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RESEARCH ARTICLE

Dose comparative evaluation of analgesic activity of simvastatin in wistar rats

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ABSTRACT

Background: Pain is defined as an unpleasant sensation and emotional experience associated with or without tissue damage. Analgesics are the drugs that relieve pain. Statins are mainly employed in the treatment of hyperlipidaemias. Simvastatin belongs to HMG-CoA reductase inhibitors, which is the rate limiting step in the cholesterol synthesis. Analgesic effect of Simvastatin is a pleotropic effect, but the exact mechanism is not known. During our literature search we came across limited number of studies that evaluated the analgesic activity of simvastatin at different doses; however, the results were controversial at lower doses. Hence this study was under taken to evaluate analgesic activity Simvastatin at different doses in Wistar rats and also to compare its analgesic activity with Tramadol. **Aims and Objectives:** (i) To evaluate analgesic activity Simvastatin at different doses in Wistar rats; (ii) To compare the analgesic activity of Simvastatin with Tramadol. **Materials and Methods:** Analgesic activity of simvastatin was evaluated wistar rats using Tail Flick Model and Eddy's Hot Plate Model. Normal saline with Polyethylene glycol (2 ml/kg), Tramadol (10 mg/kg), Simvastatin (5 mg/kg, 10 mg/kg and 30 mg/kg) dissolved in Polyethylene glycol, were given orally to the randomly divided 5 groups of 6 animals each. Maximum possible analgesia was calculated at 30, 60 and 90 min in both the models and compared between the 5 groups. Observations were analysed using ANOVA and *post hoc* Tukey's test. **Results:** Simvastatin at doses 5 mg/kg and 10 mg/kg body weight produced significant Maximal possible analgesia at 30 and 60 min in both the models (<0.001). Whereas dose of simvastatin i.e 30 mg/kg body weight produced significant Maximal possible analgesia at 30, 60 and 90 min in both models. (<0.001). These results were comparable to tramadol in both the models. **Conclusions:** Simvastatin showed analgesic activity in both Tail Flick model and Eddy's Hot Plate.

KEY WORDS: Analgesic Activity; Simvastatin; Tramadol; Tail Flick Model; Eddy's Hot Plate

INTRODUCTION

Pain is defined as an unpleasant sensation and emotional experience associated with or without tissue damage.[1] Pain can be categorised into various types like acute pain, chronic pain, nociceptive pain, neuropathic pain, cancer pain, etc.[2]

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Analgesics are the drugs that can relieve the sensation of pain. The word analgesic is derived from Greek *an-* ("without") and *algos* ("pain"). These drugs may act on the peripherally i.e at the site of the pain sensation and centrally i.e in the central nervous system where pain signals are processed. Analgesics are generally divided into 2 broad groups, the Opioid analgesics- those that act like morphine and the Non-Opiods/Nonsteroidal anti-inflammatory drugs – those that act peripherally inhibiting cyclo oxygenase. Long term use of currently available analgesics are associated with serious adverse effects.[3] Hence, the search for a new, safe analgesics drug is ongoing.

Statins, first introduced in 1980, are the most efficacious and well tolerated drugs in the treatment of hyperlipidaemia and

are commonly employed in prevention of cardiovascular diseases including coronary atherosclerosis. The Statins including Simvastatin are HMG-CoA reductase inhibitors, which block the rate limiting step in the cholesterol synthesis.[4] In addition they may have various pleotropic effects like anti-inflammatory, analgesic, immunomodulatory, etc.[5]

Patients of hyperlipidaemia are often overweight and more likely to suffer from osteoarthritis.[6] Long term treatment of the patients with analgesics provide only symptomatic relief and are associated with serious adverse effects. Considering various reports about anti-inflammatory and analgesic activity of statins, it is worthwhile to further evaluate these activities. Atorvastatin has also been evaluated for its anti-inflammatory and analgesic activities.[7]

During our literature search we came across limited number of studies that evaluated the analgesic activity of simvastatin at different doses; however, the results were controversial at lower doses. Hence this study was under taken to evaluate analgesic activity Simvastatin at different doses in Wistar rats and also to compare its analgesic activity with Tramadol.

Objectives

- To evaluate analgesic activity Simvastatin at different doses in Wistar rats.
- To compare the analgesic activity of Simvastatin with Tramadol.

MATERIALS AND METHODS

Selection of Animals

After obtaining permission from Institutional Animal Ethical Committee, Wistar rats were obtained from J J M Medical College, Animal house attached to Pharmacology Department. Total of 30 rats weighing 150–200 g of either sex were taken. Animals were fed standard pellet diet and water.

They were acclimatized for 7 days before commencement of study in standard laboratory condition 12 h day and night rhythm, maintained at 25 ± 30°C and 50–70% humidity.

Inclusion Criteria

- Healthy Wistar rats
- Weighing 150–200 g
- Previously unused rats for any other experiments.

Exclusion Criteria

- Pregnant and diseased animals.

Ethical Approval

Ethical committee permission was obtained from *IAEC* and the *Ref. no.: JJMMC/IAEC/13-2017.*

Duration of Study

Study was completed within 4 weeks.

Drugs and Chemicals

- Normal saline 2 ml/kg.
- Simvastatin (5 mg/kg, 10 mg/kg and 30 mg/kg).[8]
- Polyethylene glycol.
- Tramadol 10 mg/kg.

Instruments Required

1. Tail flick model.
2. Eddy's hot plate model.
3. Syringes.
4. Feeding needles.
5. Stopwatch.

Procedure

Screened animals were divided into 5 groups of 6 animals each.

Drugs were administered as shown below:

- Group I: Control (Normal saline 2 ml/kg with polyethylene glycol Orally).
- Group II: Standard (Tramadol 10 mg/kg Orally)
- Group III: Simvastatin (5 mg/kg orally dissolved in polyethylene glycol).
- Group IV: Simvastatin (10 mg/kg orally dissolved in polyethylene glycol).
- Group V: Simvastatin (30 mg/kg orally dissolved in polyethylene glycol).

Drugs were given orally with the help of gastric catheter sleeved to syringe.

Analgesic activity assessed by:

a) Tail Flick Method.
b) Eddy's hot plate Method.

Tail Flick Method

Analgesia was measured using modified method of D Amour and Smith called as tail flick method using an analgesiometer. Reaction time (latency time) in seconds was used as the unit for measurement of pain and an increase in reaction time was indicative of analgesia. "Reaction time" is noted as time between placing the tail of the rat on the radiant heat source and sharp withdrawal of the tail and was recorded. Cut off time of ten seconds was taken as maximum latency so as to rule out thermal

injury while noting down the reaction time. In all the groups, tail-flick test was performed prior to drug administration, and at 30, 60 and 90 min after drug administration and the reaction time at each time interval (test latency) was calculated.[9]

The maximum possible analgesia (MPA) was calculated as follows:

MPA=Reaction time for treatment − basal reaction time for × 100.[10]

Maximum latency – basal reaction time

Eddy's Hot Plate Method

The hot plate consists of an electrically heated surface which is either copper plate or a heated glass surface. The temperature was controlledat 55°C–56°C. The animals were placed on the hot plate. "Reaction time" was taken as the time until either licking or jumping occurs and was recorded by a stop-watch before and after 30, 60 and 90 min after drug administration.[9]

The MPA was calculated as follows:

MPA=Reaction time for treatment − basal reaction time for × 100.[10]

Maximum latency – basal reaction time

RESULTS

Reaction time for treatment and basal reaction time were noted. These values were expressed as mean ± standard error mean. Then the percentage of MPA was calculated. Intergroup difference was statistically determined by ANOVA followed by Tukey's *post-hoc* test analysis. Level of significance was taken as $P < 0.05$.

Tail Flick Model

Table 1 shows that, when compared to control group simvastatin at 5 mg/kg and 10 mg/kg body weight showed significant percentage of MPA after 30 and 60 min of drug administration($P < 0.001$), but not after 90 min of drug administration. Whereas simvastatin at dose 30 mg/kg body weight showed significant percentage of MPA after 30, 60 and 90 min of administration when compared to control ($P < 0.01$). These values were comparable with tramadol at 10 mg/kg body weight.

Eddy's Hot Plate

Table 2 and Graph 2 shows that, when compared to control group simvastatin at 5 mg/kg body weight showed significant percentage of MPA after 30 and 60 min of drug administration($P < 0.001$), but not after 90 min of drug administration. Whereas simvastatin at doses 10 mg/kg and 30 mg/kg body weight showed significant percentage of MPA after 30, 60 and 90 min of administration when compared to control ($P < 0.01$). These values were comparable with tramadol at 10 mg/kg body weight.

DISCUSSION

In this study analgesic activity of Simvastatin at different doses was evaluated using Tail Flick Model and Eddy's hot plate in Wistar rats. Here combination of Normal saline and polyethylene glycol was used as control and Tramadol as standard. Increase in MPA was considered as parameter to evaluated analgesic activity of Simvastatin.

Simvastatin showed dose dependent analgesic activity in both models. Simvastatin at 30 mg/kg body weight showed better analgesic activity at 30 min, 60 min and 90 min when compared control and was similar to analgesic activity of Tramadol. Analgesic activity of Simvastatin at 5 mg/kg and 10 mg/kg body weight were better at 30 min and 60 min in both models. These responses were not inferior to standard drug Tramadol.

Table 1: Percentage of MPA (Mean±SD) in tail flick model

Groups	Group 1	Group 2	Group 3	Group 4	Group 5
30 min	-	51.89±14.85	53.78±12.38	52.57±8.76	49.76±6.77
60 min	-	43.26±7.98	43.42±16.62	38.6±4.84	52.54±4.16
90 min	-	42.3±7.5	6.3±7.94	10.89±6.79	38.65±21.32

SD: Standard deviation, MPA: Maximum possible analgesia

Table 2: Percentage of MPA (Mean±SD) in eddy' hot plate

Groups	Group 1	Group 2	Group 3	Group 4	Group 5
30 min	-	29.51±9.55	20.08±7.02	37.35±14.58	34.07±9.36
60 min	-	30.63±5.72	25.89±4.82	39.24±11.88	35.02±8.48
90 min	-	36.16±5.92	14.79±11.66	25.98±13.30	35.65±14.10

MPA: Maximum possible analgesia, SD: Standard deviation

These results correlates with study done by Dr Dwajani *et al*.,[1] where analgesic activity of Simvastatin and Atorvastatin were evaluated in Tail clip model, Eddy's Hot plate and Hot water tail immersion test. In all the three models the analgesic activity of Simvastatin and Atorvastatin were comparable with Tramadol.[1]

A similar study done by Jaiswal and Sontakke showed analgesic activity of simvastatin in Tail Flick Model and Acetic acid induced writhing model. In that study the analgesic activity of both Simvastatin and Atorvastatin were evaluated and simvastatin showed activity comparable with aspirin in both the models of analgesic activity.[2]

Statin group of drugs, among the most widely prescribed drugs for hyperlipidemia and coronary atherosclerosis, belongs to HMG-CoA reductase inhibitors, which is the rate limiting step in the cholesterol synthesis.[4] These drugs prevent formation of atherosclerptic plaques there by reducing the morbidity and mortality of cardiovascular events.[11] The statins have also been ascribed other effects like anti-inflammatory, analgesic, immunomodulatory, etc.[5]

Our study shows that Simvastain has analgesic activity. The exact mechanisms of the anti-inflammatory and analgesic activity of Statins are still not clearly defined. However the mechanisms proposed are related to opiodergeic type activity and to a decrease in the secretion of pro-inflammatory cytokines interleukin (IL)-6 and IL-8 from the macrophages. [4,13,14]

Since proposed analgesic mechanism of simvastatin is through opioid mediated, both screening models used are the standard models to evaluate the centrally acting analgesic activity of the drugs. One limitation of our study is that the mechanism involved in analgesic activity couldn't be evaluated. Further we have tested the activity only in the acute models of pain.

CONCLUSIONS

To conclude it is clear from this and previous studies that simvastatin has analgesic activity, but further studies are required to evaluate the action in different models and to understand the exact mechanism of action. Since the drug is already approved for use in humans with hyperlipidemia it may tested for analgesic activity in humans as well. Positive results in human trials may make it to be a suitable option in overweight patients with hyperlipidaemia and osteoarthritis.

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