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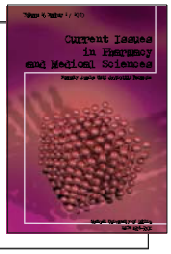

Influence of combined treatment with mianserin and simvastatin on selected biochemical serum parameters of liver and kidney function in rats

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ABSTRACT

The aim of the present study was to assess the impact of combined 14-day treatment with mianserin (10 mg/kg) and simvastatin (1 or 10 mg/kg) on selected biochemical liver and kidney parameters in rats (AST and ALT activities and the concentrations of AFP, total protein, urea, creatinine and ß2-M). The results showed the increase in both transaminases activities, creatinine concentration and the decrease of AFP, total protein and ß2-M concentrations. The results indicate that 14-day combined administration of mianserin with simvastatin negatively affects the liver functioning. The observed changes in kidney biochemical parameters may suggest a risk of renal dysfunction during long-term combined treatment with these drugs.

Keywords: mianserin, simvastatin, biochemical liver and kidney parameters, rats

INTRODUCTION

In recent years, the problem of depression has been growing steadily. WHO ranks depression as the world's fourth greatest public health problem and a prognosis for 2020 predicts depression to be the second cause of disability [22]. The treatment of depression requires long and intensive therapy based mainly on antidepressant drugs with different pharmacological profile. One of frequently used atypical antidepressant medicines is mianserin, which is generally well tolerated by elderly patients and those with cardiovascular disease [21]. However, it causes certain side effects and interacts with simultaneously used other drugs [9,19]. Side effects of mianserin are rare and weaker than tricyclic antidepressants (TCAs) and include excessive sedation, disorders of the liver, dry mucous membranes, weight gain and allergic skin reactions [9,29,31]. Patients suffering from depression and cardiovascular disease often require polytherapy. Therapy with statins (3-hydroxy-3-methylglutaryl-CoA reductase inhibitors) is an important factor in the treatment and prevention of cardiovascular diseases [2,27,30]. Simvastatin is one of the most frequently prescribed statin. Statins are generally well tolerated. However, adverse effects associated with their use such as myopathy, myositis and elevation of serum liver enzyme levels are well known [7,3,25].

There are some reports on simultaneous usage of antidepressants and statins [14,23,10,11]. The lack of clinical data about the impact of combined use of mianserin and simvastatin on the liver and kidney function inspired this study. The aim of this study was to asses the effect of 14-day combined treatment with mianserin and simvastatin on selected parameters of liver and kidney function in the serum of rats.

MATERIAL AND METHODS

Drugs, chemicals and methods. The following substances and commercial test kits were used: mianserin (Miansec, Jelfa, Poland), simvastatin (Simvacard, Zentiva), aqua pro injectione (Polfa, Lublin, Poland), aspartate (AST) and alanine (ALT) aminotransferases – Liquick Cor-ALT-60 and Liquick Cor-AST-60, total protein – Liquick Cor-TOTAL PROTEIN 120 (the method is based on the biuret reaction), creatinine – Liquick Cor-CREATININE 60 (modificated Jaffe´s method), urea–

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Liquick Cor-UREA 120 (kinetic, enzymatic method with urease and glutamate dehydrogenase) – (CORMAY, Lublin, Poland), α-fetoprotein – AFP-ELISA – DIMA GmbH (Goettingen, Germany) and β2-microglobulin (β2-M) – Beta-2-Microglobulin ELISA (Immundiagnostic AG, Bensheim, Germany).

Animals. The study was carried out on male Wistar rats weighing 195-275 g (purchased from licensed breeding farm of Brwinów, Poland). Animals were kept under standard laboratory conditions and maintained on a 12 h day/ 12 h night cycle with free access to food and water. The Ethical Committee on Animal Experimentation of the Medical University of Lublin approved the studies.

Treatments. The drugs were suspended in distilled water with one drop of Tween 80 and injected intraperitoneally (ip) in volumes of 0.5ml/100g. The rats received mianserin, simvastatin and the combination of mianserin and simvastatin (i.p.) once a day for 14 days. Groups of rats (1-6) were administered sequentially: 1. control animals – aqua pro injectione; 2. mianserin 10 mg/kg; 3. simvastatin 1 mg/kg; 4. simvastatin 10 mg/kg; 5. mianserin 10 mg/kg with simvastatin 1 mg/kg; 6. mianserin 10 mg/kg with simvastatin 10 mg/kg. The drugs were applied in effective doses [21,25].

Experimental protocols. Each experimental group consisted of eight animals. The rats were decapitated 24 h after the last injection and blood from each animal was taken. The blood was allowed to clot, the serum fraction was separated and subsequently stored at -20°C until biochemical assays were performed.

Statistical analysis. Results are expressed as mean± SEM. Statistical significance among groups was determined by ANOVA test. The differences were considered as statistically significant if p-values were less than 0.005.

RESULTS AND DISCUSSION

Depression is often accompanied by cardiovascular diseases, which requires treatment with both antidepressants and statins [20, 17, 28]. Combined treatment may adversely affect functioning of internal organs, especially the liver and kidneys.

Our studies indicated that combined 14-day treatment with mianserin and simvastatin can cause a few changes in the biochemical liver parameters in rats. The present study indicated that simultaneous treatment with mianserin (10 mg/kg) and simvastatin (1 or 10 mg/kg) caused an increase in AST activity compared to the groups of rats receiving only mianserin or simvastatin (Fig.1). Neither of the drugs administered separately affected AST activity in comparison to the control group. Mianserin administered simultaneously with simvastatin only in a dose 10 mg/kg caused a significant increase in ALT activity in comparison to mianserin or simvastatin (10 mg/kg) (Fig.2).

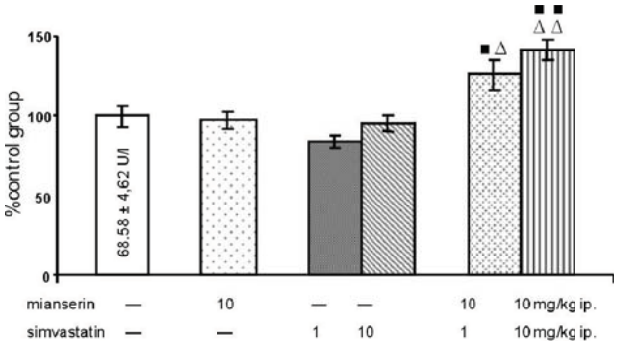

Fig. 1. The activity of AST in the serum of rats after 14-days treatment with mianserin, simvastatin and their combination

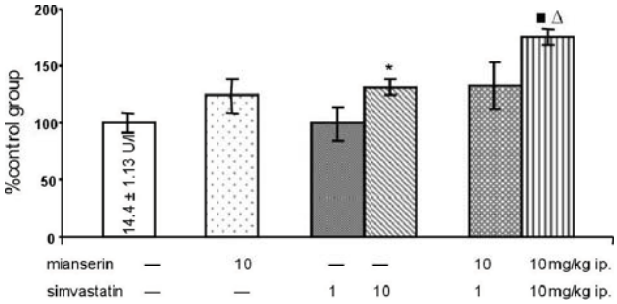

Fig. 2. The activity of ALT in the serum of rats after 14-days treatment with mianserin, simvastatin and their combination

It should be noted that only the higher dose of simvastatin (10 mg/kg) increased ALT activity in comparison to the control group. Our previous studies showed that 14-days simultaneous treatment with simvastatin (10 mg/kg) and amitriptyline (10 mg/kg) increased the activity of AST while combined treatment with simvastatin (20 mg/kg) and doxepine (20 mg/kg) increased the activity of both AST and ALT [10,11]. Numerous scientific articles and publications prove that the probability of liver functioning disorder while using statins is slight [5,24,26]. According to many authors, the growth of transaminases activity is reversible and it is dependant on the dosage – the highest doses of statins generally have higher activities of transaminases [4,6,13]. Clinical research data [8] shows that the frequency of the occurrence of higher activities of AST and ALT in the serum of the examined and treated patients as well as in the placebo group were comparable. According to these authors, lovastatin, simvastatin and pravastatin do not trigger the risk of liver functioning disorder, implying liver damage [8]. The 14-day combined treatment with mianserin and simvastatin in the 10 mg/kg dose only significantly decreased the concentration of AFP in the rat serum in comparison to the groups of animals receiving only one of these drugs (Fig.3). It was found, that mianserin alone caused a significant decrease in the concentration of AFP in comparison to the control group. The combined treatment with mianserin and simvastatin (1 or 10 mg/kg) in rats significantly decreased the concentration of total protein in comparison

to only mianserin or simvastatin (Fig.4). A significant decrease in the concentration of this protein was observed in the groups of animals pretreated with only mianserin or simvastatin (10 mg/kg) in comparison to the control group. The observed changes may suggest disorders in liver functioning when mianserin and simvastatin are administered simultaneously, especially in a high doses. This cannot be ignored, because both applied drugs used in this research are similarly metabolized [12,18].

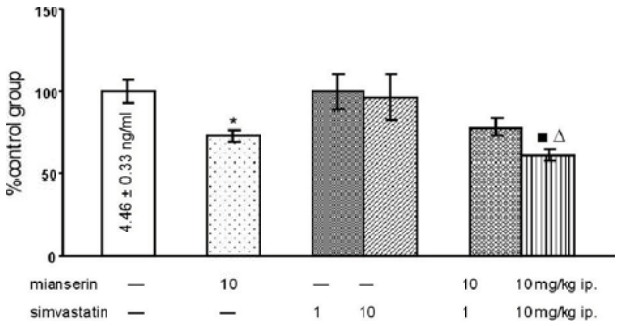

Fig. 3. The concentration of AFP in the serum of rats after 14-days treatment with mianserin, simvastatin and their combination

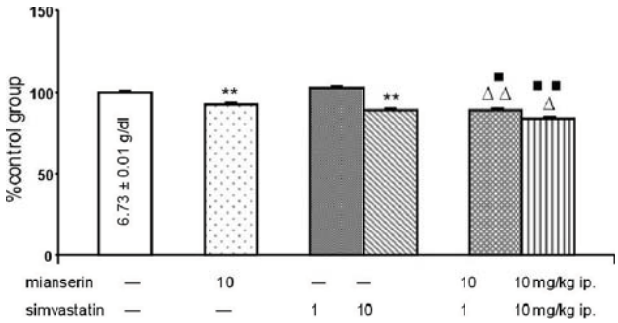

Fig. 4. The concentration of total protein in the serum of rats after 14-days treatment with mianserin, simvastatin and their combination

The study also examined parameters of kidney functioning. On the basis of the literature data, statins therapy does not impair kidney functioning [13,15]. It is even advised to use these drugs in chronic kidney disease [1,4,16]. Our research showed, that the combined 14-day treatment with mianserin and both doses of simvastatin had no influence on the concentration of urea as compared to treatment with only mianserin or simvastatin (Fig.5). A significant increase in the concentration of urea was observed only in the serum of rats treated with simvastatin (10 mg/kg) in comparison to the control group. A significant increase of creatinine concentration was notified in the rats serum pretreated with mianserin and simvastatin (10 mg/kg) compared to the groups receiving only one of these drugs (Fig.6). However, the level of creatinine concentration in this group was rated within the control group limits. The combined treatment with mianserin and simvastatin (1 mg/kg) caused significant decrease of creatinine concentration as compared to simvastatin. Neither mianserin nor simvastatin changed the creatinine concentra- tion in comparison to the control group. Mianserin administered simultaneously with simvastatin (10 mg/kg) caused a significant decrease in the concentration of ß2-M in the rats serum in comparison to only mianserin or simvastatin (Fig.7).

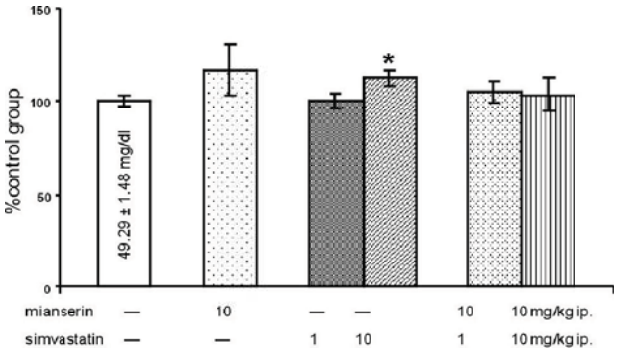

Fig. 5. The concentration of urea in the serum of rats after 14-days treatment with mianserin, simvastatin and their combination

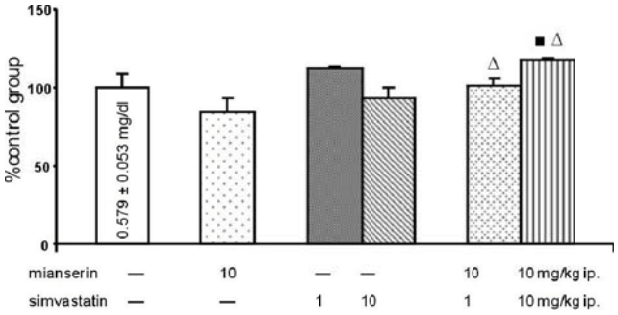

Fig. 6. The concentration of creatinine in the serum of rats after 14-days treatment with mianserin, simvastatin and their combination

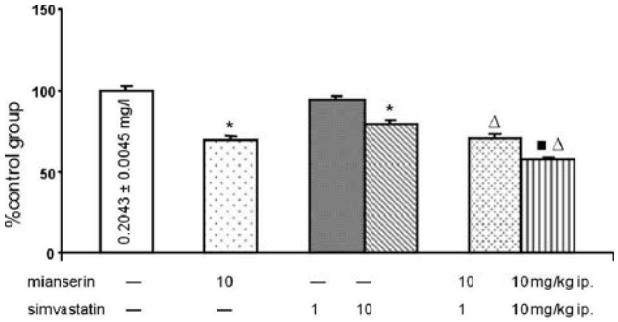

Fig. 7. The concentration of β_2 – microglobuline in the serum of rats after 14-days treatment with mianserin, simvastatin and their combination

*Δ ■ – p<0.05
ΔΔ■■ – p<0.001
* – comp. with control group
■ – comp. with mianserin
Δ – comp. with simvastatin

The administration of combined mianserin with simvastatin (1 mg/kg) decreased β2-M concentration in comparison to administration of only simvastatin. The decrease in β2-M concentration was observed in the serum of rats receiving only mianserin or simvastatin (10 m/kg) in

comparison to the control group. The results do not indicate unambiguously that 14-day combined administration with these drugs unfavorably influences kidney function; however the observed changes may suggest the possibility of renal disorder during the long-term treatment.

On the basic of our data, we have found that combined administration of mianserin and simvastatin causes changes in the liver and kidney parameters, which should be disregarded in long-term therapy.

CONCLUSIONS

1. The combined 14-day treatment with mianserin and simvastatin caused a significant increase in the AST and ALT activities and the concentration of creatinine but a decrease in concentrations of AFP, total protein and β2-M.
2. The observed changes in liver biochemical parameters may indicate the possibility of toxic interaction between mianserin and simvastatin, especially when used in high doses for a long time.
3. The fluctuations in the studied kidney parameters may suggest a risk of renal dysfunction during long-term combined treatment with these drugs.

REFERENCES

1. Agarwal R.: Effects of statins on renal function. *Am. J. Cardiol.*, 97, 748, 2006.
2. Almuti K. et al.: Effects of statins beyond lipid lowering: Potential for clinical benefits. *Int. J. Cardiol.*, 109, 7, 2006.
3. Bays H.: Statin Safety: An Overview and Assessment of the Data – 2005. *Am. J. Cardiol.*, 97, 6C, 2006.
4. Chalasani N. et al.: Patients with elevated liver enzymes are not at higher risk for statin hepatotoxicity. *Gastroenterology*, 126, 1287, 2004.
5. Charles E. C. et al.: Evaluation of cases of severe statin-related transaminitis within a large health maintenance organization. *Am. J. Med.*, 118, 618, 2005.
6. Cohen D.E. et al.: An Assessment of Statin Safety by Hepatologists. *Am. J. Cardiol.*, 97 (1), S77, 2006.
7. Degreef L.E. et al.: The tolerability and efficacy of low-dose simvastatin in statin-intolerant patients. *Eur. J. Intern. Med.*, 21, 293, 2010.
8. Denus S. et al.: Statins and liver toxicity: a meta-analysis. *Pharmacotherapy*, 24, 584, 2004.
9. Girard M. et al.: Mianserin side-effects. *J Lancet*, 336, 1439, 1990.
10. Herbet M. et al.: Evaluation of selected biochemical parameters in the serum of rats pretreated with simvastatin, doxepin or their combination. *Ann. Umcs Sect. DDD*, 24, 107, 2011.
11. Herbet M. et al.: The influence of combined treatment of simvastatin and amitriptyline on some biochemical parameters in rat serum. *Ann. Umcs Sect. DDD*, 23, 121, 2010.
12. Herman R.J.: Drug interactions and the statins. *CMAJ*, 16, 1281, 1999.
13. Jacobson T.A.: Statin Safety: Lessons from New Drug Applications for Marketed Statins. *Am. J. Cardiol.*, 97, 44, 2006.
14. Karnik N.S., Maldonado J. R.: Antidepressant and statin interactions: a review and case report of simvastatin and nefazodone-induced rhabdomyolysis and transaminitis. *Psychosomatics*, 46, 565, 2005.
15. Kasiske B.L. et al.: An Assessment of Statin Safety by Nephrologists. *Am J Cardiol*, 97(8A): 82C, 2006.
16. Kassimatis T.I., Konstantinopoulos P.A.: The role of statins in chronic kidney disease (CKD): Friend or foe? *Pharmacol. Ther.*, 122, 312, 2009.
17. Musselman D.L. et al.: The relationship of depression to cardiovascular disease: epidemiology, biology and treatment. *Arch. Gen. Psychiatry*, 55, 580, 1998.
18. Paoletti R. et al.: Pharmacological interactions of statins. *Atherosclerosis*, 3, 35, 2002.
19. Rajewska J., Rajewski A.: Mianserin therapy of depressive patients with coexisting cardiovascular diseases. *Eur Neuropsychopharmacol*, Vol 6, Suppl 4, S4-87, 1996.
20. Roose S.P. et al.: Pharmacologic treatment of depression in patients with heart disease. *Psychosom Med.*, 67, 54, 2005.
21. Rudnik-Szałaj I.. et al.: Zastosowanie mianseryny w leczeniu depresji. *Psychiatria Polska*, 34, 71, 2000.
22. Rybakowski J.K. et al.: One-year course of the first vs multiple episodes of depression – Polish naturalistic study. *Eur. Psychiatry*, 19, 258, 2004.
23. Skrabal M.Z. et al.: Rhabdomyolysis associated with simvastatin-nefazodone therapy. *South Med. J.*, 96, 1034, 2003.
24. Smith C.C. et al.: Screening for Statin-Related Toxicity: The Yield of Transaminase and Creatine Kinase Measurements in a Primary Care Setting. *Arch. Intern. Med.*, 163, 688, 2003.
25. Talbert R.L.: Safety issues with statin therapy. *J Am Pharm Assoc*, 46, 479, 2006.
26. Tolman K.G.: The liver and lovastatin. *ACC Curr J Rev*, 89, 1374, 2002.
27. Tousoulis D. et al.: Statins in heart failure. Beyond the lipid lowering effect. *Int J Cardiol*, 115, 144, 2007.
28. Vikram K. et al.: Major Depression with Ischemic Heart Disease: Effects of paroxetine and nortriptyline on long-term heart rate variability measures. *Biol Psychiatry*, 52, 418, 2002.
29. Wakeling A.: Efficacy and side effects of mianserin, a tetracyclic antidepressant. *Postgrad. Med. J.*, 59, 229, 1983.
30. Wang C.Y. et al.: Pleiotropic effects of statin therapy: molecular mechanisms and clinical results. *Trends Mol. Med.*, 14, 37, 2008.
31. Wille S.M. et al.: Relevant issues in the monitoring and the toxicology of antidepressants. *Crit. Rev. Clin. Lab. Sc.i*, 45, 25, 2008.