



Effect of Azithromycin and Rosuvastatin on animal models for skeletal muscle relaxant activity in Swiss albino mice

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ABSTRACT

The objective of the study was to evaluate the effect of Azithromycin and Rosuvastatin on animal models for skeletal muscle relaxant activity in Swiss Albino Mice by using Rotarod and actophotometer. Statins affect skeletal muscle contraction and it is metabolized by CYP3A4. Macrolide antibiotics inhibit CYP3A4 and it can be co-administered along with statins. For this study 30 healthy albino mice were randomly selected and divided into 5 equal groups. Rota rod test and Locomotor activity by Actophotometer was observed for 5mins before and after intragastric administration of distilled water 0.5ml, Diazepam (4 mg/kg), Azithromycin 100mg/kg, Rosuvastatin 2mg/kg and combination of Azithromycin (100mg/kg) + Rosuvastatin (2mg/kg) to mice of group 1 to 5 respectively. The results were analyzed statistically. Rosuvastatin and Azithromycin produced no significant effect on motor coordination and locomotor activity in albino mice.

Key Words: Statins, Macrolides, Rota rod, Actophotometer.

INTRODUCTION

Statins are the most efficacious and the best tolerated hypolipidaemic agent, [1] but which are more frequently associated with mild muscle complaints, including myalgia, cramps, and weakness, which may compromise medication compliance and quality of life. The reported incidence of myalgia during statin therapy ranges from 1% in controlled studies [2] to 25% in clinical reports [3]. Muscle weakness has also been reported with statin therapy [4]. Inhibition or induction of CYP3A4 by a variety of pharmacologic agents provides rationales for drug-drug interactions involving statins [1]. Macrolide antibiotics are one of the commonly used agents in various clinical conditions. Macrolide antibiotics like Erythromycin and clarithromycin inhibit CYP3A4 and are associated with clinically significant drug interactions. Caution is advised, nevertheless, when using azithromycin in conjunction with drugs known to interact with erythromycin [5]. Drugs which affect skeletal muscle contraction are therapeutically important. In many situations co-administration of Azithromycin and Rosuvastatin are unavoidable. Nevertheless, the combined effect of these drugs on muscle

performance and exercise performance have not been carefully studied. Hence this study was designed to evaluate the effect of Azithromycin and Rosuvastatin on animal models for skeletal muscle relaxant activity in Swiss Albino Mice.

METHODOLOGY

For this study 30 healthy Wister albino mice weighing 20 to 30 gm., were procured from the Central animal house of Sri Muthukumaran Medical College & RI, Chennai, and were kept in the Pharmacology experimental laboratory for about 10 days. They were maintained at room temperature (25±2°C) under standard 12:12 hr. Light Dark cycle, fed on germinating grams, rodent diet and water ad libitum. All the drugs were administered via intragastric route. Rota rod test and locomotor activity by Actophotometer was conducted to mice of group 1 to 5 after intragastric administration of Standard and test drugs. The study protocol was approved by the Institutional animal ethics committee. (Table 1)

Rota rod test: The loss of muscle-grip is an indication of muscle relaxation and this effect can be easily studied by Rota-rod. Animals remain on Rota-Rod (25 rpm) for 5 min or more after low

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successive trials were included in the study. After the administration of control, standard and test drugs the fall off time from the rotating rod were noted after 2 hrs. The difference in the fall off time from the rotating rod between the control and the treated mice were taken as an index of muscle relaxation [6].

Locomotor activity by Actophotometer: To assess the locomotor activity, the mice were placed individually in the activity cage for 5 minutes. When the beam of light falling on the photocell is cut off by the animal, a count is recorded. The basal activity score for all the animals were noted for 5 minutes. The locomotor activity score for each animal was observed again 30 mins after administration of standard, test and control drugs [7].

Statistical Analysis: The results were analyzed statistically by One-way ANOVA followed by Dunnet's multiple comparison tests using SPSS 16.0 software. The data were expressed as mean \pm standard deviation (SD) and $P < 0.05$ was considered significant.

RESULTS

Rota rod test: In this test, Diazepam (4 mg/kg) showed highly significant reduction in the time spent by the animals on revolving rod when compared to control ($P < 0.05$). The test drugs, namely Azithromycin 100mg/kg, Rosuvastatin 2mg/kg and combination of Azithromycin (100mg/kg) + Rosuvastatin (2mg/kg) did not produce significant effect on rota rod test when compared to control. (Table 2)

Locomotor activity by Actophotometer: The percentage of reduction in locomotor activity with Diazepam (4 mg/kg) after 30 mins is 57.33 i.e. there is significant ($P < 0.05$) decrease in locomotor activity compare to control, whereas Azithromycin 100mg/kg, Rosuvastatin 2mg/kg and combination of Azithromycin (100mg/kg) + Rosuvastatin(2mg/kg) did not show significant decrease in locomotor activity when compared to control. (Table 2)

DISCUSSION

Statins (Hydroxy-methyl-glutaryl CoA reductase inhibitors) are the most effective medications for reducing elevated concentrations of low-density lipoprotein (LDL) cholesterol and produce

remarkable reductions in cardiovascular events [8]. Statins can produce life-threatening rhabdomyolysis, but this is rare. Statins are more frequently associated with mild muscle complaints, including myalgia, cramps, and weakness, which may compromise medication compliance and quality of life [9]. Macrolide antibiotics namely, Erythromycin and clarithromycin inhibit CYP3A4 and are associated with clinically significant drug interactions. Caution is advised, nevertheless, when using azithromycin in conjunction with drugs known to interact with erythromycin [5]. In many situations co-administration of Azithromycin and Rosuvastatin are unavoidable and its effect on muscle performance have not been carefully studied. Hence this study was designed to assess the effect of Azithromycin and Rosuvastatin on animal models for skeletal muscle relaxant activity in albino mice. In our study, we have found that diazepam (standard drug) 4mg/kg, significantly ($P < 0.05$) affect motor coordination in rotating rod at a speed of 25rpm. Whereas Azithromycin 100mg/kg alone, Rosuvastatin 2mg/kg alone and combination of Azithromycin (100mg/kg) plus Rosuvastatin (2mg/kg) treated mice produced no significant effect on motor coordination in albino mice. Its suggesting that azithromycin alone or coadministration of azithromycin and rosuvastatin did not significantly affect skeletal muscle contraction and this combination is found to be safe. In actophotometer test, only Diazepam 4mg/kg produced significant effect on locomotor activity compared to Azithromycin 100mg/kg alone, Rosuvastatin 2mg/kg alone and combination of Azithromycin (100mg/kg) plus Rosuvastatin(2mg/kg) treated mice (Table.2). The percentage of reduction in locomotor activity with diazepam (4 mg/kg) 57.33. So, Azithromycin can be prescribed along with Rosuvastatin when it is needed.

CONCLUSION

To conclude, Azithromycin, Rosuvastatin and combination of Azithromycin plus Rosuvastatin treated mice did not produce significant effect on locomotor activity and muscle coordination. Hence, co-administration of Azithromycin and Rosuvastatin found to be safe.

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Table 1: Plan of study

| Groups | Drug | Dose |
|--------|-----------------------------|-------------------|
| 1 | Distilled water | 0.5ml |
| 2 | Diazepam | 4mg/kg |
| 3 | Azithromycin | 100mg/kg |
| 4 | Rosuvastatin | 2mg/kg |
| 5 | Azithromycin + Rosuvastatin | 100mg/kg + 2mg/kg |

Table 2: Effect of drugs on locomotor activity in Actophotometer and muscle coordination in rota rod apparatus in Albino Mice

| Groups n=6 | Locomotor Activity Score | | | Time spent on rota rod (sec) |
|------------------------------------------------------------------|--------------------------|-------------------|-------------------|---------------------------------|
| | Before treatment | After treatment | % of reduction | |
| Group 1 (Control) Distilled water 0.5ml | 453.00 ± 76.67 | 321.67 ± 92.86 | 28.99 | 285.50 ± 16.61 |
| Group 2 (Standard) Diazepam 4mg/kg | 403.50 ± 52.23 | 172.17 ± 124.92 * | 57.33 | 32.17 ± 13.99 * |
| Group 3 Azithromycin 100mg/kg | 421.33 ± 49.66 | 359.33 ± 36.40 | 14.71 | 290.17 ± 11.72 |
| Group 4 Rosuvastatin 2mg/kg | 396.50 ± 80.73 | 313.00 ± 55.44 | 21.06 | 276.83 ± 20.94 |
| Group 5 Azithromycin 100mg/kg + Rosuvastatin 2mg/kg | 465.33 ± 79.54 | 427.33 ± 51.54 | 08.17 | 287.40 ± 6.66 |

*One-way ANOVA followed by Dunnet's multiple comparison tests*compared to control P<0.05*

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