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RESEARCH ARTICLE

Evaluation of analgesic activity of simvastatin and atorvastatin in Wistar rats: An experimental study

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ABSTRACT

Background: The statins are a group of hypolipidemic drugs that are commonly prescribed in cases of altered lipid profile mainly raised low-density lipoprotein levels. They stabilize atherosclerotic plaques and are useful in preventing coronary and cerebrovascular accidents. In addition to these effects, few studies have shown that statins such as atorvastatin and simvastatin have analgesic and anti-inflammatory activities. **Aims and Objectives:** This study has been undertaken to confirm the analgesic activity of these statins which might prove to be better-tolerated alternatives to the non-steroidal anti-inflammatory drugs which though are efficient in reducing pain but lead to a large number of adverse effects on the long term and injudicious use. **Materials and Methods:** Atorvastatin and simvastatin, in doses of 10 mg/kg each, were administered orally to two groups (n = 6) of rats (experimental groups) against a control group receiving normal saline (n = 6) and a standard group receiving aspirin (n = 6). The animals were then subjected to tail-flick test at 0, 30, 60, 90, and 120 min after drug administration, and the parameters were recorded. **Results:** Both the experimental groups receiving atorvastatin and simvastatin showed a significant increase in mean reaction time in the tail-flick test as compared to the control group receiving normal saline ($P < 0.05$). The increase in reaction time for the group receiving simvastatin was comparable with that of aspirin, a well-known analgesic. **Conclusion:** Both atorvastatin and simvastatin are found to have analgesic activities in Wistar rats, and the analgesic activity of simvastatin is comparable to that of aspirin.

KEY WORDS: Atorvastatin; Simvastatin; Analgesic Activity; Tail-Flick Test

INTRODUCTION

The statins are a well-known class of lipid-lowering agents that inhibit the enzyme 3-hydroxy-3-methylglutaryl coenzyme A reductase.[1,2] They are most effective in reducing low-density lipoprotein. Hence, they are widely used as hypolipidemic agents in treating dyslipidemia and preventing the occurrences of atherosclerosis and coronary heart diseases.[3,4] The statins also lower the oxidative stress and vascular inflammation with increasing the stability of atherosclerotic plaques.[1,2]

Analgesics such as non-steroidal anti-inflammatory drugs (NSAIDs) are the commonly prescribed medications, used to treat mild pain and body aches to severe pain like that of osteoarthritis. However, unfortunately, the NSAIDs are associated with a number of adverse effects,[1,5] resulting in increased gastritis causing peptic ulcerations, aggravated asthmatic attacks, altered liver enzymes, renal insufficiency, and many more. Hence, there has been a continuous search

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for a better alternative to NSAID, which will suppress the symptoms of pain as well as will be well tolerated in the body without showing much adverse effects.

Statins such as atorvastatin, simvastatin, and rosuvastatin, commonly used in treating hyperlipidemia, are well tolerated by our body. There are very few studies on the analgesic and anti-inflammatory property of statins.[6,7] The stains are found to act by decreasing the secretion of proinflammatory cytokines interleukin-6 (IL-6) and IL-8 from macrophages and inhibit the release of the chemokine CCL2/macrophage chemotactic protein-1 from these cells.[6,8] However, for prescribing statins as analgesics, it calls forth further experimental studies.

Hence, the present study had been designed for exploring the analgesic potential of atorvastatin and simvastatin in Wistar rats, which may widen the therapeutic horizon for the said agents.

Objectives

1. To evaluate the analgesic effect of atorvastatin and simvastatin.
2. To compare the analgesic activity of these drugs with aspirin.

MATERIALS AND METHODS

Ethical Consideration

The study was started after getting approval from the Institutional Animal Ethical Committee.

Animals Used

Healthy Wistar rats (150-250 g) of either sex, bred locally in the animal house of Jawaharlal Nehru Medical College, Sawangi (Meghe), were used for the study. They were housed under controlled condition of temperature 23 ± 2°C and 12 h light and dark cycles, respectively. They were maintained on normal diet and water *ad libitum*. Animals were grouped into four, each group comprising 6 animals (n = 24).

Rationale for the Use of Animals

Since these were the preliminary studies, the activity of above drugs had to be confirmed by animal experiments. As the rats were easy to handle, easily available, easy to subject them for testing, and their nutrition resembled that of human, so, they were preferred for the usage in this study.

Drugs used

The drugs atorvastatin and simvastatin manufactured by the company Lupin Ltd. and the drug aspirin manufactured by USV Ltd. were obtained from the local market.

Study design

The animals were allocated randomly into 4 groups, containing 6 animals in each group. All the drugs were administered orally in the following dosage.[7,9]

Group I: Received normal saline (NaCl) 0.5 ml – served as control
Group II: Received aspirin 300 mg/kg – served as standard
Group III:Received atorvastatin 10 mg/kg – served as experimental
Group IV: Received simvastatin 10 mg/kg – served as experimental

The animals were subjected to tail-flick test at different time intervals, i.e., at 0, 30, 60, 90, and 120 min after administration of the drugs, and the parameters were noted.

Tail Flick Analgesiometer Test

The tail-flick test is a test of the pain response in animals. Here, the rat was first put inside a restrainer, and its tail was placed on the radiant heat source, and sharp withdrawal of the tail was recorded as "reaction time." Cutoff time of 20 s was imposed so as to avoid any thermal injury while noting down the reaction time. We selected to do the D'Armour and Smith tail-flick test as this test unlike the hot-plate test can be repeated several times on the same animal (with the condition to respect a minimum resting time between each evaluations – around 5 min), before and after drug administration for instance. In all the groups, tail-flick test was performed at 0, 30, 60, 90, and 120 min after drug administration, and the reaction time at each time interval was calculated.

Statistical Analysis

SPSS software[10] was used for analyzing the data collected after the experiment, which was subjected to different appropriate statistical tests. $P < 0.05$ was considered to be statistically significant in this study.

RESULTS

In the present study, we have evaluated the analgesic activity of atorvastatin and simvastatin and compared its property with that of a standard NSAID, aspirin. Here, an increase in the mean reaction time in tail-flick test was considered indicative of analgesia.

The tail-flick tests were applied at 0, 30, 60, 90, and 120 min after administration of each drug in specified doses, and the mean reaction time (in seconds) in all the four groups of animals, which have received NaCl (Group I - control), aspirin (Group II - standard), atorvastatin (Group III - experimental group), and simvastatin (Group IV - experimental group), respectively, was noted as shown in Table 1.

Figure 1 showed the findings from the tail-flick test. It revealed increasing mean reaction time of each of the test Groups III and IV and the standard (II) as compared to the control Group I.

We used analysis of variance to analyze the difference in mean reaction time among all the four groups after the administration of the drugs and found that there exist significant differences between and within all the test groups at 30, 60, 90, and 120 min after the drug administration ($P < 0.01$) (Table 2).

Then we applied *post hoc* Tukey test among the different groups at different time intervals to do a pair-wise comparison, where, we found that there exists significant difference (Table 3) in the mean reaction time between the groups receiving atorvastatin and simvastatin, respectively, when compared with the group receiving NaCl ($P < 0.05$), confirming the analgesic property of both the statins.

The test drugs (atorvastatin and simvastatin) were now compared with the standard drug (aspirin) as shown in Table 4. Here, we found a significant difference ($P < 0.05$) among atorvastatin and aspirin at all the different time intervals. However, contrarily, we did not find any significant difference to occur between simvastatin and aspirin at 30 min ($P > 0.05$; CI: −0.05-1.06), 90 min ($P > 0.05$; CI: 0.56-2.60), and 120 min ($P > 0.05$; CI: 0.37-2.29). Hence, simvastatin had a better analgesic property than that

Table 1: Mean reaction time (in seconds) in tail-flick experiment after drug administration at different time intervals (mean±SD)

Group	0 min	30 min	60 min	90 min	120 min
NaCl (Group I)	5.5±0.5	5.9±0.6	6.1±0.6	6.1±0.7	5.9±0.8
Aspirin (Group II)	5.8±0.9	10.5±0.4	13.5±0.5	14.9±0.4	15.3±0.7
Atorvastatin (Group III)	5.4±0.5	7.5±0.5	09±0.6	10.6±0.7	11.6±0.5
Simvastatin (Group IV)	5.8±0.8	10.3±0.4	12.3±0.4	13.3±0.8	13.9±0.2

SD: Standard deviation

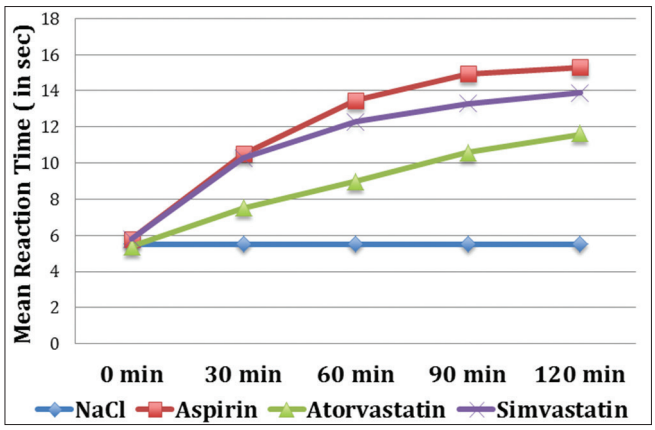

Figure 1: Findings from the tail-flick test

Table 2: ANOVA table showing differences in mean reaction time

Time interval after drug administration	Sum of squares	df	Mean square	F	Significant
0 min					
Between groups	0.5	03	0.2	0.4	>0.05
Within groups	9.4	20	0.4		
Total	9.9	23			
30 min					
Between groups	88.3	03	29.4	115.9	<0.01
Within groups	5.1	20	0.2		
Total	93.5	23			
60 min					
Between groups	214.5	3	71.5	241.7	<0.01
Within groups	5.9	20	0.2		
Total	220.4	23			
90 min					
Between groups	269.5	03	89.8	225.8	<0.01
Within groups	7.9	20	0.3		
Total	277.5	23			
120 min					
Between groups	305.8	03	101.9	291.3	<0.01
Within groups	7.0	20	0.3		
Total	312.8	23			

ANOVA: Analysis of variance

Table 3: Comparison of control (NaCl) with the statins (*post hoc* Tukey test)

Group	Comparison group	Mean difference	Standard error	*P* value	95% CI
I – NaCl (30 min)	III (atorvastatin)	−1.5	0.2	<0.01	−2.4 to−0.7
	IV (simvastatin)	−4.3	0.2	<0.01	−5.1 to−3.5
I – NaCl (60 min)	III (atorvastatin)	−2.9	0.3	<0.01	−3.8 to−2.0
	IV (simvastatin)	−6.1	0.3	<0.01	−7.0 to−5.7
I – NaCl (90 min)	III (atorvastatin)	−4.5	0.3	<0.01	−5.5 to –3.4
	IV (simvastatin)	−7.2	0.3	<0.01	−8.2 to –6.2
I – NaCl (120 min)	III (atorvastatin)	−5.6	0.3	<0.01	−6.6 to –4.7
	IV (simvastatin)	−8.0	0.3	<0.01	−8.9 to –7.0

CI: Confidence interval

Table 4: Comparison of standard (aspirin) with the statins (*post hoc* Tukey test)

Group	Comparison Group	Mean difference	Standard error	*P* value	95% CI
II – Aspirin (30 min)	III (atorvastatin)	3.0	0.2	<0.01	2.2 to 3.8
	IV (simvastatin)	0.2	0.2	>0.05	−0.5 to 1.1
II – Aspirin (60 min)	III (atorvastatin)	-4.8	0.3	<0.01	3.9 to 5.7
	IV (simvastatin)	-3.2	0.3	<0.01	−4.1 to−2.3
II – Aspirin (90 min)	III (atorvastatin)	4.3	0.3	<0.01	3.3 to 5.3
	IV (simvastatin)	1.5	0.3	>0.05	0.5 to 2.6
II – Aspirin (120 min)	III (atorvastatin)	3.6	0.3	<0.01	2.7 to 4.6
	IV (simvastatin)	1.3	0.3	>0.05	0.3 to 2.3

CI: Confidence interval

of atorvastatin and was found to be comparable with that of aspirin.

DISCUSSION

In this experimental study, we tried to explore the analgesic effect of the statins. We have chosen atorvastatin and simvastatin because they are the most widely prescribed statins with a wide safety margin among the different available statins. These drugs are prescribed in the prevention or management of atherosclerotic vascular events. These drugs are well tolerated by patients with minimal adverse effects as minimal as placebo with standard therapeutic doses.[11] These drugs can be safely used in the patients of elevated liver enzymes where NSAIDs are contraindicated. Adverse effects of statins are seen only at higher doses when they are prescribed with other drugs such as ketoconazole and itraconazole which are enzyme inhibitors causing increased levels of statins leading to adverse effects of statins; these adverse effects are also more common in the patients with genetic predisposition.[12]

Tail-flick test was effective in determining the efficacy and potency of centrally acting analgesics. This was very clear in our experiment, where we found a significant increase in the mean reaction time with gradual passage of time in both the test drugs. The effect was observed to be highest in the aspirin group. These results are in conjunction with the findings of other studies.[6,7,12]

Dwajani et al.[7] also found that the analgesic activity of both the statins starts quite early, which was in conjunction to our findings. Hence, they can be used in acute painful conditions.

In the current study, we found that though atorvastatin has significant analgesic property, but its analgesic property cannot be compared with that of Aspirin. On the other hand, simvastatin has significant analgesic property and its activity is comparable with the analgesic property of aspirin. Hence, simvastatin can be said to have a better analgesic property than atorvastatin.

In this study, reaction time was noted for four time intervals only, where the analgesic effect of atorvastatin and simvastatin

was found to be rising. Few more readings could have helped in knowing the peak analgesic activity of the statins, which was our limitation in the study.

CONCLUSION

From this study, we came to the conclusion that both atorvastatin and simvastatin has significant analgesic activity in the rats, and the analgesic activity of simvastatin is comparable to that of aspirin at 30, 90, and 120 min after administration, respectively, hence these statins may be a safe alternative to known NSAIDs for long-term treatment of chronic painful conditions such as osteoarthritis. They may be useful as analgesics in conditions in which NSAIDs are contraindicated, but further studies are required for confirmation.

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