Full Length Research Paper

Comparison of the efficacy and safety of an oral combination of losartan, hydrochlorothiazide and simvastatin against separated components, in hypertensive and dyslipidemic patients

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Received 29 October, 2014; Accepted 25 March, 2015

Hypertension is an important health problem that frequently requires multidrug treatment, whether due to monotherapy failure or in a concomitant manner. This situation has impulsed the development of some fixed dose combination products with the idea of improve the efficacy, the safety or the adherence of the treatment. In this study, the efficacy and safety of a fixed dose combination product composed by losartan, hydrochlorothiazide and simvastatin was compared with the mixture of losartan and hydrochlorothiazide plus simvastatin, in hypertensive and hypercholesterolemic patients. In this double-blinded, randomized and controlled clinical trial, one hundred and forty four (144) hypertensive and hypercholesterolemic patients received a daily capsule with losartan 50 mg, hydrochlorothiazide 12.5 mg and simvastatin 20 mg plus a tablet of placebo; or a daily tablet with losartan 50 mg and hydrochlorothiazide 12.5 mg plus a capsule of simvastatin 20 mg, during 81 days. Both treatments produced similar reductions on blood pressure and low-density lipoprotein-cholesterol levels, and more than 90% of treated patients achieved recommended values in these parameters. It is concluded that the fixed dose combination of losartan, hydrochlorothiazide and simvastatin, is as effective and safe as the fixed dose of losartan and hydrochlorothiazide plus simvastatin, in hypertensive and hypercholesterolemic patients.

Key words: Hydrochlorothiazide, hypercholesterolemia, hypertension, losartan, simvastatin.

INTRODUCTION

Hypertension is an important medical and public health problem, which approximately affects one billion people worldwide (Chobanian et al., 2003). The correlation between a high level of blood pressure with heart attack,
heart failure, stroke and kidney diseases is consistent (Anderson et al., 1991); on this way, the treatment of hypertension to <140/90 mmHg is associated with a decrease in cardiovascular disease complications (Hansson et al., 1998). Although, several drugs, including beta adrenergic blockers, angiotensin converting enzyme inhibitors, calcium channel blockers and angiotensin II receptors blockers are used for reducing blood pressure, the underused thiazide-type diuretics have been considered the basic drugs for the initial treatment of hypertension (Chalmers and Zanchetti, 1996; Psaty et al., 1997; 2003). Anyway, only 30% of hypertensive patients are adequately controlled with the administration of one drug, and two or more drugs are used to control the level of blood pressure in the rest of patients, either as separate prescriptions or in fixed-dose combinations (Sica, 2002).

The combination of losartan plus hydrochlorothiazide is currently approved in some countries as a second line therapy for hypertension, or, inclusive, as initial therapy in severe hypertension cases. On the other hand, the recommendation that a global anti-hypertensive therapy should include other measures including smoking cessation, management of diabetes, lipid lowering products, anti-platelet agents, exercise training, and weight reduction in obese patients (Chobanian et al., 2003), it has impulse the development of some fixed-dose combination products including antihypertensive with other drugs of a different therapeutic activity, which could improve the treatment adherence. In this study, we were interested in the preliminary evaluation of a fixed dose combination product composed by losartan, hydrochlorothiazide and simvastatin, in comparison with the mixture of losartan and hydrochlorothiazide plus simvastatin, in hypertensive and hypercholesterolemic patients.

**METHODOLOGY**

**Subjects**

To evaluate the efficacy and safety of oral administration of a fixed-dose combination product composed by losartan, hydrochlorothiazide and simvastatin, in comparison with the mixture of losartan and hydrochlorothiazide plus simvastatin, one hundred and forty four hypercholesterolemic (LDL cholesterol ≥ 130 mg/dL) patients with either untreated grade 1 or 2 essential hypertension or uncontrolled on monotherapy (systolic blood pressure 140 to 179 mm Hg and diastolic blood pressure 90 to 109 mmHg), and 18 to 65 years old, were recruited to perform a phase III, double blinded, randomized and placebo-controlled clinical trial study. Subjects with a history of allergic reactions to thiazide diuretics, angiotensin II receptor blockers or statins, diabetes, pregnant, alcoholism, secondary hypertension, severe hypertension, unstable angina, acute myocardial infarction, hepatic disease or renal insufficiency, were excluded from the study. The protocol was carried out following the recommendations of the latest version of the World Medical Association Declaration of Helsinki – Ethical Principles for Medical Research Involving Human Subjects. All participants read the protocol, which was approved by the Institutional Research and Ethics Committee, and provided written informed consent for their participation in the study.

**Study design**

This randomized, double blind placebo-controlled study of 81 days was approved by The General Hospital “Dr. Enrique Cabrera” Review Board. After obtaining written informed consent, patients were instructed to withhold anti-hypertensive or anti-lipemic drug, and were randomly assigned to one of 2 treatments: a night daily tablet with losartan 50 mg and hydrochlorothiazide 12.5 mg and a capsule of simvastatin 20 mg, or a night daily capsule with losartan 50 mg, hydrochlorothiazide12.5 mg and simvastatin 20 mg, plus a tablet of placebo. All investigation products were provided by Landsteiner Scientific, S.A. de C.V., Mexico City. Sample size calculation was estimated to provide 80% power to detect treatment differences in absolute body weight loss with an alpha level of 0.05, and a mean difference of 12.0 mg/dL LDL-cholesterol with a standard deviation of 23.1 mg/dL LDL-cholesterol (Ronceros et al., 2012), being 58 patients, which is the minimum number of patients required in each group. Sample size calculation included an estimation of 25% patient withdrawals. Figure 1 shows the general outline of the trial phase. The patients were seen in six visits during this study of 81±3 days (visit 1 of selection at day 0, visits 2 to 5 of treatment at days 1, 14, 44 and 74 days, and visit 6 of final revision at day 81, respectively). During all visits, general measurements, including weight, height, waist circumference, body mass index (BMI), respiratory frequency, temperature, heart rate, systolic blood pressure (SBP) and diastolic blood pressure (DBP) were obtained. In addition, during the visits 1 and 5 an electrocardiogram of 12 derivations was also performed, and a blood sample was taken for blood chemistry and hemat biometry assays. In each determination, patients upon arrival voided their bladder, wore only a clinical robe and a nude body weight was obtained on a calibrated scale. Height was determined with the patients placed with the heels together; and the buttocks, shoulders and head in contact with the stadiometer. Waist circumference was measured placing a tape in the midway between the top of hip bone and the bottom of ribs and wrapping around the waist at the mark level. Measurements of systolic and diastolic blood pressure were obtained using a mercury sphygmomanometer (mean of three measurements in the right arm in seated position), and blood samples for laboratory assays were obtained at approximately 8 AM after patients fasted overnight.

**Data analysis**

Baseline characteristics are summarized as number of patients and percentage (%) for categorical variables, and as mean ± standard deviation continuous variables. The analysis was performed on a per-protocol analysis. The underlying assumption of the statistical analysis was that all variables had a normal probability of distribution according to Shapiro-Wilk’s test. Values for baseline blood pressure and blood pressure reduction from baseline to 1, 14, 44, 74 and 81 days are presented as means of systolic and diastolic pressure ± standard deviation (mmHg).
Likewise, values for baseline LDL-cholesterol and end LDL-cholesterol are presented as means ± standard deviation (mg/dL). Statistical analysis of the time-course of blood pressure and LDL-cholesterol values for both treatments was performed by repeated measures analysis of variance followed by the Tukey’s test. Blood pressure control in each treatment (<140/90 mmHg) was summarized as numbers of patients and percentages (%). Potential differences of demographic data between groups were assessed by the Student t-test or χ²-test. In addition, a paired t-Student test was used to assess significant changes in the laboratory parameters from baseline to 81 days. Patients with less than 80% of treatment adherence were not included in the analysis. Differences were considered statistically significant when P was <0.05. Data were analyzed using the statistical software statistical package for the social sciences (SPSS), version 20.0.

RESULTS

Demographic data

A comparison of the main demographic data is shown in Table 1. Patients of both groups resulted equilibrated regarding sex, age, weight, waist circumference, body mass index (BMI), respiratory frequency, temperature, heart rate, diastolic blood pressure (DBP) and systolic blood pressure (SBP) variables. There were no violations to the protocol that may have interfered with the study variables. Four patients were withdrawn from the study; in the losartan-hydrochlorothiazide plus simvastatin group (LH-S), one of them was withdrawn because of lack of treatment efficacy and two due to poor treatment adherence whereas in the losartan-simvastatin-hydrochlorothiazide group (LSH) one patient was withdrawn due to poor adherence treatment. 54.16% of population had a complete treatment adherence (100%), 42.36% had a very good adherence (90 to 99%), 0.69% had a good adherence (80 to 89%), and only 2.77% had a poor treatment adherence (< 80%).

Anti-hypertensive effect

The time-course of mean SBP and DBP values are shown in Figure 2. Baseline SBP/DBP values for (LH-S) group corresponded to 147.5±6.0 / 95.8±3.77 mmHg and 148.2±6.0 / 96.0±3.21 mmHg for LSH group. Both treatments produced significant reductions of both SBP and DBP values in a gradual and similar manner, from the second to the sixth visit (P < 0.0001). There were no significant differences between treatments at any time. At the sixth visit, approximately after 12 weeks, 64/69 (92.8%) patients of LHS group and 67/71 (94.3%) patients of LSH group achieved an adequate blood pressure control (SBP < 140 mm Hg / DBP < 90 mmHg).

Low-density lipoprotein cholesterol (LDL-C) lowering effect

The LDL-C level changes of patients at visits 1 and 6 are shown in Figure 3. All patients had a baseline LDL-C value less than 190 mg/dL. Patients of LH-S group had a reduction from 144.8 ± 24.8 mg/dL to 97.3 ± 24.5 (P < 0.0001), while patients of LSH group had a significant statistically reduction from 143.2 ± 24.1 to 101.2 ± 24.7 (P < 0.0001). On the same way, 61/69 patients of LH-S group vs 64/71 patients of LSH group achieved the recommended level of LDL-C < 130 mg/dL. Additionally, the mean atherogenic index LDL-C/HDL-C was reduced from 4.68±1.0 to 3.85 ± 0.94 in patients of LH-S group (P <0.0001) and from 4.67 ± 0.76 to 3.9 ± 0.85 in patients of

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>LH-S (n=72)</th>
<th>LSH (n=72)</th>
<th>P -value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex (male/female)*</td>
<td>29/43</td>
<td>29/43</td>
<td>0.7340</td>
</tr>
<tr>
<td>Age (years)**</td>
<td>47.1±9.4</td>
<td>46.7±9.5</td>
<td>0.8377</td>
</tr>
<tr>
<td>Height (cm)**</td>
<td>162.7±8.2</td>
<td>163.2±9.3</td>
<td>0.7678</td>
</tr>
<tr>
<td>Weight (kg)**</td>
<td>76.3±12.3</td>
<td>78.9±16.1</td>
<td>0.2715</td>
</tr>
<tr>
<td>Body mass index (kg/m²)**</td>
<td>28.8±4.2</td>
<td>29.7±5.9</td>
<td>0.3240</td>
</tr>
<tr>
<td>Waist circumference (cm)**</td>
<td>94.7±11.6</td>
<td>96.0±11.8</td>
<td>0.4810</td>
</tr>
<tr>
<td>Heart rate (beats per minute)**</td>
<td>72.1±7.1</td>
<td>72.1±8.0</td>
<td>0.9913</td>
</tr>
<tr>
<td>Respiratory frequency (breaths per minute)**</td>
<td>19.5±2.2</td>
<td>19.7±2.4</td>
<td>0.6870</td>
</tr>
<tr>
<td>Temperature (°C)**</td>
<td>36.5±0.2</td>
<td>36.5±0.2</td>
<td>0.7338</td>
</tr>
<tr>
<td>Systolic arterial pressure (mmHg)**</td>
<td>147.6±5.5</td>
<td>148.3±6.1</td>
<td>0.4464</td>
</tr>
<tr>
<td>Diastolic arterial pressure (mmHg)**</td>
<td>96.1±4.1</td>
<td>96.6±3.4</td>
<td>0.4011</td>
</tr>
<tr>
<td>LDL-Cholesterol (mg/dL)**</td>
<td>144.9±24.8</td>
<td>143.3±24.2</td>
<td>0.6988</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. There were no significant differences between studied groups by *χ² or ** t-Student test.
Figure 1. General outline of the study. LH-S = fixed dose combination of losartan and hydrochlorothiazide plus simvastatin. LSH = fixed dose combination of losartan, simvastatin and hydrochlorothiazide.

Figure 2. Mean of plasmatic concentrations of low density lipoprotein – cholesterol (LDL-C) ± standard deviation, in hypertensive and dyslipidemic patients treated with a tablet of a fixed dose combination of losartan and hydrochlorothiazide plus a capsule of simvastatin (LH+S, closed circles) or a capsule with a fixed dose combination of losartan, simvastatin and hydrochlorothiazide and a tablet of placebo (LSH, open circles). *Significantly different from baseline values (P<0.0001), as was determined by two-way analysis of variance with repeated measures, followed by the Tukey’s test.

Adverse events

The frequency of adverse event was similar for both groups. Twenty four patients reported adverse events; 14 from LH-S group and 10 from LSH group. The most frequent adverse events were mild and consisted of tonsillitis, headache and abdominal pain (4, 1, and 0, for LH-S group and 2, 4, 2 for LSH group respectively). After 81 days treatment, both treatments significantly improved total cholesterol, LDL-cholesterol and atherogenic index, as well as creatinine and uric acid levels, and lactate dehydrogenase activity. There were no other clinically significant changes in the laboratory parameters. More
DISCUSSION

Interest in using fixed-dose combination therapy has been particularly increased in hypertension, including those cases of patients with concurrent medical problems such as hyperlipidemia, diabetes and renal disease. The combination therapy looks for the additive or synergistic effect of two or more drugs with different mechanisms of action, mainly in the case of the fixed-dose combinations.
with drugs with complementary mechanism of action increase the efficacy of each drug against either as monotherapy. Actually, in some countries the combination of losartan and hydrochlorothiazide is approved for the treatment of hypertension as a second line therapy, or as initial therapy for severe hypertension. On the other hand, based on the idea that angiotensin II is very potent endogenous vasoconstrictor, whereas LDL induces up-regulation of the AT1 receptor (Nickenig et al., 1997). A comparative study was performed in patients with hypertension and hypercholesterolemia, who received simvastatin 20 mg or losartan 20 mg alone or in combination, in this study, individual drugs produced the expected anti-hypertensive or hypcholesterolemic effect, but the mixture significantly improved the effect of individual drugs on endothelial function and inflammatory markers, such as plasma malondialdehyde, C-reactive protein and monocyte chemoattractant protein-1 levels, which suggest that the fixed combination of simvastatin-losartan could reduce cardiovascular events in hypercholesterolemic and hypertensive patients more than monotherapy with either drug alone (Kwang et al., 2004). Although, the current study focused on the preliminary comparison of a fixed-dose combination of losartan, hydrochlorothiazide and simvastatin versus the mixture of a fixed-dose combination of losartan and hydrochlorothiazide plus simvastatin, remarkable levels of effectiveness in terms of an adequate blood pressure control and a recommended level of LDL-C, in more than 90% of hypertensive and hypercholesterolemic patients were found.

### Table 2. Baseline and final metabolic parameters measured in hypertensive and dyslipidemic patients that received a daily capsule of losartan / hydrochlorothiazide / simvastatin and a placebo tablet (LSH), or a tablet of losartan / hydrochlorothiazide and a capsule of simvastatin (LH-S) during 81 days.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>LH-S Basal</th>
<th>LH-S Final</th>
<th>P-value</th>
<th>LSH Basal</th>
<th>LSH Final</th>
<th>P-value</th>
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</tr>
<tr>
<td>Glucose (mg/dL)</td>
<td>87.6±10.89</td>
<td>90.26±12.04</td>
<td>0.1582</td>
<td>87.14±12.11</td>
<td>90.63±12.65</td>
<td>0.0977</td>
</tr>
<tr>
<td>Total cholesterol (mg/dl)</td>
<td>212.30±30.08</td>
<td>167.33±27.25</td>
<td>&lt;0.0001</td>
<td>212.17±25.18</td>
<td>175.08±30.97</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol-LDL (mg/dl)</td>
<td>144.85±24.83</td>
<td>97.32±24.58</td>
<td>&lt;0.0001</td>
<td>143.26±24.18</td>
<td>101.20±27.74</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cholesterol-HDL (mg/dl)</td>
<td>47.39±12.05</td>
<td>45.19±10.81</td>
<td>0.2402</td>
<td>46.57±9.54</td>
<td>46.07±8.71</td>
<td>0.6483</td>
</tr>
<tr>
<td>Triglycerides (mg/dl)</td>
<td>163.03±56.56</td>
<td>146.75±55.97</td>
<td>0.0076</td>
<td>173.29±53.32</td>
<td>160.93±69.64</td>
<td>0.1463</td>
</tr>
<tr>
<td>Atherogenic index</td>
<td>4.68±1.00</td>
<td>3.85±0.94</td>
<td>&lt;0.0001</td>
<td>4.67±0.76</td>
<td>3.90±0.85</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urea (mg/dL)</td>
<td>24.64±11.78</td>
<td>22.62±17.01</td>
<td>0.2950</td>
<td>23.86±18.92</td>
<td>25.42±12.04</td>
<td>0.1257</td>
</tr>
<tr>
<td>Uric acid (mg/dl)</td>
<td>5.33±1.22</td>
<td>4.92±1.25</td>
<td>0.0004</td>
<td>5.35±1.43</td>
<td>4.97±1.39</td>
<td>0.0011</td>
</tr>
<tr>
<td>Creatinine (mg/dl)</td>
<td>0.86±0.16</td>
<td>0.79±0.13</td>
<td>&lt;0.0001</td>
<td>0.88±0.15</td>
<td>0.80±0.15</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Lactate dehydrogenase (UI/L)</td>
<td>185.74±32.51</td>
<td>171.57±32.46</td>
<td>0.0004</td>
<td>187.08±32.68</td>
<td>169.17±30.46</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Alkaline phosphatase (UI/L)</td>
<td>89.78±24.14</td>
<td>84.16±23.80</td>
<td>0.0074</td>
<td>94.79±24.47</td>
<td>95.03±26.70</td>
<td>0.9707</td>
</tr>
<tr>
<td>Aspartate transaminase (UI/L)</td>
<td>24.64±11.78</td>
<td>22.62±17.01</td>
<td>0.2950</td>
<td>23.86±18.92</td>
<td>25.42±12.04</td>
<td>0.1257</td>
</tr>
<tr>
<td>Alanine transaminase (UI/L)</td>
<td>31.35±21.53</td>
<td>32.99±26.19</td>
<td>0.5896</td>
<td>38.07±40.27</td>
<td>33.28±21.75</td>
<td>0.1809</td>
</tr>
<tr>
<td>Creatine phosphokinase (UI/L)</td>
<td>116.57±57.32</td>
<td>137.97±79.48</td>
<td>0.1495</td>
<td>123.26±77.73</td>
<td>134.49±94.88</td>
<td>0.4590</td>
</tr>
</tbody>
</table>

Data are expressed as mean ± standard deviation. Differences were considered statistically significant when P < 0.05 by paired t-Student test.
One of the objectives of a fixed-dose combination is the attenuation of adverse events induced by single agents, both clinic and metabolic. In this study, the frequency of adverse event was similar for both groups being tonsillitis, headache and abdominal pain the more frequent adverse effects. All of them were mild and transient, and they were consistent with those seen with losartan, hydrochlorothiazide or simvastatin as monotherapy. Moreover, there were no new adverse events due to the combination. Both treatments were well-tolerated since both treatments improved significantly lipid profile, creatinine and uric acid levels, and there were no other clinically significant changes in the laboratory parameters. Tolerability and safety of the fixed-dose combination of losartan, hydrochlorothiazide and simvastatin or the mixture of a fixed-dose combination of losartan and hydrochlorothiazide plus simvastatin could be explained on the following basis: there is no clinically significant pharmacokinetic interaction between losartan and hydrochlorothiazide (McCrea et al., 1995); there seems no identified significant pharmacokinetic interactions between simvastatin and losartan, which is mainly metabolized by CYP2C6 as irbesartan (Marino and Vachharajani, 2001; the combination of losartan plus simvastatin improve the anti-atherosclerotic effect of each drug as monotherapy (Nomura et al., 2004); losartan may attenuate some of the deleterious metabolic effects of hydrochlorothiazide because losartan may counterbalance the augment of uric acid (Soffer et al., 1995, MacKay et al., 1996) and glucose intolerance (Rulope et al., 1996) induced by hydrochlorothiazide; while hydrochlorothiazide may reduce the potassium-increased levels induced by losartan (Soffer et al., 1995; Palmer, 2008). In line with the results, a randomized double-blind placebo-controlled crossover trial of a Polypill (containing amlodipine 2.5 mg, losartan 25 mg, hydrochlorothiazide 12.5 mg and simvastatin 40 mg) was performed in individuals aged > 50 years old without a history of cardiovascular disease, the study showed that the fixed-dose combination was effective, safety and well-tolerated (Wald et al., 2012).

In general, the use of fixed-dose combinations show a better patient compliance due to simplification of the regimen, reduction of the pill burden and a potential reduction of cost, due to a fixed-dose combination is often less expensive than buying each drug individually and reduces costs associated with cardiovascular events and productivity loss due reduces their incidence. In fact, it is well known that patient compliance is inversely related to the number of drugs being administered. To overcome this problem, several dual and triple-drug, fixed-dose combinations have been developed and marketed, which are easier to administer, and they have been shown to increase patient compliance and adherence to treatment (Ram, 2013). In this regard, there is evidence that show the proven cost-effectiveness and patient compliance of a fixed-dose combination of a statin-like drug plus an anti-hypertensive drug (Delgado-Montero and Zamorano, 2012) or an AT1-receptor antagonist plus a thiazide diuretic (Coca, 2008). Moreover, the fixed-dose losartan/hydrochlorothiazide is more cost-effective than candesartan/amlodipine (Shimosawa et al., 2007), and similar to other fixed-dose AT1-receptor antagonists/hydrochlorothiazide combinations (Ekman et al., 2008). Currently, a study demonstrating the cost-effectiveness of the current fixed-dose combination is lacking, but 97.2 and 98% patients had good treatment adherence in this study and in the study of Wald et al. (2012), respectively, since they took more than 80% of their allocated pills.

On the other hand, the fixed-dose combinations have also disadvantages as the loss of dose flexibility or the difficulty in identifying the active ingredient responsible for adverse reaction in the fixed-dose combination. In the former disadvantage, the fixed-dose of losartan 50 mg/hydrochlorothiazide12.5 mg/simvastatin 20 mg could be only increased twice daily in patients unable to achieve LDL-C goal and blood pressure control according to recommended dose for hypertension and dyslipidemia by Food and Drug Administration (Hsu et al., 1995; Ripley and Hirsch, 2010; Palmer, 2011). However, for those who has blood pressure control but not LDL-C goal or vice versa, should consider alternative therapy. With respect to the difficulty in identifying the active ingredient responsible of an adverse reaction, the three drugs that belong to the fixed-dose losartan/hydrochlorothiazide/simvastatin combination are well tolerated and its more common adverse events are mild to moderate and transient, so they do not have clinic relevance.

However, it has been reported that some uncommon adverse events with each drug should be taken in account for the control patient. Losartan induces uricosuric and hyperkalemic effects (Ripley and Hirsch, 2010), while thiazide diuretics as hydrochlorothiazide can provoke hyperglycaemia and diabetes, as well as hypokalemia and hyperuricemia (Palmer, 2011). Simvastatin, as other statins, has been associated with rare cases of severe myopathy and rhabdomyolysis, which is accompanied by elevations in creatine kinase, as well as renal failure (Alonso et al., 2005). In this fixed-dose combination, some adverse events are counterbalanced as earlier stated, but patients should be monitored for creatine kinase activity, as well as for creatinine, uric acid, glucose and K+ levels. Finally, this problem might be alleviated by starting the medications individually and monitoring for reactions, and then switching to a fixed-dose combination when no problems have been observed.

**Conclusion**

The results show that fixed dose combination of losartan,
hydrochlorothiazide and simvastatin is as effective and safe as the fixed-dose combination of losartan and hydrochlorothiazide, plus simvastatin, in the treatment of mild and moderate essential hypertension and hypercholesterolemia. This combination could be used as substitutive therapy in the treatment of hypertensive and hypercholesterolemic patients already treated with the association of losartan, hydrochlorothiazide and simvastatin at the same doses, in who a better compliance is desirable.

AKNOWLEDGMENTS

Authors kindly acknowledge Landsteiner Scientific, S.A. de C.V., Mexico City, Mexico for the formulations provided for this study.

Conflict of interest

The authors declare that they have no conflicts of interest.

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