Original Article

Evaluation of analgesic effect of Atorvastatin in rats

Bhete S B[1*], Pandit P R[2], Satpute Sachin[3], Vikas N Solunke[4]

[1,3]Assistant Professor, Department of Pharmacology, Topiwala National Medical College and BYL Nair Ch Hospital, Mumbai, Maharashtra, INDIA.
[2]Associate professor, Department of Pharmacology, HHSBT and cooper hospital, Mumbai, Maharashtra, INDIA.
[4]Assistant Professor, Department of Pediatrics, Government Medical College, Latur, Maharashtra, INDIA.
Email: drsandeepbbhete@gmail.com

Abstract

Aim: The aim of this study is to evaluate the analgesic activity of atorvastatin in tail clip model of rat. **Methods and Material:** Analgesic activity of atorvastatin 3mg/kg and 8mg/kg were assessed in in tail clip model of rat where they were compared with control and ibuprofen group. **Results**: In tail clip method of rats, Atorvastatin 8 mg/kg group showed significant analgesic activity as compared with control group on day 3 and 6. However, atorvastatin 3 mg/kg group did not show any analgesic effect. Analgesic activity of both group of atorvastatin showed improvement as the study progressed from day 3 to day 6. **Conclusion:** The result of this study if substantiated by further experimental and clinical research suggest that atorvastatin may play important role in treating painful condition like osteoarthritis and rheumatoid arthritis specially when there is coexisting hypercholesterolemia.

Key words: tail clip, analgesic.

[*]**Address for Correspondence:**
Dr. Bhete S. B., Assistant Professor, Department of Pharmacology, Topiwala National Medical College and BYL Nair Ch. hospital, Mumbai, Maharashtra, INDIA.
Email: drsandeepbbhete@gmail.com

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INTRODUCTION

Pain is a major symptom of inflammatory disease. Inflammation is said to be a complex protective reaction in the vascularized connective tissue due to variety of endogenous and exogenous stimuli causing cell injury in the body and is characterized by the reaction of blood vessels, leading to accumulation of fluids and leukocytes in the extravascular tissue. This complex phenomenon involves endogenous chemical mediators such as histamine, bradykinin, 5-hydroxytryptamine, various chemotactic factors, leukotrienes and prostaglandins (Kumar V *et al.*, 2004). Many NSAIDs like aspirin, phenylbutazone, indomethacin and corticosteroids are in clinical use to suppress pain and inflammation. But, all of these are not completely devoid of adverse effects. Hence the search for safer and better analgesic and anti-inflammatory agents other than NSAIDs continues. However, drugs which are not structurally related to NSAIDs like penicillamine, allopurinol have also been in clinical use to treat inflammatory and very painful conditions like rheumatoid arthritis, gout etc (Burke A. *et al.*, 2006). Some drugs unrelated to NSAIDs like HMG-CoA reductase inhibitors (statins) like atorvastatin, lovastatin and rosuvastatin (Schmidt GW, 2002; Tondon V *et al.*, 2005) have been reported to posses anti-inflammatory activity in experimental models though they are not routinely used in the treatment of inflammatory disorders. Moreover, clinical study on rheumatoid arthritis (McCarey DW *et al.*, 2004) indicates reduction in pain by inhibiting inflammation. Paradoxically, statins like lovastatin (Schmidt A *et al.*, 2002) and atorvastatin (Kiener PA *et al.*, 2001) have been reported to possess pro-inflammatory activity in *in-vitro* studies. Statins are the class of drugs most widely used for the prevention of primary and secondary coronary heart disease (Corsini A *et al.*, 1995). Highly selling and most commonly prescribed drug is atorvastatin (Youssef S *et al.*, 2002). In view of the controversial reports regarding analgesic activity of statins, the present study was planned to explore analgesic activity of atorvastatin in male *Wistar* rats using their clinical equivalent doses in tail clip model.

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MATERIALS AND METHODS

The animal experiments were carried out in accordance with the guidelines set by the "Committee for the Purpose of Control and Supervision on Experiments on Animals" (CPCSEA). The study was approved by the Institutional Animal Ethics Committee.

Animals

A total 30 male albino *Wistar* rats of age 6-8 weeks and weight 120-150 grams were used in rat model of tail clip method for evaluating analgesic activity. The animals were from the same stock and were acquired from Haffkine Biopharma Corporation Parel. Six rats were included per group. The rats were accommodated in polypropylene cages with grill on top. Food, water and bedding of clean paddy husk were provided. The rats were allowed one week period of acclimatization in animal laboratory at room temperature. Body weight of the rats was recorded on first day of initiation of study. Animals were fed on standard pellet diet. Water was provided in glass bottles with stainless steel sipper tubes. Food and water were given *ad libitum*.

Drugs

Atorvastatin powder (pure form) and ibuprofen powder (pure form) were obtained from Cipla pharmaceuticals. The suspension of atorvastatin and ibuprofen powders were made in distilled water by using 2% gum acacia.

Tail clip method

PROCEDURE

Rats (n=30) were used for Tail clip method described by Bianchi and Franceschini *et al.*, (1954). The animals were initially screened by applying the Bull dog clamp of appropriate size to the root of the tail approximately 1 cm from the body to induce the pain. The reaction time of the animal in the form of biting the clip or the tail near the location of the clip was recorded. On DAY 0, rat artery clip was applied to the base of tail for 30 seconds. The time required for each rat to respond was noted. Those rats which respond within 30 second were selected (n=24) and divided into four groups containing 6 rats each.

The rats received oral saline 2.5ml/kg(group 1), ibuprofen 108mg/kg(group 2), atorvastatin 3mg/kg and atorvastatin 8mg/kg(group 4) for 6 days daily On day 0, tail clip applied at 1hr, 2hr, and 4hr after administration of drugs and readings of reaction time were recorded.

On DAY 3, tail clip applied 2hr after drug administration and readings of reaction time were taken. Same procedure repeated on day 6.

Parameters analyzed for evaluation of analgesic activity were

1) Comparison of reaction time at various time intervals within the groups on day 0.
2) Comparison of reaction time at various time intervals between groups on day 0.
3) Comparison of reaction time in between groups at 2 hr on day 3 and 6.
4) Comparison of Reaction time at baseline, day 3 and day 6 within the groups.

Statistical Analysis

The difference of reaction time within the group was estimated using Repeated Measures ANOVA followed by Dunnett test and between different groups was estimated using One Way ANOVA followed by Tukey multiple comparison test. p value less than 0.05 was considered as significant.

RESULTS

Table 1: Comparison of reaction time at baseline, 1 hr, 2 hr and 4 hr within the group on day 0

Study groups	Reaction Time (mean ±SEM) in seconds			
	baseline	1 hr	2 hr	4 hr
Control	6.66 ±0.49	7 ± 0.37	7.16 ± 0.31	7.17± 0.47
Ibuprofen	6.83± 0.48	15 ± 0.58***	12 ± 0.68***	10 ± 0.52***
Atorvastatin 3mg/kg	6.16 ± 0.48	6.67 ± 0.56	6.67 ± 0.49	6.33 ± 0.6
Atorvastatin 8mg/kg	6.66 ± 0.49	7.5 ± 0.62	7.5 ± 0.43	7.5 ± 0.21

*** p<0.001

From table 1, it is seen that Atorvastatin 3 mg/kg and 8 mg/kg groups have not shown any significant difference in reaction time at any point of time interval from baseline. Only Ibuprofen group has shown significant difference from baseline at various time intervals. Results were analysed by using repeated measure ANOVA followed by Dunnett test.

Table 2: Comparison of Reaction time between groups at 1 hr, 2 hr and 4 hr on day 0

Time (hr)	Control	Ibuprofen	Atorvastatin 3mg/kg	Atorvastatin 8 mg/kg
1 hr	7 ± 0.37	15 ± 0.58	6.67 ± 0.56	7.5 ± 0.62
p value		control Vs Ibuprofen <0.001	Control Vs Atorvastatin 3mg >0.05 Ibuprofen Vs Atorvastatin 3 mg <0.001	control Vs Atorvastatin 8mg >0.05 Ibuprofen Vs Atorvastatin 8mg <0.001
2 hr	7.16± 0.31	12 ± 0.68	6.67 ± 0.49	7.5 ± 0.43
p value		control Vs Ibuprofen <0.001	control Vs Atorvastatin 3 mg >0.05 Ibuprofen Vs Atorvastatin 3 mg <0.001	control Vs Atorvastatin 8mg >0.05 Ibuprofen Vs Atorvastatin 8mg <0.001

4 hr	7.17± 0.47	10 ± 0.52	6.33 ± 0.6	7.5± 0.21
p value		control Vs Ibuprofen <0.01	control Vs Atorvastatin 3 mg >0.05 Ibuprofen Vs Atorvastatin 3 mg <0.01	control Vs Atorvastatin 8mg >0.05 Ibuprofen Vs Atorvastatin 8mg <0.01

Reaction time(mean± SEM) in seconds

From table 2, it is seen that Atorvastatin 3mg/kg and 8mg/kg groups have not shown any significant difference with control group at any point of time (p>0.05). Ibuprofen group has shown significant difference with other groups. The test applied here was One way ANOVA followed by Tukey multiple comparison test.

Table 3: Comparison of Reaction time between groups on day 3

	Control	Ibuprofen	Atorvastatin 3 mg/kg	Atorvastatin 8 mg/kg
Reaction time at 2 hr	6.66 ± 0.49	17.17± 0.54	8.33 ± 0.61	9 ± 0.45
p value		control Vs Ibuprofen <0.001	control Vs Atorvastatin 3 mg >0.05 Ibuprofen Vs Atorvastatin 3 mg <0.001	control Vs Atorvastatin 8 mg <0.05 Ibuprofen Vs Atorvastatin 8 mg <0.001

Values expressed as mean ± SEM (seconds)

From table 3, it is seen that Atorvastatin 8 mg/kg group has shown significant difference with control group. The test applied was one way ANOVA followed by Tukey multiple comparison test.

Table 4: Comparison of Reaction time between groups on day 6

	control	Ibuprofen	Atorvastatin 3 mg/kg	Atorvastatin 8 mg/kg
Reaction time at 2 hr	7.17 ± 0.31	20.33 ± 0.88	9.33 ± 0.61	11 ± 0.52
p value		control Vs Ibuprofen <0.001	control Vs Atorvastatin 3 mg >0.05 Ibuprofen Vs Atorvastatin 3 mg<0.001	control Vs Atorvastatin 8 mg <0.01 Ibuprofen Vs Atorvastatin 8 mg <0.001

Values expressed as mean ± SEM (seconds)

Atorvastatin 8 mg/kg group has shown significant difference with control group. Ibuprofen group showed significant difference with all other groups. The test applied was one way ANOVA followed by Tukey multiple comparison test.

Table 5: Comparison of Reaction time at baseline, day 3 and day 6 within the groups

Study groups	Reaction time (mean ± SEM) in seconds		
	baseline	day 3	day 6
Control	6.66 ± 0.49	6.66± 0.49	7.17 ± 0.31
Ibuprofen	6.83 0.48	17.17 ± 0.54**	20.33 ± 0.88**
Atorvastatin 3mg/kg	6.16 ± 0.48	8.33 ± 0.61**	9.33 ± 0.61**
Atorvastatin 8mg/kg	6.66 ± 0.49	9 ± 0.45**	11 ± 0.52**

** p < 0.01

Ibuprofen group showed significant difference in reaction time from baseline on day 3 and 6. Atorvastatin 3 mg/kg and 8 mg/kg groups also showed significant difference in reaction time from baseline on day 3 and 6. (table 5 and fig.1). Results were analysed by using repeated measure ANOVA followed by Dunnett test.

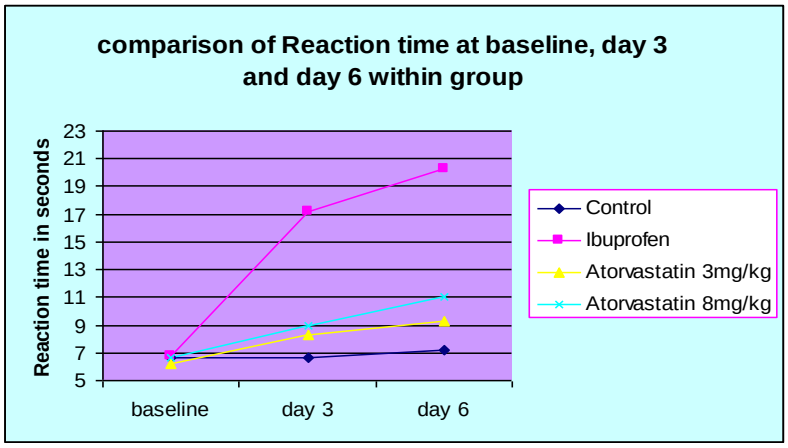

Figure 1: Graph showing Comparison of Reaction time at baseline, day 3 and day 6 within the groups

DISCUSSION

We investigated the analgesic effect of atorvastatin in rats by tail clip method. In the present study, on day 0, Atorvastatin 3 mg/kg and 8 mg/kg groups did not show any significant difference in reaction time with control group at all point of time intervals (table 2). But the reaction time of Atorvastatin 8 mg/kg group increased from 6.66 ± 0.49s at baseline to 9 ± 0.45s on day 3 and 11 ± 0.52s on day 6 (table 5). Thus Atorvastatin 8 mg/kg showed analgesic activity as compared with control group on day 3 and 6. Atorvastatin 3 mg/kg did not show analgesic activity as compared with control group. But as study progressed from day 0 to day 6, Atorvastatin 3mg/kg and 8 mg/kg groups showed increase in reaction time which is shown in fig.1.

Similar findings were reported by Santodomingo-Garzon T *et al.* (2006) who studied the analgesic effect of atorvastatin in mechanically induced inflammatory hypernociception in mouse paws. Treatment with atorvastatin for 3 days dose-dependently reduced hypernociception induced mechanically by lipopolysaccharide (LPS). Treatment for 1 or2 days did not show reduction in hypernociception.

These findings were similar to our finding, as high dose atorvastatin 8 mg/kg showed analgesic effect on day 3 and 6 as compared with control group.

Inflammatory hypernociception involves the release of several inflammatory mediators. Those hypernociceptive mediators considered to be directly acting (PGs and sympathetic amines) act on their specific metabotropic receptors present on the primary sensory neurons, triggering a cascade of intracellular events responsible for lowering the nociceptive threshold (Ferreira and Nakamura, 1979; Nakamura and Ferreira, 1987; Taiwo *et al.*, 1989; Khasar *et al.*, 1999). The release of these hypernociceptive mediators is generally preceded by the initiation of a cytokine cascade (Cunha *et al.*, 1991, 1992, 2005). In rats, the release of TNF-α is preceded by the generation of bradykinin (Ferreira *et al.*, 1993). Thus, bradykinin stimulates the release of TNF-α, which in turn stimulates two distinct hypernociceptive pathways. TNF-α stimulates IL-1β production and that induces the expression of COX-2, responsible for prostanoid biosynthesis. TNF-α also stimulates release of chemokines that induce the release of sympathomimetic amines (Ferreira *et al.*, 1988; Cunha *et al.*, 1991, 1992; Lorenzetti *et al.*, 2002). In mice, IL-1β is responsible for the release of prostanoids (Cunha *et al.*, 2005). Santodomingo-Garzon T *et al.*,(2006) had found that atorvastatin inhibited the mechanical hypernociception induced by bradykinin, TNF-α, IL-1β in mice. Furthermore, atorvastatin also inhibited the release of IL-1ß and PGE_2 in the mouse paw skin treated with lipopolysaccharide (LPS). Therefore, the antinociceptive effect of atorvastatin upon inflammatory hypernociception seems to be owing to the inhibition of the release of cytokines and PGs (Santodomingo-Garzon T *et al.*, 2006). The release of proinflammatory cytokines and also COX-2 induction are largely dependent on Nuclear Factor- kappa B (NF-κB) transcription pathway (Li and Verma, 2002; Ali and Mann, 2004; Wu, 2005). There is also evidence that statins diminish the activity of Nuclear Factor- kappa B (NF-κB) (Hilgendorff *et al.*, 2003; Lin *et al.*, 2005; Planavila *et al.*, 2005; Prasad *et al.*, 2005).

A peripheral site for the antinociceptive action of atorvastatin is more likely as this statin does not cross the blood–brain barrier (Sparks *et al.*, 2002). However, atorvastatin acting peripherally may also lead to a reduction of central sensitization as reduction of peripheral nociceptive input to the central nervous system could reduce central sensitization (Millan, 1999).

Some analgesic drugs that inhibit PG-induced hypernociception, such as peripherally acting opioids and dipyrone, act, at least in part, by stimulating the L-arginine/NO/cGMP pathway. Also, subcutaneous

injection of NO donors inhibited PGE_2-induced hypernociception (Duarte *et al.*, 1992). Statins induce upregulation of eNOS expression in vascular endothelial cells (Endres *et al.*, 1998; Amin-Hanjani *et al.*, 2001). Other studies have shown that statins could also upregulate the expression of inducible NOS through inhibition of geranylgeranyl pyrophosphate in vascular smooth muscle cells, airway epithelial cells, fibroblasts and cardiac myocytes (Chen *et al.*, 2000; Muniyappa *et al.*, 2000; Ikeda *et al.*, 2001). Atorvastatin is known to decrease expression of prostaglandin E2 receptors in human carotid atherosclerotic plaques and monocytic cells (Gomez-Hernandez *et al.*, 2006).

The increase of NO production by statins can be both dependent on and independent of cholesterol inhibition (Laufs, 2003). Inhibition of the enzymatic activity of HMG-CoA reductase depletes downstream isoprenoids such as geranylgeranyl pyrophosphate and farnesyl pyrophosphate. The synthesis of these compounds is dependent on mevalonate but sterol-independent (Hernandez-Perera *et al.*, 1998). These isoprenoids not only serve as intermediates for cholesterol biosynthesis, but modify proteins to facilitate their attachment to cell membranes (Amin-Hanjani *et al.*, 2001). Exogenous mevalonate reversed the antinociceptive effect of atorvastatin, suggesting that a product downstream of HMG-CoA reductase, but not cholesterol, involved in modulating the hypernociception (Santodomingo-Garzon T *et al*., 2006). Inhibition of isoprenoid production by statins has been shown to increase NOS expression and activity in culture, with consequent production of NO, which has anti-hypernociceptive activity (Laufs and Liao, 1998; Laufs, 2003).

It was interesting to note that analgesic activity of atorvastatin showed improvement as the study progressed from day 3 to day 6. This perhaps indicates that administration of atorvastatin for a prolonged period as is used for treating hypercholesterolemia may show more pronounced analgesic effect. As a corollary of the present observations, an atherosclerotic patient with inflammatory co-morbidities like rheumatoid arthritis and osteoarthritis may require reduced doses of NSAIDs to relieve the pain. However this speculation needs to be confirmed clinically.

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