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PRACA ORYGINALNA

Nine month follow-up of amlodipine maleate and amlodipine besylate treatment in patients with essential hypertension: does the salt form matter?

Ocena i porównanie skuteczności hipotensyjnej i tolerancji maleinianu amlodypiny i benzenosulfonianu amlodypiny u chorych z nadciśnieniem tętniczym pierwotnym

Streszczenie

Wstęp Celem przeprowadzonego, wieloośrodkowego, trwającego sześć miesięcy badania była ocena skuteczności hipotensyjnej i tolerancji maleinianu amlodypiny u chorych na nadciśnienie tętnicze.

Materiał i metody W pierwszej części badania porównano skuteczność hipotensyjną maleinianu amlodypiny (Tenox, Krka) i benzenosulfonianu amlodypiny (Norvasc, Pfizer) w trwającym trzy miesiące badaniu przeprowadzonym metodą podwójnie ślepej próby w grupach równoległych. W drugiej części badania oceniano skuteczność hipotensyjną i tolerancję maleinianu amlodypiny w trwającym sześć miesięcy badaniu przeprowadzonym metodą otwartą. Badaniem objęto 245 chorych (w pierwszej części) i 202 chorych (w drugiej części) z nadciśnieniem tętniczym zdefiniowanym jako rozkurczowe ciśnienie tętnicze 95–114 mm Hg. Kryterium skuteczności leczenia było obniżenie ciśnienia rozkurczowego do wartości 89 mm Hg i mniej lub obniżenie ciśnienia rozkurczowego o 10 mm Hg i więcej. Do drugiej części badania włączono chorych u których uzyskano zadawalającą kontrolę ciśnienia tętniczego w pierwszej części.

Wyniki W trakcie pierwszej części badania leczenie obydwoma lekami było związane z istotnym, porównywalnym obniżeniem ciśnienia tętniczego. Leczenie benzenosulfonianem amlodypiny związane było z większym obniżeniem rozkurczowego ciśnienia tętniczego o 1,27 mm Hg w porównaniu z leczeniem maleinianem amlodypiny (różnica ta była jednak nieistotna stastycznie i mieściła się w 90% przedziale ufności braku różnic pomiędzy porównywanymi lekami). Nie zaobserwowano różnic pomiędzy chorymi leczonymi badanymi solami amlodypiny w odniesieniu do częstości osiągnięcia docelowych wartości rozkurczowego ciśnienia tętniczego(90,91%

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i 89,52% odpowiednio dla maleinianu i benzenosulfonianu amlodypiny). W drugiej części badania, po 6 miesiącach, leczenie maleinianem amlodypiny związane było z obniżeniem rozkurczowego i skurczowego ciśnienia tętniczego o –17,5/–21,2 mm Hg w porównaniu z wartościami wyjściowymi. W trakcie pierwszej części badania u 35 chorych w grupie otrzymującej maleinian amlodypiny i 47 chorych w grupie otrzymującej benzenosulfonian amlodypiny wystąpiły zdarzenia niepożądane (28,9% *vs.* 37,9%, p = NS). Częstość występowania zdarzeń niepożądanych w drugiej części badania wynosiła 8,4%.

Wnioski Uzyskanie wyniki wskazują, że maleinian amlodypiny i benzenosulfonian amlodypiny stosowane w monoterapii u chorych z łagodnym i umiarkowanym nadciśnieniem tętniczym charakteryzują się porównywalną wysoką skutecznością hipotensyjną i porównywalną częstością zdarzeń niepożądanych. Leczenie maleinianem amlodypiny przez dalsze sześć miesięcy charakteryzowało się wysoką skutecznością hipotensyjną i dobrą tolerancją.

słowa kluczowe: amlodypina, badanie wieloośrodkowe, skuteczność hipotensyjna, działania niepożądane, nadciśnienie tętnicze

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Introduction

Calcium antagonists are the mainstay in the therapy of hypertension, constituting a pharmacologically heterogeneous group. According to the 2003 guidelines of the European Society of Hypertension and the European Society of Cardiology (ESH and ESC) and as well as national Societies of Hypertension guidelines, calcium antagonists are among the first choice of medication for mild and moderate hypertension — along with diuretics, beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, and AT1 receptor antagonists [1, 2].

Amlodipine, a dihydropyridine derivative, is one of the longest acting calcium antagonists; it is characterized by the slow onset of an antihypertensive effect that lasts over 24 hours, a highly selective effect on peripheral vessels and a favorable influence on coronary circulation [3]. Due to the above mentioned properties, it has become one of the most frequently prescribed calcium antagonists, both in monotherapy and combination, in more severe forms of arterial hypertension [3, 4].

Amlodipine in the form of a maleate salt began to be used in a clinical setting in the late 1980s and early 1990s. It should be stressed that this particular form of calcium antagonist was used in a branch of the TOHMS trial (Treatment of Mild Hypertension Study), which compared the efficacy of basic groups of antihypertensive drugs [5]. Later, during the process of marketing approval, amlodipine maleate was replaced by amlodipine besylate, which has been, until recently, the only amlodipine salt on the market. Earlier phase I studies suggested an equal pharmacokinetic profile of the two salt forms [6–8]. Amlodipine maleate and besylate administered to healthy volunteers were characterized by a long half-life (31–37 h) [6, 7]. A formulation with a maleate salt of amlodipine was developed, based on the preposition of the equivalent therapeutic features of amlodipine, regardless of the salt form in which the active substance exists in the formulation. However, changing the salt form of a drug may alter substantially its chemical and biological properties that underlie differences in their clinical efficacy and safety [9]. However there is, as yet, no reliable way of predicting exactly the effect of changing the salt form of an active drug will have on its biological activity. The supposition that the same salt form of two related parent compounds will behave in exactly the same way may not be always correct [9].

The objective of our study was, therefore, to evaluate the antihypertensive efficacy and tolerability of amlodipine maleate during a 9-month study including a 3-month equivalence assessment with the reference amlodipine salt and a 6-month open non-comparative extension to the equivalence part in order to provide further information on clinical efficacy and tolerability during prolonged treatment with amlodipine maleate in hypertensive patients. The preliminary results of the 3-month equivalence assessment in a per protocol study population have been already published in Arterial Hypertension [10].

Material and methods

The study was conducted in 7 centers in Poland, and was composed of two phases. The first phase was randomized, double-blind and parallel, enrolling 263 patients with mild and moderate essential hypertension. This 3-month comparative phase was followed by a second one, in which 220 eligible patients were proposed to continue with amlodipine maleate in an open non-comparative fashion for additional 6 months. Each patient received detailed information about the study and signed an informed consent form to participate before entering the trial. The protocol of the study was in accordance with the Declaration of Helsinki recommendations. The study received approval from the local Ethics Commit-

tee. The study was audited by independent experts in clinical studies.

The inclusion criteria in the first phase of the study comprised male or female patients with essential hypertension defined as a sitting diastolic blood pressure (DBP) being within the range of 95––114 mmHg and systolic blood pressure (SBP) below 180 mm Hg. The study enrolled patients with recently diagnosed, untreated hypertension or patients with hypertension having been diagnosed earlier, in whom antihypertensive treatment had been discontinued for at least a month before being included into the study. Patients were disqualified in cases of secondary or malignant hypertension, significant cardiac, renal, hepatic or other serious diseases that could have interfered with the study protocol. Diabetics receiving insulin and pregnant, breast-feeding women and women of reproductive age not using contraceptives were also excluded from the trial.

The inclusion criteria for the prolonged follow--up period was adequate blood pressure control defined as reaching the target DBP of 89 mm Hg or at least a 10 mm Hg reduction of DBP compared to the baseline values (week 2).

The first phase started with a 2-week placebo run-in period after which patients were randomly assigned to receive amlodipine maleate or amlodipine besylate for 12 weeks. The starting dose of the active treatment was 5 mg once daily. After 6 weeks of treatment the dose was increased to 10 mg of amlodipine maleate or amlodipine besylate in patients who failed to attain an adequate blood pressure response, defined as the reduction of DBP below 90 mm Hg. The dosing schedule during the second phase was similar to that during the first phase; during the first three months, the patients received amlodipine maleate in the maintenance dose they had had at the end of the double blind phase. After three months the dose was increased to 10 mg in patients with inadequate blood pressure control. Patients who already received the maximal dose of amlodipine were excluded from the study due to the lack of efficacy. The structure and the timeline of the study are displayed in Figure 1.

The medication applied in the first phase was amlodipine maleate 5 mg tablets (Tenox®, Krka d. d.) and the reference drug amlodipine besylate 5 mg tablets (Norvasc®, Pfizer Inc.). The drugs were placed into capsules of identical appearance. In the study, capsules of 5 and 10 mg with evaluated and reference drugs were used. During the second phase all patients received amlodipine maleate tablets 5 or 10 mg (Tenox®, Krka d. d.).

Patients were instructed to take the medication early in the morning between 7 and 10 a.m. During the active treatment period of the first phase patients had check-ups with efficacy and safety evaluation after 3, 6, 9 and 12 weeks. During the second phase patients had one check-up after three months and a final check-up after six months. The check-ups included, apart from blood pressure and heart rate measurements, a physical examination, and an assessment of treatment tolerability. At the beginning of

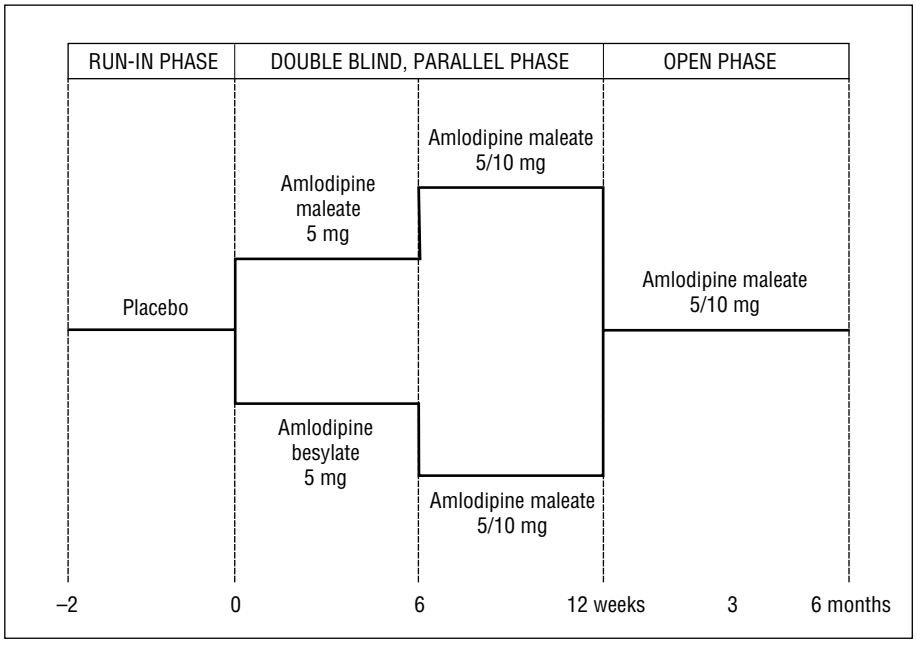

Figure 1. Study structure
Rycina 1. Schemat badania

the study the following tests were performed: electrocardiography, ophtalmoscopy, blood cell count and biochemical examinations (sodium, potassium, calcium, creatinine, glucose, bilirubin, transaminase and lipid levels). Electrocardiography was repeated during the last check-up of each phase. Biochemical parameters were assessed during each consecutive check-up. Blood pressure was measured by a mercury sphygmomanometer (on the right arm, at sitting position, measurements after 5 minutes rest, readings were taken 3 times at 2 minutes intervals, 24 h after taking the last dose of the medication).

The primary endpoint (primary efficacy variable) of the first phase was a comparison of the mean absolute reduction of diastolic blood pressure in the studied groups expressed as the difference between diastolic blood pressure values measured during the baseline visit at the beginning of the active treatment (week 2) and at the end of the first phase (week 14). The efficacy threshold was not determined in this study. Instead, the margins of equivalence for the primary efficacy variable were set at +4 mm Hg and –4 mm Hg. In order to be claimed to be equivalent, the mean value of the primary efficacy variable in the group taking amlodipine maleate must not differ from the mean value in the group taking amlodipine besylate by 4 mm Hg or more.

The secondary efficacy variables of the study were comparisons of the mean absolute reduction levels of systolic blood pressure (SBP) and heart rate (HR) between the groups, the percentage of patients with blood pressure normalization and the number of respondents. The normalization of blood pressure was defined as a DBP reduction below 90 mm Hg and respondents were those who did not reach the target DBP, although DBP had been reduced by 10 mm Hg or more.

Efficacy variables during the second phase were similar to those during the first phase. We compared DBP, SBP and HR changes, the percentage of patient with normalization as well as the percentage of respondents at the end of second phase with baseline values and with values at the end of the first phase.

An assessment of treatment tolerability was conducted, based on the analysis of adverse reactions reported during visits that had occurred while taking the medication. If there was a possible relation between an adverse reaction and the medication, it was assumed that it could not be excluded. During the first phase, we compared the safety profiles of amlodipine maleate and amlodipine besylate by assessing the incidences of drug-related adverse events, the number of patients excluded from the study and changes in laboratory parameters or electrocardiograms.

During the second phase we followed-up all the safety variables of the first phase and compared optical fundi changes assessed at the end of second phase and at the beginning of the study.

Data analysis

The SAS statistical package (version 8.1; SAS Institute, USA) was used for the calculation of results. In the primary efficacy analysis of the equivalence assessment between the drugs two one-sided t test procedures were used, with the adjustment of the final measurement in the Intention-To Treat (ITT) population (all randomized patients with at least one post- randomization measurement). The endpoint value was the last recorded measurement. Analysis of the per protocol (PP) population was then performed to confirm the results of the ITT analysis. The PP population was defined as patients who had completed the first phase within the planned time and study visits schedule with a compliance of > 80% and no major protocol deviations. Regarding the equivalence margins for the 90% confidence interval of ±4 mm Hg it was calculated that 114 patients were required per group to ensure the study power of ≥ 80%. In the secondary efficacy analysis a two-sided t test was used for quantitative variables and Pearson's Chi-squared test for categorical variables. In the descriptive statistics, the mean and standard deviation was presented for quantitative variables. The frequencies and percentages of the patients were presented by the treatment group for the qualitative variables. Within each treatment group the significance of the differences in DBP, SBP, and heart rate were analysed using the paired t-test.

In the safety analysis, a comparison was made using similar statistical methods for the corresponding type of variables as for the efficacy analysis. The results throughout are presented as mean ± standard deviation.

Results

Efficacy

Altogether, 263 patients were enrolled in the first phase. Of the 263 patients 13 did not fulfill randomization criteria, noncompliance to inclusion criteria, adverse events, or because they did not appear at the following check-up (lost to follow-up). The remaining 250 patients were randomly assigned to two groups receiving the evaluated or reference medication. Two hundred and twenty-six patients completed the first phase of the trial. 24 patients were withdrawn from this part of the study (table I).

Table I. Patients distribution
Tabela I. Rozkład chorych

Patients	A. maleate	A. besylate	All
First phase			
Enrolled	—	—	263
Randomized	125	125	250
Completed	114	112	226
Withdrawals:	11	13	24
— *lost to follow up*	5	1	6
— *adverse events*	3	2	5
— *withdrawn consent*	0	1	1
— *protocol violation*	3	9	12
Analysed (ITT)	121	124	245
Analysed (PP)	110	109	219
Second phase			
Enrolled	208	—	—
Completed	198	—	—
Withdrawn:	10	—	—
— *lost to follow-up*	7	—	—
— *adverse events*	2	—	—
— *inadequate blood pressure control*	1	—	—
— *protocol violation*	1	—	—
Analysed (ITT)	202	—	—

Five patients were withdrawn (lost to follow-up) before the first evaluation of efficacy. The remaining 245 patients constituted the ITT population. Out of 226 patients who concluded the study, 219 constituted the PP population, while in 7 patients, violation of the study protocol prevented their inclusion in the PP analysis.

Two hundred and twenty patients were deemed eligible for participation in the second phase, while 6 patients were not included due to inadequate blood pressure control. Two hundred and eight were actually included, since twelve patients withdrew their consent. One hundred and ninety-eight patients completed the trial. Ten patients were withdrawn during the second phase. We performed an ITT analysis of the second phase in 202 patients who had had at least one clinical evaluation during the second phase. One hundred and five analysed patients were given amlodipine maleate throughout the whole study, while 97 had previously been taking amlodipine besylate. The distribution of patients in the study is displayed in table I.

Baseline characteristics at randomization did not differ significantly between the treatment groups (table II).

Table II. Baseline characteristics of the randomized population (n = 250)
Tabela II. Charakterystyka wyjściowa chorych (n=250)

	A. maleate n = 125	A. besylate n = 125
Age (years)	43.0 ± 12.4	43.7 ± 12.7
Male gender (%)	84.0	83.0
Body mass index [kg/m^2]	26.8 ± 4.2	27.4 ± 3.9
SBP [mm Hg][1]	154.3 ± 10.4	153.5 ± 9.8
DBP [mm Hg][1]	101.4 ± 3.6	101.8 ± 3.7
HR [beats/min]	74.3 ± 7.0	74.7 ± 7.8
Previous antihypertensive therapy (%)	53.7	55.7

p = NS for all the comparisons between the groups
[1]SBP and DBP values after two-weeks of placebo run-in period

Table III. Analysis of the primary efficacy variable
Tabela III. Ocena skuteczności leczenia — rozkurczowe ciśnienie tętnicze

	A. maleate	A. besylate
N	121	124
DBP reduction [mm Hg]		
mean ± SD	–16.67 ± 6.80	–17.94 ± 6.10
Range	od –31 do +5	od –40 do +2
p (equivalence margin = = –4 mm Hg)	< 0.001	
p (equivalence margin = = +4 mm Hg)	0.001	
90% confidence interval [mm Hg]	–0.35 + 2.90	

One hundred and thirty-four (54.69%) patients had been previously treated with at least one antihypertensive agent: ACE inhibitors (40.09%), calcium antagonists (24.57%), beta-blockers (10.78%), AT receptor antagonists (10.34%), diuretics (9.91%), alpha-blockers (0.86%) or others (3.45%).

A primary efficacy variable analysis of 245 patients (ITT) has shown equal efficacy of the two salts in terms of the DBP reduction (table III). The difference in DBP reduction between the groups was 1.27 mm Hg in favour of amlodipine besylate and the 90% CI fell entirely within the equivalence margins. The PP results have confirmed the ITT analysis (data not shown).

An analysis of secondary efficacy variables did not reveal any differences between the two groups (table IV). Both drugs significantly lowered DBP and SBP after 12 weeks of treatment compared with the

Table IV. A comparison of secondary efficacy variables between the groups
Tabela IV. Ocena skuteczności leczenia — skurczowe ciśnienie tętnicze i częstość akcji serca

	A. maleate (n = 121)	A. besylate (n = 124)	p for the comparison between the drugs
SBP reduction [mm Hg]	–20.60 ± 12.6*	–20.39 ± 12.94*	0.9403
HR change [beats/min]	–0.89 ± 9.10	–0.51 ± 9.49	0.7466
BP normalisation (% pts)	90.91	89.52	0.7138

*p < 0.0001 compared to baseline

baseline values while HR was significantly not changed in any of the groups. The percentage of patients whose DBP was adequately controlled showed no significant difference between the groups and the number of respondents (patients who did not reach the target DBP and whose DBP reduction was 10 mm Hg or more) was too small to perform a relevant analysis of data. The curves of blood pressure reduction during the first phase were similar in both drugs (Fig. 2).

Altogether 129 patients (55.6%) in the ITT population continued the therapy with a 5 mg dose after 6 weeks of active treatment during the first phase. Forty-nine patients (43%) treated with amlodipine maleate and 54 (46%) patients treated with amlodipine besylate required an increase of the dose to 10 mg after 6 weeks. This difference was not significant (p = 0.67). The results of the PP analysis corroborated those of the ITT analysis. Since safety was a primary concern in the second phase, the efficacy analysis served only to assess the longer term blood pressure control that could have been important for safety reasons.

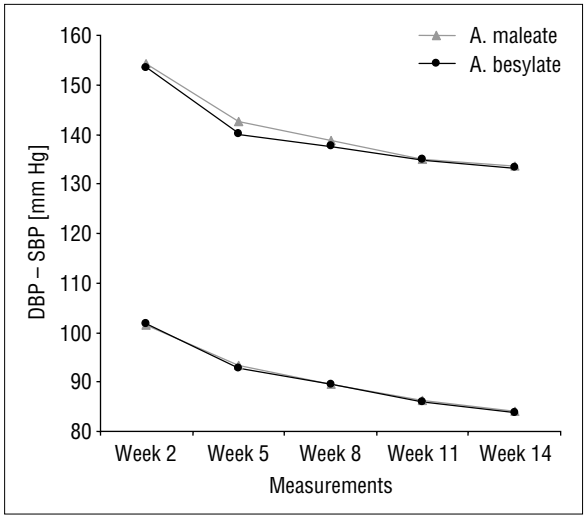

Figure 2. Changes in SBP and DBP during the active treatment period of the first phase

Rycina 2. Zmiany w wysokości skurczowego (SBP) i rozkurczowego (DBP) ciśnienia tętniczego w trakcie pierwszej części badania

The DBP/SBP reduction at the end of the second phase was –17.5/–21.2 mm Hg compared to the baseline values (paired t test, p < 0.0001). During the second phase both the mean DBP and the mean SBP were increased by 0.9 mm Hg in comparison with the beginning of the second phase (paired t test, p = 0.0062 and 0.043 for DBP and SBP, respectively). Comparing these parameters in the group of patients having received amlodipine maleate during the whole trial with those who switched from amlodipine besylate to amlodipine maleate at the end of the first phase there were no significant differences between the two groups (table V). HR was not significantly changed at the end of the second phase compared to the baseline value, while it increased by 1.24 beats/min in comparison with the beginning of the phase (p = 0.029).

Out of 202 patients analysed, 163 (80.7%) maintained the target DBP below 90 mm Hg at the end of the second period. One patient was excluded due to inadequate control of blood pressure representing 0.49% of the ITT population.

Safety

A comparative analysis of treatment tolerability was performed on the ITT population of 245 patients.

During the first phase there were 129 adverse reactions, i.e. adverse events probably or most probably related to the study drug, recorded in the study, that occurred in 35 patients in the amlodipine maleate group and in 47 patients in the amlodipine besylate group (28.9% *vs.* 37.9%; p = NS). The most common adverse reactions were: headache, lower extremity edema, facial flushes and transaminase activity elevations. The frequencies of adverse reactions did not differ significantly between the treatment groups (table VI). Most of the adverse reactions were mild or moderate pronounced and occurred during the first six weeks of treatment. Adverse reactions led to the discontinuation of therapy in 3 patients (2.4%)

Table V. Blood pressure changes in the second phase
Tabela V. Zmiany w wysokości ciśnienia tętniczego w trakcie drugiej części badania

	A. maleate — A. maleate (n = 105)	A. besylate — A. maleate (n = 97)	p for the comparison between the drugs
DBP reduction [mm Hg]$^{+}$	–17.4 ± 6.3	–17.5 ± 6.1	0.9099
SBP reduction [mm Hg]$^{+}$	–21.4 ± 11.5	–20.9 ± 12.2	0.7320
DBP change [mm Hg]$^{++}$	0.77 ± 5.21	1.07 ± 4.12	0.6513
SBP change [mm Hg]$^{++}$	0.69 ± 6.23	1.04 ± 5.72	0.6513

$^{+}$ Reduction at the end of the second phase with regard to the baseline values
$^{++}$ Change at the end of the second phase compared to the beginning of the second phase

Table VI. Adverse reactions during the first phase
Tabela VI. Zdarzenia niepożądane w trakcie pierwszej części badania

Adverse reaction	A. maleate n = 121	A. besylate n = 124	Total n = 245
Headache	11 (9.1)	16 (12.9)	27 (11.0)
Peripheral edema	10 (8.3)	8 (6.5)	18 (7.3)
Flushing	7 (5.8)	8 (6.5)	15 (6.1)
Increased ALT	8 (6.6)	10 (8.1)	18 (7.3)
Increased AST	5 (4.1)	7 (5.6)	12 (4.9)
Palpitation	2 (1.6)	4 (3.2)	6 (2.4)
Skin rash	2 (1.6)	4 (3.2)	6 (2.4)
Fatigue	1 (0.8)	2 (1.6)	3 (1.2)
Tachycardia	0 (0.0)	3 (2.4)	3 (1.2)
Constipation	2 (1.6)	0 (0.0)	2 (0.8)
Dizziness	2 (1.6)	0 (0.0)	2 (0.8)

The table contains number and percentage (in brackets) of patients with adverse reactions; p = NS for all the comparisons between the groups

in the group receiving amlodipine maleate and in 2 patients (1.6%) in the group receiving amlodipine besylate. Some of the patients had several complaints listed in the Table IV.

During the second phase, out of 202 patients treated with amlodipine maleate, 17 patients had 19 adverse reactions, yielding an overall incidence of 8.4%. Thirteen adverse reactions were mild in intensity, 5 adverse reactions were moderate and one adverse reaction was severe. The most common adverse reactions were peripheral edema (4.5% of patients) and increased ALT (2.5%) and increased AST (1%). There were two patients excluded due to adverse reactions. An analysis of ECG did not show any differences in ECG abnormalities at the end of each phase compared to the baseline examination.

Discussion

Amlodipine, a dihydropyridine derivative, a third generation calcium channel blocker, has the properties that enable the smooth and gradual onset of its antihypertensive effects, the prolonged duration of these effects [11]. High efficacy and good tolerability of amlodipine have been demonstrated in numerous clinical trials. Amlodipine has been studied in many large, multicentre clinical studies including TOHMS [5], Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and the recently completed Valsartan Antihypertensive Long-term Use Evaluation [12, 13]. In these studies two different salts of amlodipine were administered — amlodipine besylate and amlodipine maleate. The amlodipine maleate was assessed in the TOMHS study while in other trials amlodipine besylate was used.

The TOMHS study, the only large long-term study in which amlodipine maleate has been used, included over 900 patients with essential mild hypertension during a 4 year observation. It evaluated antihypertensive action, tolerability and influence on target organ damage and the metabolic profile of the representatives of five basic groups of antihypertensive drugs: diuretic, beta-blocker, alpha-blocker, calcium antagonist and converting enzyme inhibitor, represented respectively by chlorthalidone, acebutolol, doxazosine, amlodipine and enalapril. The TOMHS study demonstrated the adequate antihypertensive efficacy of amlodipine maleate, the favorable influence of its lipids profile and the highest proportion of patients (83%) receiving 5 mg of the medication once daily, who continued the treatment with the evaluated calcium antagonist [5].

Recently, amlodipine maleate was introduced for the clinical use and is expected to have identical pharmacological and clinical properties as amlodipine besylate. The main issues involving the problem

of the salt switch are the possible difference in pharmacokinetic properties, including differences in solubility and permeability, *i.e.* absorption of the active substance, and safety issues due to presumably different toxicological profile of the two salts. Ideally, pharmacological and toxicological activities of a given drug should not be influenced by the selection of a particular salt type used, however differences may appear in some cases [14]. We have tested the pharmacokinetic properties of the both salts in a bioequivalence study and have proven the same profile of blood concentration, *i.e.* the rate and extent of absorption of both drugs (data on file). The preclinical toxicological tests did not show any significant differences between the two salts [15–18].

The results of our study have shown the equivalent efficacy of both salts. The equivalence margin, based on DBP, has been stated to be somewhat narrower than in similar equivalence studies [19, 20] in order to assure a reliable criterion for the equivalence of the antihypertensive effect. The study was designed to simulate normal clinical practice by titrating the doses of study medication according to the blood pressure response and by performing an ITT analysis of the data. The results were also confirmed by the previously published PP analysis [10], which increases the reliability of claims regarding equivalence. The SBP data, heart rate and percentage of patients who reached the target blood pressure after 12 weeks of active therapy further supported the therapeutic equivalence of the two amlodipine salts. The size of the therapeutic effect was not substantially different from the other amlodipine studies with similar dosing regimens [20–22].

The antihypertensive efficacy of amlodipine maleate was maintained during the extended follow-up phase, proving the absence of therapeutic escape. The blood pressure reduction at the end of the nine-month follow-up was adequate and significant compared to the baseline values. Blood pressure reduction, a minor increase of DBP and SBP at the end of the study in comparison with the beginning of the extended follow-up (second phase) and the percentage of patients in whom blood pressure was adequately controlled were all comparable with other studies of a similar design [23]. The absence of a significant difference in a minute increase in blood pressure at the end of the 9 month follow-up between the patients who had been receiving amlodpine maleate throughout the entire trial and those who had switched from amlodipine besylate to amlodipine maleate after the first phase, strongly suggests that a switch from amlodipine besylate to the maleate salt of amlodipine does not result in any clinically significant changes in blood pressure control. For these results to be confirmed they would have to be compared with data on patients who would have received amlodipine besylate during the whole study, which is beyond the scope of this trial.

The safety profiles of the two salts were comparable with no significant differences in the parameters investigated, including overall incidence of adverse events, incidences of individual adverse events and the number of patients excluded due to adverse events. In general, the safety profile of study drugs in this study was similar to the profile described in the literature [20, 21, 24]. Our study showed the relatively high incidence of AST and ALT slight increase in both treatment groups, however the initial activity of the liver enzymes had already been increased in a substantial proportion of patients with abnormal values at the end of the first phase. There were no differences in the proportion of patients with abnormal activity ALT or/and AST at the end of first phase, compared with the initial check-up, as assessed by the particular statistical methodology [25].

The incidence of drug-related adverse events with amlodipine maleate during the extended follow-up was much lower than in the first three months of the study, indicating the stabilization of the patient's tolerance to the drug. The latter, together with low number of patient exclusions due to adverse events, corroborate the satisfactory safety results of the first phase and indicate that amlodipine maleate is a well-tolerated and safe drug.

In conclusion, our study has shown the equivalent efficacy and comparable safety profiles of two amlodipine salts, which indicates that a different salt form of the active substance amlodipine does not have any clinical implications with respect the an altered antihypertensive effect or a difference in the safety profile. The extended follow-up period confirmed the adequate blood pressure control and satisfactory safety profile of amlodipine maleate.

Summary

Background A nine-month follow-up, multicenter study was carried out to assess the efficacy and safety of amlodipine maleate, a recently launched amlodipine salt in 263 patients with essential hypertension.

Material and methods In the first phase of the trial, a 3-month equivalence assessment with the reference besylate salt has been carried out in a randomised double-blind fashion including placebo run-in period. The equivalence margins were set to be ± 4 mm Hg. The second

phase was a 6-month open non-comparative extension of the equivalence phase to provide additional information on clinical efficacy and acceptability during prolonged treatment with amlodipine maleate. Essential hypertension was defined as a sitting diastolic blood pressure (DBP) being within the range of 95–114 mm Hg and systolic blood pressure below 180 mm Hg. An adequate blood pressure control defined as reaching the target DBP of 89 mm Hg or at least 10 mm Hg reduction of DBP compared to the baseline values, was the inclusion criterion for the second phase. The primary endpoint was the mean absolute reduction of DBP at the end of the active treatment in relation to the baseline.

Results Altogether, 245 patients were analyzed in the equivalence comparative part, while 202 patients were included in the analysis of the open follow-up period. Both drugs have significantly lowered DBP and SBP after 3 months of treatment compared with the baseline values while heart rate has not been significantly changed in any of the treatment groups. The difference in these parameters between the salts was not significant. The difference in DBP reduction between the treatments was 1.27 mm Hg in favour of the besylate salt and the 90% confidence interval fell entirely within the equivalence margins.

There was no difference between the salts in the percentage of patients reaching the target DBP (90.91% and 89.52% for maleate and besylate, respectively). The DBP/SBP reduction after the amlodipine maleate at the end of the 6-month second phase was –17.5/–21.2 mm Hg compared to the baseline values (paired t test, $p < 0.0001$). Blood pressure control was adequate during the second phase.

Thirty-five patients in the amlodipine maleate group and 47 patients in the amlodipine besylate group reported adverse reactions during the 3-month comparative (28.9% and 37.9%, for maleate and besylate, respectively, p = NS). The overall incidence of amlodipine maleate-related adverse events during the second phase was 8.4%.

Conclusions In conclusion, amlodipine maleate was shown to be equivalent to the reference besylate salt in terms of antihypertensive efficacy, and safety profiles of the two salts were not significantly different. Amlodipine maleate enabled adequate blood pressure control and was shown to be well tolerated during the entire 9-month follow-up.

key words: amlodipine, multicenter study, antihypertensive efficacy, side effects, essential hypertension

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