Cardiovascular Drugs and Therapy 16 221–226 2002

CLINICAL PHARMACOLOGY AND DRUG STUDIES

Assessment of Quality of Life in a Double-Blind, Randomized Clinical Trial of Imidapril and Captopril for Hypertensive Chinese in Taiwan

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Summary. Purpose. **Although the role of angiotensin-converting enzyme (ACE) inhibitors for the treatment of hypertension has been well established, no data has been generated regarding the influence of ACE inhibitors for health-related quality-of-life (QOL) dimensions for Chinese patients.**

Materials. **A double-blind, active-control, randomized clinical trial was used to compare the effects of two ACE inhibitors, imidapril and captopril, on quality-of-life dimensions in one outpatient clinic in one tertiary clinical-care facility. After a 2–3 week washout period with placebo, 59 patients with mild-to-moderate hypertension were randomly assigned to receive imidapril (5 to 10 mg per day) or captopril (25 to 50 mg twice per day) for 12 weeks. Patients completed the Short-form 36 (SF 36) health survey questionnaire, which evaluates 8 QOL dimensions, just before treatment, during the 8th week, and at the end of treatment (12th week). ANOVA for repeated measures was used to analyze the QOL-score changes over time and compare treatments, and to assess the interaction of treatment duration and group on these scores.**

Results. **No significant differences were demonstrated for changes in blood-pressure, frequency of adverse effects and withdrawal of patients from the study comparing the two drugs. Significant improvement, however, was demonstrated for mental-component summary scores after 12 weeks of treatment for both drugs ($P = 0.029$). No significant differences were established for individual QOL dimensions comparing the two drugs. A significantly higher baseline systolic blood pressure was found in the participants who did not complete the questionnaire than in those who did.**

Conclusions. **Similar and significant improvements were determined for the mental-component QOL summary scores for the two ACE inhibitors, imidapril and captopril, and no significant differences were demonstrated comparing treatments.**

Key Words. **angiotensin-converting enzyme inhibitors, ACE, quality of life, clinical trial**

Introduction

Improvements in mortality and morbidity due to hypertension have been confirmed in large-scale clinical trials of antihypertensive treatments. The enhancement of quality of life (QOL) has also been the theme of a number of research studies. The development of angiotensin-converting enzyme (ACE) inhibitors appears to have constituted the greatest advance in hypertension treatment, and these inhibitors have proven beneficial across a number of proposed QOL dimensions [1,2]. Various ACE inhibitors that were subsequently developed have been the subject of intensive clinical study for hypertension treatment and congestive heart failure. ACE inhibitors are recognized as one of the first treatment choices made in the step-wise therapy advocated for hypertension by the WHO Guidelines Subcommittee [3]. Imidapril (imidapril hydrochloride; Tanabe Seiyaku Co., Ltd.), which contains no sulfhydryl groups in its chemical structure, is a newly developed ACE inhibitor. It is a pro-drug which becomes active as it is hydrolyzed and converted to a diacid metabolite (imidaprilat). The potency of imidaprilat for humans is about twice that of enalaprilat (the active metabolite of enalapril) and about 10 times that of captopril [4]. The efficacy and safety of imidapril for humans, administered once a day, have been confirmed in a Phase I clinical trial using healthy subjects and patients diagnosed with mild to moderate hypertension [5].

Recent research has emphasized the use of QOL measures to evaluate antihypertensive therapy [6–8], as adverse side effects and impairment of psychosocial function may reduce patient compliance [6,9]. Thus, QOL-guided treatment may improve this compliance and prevent deterioration of psychosocial function [10]. The QOL for hypertensive patients can be assessed using generic and/or disease-specific questionnaires. In particular, it has been demonstrated that the Short-form 36 (SF-36) questionnaire is a reliable and sensitive tool for the evaluation of QOL dimensions for various

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populations and diseases [11–13]. The 36-item design is used to evaluate eight QOL dimensions: physical and social functioning, role limitations due to emotional and physical problems, mental health, energy/vitality, pain level, and general-health perception. Good sensitivity and specificity have been demonstrated for this research instrument [14–16]. The validity of the SF-36 questionnaire for the pre-test was good. Due to the multiple correlations that are derived from the eight QOL dimensions explored in the SF-36, two composites, physical and mental component scales (PCS, MCS), are used to summarize the results [17]. These two composite scores are shown to be better indicators of general health both in the general population and in disease-specific groups [17]. To date, there have been relatively few reports using the SF-36 questionnaire for QOL evaluation for hypertensive populations [2,18].

Testa et al. [1] have determined different effects for the two ACE inhibitors, captopril and enalapril, for a number of QOL dimensions. They conclude that captopril treatment was associated with more favourable changes for overall QOL, mental health, sleep and vitality dimensions. In this report, we compare captopril with the new ACE inhibitor imidapril to evaluate QOL-dimension changes for Chinese hypertensive patients treated over a 3-month study period.

The randomized, double-blind, parallel study was designed to compare the efficacy and safety of imidapril and captopril for the treatment of mild-to-moderate essential hypertension for Chinese patients in Taiwan. The SF-36 questionnaire was used to evaluate QOL changes during treatment.

Materials and Methods

Study design

This QOL-dimension clinical trial was performed concurrently with a randomized, double-blind, clinical trial, entitled "Efficacy and Safety of Imidapril, A New Angiotensin-Converting Enzyme Inhibitor, in Chinese Patients with Mild to Moderate Hypertension: A Double-Blind Comparison with Captopril" [19]. All 59 patients in the clinical trial were considered participants in the QOL study. With help of an assistant, all finished the initial QOL questionnaire. The study design included a placebo washout period of 2–3 weeks and an active treatment period of 12 weeks. This clinical trial was approved by the Independent Review Board of the National Taiwan University Hospital and the informed consent signed by every patient.

Adult hypertensive patients from the outpatient clinic of one university hospital were enrolled in this study. Hypertension was defined as seated diastolic blood pressure (DBP) ranging from 95–115 mm Hg during the washout period. Exclusion criteria included secondary or more severe hypertension (seated DBP over 115 mm Hg or systolic blood pressure (SBP) over 240 mm Hg during the washout period), potential pregnancy, severe heart failure or myocardial infarction during the previous three months. Further exclusion criteria were evident coronary heart disease, such as unstable angina pectoris with poorly controlled diabetes, renal or hepatic disease and antihypertensive drug treatment was also excluded to prevent interference with the ACE treatment.

Patients on the imidapril regimen received a 5 mg imidapril capsule in the morning and a placebo capsule in the evening for 4 weeks. The imidapril dosage was increased to 5 mg 2 times per day for the next 8 weeks if the DBP was still ≧90 mm Hg after the first phase of treatment. Patients on the captopril regimen received a 25 mg captopril capsule twice per day for 4 weeks, and the dosage was doubled for the next 8 weeks if DBP was still ≧90 mm Hg after the first treatment phase. The total duration of the treatment period was 12 weeks.

Blood pressure measurements

A standard mercury sphygmomanometer was used for all BP measurements taken by the same nurse during outpatient visits. The BP was recorded after 10 minutes of rest in a sitting position. Two seated measurements were performed subsequently, separated by a 5-minute interval. The mean of the two measurements was used as the reference value.

Measurement of quality-of-life dimensions

The QOL dimensions were measured using the SF-36 questionnaire which was completed during each of the three visits [17,20]. The clinical assistant collected the self-administered questionnaires. The SF-36 was designed to survey health-related QOL issues for clinical research [20]. It consists of 36 questions grouped and scored on eight dimensions: physical functioning, physical and emotional roles, bodily pain, general and mental health, vitality, and social functioning. The validity, reliability and utility of the instrument have been established across various clinical trials and cohort studies [13,17,20].

Statistical analysis

As the QOL dimensions are continuous variables, data were presented as mean ± standard error. Repeated-measures ANOVA was used to test the effects of drug group and treatment duration on QOL dimension scores, incorporating the interaction of treatment duration and drug group. Polynomial transformations were used to fit the duration effect, and the time period as 0, 8, or 12 units. The GLM procedure of the SAS program was used for all statistical analyses [21]. Differences comparing drug group, treatment duration and their interaction were considered statistically significant when P value was <0.05. The means for the various QOL scores were also estimated from data gathered at baseline and weeks 8 and 12 to express the trend for each dimension during the two treatment phases. For the comparison of baseline data in responsive and missing

groups, we used the unpaired Student t-test to test the continuous variables and the χ^2 test to test the significant level of the categorical data.

We set Type I error for the two-tailed test as 0.05 and type II error as 0.20. A deviation of 3.0 and the population standard deviation of 5.8 of PCS were assumed from literature reviews. The estimated sample size in each treatment group was 29.3, or round up to 30.

Results

A total of 59 patients were enrolled in this antihypertensive clinical trial and QOL study. Two patients were excluded because of abnormally high liver function values. Of the remaining 57 patients, 29 received imidapril and 28 received captopril. The ages of the participants ranged from 38 to 67 (mean 52.3, standard deviation 6.9) years. No differences were determined comparing the two drugs for gender, age, history of hypertension, concomitant medication or adverse drug reactions. Adverse drug reactions during the treatment period were reported by 27.6% of patients in the imidapril group and by 46.4% of patients in the captopril group. Drug-related coughing occurred more in the captopril (35.7%) than in the imidapril (13.8%) group, with borderline significance ($p = 0.055$). Also, one patient in the imidapril group had mild proteinuria, and another patient in the captopril group had mild elevation of aminotransferase. No serious adverse events were reported. Patient compliance and dosage titration for both drugs were compatible. Comparing the efficacy for DBP normalization, there was no significant difference between drugs. There were similar percentages of dose titration in both drugs (55% in imidapril vs. 46% in captopril for double dosage) after the treatment period.

The changes in QOL-dimension scores for the two treatment groups, including PCS and MCS scores derived for baseline, week-8 and week-12 results in the responsive 40 participants, are presented in Table 1, with the levels of significance for treatment group and duration, and interaction effects presented in Table 2. The scores for the eight QOL dimensions increased modestly or remained relatively stable for both drug groups. The PCS scores increased for captopril, and decreased for imidapril, however, the difference was not statistically significant. The MCS scores increased for both ACE inhibitors, with significant differences from baseline demonstrated after 12 weeks of treatment ($P = 0.029$). No difference was demonstrated comparing the treatment groups (Fig. 1). We also monitored the other possible co-morbid disorders, such as congestive heart failure or cardiovascular events during the course of the study. We could not find any

Table 1. *SF-36 QOL-dimension scores specified by treatment periods and drug regimens of captopril and imidapril*

	Captopril			Imidapril		
	Baseline	Week 8	Week 12	Baseline	Week 8	Week 12
Physical component	51.08 ± 6.39	51.70 ± 4.24	52.75 ± 5.44	52.47 ± 7.55	51.39 ± 6.34	50.82 ± 6.23
Mental component	45.04 ± 9.22	47.17 ± 8.96	46.31 ± 8.84	43.04 ± 9.72	45.73 ± 10.29	47.45 ± 10.95
Physical functioning	86.60 ± 12.32	86.39 ± 12.58	87.19 ± 13.40	86.30 ± 13.61	87.78 ± 10.60	84.81 ± 17.42
Physical role	75.00 ± 38.35	84.72 ± 29.88	88.89 ± 26.04	75.00 ± 39.09	73.68 ± 36.77	80.26 ± 31.82
Bodily pain	78.39 ± 20.45	80.89 ± 16.22	79.44 ± 16.63	74.84 ± 22.15	77.63 ± 20.71	76.58 ± 19.25
General health	51.56 ± 21.02	59.75 ± 18.40	61.31 ± 23.79	64.94 ± 16.66	60.76 ± 23.92	64.41 ± 24.22
Vitality	66.11 ± 15.86	65.00 ± 13.61	65.56 ± 13.38	58.82 ± 21.33	60.29 ± 20.95	60.88 ± 22.34
Social functioning	79.86 ± 21.06	87.50 ± 12.86	82.64 ± 17.22	82.24 ± 18.31	81.58 ± 16.33	82.24 ± 18.31
Emotional role	70.59 ± 43.91	78.43 ± 33.21	78.43 ± 39.98	62.96 ± 41.05	68.52 ± 40.38	77.78 ± 37.92
Mental health	61.61 ± 21.58	63.48 ± 21.30	63.85 ± 17.87	65.41 ± 19.49	65.41 ± 22.76	65.06 ± 23.96

Table 2. *Hypothesis testing by SF-36 QOL dimension*

P value	Treatment: Captopril vs. imidapril	Duration: Week 0, 8, and 12	Interaction for treatment duration and drug regimen
Physical functioning	0.918	0.769	0.455
Physical role	0.459	0.290	0.633
Bodily pain	0.574	0.578	0.991
General health	0.400	0.235	0.055
Vitality	0.337	0.924	0.751
Social functioning	0.804	0.241	0.130
Emotional role	0.590	0.205	0.749
Mental health	0.739	0.831	0.755
Mental component	0.793	**0.029**	0.337
Physical component	0.867	0.957	0.198

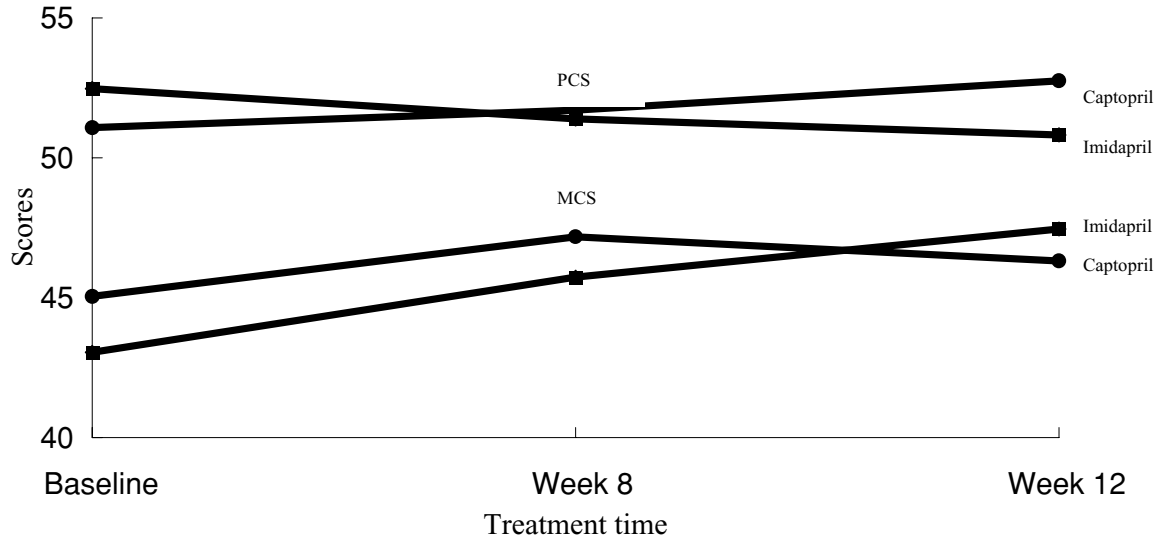

Fig. 1. *PCS and MCS score changes, specified by drug treatment.*

co-morbid disorders that might have impacted on QOL evaluation.

Among the 59 participants in the clinical trial, there were 19 patients who did not complete the questionnaire (missing group) and 40 patients who completed the questionnaire (responsive group) in this QOL trial. Table 3 shows the distribution of selected variables between the two groups. We found that the patients in the missing group were slightly older, had a higher baseline blood pressure, a longer duration of hypertension and higher body mass index values. Only baseline systolic blood pressure in the missing group was significantly higher than in the responsive group. The proportions of female gender, treatment drug and titration dosage were similar in both groups.

Discussion

This clinical trial clearly demonstrates that both imidapril and captopril can improve SF-36 mental-component summary scores after 12 weeks of treatment. No significant difference was demonstrated for either drug for the various QOL dimensions.

Although it has been demonstrated that antihypertensive treatment decreases cardiovascular morbidity and mortality, some drugs, especially methyldopa and propranolol, produce side effects and impairment of QOL dimension, such as sexual dysfunction, sleeping problems and depression [6,9]. To improve drug compliance for hypertensive patients it is important to monitor QOL changes and remain vigilant for adverse effects. Clinicians have an additional tool to aid

Table 3. *Basic demographic, hypertension history, and blood pressure in this clinical trial, specified by completing the questionnaire or missing status*

	Missing groups ($N = 19$)		Completed groups ($N = 40$)		
	Mean	SEM	Mean	SEM	*P* value
Age (years)	53.5	1.66	51.8	1.07	0.359
Baseline systolic BP (mmHg)	157.7	3.41	147.5	2.18	0.012
Baseline diastolic BP (mmHg)	100.5	0.94	98.6	0.60	0.091
Duration of hypertension (year)	6.6	1.55	4.8	0.84	0.269
Body height (cm)	160.6	1.38	162.8	1.40	0.322
Body weight (kg)	67.7	3.19	67.0	1.57	0.804
Body mass index (kg/m^2)	26.1	0.96	25.2	0.48	0.363
Gender (women, %)	12	63.2%	15	37.5%	0.205
Treatment drug (Imidapril, %)	8	42.1%	22	55.0%	0.355
Titration (yes, %)	10	52.6%	19	47.5%	0.713

SEM: Standard error of means.

in drug selection for the hypertensive patient. In addition to efficacy predictions and the identification of significant physical symptoms, information is available regarding the potential impact of a particular drug on patient QOL. Use of this information may help to improve treatment compliance and the associated economic impact by improving work performance and reducing drop-out as a result of side-effects.

In 1986, Croog et al. [6] documented the applicability of these techniques for the assessment of the impact of antihypertensive therapy on the QOL of patients enrolled in a clinical trial. Adopting a standard clinical format, over 600 patients were randomly assigned to 3 treatment groups after a 4-week washout period. The results indicated that captopril might improve general well-being, work performance and cognitive function, while both methyldopa and propranolol worsened physical symptoms, sexual dysfunction and life satisfaction.

The baseline PCS and MCS magnitudes in this clinical trial were similar to the results from a survey of hypertensive patients [17]. After a 1-year treatment for hypertension, the PCS decreased by 0.40 and MCS increased by 0.20 with ACE inhibitor treatments in general clinics. The reason that mental component scores improve is supposed to be due to ACE inhibitor effects on inhibition of renin-angiotensin system [17]. ACE inhibitors are preferred in some subsets of hypertensive patients, such as congestive heart failure or diabetes and can improve QOL [22]. In our clinical trial, although the changes of PCS and MCS were different for both ACE-inhibitors, these did not reach significant levels. It might be due to the small sample size and short follow-up time in our study.

The composite PCS and MCS scores, as determined by the SF-36 questionnaire, can improve measurement precision for psychometric evaluation in comparison to the eight individual SF-36 scales [17]. Also, reproducible and useful summaries of results for individual patients can be derived from these scores. Further, repeated, longitudinal assessment of QOL can produce interpretable estimates of health-status change, which would otherwise not be available to clinicians [23]. Thus, our design incorporated three discrete QOL assessments for each patient to investigate QOL changes intrinsic to hypertension treatment.

This clinical trial had a limitation. The power of the statistical comparisons of the drugs was limited as a consequence of the relatively short study period and small sample population. Although the recruitment number was adequate for sample size estimation, the study was still underpowered due to the fact that only 40 patients complete the study. Also, missing data in a clinical trial is an important issue. In this trial, we found significantly higher baseline systolic blood pressure in the missing group. It implied that patients with higher blood pressure might drop out earlier, if not treated adequately. The non-respondents did not fill out their questionnaire because they dropped out of the clinical trial. Other factors, such as age, medical history of hypertension and treatment plans were not significantly different between responsive and missing groups. The effects of treatment, such as the degree of blood pressure decrease and percentage of achieving adequate blood pressure control did not reach a statistically significant level between the two groups during the course of treatment. We considered that exclusion of missing data in this trial would not impact much on the demonstrated trends.

Improvements were demonstrated for the QOL mental-component composite score for both imidapril and captopril, which were otherwise indistinguishable according to standard clinical assessments for efficacy and safety. No significant differences were demonstrated for individual quality-of-life dimensions, although improved QOL scores were noted.

Acknowledgment

The study was partially sponsored by Taiwan Tanabe Seiyaku Co., Ltd., Taipei, Taiwan.

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