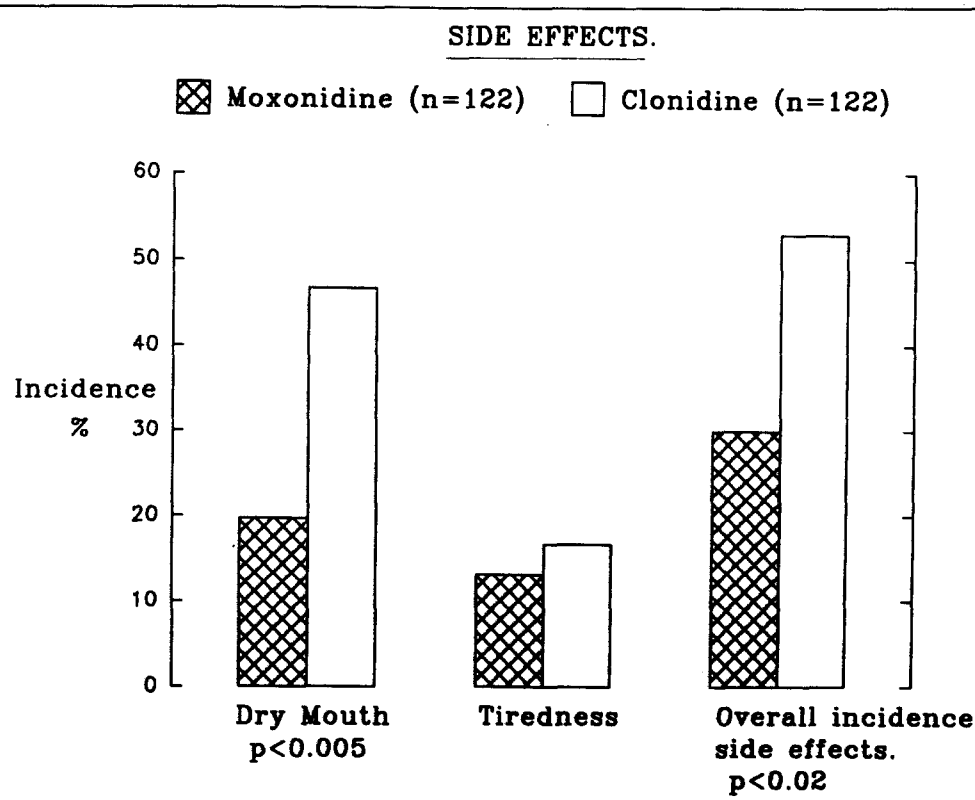

Fig. 9. Incidence of side effects in a 6-week double-blind study comparing moxonidine and clonidine. After Plänitz [25], with permission.

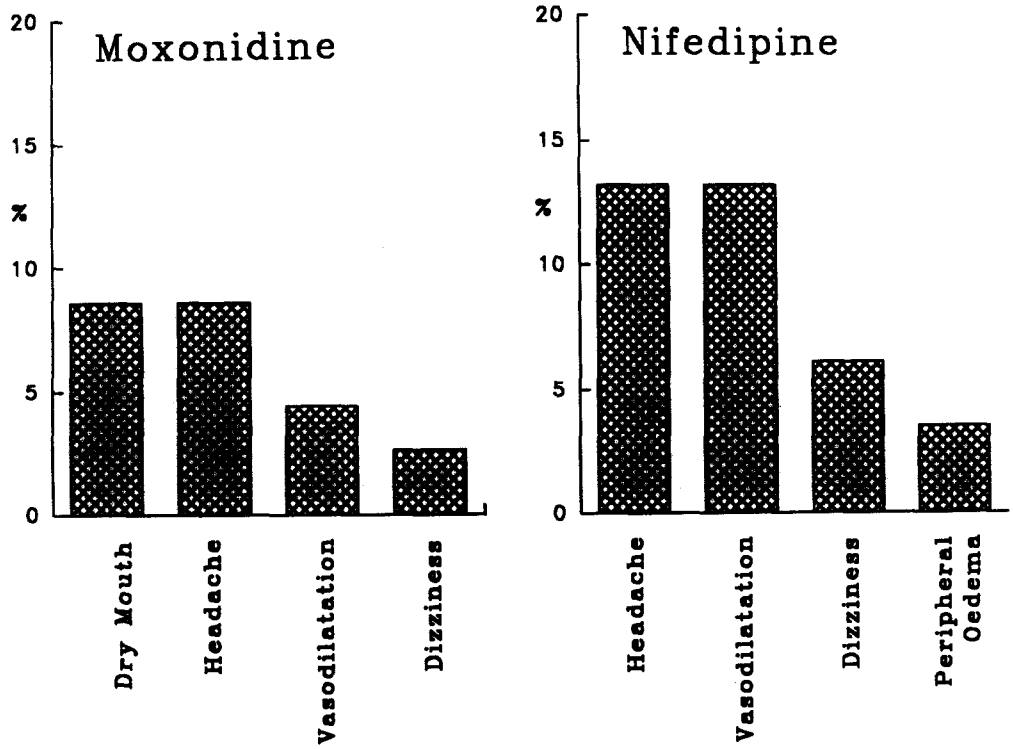

Fig. 10. *Adverse event profile in a double-blind study comparing moxonidine (n = 116) and nifedipine (n = 113). A total of 28% of patients experienced an adverse event on moxonidine and 37.2% on nifedipine. After Wolf [17], with permission.*

Conclusions

Moxonidine is an effective antihypertensive agent, and its tolerance compares satisfactorily with other antihypertensive drugs and in several instances appears superior. Comparative studies with representatives of all major classes of drugs have indicated that moxonidine is of similar efficacy as these drugs. Such studies have been performed against atenolol, captopril, nifedipine, clonidine, hydrochlorothiazide, and prazosin. These studies do suggest, thus far, that I_1-imidazoline receptor selectivity, in contrast to its weak agonist action at the α_2-receptor of moxonidine [2], does appear to fulfill predictions, which is reflected in the lower incidence of sedation with this agent [25, 26]. This contrasts with clonidine, which exhibits a low efficacy at the I_1-imidazoline receptor, compared to its α_2-receptor agonism [2], and its higher incidence of sedation [24, 25].

Acknowledgments

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