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

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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

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The efficacy of moxonidine in the management of essential hypertension was examined in a study conducted in 138 general practice centres in the UK. Slightly more than half of the patients who completed 8 weeks of open-label once-daily moxonidine therapy (294 out of 566) achieved good control of blood pressure (defined as sitting DBP < 90 mmHg or reduction from baseline of at least 10 mmHg) with moxonidine 200 or 400 mcg, administered once daily. The remaining 272 patients were randomized to 4 weeks of double-blind therapy during which they received, in addition to moxonidine 400 mcg o. d., amlodipine 5 mg (n = 87), enalapril 10 mg (n = 88), or hydrochlorothiazide 12.5 mg (n = 97). Satisfactory blood pressure responses were recorded in 46.9 % of patients treated with moxonidine/amlodipine, 26.8 % of patients treated with moxonidine/enalapril and 21.1 % of patients treated with moxonidine/hydrochlorothiazide.

The results of this study indicate that moxonidine is effective when used either alone or in combination for the management of essential hypertension in the patient population encountered in UK general practice. Further evaluation of the combination of moxonidine plus amlodipine, which was both effective and well tolerated, is desirable. J Clin Basic Cardiol 1999; 2: 219–24.

Key words: moxonidine, amlodipine, enalapril, hydrochlorothiazide, primary care, hypertension

Moxonidine (Physiotens® Solvay Healthcare Ltd.) is the first drug of its class – the selective imidazoline receptor agonists (SIRAs) – to have been approved in the UK for the management of essential hypertension. The drug has been available in continental Europe since 1991. Moxonidine exerts its blood pressure-lowering effect through stimulation of imidazoline type 1 (I1) receptors in the cardiovascular regulatory centres of the medulla oblongata [1–3]. As a selective agonist for these receptors moxonidine is an effective antihypertensive agent, with less potential for significant side effects than less selective agents that give rise to alpha-adrenoceptor-mediated adverse effects [4, 5].

The pharmacology and clinical profile of moxonidine have been the subject of a recent review [6]. Cardiac output is unaffected either at rest or during exercise and haemodynamic reflexes are not impaired. The drug is administered either once or twice daily. Doses of 200–400 mcg are usual: the recommended maximum daily dose is 600 mcg. Moxonidine has not been associated with undesirable metabolic effects in hypertension and potentially favourable effects on glucose tolerance and insulin sensitivity have been suggested.

Moxonidine has been evaluated in both placebo- and active-controlled trials and has demonstrated consistent and sustained blood pressure-lowering efficacy comparable to that of other major classes of antihypertensives [6–14]. The expectation of good tolerability has been substantiated in clinical use [15, 16].

Experience with moxonidine in combination therapy in clinical trials has been encouraging, but is limited [17]. The present study – TOPIC (Trial Of Physiotens In Combination) – was undertaken to gain additional experience with moxonidine in combination regimens with well-characterized agents from three major classes of antihypertensives (calcium channel blockers, ACE inhibitors and thiazide diuretics). Inter alia the design and conduct of the trial permitted further evaluation of moxonidine monotherapy.

Study design

TOPIC was conducted at 138 general practice centres in the UK and was designed to evaluate once-daily antihypertensive therapy, consisting of moxonidine alone or moxonidine plus either amlodipine, enalapril or hydrochlorothiazide. The trial consisted of a 4-week single-blind placebo run-in, followed by an 8-week phase of open-label moxonidine therapy. Patients who responded to moxonidine during the open-label phase continued to receive moxonidine monotherapy (MM group). Other patients were randomized to a 4-week phase of combination antihypertensive therapy (CT group). The total duration of active treatment was thus 12 weeks. The study design is illustrated in Figure 1.

Figure 1. Study plan for TOPIC. A = placebo run-in phase (4 weeks; n = 792). B = open-label monotherapy phase (8 weeks; n = 678; moxonidine 200 mcg/day for 4 weeks, then 200 or 400 mcg/day as required). C = moxonidine monotherapy (4 weeks; n = 303; moxonidine 200 or 400 mcg/day as required for 4 weeks). D, E, F = combination therapy (4 weeks; moxonidine [400 mcg/day] plus other agent as specified below). D = moxonidine plus amlodipine (5 mg/day) (n = 87). E = moxonidine plus enalapril (10 mg/day) (n = 88). F = moxonidine plus hydrochlorothiazide (12.5 mg/day) (n = 97).
Patients
Patients were eligible for inclusion if they were 18–80 years old and had stage 1–II essential hypertension according to World Health Organization criteria (DBP ≥ 95 and ≤ 114 mmHg, SBP ≤ 220 mmHg) at the beginning and end of the 4-week run-in period and on the first day of active therapy. Patients were not eligible for the active treatment phase if their DBP differed by more than 10 mmHg in two measurements taken in the week immediately preceding the start of active therapy. All participating patients were either previously untreated or were earmarked to switch from antihypertensive therapy because of the inefficacy or poor tolerability of previous medications.

Patients were ineligible if they had severe concomitant disorders affecting major organ systems (eg, cardiovascular disease [other than hypertension], respiratory, digestive, endocrine, neurologic/psychiatric or immunologic disease), other relevant diseases as revealed by history, physical examination and/or laboratory assessments, or had undergone (or were scheduled to undergo) major surgery. Other exclusion criteria comprised secondary hypertension, sick sinus syndrome, severe bradycardia (< 50 beats/min), history of unstable angina in the last 3 months, reliance on antihypertensive medication that could not be withdrawn at pre-treatment assessment, history of drug abuse (including alcohol), history of previous allergic reactions to any antihypertensive drug, intake of a non-registered drug within 8 weeks prior to the run-in period and unsuitability for inclusion in the study in the opinion of the investigator. Pregnant or breast-feeding women were not eligible to take part in the study.

Endpoints of the study
The primary endpoint of the study was the difference in sitting blood pressure and heart rate in the MM and CT groups, response rates in the MM and CT groups and change in diastolic sitting blood pressure in the MM group. Response to therapy was defined as attainment of sitting DBP < 90 mmHg or a reduction in sitting DBP of at least 10 mmHg.

Blood pressure was measured according to the Riva-Rocci method at each visit on the same arm, using always the same standard, recently serviced, sphygmomanometer and the same cuff. Phase V of Korotkoff was used to determine DBP. At each centre, measurements were made by a single nominated individual (physician or study nurse). Measurements were commenced after patients had rested for 10 minutes in the clinic. Sitting DBP was calculated as the arithmetic mean of three measurements taken at 2-minute intervals. Heart rate was measured while the patient was seated. The patient was then invited to stand for 1 minute, after which blood pressure was measured once.

Statistics
Statistical analysis was performed at the Biometrics Department of Solvay Pharmaceuticals, Weesp, The Netherlands. Analyses were based primarily on the intention-to-treat (ITT) cohorts.

The primary efficacy variable was the difference between the standard surgery measurement of sitting DBP (mean of three successive measurements made before the morning dose) before and after 4 weeks of combination therapy. The ITT patient sample for this analysis comprised all patients who received at least one dose of combination therapy and for whom sitting DBP assessments were made at the start and conclusion of the combination treatment phase. Analysis of variance including the factors, centre and treatment, plus interaction of centre and treatment, was intended but, because of the large number of centres and correspondingly small number of patients per centre, was restricted to analysis for the factor treatment. The mean error was used to derive confidence intervals and p-values for treatment difference. For pair-wise comparisons, an α-level of 5 % (adapted according to the Bonferroni-Holm principles) was taken to indicate statistically significant treatment differences.

Secondary efficacy parameters and adverse events were analysed using exploratory statistics. The ITT efficacy sample for the open phase comprised patients who received at least one dose of moxonidine during the open phase and an assessment of blood pressure during that phase or within 1 day of the conclusion of that phase. The safety sample for the CT group comprised all randomized patients who received at least one dose of combined medication and at least one safety assessment while taking combination therapy. The safety sample for the open phase of the trial comprised all patients who received at least one dose of moxonidine during the open phase and at least one safety assessment during open treatment.

Ethics and patient consent
The study protocol, patient information sheet and informed consent forms were approved by the Local Research Ethics Committees of all investigators. No patient was permitted to enter the study without first completing an informed consent form. Patients were entitled to withdraw from the study at any time, without stating their reasons. Investigators were required to withdraw a patient from the study if one or more adverse events occurred that were either intolerable to the patient and/or prejudiced the patient’s health in the view of the investigator. Investigators were required to withdraw a patient from the study if the patient’s blood pressure was greater than 220/114 mmHg at any time during the trial, including the placebo run-in phase.
The study was started in September 1996 and completed in October 1997.

A total of 783 patients entered the placebo run-in phase of TOPIC. Of these, 114 either dropped out during the run-in phase (n = 36) or were excluded because they did not satisfy the eligibility criteria on the first day of active treatment (n = 78). The remaining 669 patients entered the open phase of moxonidine therapy and comprised the safety sample for that phase. At least one valid blood pressure measurement was obtained in 650 of these patients, who comprised the ITT efficacy cohort for this phase.

A total of 566 patients completed 8 weeks of open-label moxonidine monotherapy according to the protocol, of whom 294 (52 %) responded satisfactorily to moxonidine; these patients were subsequently maintained on moxonidine monotherapy (MM group). The remaining 272 patients (48 %) were randomized to combination therapy. In addition to moxonidine 400 mcg/day, these patients received amlodipine (n = 87), enalapril (n = 88) or hydrochlorothiazide (n = 97). Efficacy data were obtained from 253 of these patients.

More than half the patients who entered the open phase (n = 352; 53 %) had taken antihypertensive medications in the 12 months preceding the study. Drugs previously comprised diuretics (n = 160), beta-blockers (n = 114), ACE inhibitors or angiotensin receptor antagonists (n = 97), calcium channel blockers (n = 83) and others (n = 34). Previous use of antihypertensive drugs was higher among patients who received combination therapy than among those who continued in the MM group (57 % vs. 48 %). Medication for conditions other than hypertension was initiated in 173 patients (26 %) during the open phase and in 44 patients (16 %) who later received combination therapy; these 44 patients were spread throughout the three treatment groups. Concomitant medications were initiated in 88 patients (30 %) in the MM group.

Blood pressure data for the 294 patients in the MM group are summarized in Table 2. Statistically significant reductions in sitting DBP and SBP were recorded during the 8-week open phase and these reductions were sustained to the end of the study. Standing blood pressure was also reduced. Mean heart rate was reduced by less than 2 beats/min, although this reduction was statistically significant at week 8 and week 12.

Results for the primary endpoint of the study are presented in Table 3. The mean reduction in sitting DBP achieved with moxonidine plus amlodipine was significantly greater than those achieved with moxonidine/hydrochlorothiazide or moxonidine/enalapril, which were not statistically different from each other. Response rates to the different combination regimens were consistent with the mean reductions in DBP (Table 3).

Secondary endpoint data for the CT group are summarized in Table 4. Siting SBP was reduced significantly more by moxonidine/amlodipine than by other combination regimens, which did not differ significantly from each other. Reductions in standing blood pressure conformed to the effect on sitting blood pressure. None of the combinations studied had a significant or meaningful effect on resting heart rate.

Treatment-emergent adverse events (TEEs) were reported by 50 % of patients whilst taking moxonidine alone; the most common were dry mouth (9 %), headache and asthenia (each 7 %), dizziness, infection and somnolence (each 4 %). TEEs were recorded in 46 % of patients treated with moxonidine/amlodipine, 41 % of patients treated with moxonidine/enalapril and 28 % of patients treated with moxonidine/hydrochlorothiazide. TEEs affecting more than one system were uncommon in all three groups. The most common were upper respiratory tract infections (2 %), sinusitis (2 %) and pharyngitis (2 %). Two patients each experienced severe adverse events: one patient treated with moxonidine/hydrochlorothiazide had a gastrointestinal bleed and another patient treated with moxonidine/amlodipine had severe dyspnea.

Table 1. Demographic features of patients included in the safety samples for the combination therapy (CT) and moxonidine monotherapy (MM) groups of the TOPIC study. Data are supplied for all concomitant disease recorded in 10 % or more of patients, with the exception of cardiovascular disease (present in 100 % of both cohorts).

<table>
<thead>
<tr>
<th>CT group (n = 272)</th>
<th>MM group (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>133</td>
</tr>
<tr>
<td>Female</td>
<td>139</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>64</td>
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<tr>
<td>50–65</td>
<td>138</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>70</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>84.4</td>
</tr>
<tr>
<td>Women</td>
<td>75.4</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>27.7</td>
</tr>
<tr>
<td>Women</td>
<td>29.4</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>264</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
</tr>
<tr>
<td><strong>Concomitant diseases</strong></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>59</td>
</tr>
<tr>
<td>Urogenital</td>
<td>36</td>
</tr>
<tr>
<td>Gastrointestinal/hepatic</td>
<td>56</td>
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<tr>
<td>HEENT*</td>
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<tr>
<td>Dermatologic</td>
<td>42</td>
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<tr>
<td>Musculoskeletal</td>
<td>129</td>
</tr>
<tr>
<td>Neurologic/psychiatric</td>
<td>48</td>
</tr>
</tbody>
</table>

Table 2. Blood pressure responses among patients maintained on moxonidine monotherapy throughout the study (MM group).

<table>
<thead>
<tr>
<th></th>
<th>Day 0 (n = 294)</th>
<th>Week 4 (n = 294)</th>
<th>Week 8 (n = 293)</th>
<th>Week 12 (n = 254)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Change in mean sitting diastolic BP (mmHg)</strong></td>
<td>-10.2 ± 4.1</td>
<td>-9.2 ± 7.5</td>
<td>-13.4 ± 6.1**</td>
<td>-12.4 ± 7.4*</td>
</tr>
<tr>
<td><strong>Change in mean standing diastolic BP (mmHg)</strong></td>
<td>-10.8 ± 5.4</td>
<td>-8.1 ± 8.0</td>
<td>-12.4 ± 8.0*</td>
<td>-11.2 ± 8.5*</td>
</tr>
<tr>
<td><strong>Change in mean sitting systolic BP (mmHg)</strong></td>
<td>165.5 ± 15.1</td>
<td>-13.2 ± 15.3</td>
<td>-17.0 ± 15.7*</td>
<td>-17.7 ± 16.4*</td>
</tr>
<tr>
<td><strong>Change in mean standing systolic BP (mmHg)</strong></td>
<td>164.9 ± 16.4</td>
<td>-12.1 ± 16.1</td>
<td>-15.2 ± 17.5*</td>
<td>-15.0 ± 17.5*</td>
</tr>
<tr>
<td><strong>Change in mean resting heart rate (beats/min)</strong></td>
<td>77.7 ± 8.2</td>
<td>-1.4 ± 8.5</td>
<td>-1.7 ± 8.5**</td>
<td>-1.9 ± 8.8***</td>
</tr>
</tbody>
</table>

*p < 0.0001; **p = 0.0101; ***p = 0.0019
two patients in the CT group are summarized in Table 5. The most frequently reported TEEs in the moxonidine/amlopidine group were asthenia (7%), and dyspepsia and vasodilatation (each 5%). Asthenia (6%), headaches (5%) and infections (5%) were the most common TEEs in the moxonidine/enalapril group, while asthenia, vasodilatation and headache (each 3%) were recorded in the moxonidine/hydrochlorothiazide group.

Three patients died during the study. None of these deaths was associated with the use of study medication. In addition, 16 serious adverse events were recorded, of which four occurred during the placebo run-in, five during the open phase, five in patients in the CT groups and two in patients in the MM group. Fourteen of these events were judged to be unrelated to use of study medications. One case of diarrhoea during the open phase was judged to have a remote association to use of study medications. One case of diarrhoea during the placebo run-in, five during the open phase, five in 144 patients who had used other antihypertensive medications in the 12 months preceding their participation in TOPIC. The magnitude of the blood pressure-lowering effect of moxonidine in the open-label phase of TOPIC was consistent with that recorded in previous studies and this benefit was sustained in the patients who continued to receive moxonidine monotherapy.

TOPIC is the largest general practice-based trial of moxonidine to have been undertaken in the UK. Taken overall, the results of the study indicate that moxonidine is an effective option for the initial therapy of hypertension or an alternative to current therapies for the estimated 40–50% of patients who switch from existing therapy or discontinue antihypertensive treatment within the first 12 months [18, 19]. It is also evident from the results that initial treatment with moxonidine can provide a foundation for combination therapy in some of those patients who require it. The patients enrolled in TOPIC appear to be broadly representative of the population of hypertensive patients encountered in UK general practice, being of middle age, white and with a tendency to be overweight (although not clinically obese). Moxonidine may be regarded as a practical treatment option for many of these patients, either as monotherapy or as one element in a combination.

Approximately half the patients who completed the open-label phase of the study (294 out of 566) had their blood pressure controlled by moxonidine alone. Of those patients, approximately half (152 out of 294) had a satisfactory response to the starting dose of 200 mcg/day. The overall moxonidine response rate of 52% compares favourably with the rates for the combination regimens studied in the ensuing double-blind phase (see below). It should be noted that moxonidine monotherapy provided satisfactory control of blood pressure in 144 patients who had used other antihypertensive medications in the 12 months preceding their participation in TOPIC. The magnitude of the blood pressure-lowering effect of moxonidine in the open-label phase of TOPIC was consistent with that recorded in previous studies and this benefit was sustained in the patients who continued to receive moxonidine monotherapy.

The design of TOPIC had the effect of identifying a cadre of patients who were in some degree refractory to monotherapy. In addition to the ‘filtering’ process of the open-label phase, 53% of the patients in the CT group had previously been prescribed other antihypertensive medication and were by inference unsuited to various forms of monotherapy by reason of inadequate control of blood pressure or intolerance to medication. In all, 48% (272 out of 566) of those who completed the open-label phase were randomized to combination therapy. These data, acquired from more than 130 centres...
throughout the UK, suggest that a substantial proportion of patients with essential hypertension require polypharmacy to achieve satisfactory blood pressure control, a conclusion in keeping with the findings of the IOT study [20].

Enalapril, amlodipine and hydrochlorothiazide were chosen as combination drugs because these are well characterized, effective and widely used antihypertensive agents. The addition of a second drug to moxonidine produced neither normalization or a substantial (>10 mm Hg) reduction in sitting DBP in 46.9% of patients randomized to moxonidine plus amlodipine, 26.8% of those randomized to moxonidine plus enalapril and 21.1% of those randomized to moxonidine plus hydrochlorothiazide (P < 0.012 in favour of moxonidine/amlodipine vs. other combinations). Similarly, the blood pressure response to moxonidine/amlodipine was markedly greater than with the other combinations studied. This result is surprising; the dosages of the add-in drugs were selected as being approximately equipotent [21–23]. TOPIC is the first large-scale study of a combination of moxonidine with a calcium channel blocker. There is no obvious pharmacological basis for the marked blood pressure-lowering effect of this combination vis-à-vis the other regimens studied. The clinical results indicate, however, that moxonidine plus amlodipine is notably efficacious in the control of mild or moderate essential hypertension. Further appraisal of this combination appears warranted. Earlier experience with moxonidine/hydrochlorothiazide produced higher response rates than were recorded in the present study [17]. Differences in the patient populations – most obviously the treatment-resistant nature of many of the patients involved in TOPIC – are likely to have contributed to these different outcomes.

Tolerability of medications is increasingly regarded as an important determinant of the long-term success of therapy for hypertension, especially in the early, symptomless phases of the disease. Moxonidine monotherapy was well tolerated in this study. The pattern of adverse events was as reported in earlier studies [15, 16] and the frequency of these events was low. Similarly, all the combination regimens studied in TOPIC were well tolerated (Table 5). Characteristic adverse events, namely flushing/vasodilatation and cough, were recorded in patients who received amlodipine and enalapril respectively, but the frequency of these events was low. These data support the view that use of drugs in combination at relatively low dose can provide good therapeutic effect while minimizing the potential for adverse events [24].

In summary, the findings of this study confirm that a sizeable proportion of hypertensive patients encountered by general practice in the UK may require combination therapy to achieve satisfactory control of their blood pressure. Moxonidine is an effective, well-tolerated antihypertensive agent whether used alone or in combination with other agents. The combination of moxonidine with amlodipine appears to be especially effective in the treatment of mild or moderate essential hypertension.

References

Appendix

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J Clin Basic Cardiol 1999; 2: 223

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