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## Dose Relation of Blood Pressure Reduction with Moxonidine: Findings from Three Placebo- and Active-Controlled Randomized Studies

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Three placebo-controlled trials based on a standardized protocol and methodology have compared the blood pressure-lowering effect of once-daily moxonidine with that of the angiotensin-converting enzyme (ACE) inhibitor enalapril. Data from these studies were used to examine the dose-relation of blood pressure responses to moxonidine. Combined analysis of these studies ( $n = 461$ ), based on intention-to-treat analysis of placebo-corrected mean changes in office sitting diastolic blood pressure (SiDBP) at trough, revealed that moxonidine produced a progressive, dose-proportionate blood pressure-lowering effect across its recommended dose range (0.2–0.6 mg/day). This evidence for a dose-dependent blood pressure-lowering effect of moxonidine was confirmed by 24-hour ambulatory blood pressure recordings (ABPM). Placebo-adjusted mean changes in SiDBP during ABPM were  $-4.8$ ,  $-9.4$  and  $-10.3$  mmHg, respectively, with moxonidine 0.2, 0.4 and 0.6 mg/day ( $p < 0.001$  for comparison of each dose versus placebo). In all three studies enalapril reduced blood pressure significantly more than placebo and showed equivalence with moxonidine. We conclude that single daily doses of moxonidine in the range 0.2–0.6 mg produce dose-dependent, clinically relevant and statistically significant decreases in SiDBP at trough. *J Clin Basic Cardiol* 2003; 6: 49–51.

**Key words:** moxonidine, blood pressure, dose-response

Moxonidine is a selective agonist of imidazoline I<sub>1</sub> receptors in the rostral ventrolateral medulla [1, 2]. Through this mechanism of action, moxonidine is an effective antihypertensive therapy with a promising tolerability profile [3]. Moxonidine has been compared in controlled trials with representatives of the four classes of antihypertensives regarded as first-choice medications—diuretics [4], beta-blockers [5], angiotensin-converting enzyme (ACE) inhibitors [6–8] and calcium-channel blockers [9] and has, in each instance, exhibited consistent antihypertensive efficacy.

Three placebo-controlled trials of once-daily moxonidine have compared the blood pressure-lowering effect of this agent with the ACE inhibitor enalapril. Two of these studies have been reported previously [7, 8]; the third, a comparison of moxonidine 0.2 mg/day and enalapril 5 mg/day, is reported here for the first time. In each study, the blood pressure reduction achieved with moxonidine at the studied dosage (0.2, 0.4 [7] or 0.6 [8] mg once daily) was not statistically different to that obtained with comparison doses of enalapril (5, 10 [7] or 20 [8] mg, once daily, respectively) and was significantly superior to that seen with placebo ( $p < 0.001$ ). Consideration of data from these three studies provided an opportunity to examine dose-response relations for moxonidine across the range of currently approved daily dosages. We report the results of this investigation.

### Methods and Materials

The placebo-controlled comparative studies of moxonidine versus enalapril were based on a standardized protocol involving 8 weeks of double-blind treatment after an initial single-blind placebo-controlled run-in period. Patients enrolled in the run-in period were eligible to proceed to the active treatment phase of the study if they had office sitting diastolic blood pressure (SiDBP) in the range 95–114 mmHg and office sitting systolic blood pressure (SiSBP)  $< 200$  mmHg during the 2 weeks immediately prior to randomization and on day 0, the first day of active treatment, and ambulatory

mean diastolic blood pressure  $> 85$  mmHg. All three trials were conducted at multiple primary-care centres in Germany, with the approval of local or regional ethics authorities and the informed consent of participating patients. Details of two of these studies, which compared, respectively, moxonidine 0.4 mg/day with enalapril 10 mg/day or placebo [7], and moxonidine 0.6 mg/day with enalapril 20 mg/day or placebo have been published [8]. The third study, which involved 171 outpatients, compared moxonidine 0.2 mg/day with enalapril 5 mg/day or placebo.

Baseline and end-of-treatment office resting blood pressure measurements (evaluated at trough) and similar data from ambulatory recordings in the intention-to-treat (ITT) cohort of the three studies were included in the present analysis. (The ITT cohorts comprised all patients who underwent a baseline assessment and at least one valid efficacy assessment during the treatment period.) The primary efficacy variable in all three studies was office SiDBP at trough.

Comparison of the effects of moxonidine and enalapril was undertaken by means of analysis of variance including three fixed factors: treatment, study and interaction of both. The null-hypothesis of non-equivalence was tested against the alternative that moxonidine and enalapril were equivalent. For these purposes, equivalence was defined as a difference in SiDBP of not more than 3 mmHg. Formal equivalence limits were not defined for SiSBP, but estimates of the effect were made.

### Results

#### Patients' Characteristics

Core demographic data for the three patient populations are summarized in Table 1. These data were not pooled in order to ensure that the profile of the statistically 'average' patient was not distorted by outliers. It will be apparent from the data in Table 1 that the patients enrolled in all three studies were broadly similar.

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**Treatment Effect on SiDBP: Office Measurements**

The least squares mean changes from baseline in office SiDBP at trough are summarized in Table 2. There were significant between-study differences in the placebo response ( $p < 0.05$ ). Nevertheless, the blood pressure responses to both moxonidine and enalapril were significantly greater than to placebo in all three trials ( $p < 0.001$ ). The reductions in SiDBP achieved with moxonidine or dose-matched enalapril did not differ statistically. SiDBP responses to moxonidine, adjusted also for fixed factors (centre and treatment by centre), are illustrated in Figure 1 and reveal a clear dose-linearity in the SiDBP response to moxonidine.

**Treatment Effect on SiDBP: ABPM Measurements**

Placebo-corrected mean changes in SiDBP during 24-hour ABPM are shown in Table 3. Between-study differences were less marked than for office measurements. In all three trials, the reductions in SiDBP achieved with both moxonidine and enalapril were significantly greater than those seen

with placebo ( $p < 0.001$ ) and not significantly different from one another.

**Discussion**

This analysis confirms that in controlled trials moxonidine (0.2–0.6 mg/day) produced dose-dependent, clinically relevant and statistically significant reductions in office-recorded SiDBP and at trough, and was equivalent to enalapril (5–20 mg/day) across the dose range studied. This evidence of a dose-proportionate blood pressure-lowering effect was corroborated by ABPM measurements.

The observations that moxonidine 0.4 mg/day produced a statistically significant reduction in mean SiDBP and brought SiDBP below 90 mmHg in 53 % of patients, and produced reductions in SiDBP of at least 10 mmHg in a further 7 % of patients [9] substantiates the view that this low dose is often an effective maintenance dose.

Moxonidine can be used in combination with a variety of other antihypertensives [10]. The combination of dose-proportionate blood pressure reduction and suitability for use with other agents makes moxonidine a useful and flexible therapy appropriate to modern management strategies for

**Table 1.** Demographics of patients in three placebo-controlled trials of moxonidine versus enalapril

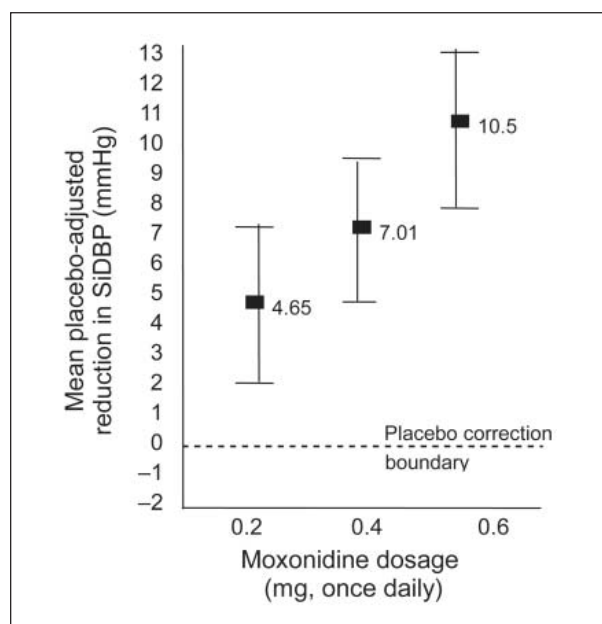
	Moxonidine (n = 54) (n = 59)	Enalapril (n = 59) (n = 56)	Placebo (n = 56)
Sex (M/F, %)	61.1/38.9	50.8/49.2	60.7/39.3
Mean age (SD)	53.6 (9.3)	51.6 (9.9)	51.2 (9.8)
Baseline SiSBP (SD)	164.0 (9.8)	162.8 (8.3)	164.1 (9.4)
Baseline SiDBP (SD)	102.4 (4.5)	100.7 (4.1)	100.3 (4.4)
Mean BMI (SD)	26.0 (2.69)	25.9 (2.30)	25.4 (2.48)
	Moxonidine (0.4 mg/day) (n = 47)	Enalapril (10 mg/day) (n = 47)	Placebo (n = 44)
Sex (M/F, %)	55.3/44.7	55.3/44.7	50/50
Mean age (SD)	54.9 (8.7)	51.2 (10.9)	53.4 (8.7)
Baseline SiSBP (SD)	163.6 (12.7)	163.5 (11.9)	159.8 (11.7)
Baseline SiDBP (SD)	101.4 (3.3)	101.5 (4.3)	101.3 (3.5)
Mean BMI (SD)	26.0 (2.44)	26.5 (3.04)	26.5 (2.68)
	Moxonidine (0.6 mg/day) (n = 51)	Enalapril (20 mg/day) (n = 53)	Placebo (n = 50)
Sex (M/F, %)	58.8/41.2	66/34	58/42
Mean age (SD)	51.2 (9.3)	52.2 (10.3)	53.6 (9.3)
Baseline SiSBP (SD)	166.0 (15.4)	165.2 (14.5)	162.8 (14.5)
Baseline SiDBP (SD)	101.1 (4.1)	101.1 (4.4)	99.9 (3.9)
Mean BMI (SD)	26.0 (2.44)	26.5 (3.04)	26.0 (2.41)

BMI = body mass index; SiDBP = office sitting diastolic blood pressure; SiSBP = office sitting systolic blood pressure

**Table 2.** Summary of response of office SiDBP at trough after 8 weeks of treatment with moxonidine (0.2–0.6 mg/day) or enalapril (5–20 mg/day) in three controlled studies in patients with hypertension

Moxonidine		Enalapril		Placebo
Dose (mg, once daily)	Change in SiDBP from baseline (mmHg)	Dose (mg, once daily)	Change in SiDBP from baseline (mmHg)	Change in SiDBP from baseline (mmHg)**
0.2 (n = 54)	-10.7*	5 (n = 59)	-12.3*	-7.0 (n = 56)
0.4 (n = 47)	-12.3*	10 (n = 47)	-11.8*	-4.7 (n = 44)
0.6 (n = 51)	-13.2*	20 (n = 53)	-11.9*	-2.3 (n = 50)

\* $p < 0.001$  versus placebo; \*\* $p < 0.05$  for differences between studies



**Figure 1.** Dose-response of reduction in office sitting diastolic blood pressure (SiDBP) at trough with moxonidine. Data illustrate placebo-corrected least mean squares changes with 95 % confidence intervals (not simple means, as shown in Table 2).

**Table 3.** Summary of placebo-adjusted changes in 24-hour ambulatory diastolic blood pressure (DBP) after 8 weeks of treatment with moxonidine (0.2–0.6 mg/day) or enalapril (5–20 mg/day) in three controlled studies in patients with hypertension (all changes  $p < 0.001$  versus placebo)

Moxonidine		Enalapril	
Dose (mg, once daily)	Change in DBP from baseline (mmHg)	Dose (mg, once daily)	Change in DBP from baseline (mmHg)
0.2 (n = 47)	-4.8	5 (n = 54)	-6.4
0.4 (n = 36)	-9.4	10 (n = 36)	-9.9
0.6 (n = 40)	-10.3	20 (n = 40)	-9.2

hypertension, which emphasize the use of multiple drugs [11, 12]. The linear dose-response indicates that dose titration is a practicable option.

Experience in the individual trials suggests that adverse effects with moxonidine are also dose-related but that the frequency and severity of these events is well within sustainable limits for most patients, especially when dosage is adjusted by unforced titration [13, 14]. In particular, the tolerability profile of the 0.4 mg/day dose is compatible with its use in maintenance therapy [8]. The frequency of adverse events declines with continued use of moxonidine [14].

The value of ACE inhibitors for prevention of the cardiovascular complications of hypertension has been demonstrated in large trials and meta-analyses [15–17]. There are suggestions that ACE inhibitor therapy may have a notably benign impact on insulin and glucose homeostasis, as manifest for instance in a reduction in the development of overt diabetes in the HOPE (Hypertension Outcomes Prevention Evaluation) trial [18]. Observations in hypertensive patients suggest that moxonidine may have similar effects, notably enhancement of insulin sensitivity [18–20]. These possibilities are currently being subjected to further scrutiny in clinical trials, including MARRIAGE (Moxonidine And Ramipril Regarding Insulin And Glucose Evaluation), in which moxonidine is being compared with the ACE inhibitor ramipril, and the ALMAZ study, which involves patients with impaired glucose tolerance or diabetes mellitus managed by dietary control alone plus essential hypertension. Results of both studies are expected to become available during 2004.

## References

- Ernsberger P, Damon TH, Graff LM, Christen MO, Schäfer SG. Moxonidine, a centrally acting antihypertensive agent, is a selective ligand for I<sub>1</sub>-imidazoline sites. *J Pharmacol Exp Ther* 1992; 264: 172–82.
- Ernsberger P, Haxhiu MA, Graff LM, Collings LA, Dreshaj I, Grove DL, Graves ME, Schäfer SG, Christen MO. A novel mechanism of action for hypertension control: moxonidine as a selective I<sub>1</sub>-imidazoline antagonist. *Cardiovasc Drugs Ther* 1994; 8: 27–41.
- van Zwieten PA. Centrally acting antihypertensives: a renaissance of interest. Mechanisms and haemodynamics. *J Hypertens* 1997; 15 (Suppl 1): S3–S8.
- Frei M, Küster L, Gardosch von Krosigk PP, Koch HF, Küppers H. Moxonidine and hydrochlorothiazide in combination: a synergistic antihypertensive effect. *J Cardiovasc Pharmacol* 1994; 24 (Suppl 1): S25–S28.
- Prichard BNC, Simmons R, Rooks M, Haworth DA, Laws D, Wonnacott S. A double-blind comparison of moxonidine and atenolol in the management of patients with mild-to-moderate hypertension. *J Cardiovasc Pharmacol* 1992; 20 (Suppl 4): S45–S49.
- Kraft K, Vetter H. Twenty-four-hour blood pressure profiles in patients with mild-to-moderate hypertension: moxonidine versus captopril. *J Cardiovasc Pharmacol* 1994; 24 (Suppl 1): S29–S33.
- Küppers HE, Jäger BA, Luszick JH, Gräve MA, Hughes RA, Kaan EC. Placebo-controlled comparison of the efficacy and tolerability of once-daily moxonidine and enalapril in mild-to-moderate essential hypertension. *J Hypertens* 1997; 15: 93–7.
- Prichard BNC, Jäger BA, Luszick JH, Küster L, Verboom CN, Hughes PR, Sauermann W, Küppers HE. Placebo-controlled comparison of the efficacy and tolerability of once-daily moxonidine and enalapril in mild-to-moderate essential hypertension. *Blood Press* 2002; 11: 166–72.
- Wolf R. The treatment of hypertensive patients with a calcium antagonist or moxonidine: a comparison. *J Cardiovasc Pharmacol* 1992; 20 (Suppl 4): S45–S49.
- Waters J, Ashford J, Jäger B, Wonnacott S, Verboom CN for the TOPIC Investigators. Use of moxonidine as initial therapy and in combination in the treatment of essential hypertension – results of the TOPIC (Trial of Physiotens in combination) Study. *J Clin Basic Cardiol* 1999; 2: 219–24.
- Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Menard J, Rahn KH, Wedel H, Westerling S for the HOT Study Group. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. *Lancet* 1998; 351: 1755–62.
- Guidelines Subcommittee, WHO-ISH. 1999 World Health Organization – International Society of Hypertension Guidelines for the Management of Hypertension. *J Hypertens* 1999; 17: 151–83.
- Schachter M, Luszick J, Jäger B, Verboom CN, Söhlke E. Safety and tolerability of moxonidine in the treatment of hypertension. *Drug Safety* 1998; 19: 191–203.
- Webster J, Koch HF. Aspects of tolerability of centrally acting antihypertensive drugs. *J Clin Pharmacol* 1996; 27: S49–S54.
- Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ; Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003; 348: 583–92.
- Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. *Lancet* 2000; 355: 1955–64.
- The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000; 342: 145–53.
- Haenni A, Lithell H. Moxonidine improves insulin sensitivity in insulin-resistant hypertensives. *J Hypertens* 1999; 17 (Suppl 3): S29–S35.
- Sanjuliani AF, Genelhu-Fagunde V, Rodrigues LLG, Moulin CS, Netto JF, Francischetti EA. Effect of an imidazoline agonist on sympathetic activity and components of the insulin resistance syndrome in obese hypertensive Brazilian patients. *J Hypertens* 2002; 20 (Suppl 4): S206.
- Almazov VA, Shlyakhto EV, Blagosklonnaya YV, Krasnilicova EI, Vinnic TV, Ageeva VV, Isachev NI. Insulin resistance and arterial hypertension. The influence of moxonidine and metformin therapy. *J Hypertens* 2000; 18 (Suppl 2): S12.