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 participat-
ing patients were either previously untreated or were ear-
marked to switch from antihypertensive therapy because of the
inefficacy or poor tolerability of previous medications.

Patients were ineligible if they had severe concomitant dis-
orders affecting major organ systems (eg, cardiovascular dis-
case [other than hypertension], respiratory, digestive, endo-
crine, 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 crite-
ia comprised secondary hypertension, sick sinus syndrome,
severe bradycardia (< 50 beats/min), history of unstable an-
gina in the last 3 months, reliance on antihypertensive med-
cation that could not be withdrawn at pre-treatment assess-
ment, history of drug abuse (including alcohol), history of
previous allergic reactions to any antihypertensive drug, in-
take 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.

Treatment
Moxonidine 200 mcg was administered once daily for 4 weeks
at the start of the study. Patients were instructed to take the
study medication in the morning (8 a.m. ± 2 hours). This
schedule was adhered to throughout the study. At the end of
the first 4 weeks of treatment moxonidine dosage was dou-
bled (to 400 mcg o. d.) in patients deemed not to have re-
acted to the initial dose. This higher dose of moxonidine
was administered for a further 4 weeks. At the end of that
time, patients judged to have responded satisfactorily con-
tinued monotherapy with moxonidine for the remainder of
the study. Patients considered not to have responded satis-
factorily to monotherapy were eligible for randomization to
combination therapy during which they received open-label
moxonidine plus amlodipine (5 mg o. d.), enalapril (10 mg
o. d.) or hydrochlorothiazide (12.5 mg o. d.), administered
in a double-blind manner, for a further 4 weeks.

Patient compliance with the dosing schedule was checked
by monitoring the returned medication. Compliance was re-
garded as sufficient if at least 85 % of the study medication
had been taken.

Other antihypertensive medication was prohibited during
the study (including the run-in phase), even if it was intended
for treatment of a disease other than hypertension. Organic
nitrates were permitted for the treatment of stable angina pect-
oris, provided that therapy had been established for at least 3
months before entry into the study. Use of drugs for non-
cardiovascular conditions was permitted. All concomitant
medication had to be recorded on the clinical record form of
individual patients.

Endpoints of the study
The primary endpoint of the study was the difference in sit-
ting DBP after and before combination therapy.

Secondary efficacy variables included alterations in systolic
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 Depart-
ment 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 re-
ceived at least one dose of combination therapy and for whom
sitting DBP assessments were made at the start and conclu-
sion of the combination treatment phase. Analysis of variance
involving 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 pa-
tients per centre, was restricted to analysis for the factor treat-
ment. The mean error was used to derive confidence inter-
vals and p-values for treatment difference. For pair-wise com-
parisons, an α-level of 5 % (adapted according to the
Bonferroni-Holm principles) was taken to indicate statisti-
cally significant treatment differences.

Secondary efficacy parameters and adverse events were
analysed using exploratory statistics. The ITT efficacy sample
comprised all randomized patients who received at least
one dose of moxonidine during the open phase and an assess-
ment 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 as-
essment while taking combination therapy. The safety sam-
ple 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 re-
quired 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, in-
cluding the placebo run-in phase.
**Results**

The study was started in September 1996 and completed in October 1997. A total of 283 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 356 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.

Most (n = 528) of the patients who entered the initial open phase were 50 or more years old (mean age 57.7 ± 10.9 years) and almost all (97 %) were Caucasian. Just over half the patients (51 %) were women. The core demographic features of the safety samples for the CT and MM groups of TOPIC are summarized in Table 1. 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 prescribed 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 that 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. Sitting 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 1 % of patients are summarized in Table 4. The most common TEEs were related to the antihypertensive effect of moxonidine; other TEEs were related to the concomitant antihypertensive drugs used in the study. The TEE profile for moxonidine monotherapy was similar to that for combination therapy.

### 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></th>
<th>CT group (n = 272)</th>
<th>MM group (n = 294)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>133</td>
<td>142</td>
</tr>
<tr>
<td>Female</td>
<td>139</td>
<td>152</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 50</td>
<td>64</td>
<td>55</td>
</tr>
<tr>
<td>50–65</td>
<td>138</td>
<td>136</td>
</tr>
<tr>
<td>&gt; 65</td>
<td>70</td>
<td>103</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>84.4</td>
<td>84.2</td>
</tr>
<tr>
<td>Women</td>
<td>75.4</td>
<td>75.4</td>
</tr>
<tr>
<td><strong>Body mass index (kg/m²)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>27.7</td>
<td>26.7</td>
</tr>
<tr>
<td>Women</td>
<td>29.4</td>
<td>29.4</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>264</td>
<td>289</td>
</tr>
<tr>
<td>Other</td>
<td>8</td>
<td>5</td>
</tr>
<tr>
<td><strong>Concomitant diseases</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory</td>
<td>59</td>
<td>88</td>
</tr>
<tr>
<td>Urogenital</td>
<td>36</td>
<td>37</td>
</tr>
<tr>
<td>Gastrointestinal/hepatic</td>
<td>56</td>
<td>50</td>
</tr>
<tr>
<td>HEENT*</td>
<td>79</td>
<td>72</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>42</td>
<td>54</td>
</tr>
<tr>
<td>Musculoskeletal</td>
<td>129</td>
<td>118</td>
</tr>
<tr>
<td>Neurologic/psychiatric</td>
<td>48</td>
<td>52</td>
</tr>
</tbody>
</table>

*Head, ears, eyes, nose and throat

### 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>Change in mean sitting diastolic BP (mmHg) versus Day 0</td>
<td>101.2 ± 4.1</td>
<td>−9.2 ± 7.5</td>
<td>−13.4 ± 6.1*</td>
<td>−12.4 ± 7.4*</td>
</tr>
<tr>
<td>Change in mean standing diastolic BP (mmHg) versus Day 0</td>
<td>101.8 ± 5.4</td>
<td>−8.1 ± 8.0</td>
<td>−12.4 ± 8.0*</td>
<td>−11.2 ± 8.5*</td>
</tr>
<tr>
<td>Change in mean sitting systolic BP (mmHg) versus Day 0</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>Change in mean standing systolic BP (mmHg) versus Day 0</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>Change in mean resting heart rate (beats/min) versus Day 0</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/amloclidine 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 with moxonidine. One patient treated with moxonidine/enalapril experienced headache, paresthesia, blurred vision and speech disorder after 2 weeks of treatment. This cluster of TEEs was judged to be possibly related to study medication, which was withdrawn.

Table 3. Primary endpoint for the TOPIC study, plus summary of normalization and response rates

<table>
<thead>
<tr>
<th></th>
<th>Moxonidine/ enalapril</th>
<th>Moxonidine/ enalapril</th>
<th>Moxonidine/ hydrochlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 81)</td>
<td>(n = 82)</td>
<td>(n = 90)</td>
</tr>
<tr>
<td><strong>Diastolic BP at Week 8</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(end of open-label phase)</td>
<td>100.5 ± 5.1</td>
<td>100.3 ± 5.0</td>
<td>100.8 ± 5.8</td>
</tr>
<tr>
<td><strong>BP at Week 12</strong></td>
<td>153.6 ± 15.8</td>
<td>156.2 ± 18.2</td>
<td>160.9 ± 15.3</td>
</tr>
<tr>
<td>(mmHg)</td>
<td>93.1 ± 7.6</td>
<td>95.5 ± 8.0</td>
<td>97.6 ± 7.7</td>
</tr>
<tr>
<td><strong>Reduction in sitting</strong></td>
<td>−7.3 ± 7.4*</td>
<td>−4.8 ± 6.7</td>
<td>−3.2 ± 6.1</td>
</tr>
<tr>
<td>diastolic BP (mmHg)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Response rate (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Normalization</td>
<td>35.8**</td>
<td>22.0</td>
<td>15.6</td>
</tr>
<tr>
<td>Response</td>
<td>46.9***</td>
<td>26.8</td>
<td>21.1</td>
</tr>
</tbody>
</table>

*p = 0.001 versus moxonidine/hydrochlorothiazide; p = 0.016 versus moxonidine/enalapril
**p = 0.004 versus moxonidine/hydrochlorothiazide; p = 0.07 versus moxonidine/enalapril
***p = 0.001 versus moxonidine/hydrochlorothiazide; p = 0.012 versus moxonidine/enalapril

Discussion

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

**Table 5. Discontinuations and treatment-emergent adverse events (TEEs) in the CT group of TOPIC**

<table>
<thead>
<tr>
<th></th>
<th>Moxonidine/ enalapril</th>
<th>Moxonidine/ enalapril</th>
<th>Moxonidine/ hydrochlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 87)</td>
<td>(n = 88)</td>
<td>(n = 97)</td>
</tr>
<tr>
<td><strong>Discontinuations</strong></td>
<td>9</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>6</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Lack of efficacy</strong></td>
<td>2</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Other reasons</strong></td>
<td>1</td>
<td>2</td>
<td>5</td>
</tr>
<tr>
<td><strong>TEEs with frequencies &gt; 2 %</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asthenia</td>
<td>7 %</td>
<td>6 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Headache</td>
<td>3 %</td>
<td>5 %</td>
<td>3 %</td>
</tr>
<tr>
<td>Somnolence</td>
<td>–</td>
<td>–</td>
<td>3 %</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>–</td>
<td>–</td>
<td>3 %</td>
</tr>
<tr>
<td>Pain</td>
<td>3 %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Infection</td>
<td>–</td>
<td>5 %</td>
<td>–</td>
</tr>
<tr>
<td>Cough</td>
<td>–</td>
<td>3 %</td>
<td>–</td>
</tr>
<tr>
<td>Flushing/vasodilatation</td>
<td>–</td>
<td>5 %</td>
<td>–</td>
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<tr>
<td>Dizziness</td>
<td>–</td>
<td>3 %</td>
<td>–</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>5 %</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Chest pain</td>
<td>3 %</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

**Any adverse experience (%)** 46 % 41 % 28 %

*p = 0.001 versus moxonidine/hydrochlorothiazide; p = 0.016 versus moxonidine/enalapril
**p = 0.004 versus moxonidine/hydrochlorothiazide; p = 0.07 versus moxonidine/enalapril
***p = 0.001 versus moxonidine/hydrochlorothiazide

**Table 4. Secondary endpoint results for the TOPIC study**

<table>
<thead>
<tr>
<th></th>
<th>Moxonidine/ enalapril</th>
<th>Moxonidine/ enalapril</th>
<th>Moxonidine/ hydrochlorothiazide</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 81)</td>
<td>(n = 82)</td>
<td>(n = 90)</td>
</tr>
<tr>
<td><strong>Change in mean sitting systolic BP (Week 12 – Week 8) (mmHg)</strong></td>
<td>−10.7 ± 15.3*</td>
<td>−7.9 ± 13.8</td>
<td>−4.4 ± 11.3</td>
</tr>
<tr>
<td><strong>Change in mean standing systolic BP (Week 12 – Week 8) (mmHg)</strong></td>
<td>−11.9 ± 15.5**</td>
<td>−7.9 ± 15.3</td>
<td>−3.3 ± 12.6</td>
</tr>
<tr>
<td><strong>Change in mean standing diastolic BP (Week 12 – Week 8) (mmHg)</strong></td>
<td>−7.3 ± 7.6***</td>
<td>−5.7 ± 8.4</td>
<td>−3.4 ± 7.9</td>
</tr>
<tr>
<td><strong>Change in mean resting heart rate (Week 12 – Week 8) (beats/min)</strong></td>
<td>−1.3 ± 8.4</td>
<td>−0.8 ± 7.5</td>
<td>−1.7 ± 11.2</td>
</tr>
</tbody>
</table>

*p = 0.003 versus moxonidine/hydrochlorothiazide
**p < 0.001 versus moxonidine/hydrochlorothiazide; p = 0.039 versus moxonidine/enalapril
***p = 0.001 versus moxonidine/hydrochlorothiazide
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 either 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 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 that is especially effective in the treatment of mild or moderate hypertension, especially in the early, symptomless phases of the disease. Moxonidine monotherapy was well tolerated 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].

References

Appendix

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