

COMPARATIVE STUDY OF CENTRALLY ACTING SKELETAL MUSCLE RELAXANTS 'DIAZEPAM' AND 'TIZANIDINE'

*Karedla Srinivasu
*Dr. R. Ashalatha
*Dr. D. Aruna Kumari
*Dr. K. Santha bai

Abstract

Objective

This study was carried out to investigate and compare skeletal muscle relaxant effect (muscle grip strength) of Diazepam and Tizanidine in experimental animal models.

Methods:

The experimental model is rotarod test in albino mice. Nine groups of albino mice (n=8) were used Tizanidine. Group I received with 0.2ml of normal saline, Group II,III,IV received with Standard (S_1 , S_2 , S_3) 3mg/kg, 4mg/kg, 5mg/kg diazepam respectively, Group V,VI,VII received with Test (T_1 , T_2 , T_3) 3 /kg, 4mg/kg, 5mg/kg Tizanidine respectively. Then animals were placed on the rotating rod and inter drug comparisons were carried out based on the muscle grip strength.

Results: It was found that both diazepam and Tizanidine produced central muscle relaxant effect when assessed by rotarod. On inter drug comparison of diazepam and Tizanidine. It was found that by increasing concentration of drug, increased the muscle relaxant property, when assessed by rotarod.

Conclusion: Thus it was found that both diazepam and Tizanidine demonstrated muscle relaxant property but with increased doses of Tizanidine produced more muscle relaxant property than increase in doses of diazepam.

Keywords: Diazepam, Tizanidine, muscle grip, muscle relaxant property, Rotarod.

Introduction

A muscle relaxant is a drug which effects skeletal muscle function and reduces the muscle tone. It may be used to alleviate symptoms such as muscle spasm, pain and hyperreflexia. The term muscle relaxant is used to refer two major therapeutic groups, neuromuscular blockers and spasmolytics. Neuromuscular blockers act by interfering with transmission at the neuromuscular end plate and have no CNS activity. They are often used during surgical procedures and in intensive care and emergency medicine to cause paralysis. Spasmolytics, also known as "centrally acting muscle relaxants" are used to alleviate musculoskeletal pain and spasm and to reduce spasticity in a variety of neurological conditions. While both neuromuscular blockers and spasmolytics are often grouped together as muscle relaxants, the term is commonly used to refer spasmolytics only. Skeletal muscle relaxants are a heterogeneous group of medications. As a class, they are structurally and pharmacologically diverse. Increased muscle tone is a common feature of anxiety states in humans and may contribute to the aches and pains including head ache that often trouble anxious patients. The relaxant effect of benzodiazepines may therefore be clinically useful. A reduction of muscle tone appears to be possible without appreciable loss of coordination. Benzodiazepines reduce muscle tone by a central action that is independent of their sedative effect. Cats are particularly sensitive to this action and some benzodiazepines (eg: Diazepam, Lorazepam, Oxazepam) reduce decerebrate rigidity in doses that are much smaller than those needed to produce behavioural effects. In other species the difference is less clear, coordination can be tested by measuring the length of time for which mice can stay on a slowly rotating horizontal plastic rod.

Methodology

Experimental Animals

Albino mice (56) of either sex weighing 30 g used in the study (7 groups; n = 8) were obtained from the Central Animal House, ASRAM, ELURU, W.G. Dt, AP. The experimental protocol was

*Tutor, Department of Pharmacology, Government Medical College, Anantapur, Andhra Pradesh, India.

*Associate Professor, Department of Pharmacology, SVMC, Tirupathi, A.P., India.

*Assistant Professor, Department of Pharmacology, Govt. Medical College, Anantapur, A.P, India.

*Associate Professor, Department of Pharmacology, Govt. Medical College, Anantapur, A.P, India.

approved by the Institutional Animal Ethical Committee. The animals were maintained under standard husbandry conditions: temperature 22±2°C, humidity 45-55%, light: dark cycle (12:12h) for an acclimatization period of 15 days before performing the experiments.

Ethics

The experiments complied with the guidelines for animal experimentation of our laboratory and was approved by the Institutional Animal Ethical Committee (IAEC), ASRAM, ELURU, W. G. Dt, AP.

Drugs used: Diazepam (5mg), Tizanidine (2mg) .

Experimental Design:

Rota rod model:

The apparatus used for screening and comparison of muscle relaxant property of different centrally acting muscle relaxants. The rota rod assembly is immensely useful for screening drugs effecting motor coordination. It consists of four experimental compartments with a rotating rod of about 25 mm diameter and having speeds of approximately 5,10,15,20,25 revolutions/min. Time intervals are provided in each compartment. 56 mice were randomly divided into seven groups, each group consists 8 animals

Group 1 (Control): Animals were treated with normal saline and placed on rotating rod with a speed of 18 rpm (ideal speed).

Group 2 (Standard-S₁): Animals were treated with Diazepam at the dose of 3mg/kg body weight and placed on rotating rod.

Group 3 (Standard-S₂): Animals were treated with Diazepam at the dose of 4mg/kg body weight and placed on rotating rod

Group 4 (Standard-S₃): Animals were treated with Diazepam at the dose of 5mg/kg body weight and placed on rotating rod

Group 5 (Test-T₁): Animals were treated with Tizanidine at the dose of 3mg/kg body weight and placed on rotating rod.

Group 6 (Test-T₂): Animals were treated with Tizanidine at the dose of 4mg/kg body weight and placed on rotating rod.

Group 7 (Test-T₃): Animals were treated with Tizanidine at the dose of 5mg/kg body weight and placed on rotating rod.

Statistical analysis:

The results were expressed as mean ±SEM. Statistical analysis was performed by using unpaired student t-test. P<0.05 was considered statistically significant.

Result and discussion:

Previous studies suggested that the CNS depression and the non specific muscle relaxation effect can

reduce the response of motor coordination. Increased muscle tone is a common feature of anxiety states in humans and may contribute to the aches and pains including head ache that often trouble anxious patients. The relaxant effect of benzodiazepines may therefore be clinically useful. A reduction of muscle tone appears to be possible without appreciable loss of coordination. Skeletal muscle relaxants are used to treat two different types of conditions. 1) spasticity from upper motor neuron syndromes 2) muscular pains or spasms from peripheral musculoskeletal conditions. In this study centrally acting skeletal muscle relaxants diazepam and Tizanidine were used and muscle relaxant activity of Tizanidine is compared with Diazepam. The study was carried out in albino mice weighing 30 gms. Eight mice were included in each group to evaluate the muscle relaxant property in different concentrations such as 3, 4 and 5 mg/kg of both diazepam and Tizanidine. For initial screening of a drug mouse is one of the best animal as it is easy to handle can be used repeatedly since the animal is not sacrificed by rota rod method. Second choice of animal is rat. In the present study it was found that the percentage of muscle relaxant effect of diazepam is 36.32% with 3mg/kg, 75.85% with 4mg/kg and 90.61% with 5mg/kg when rota rod method was used. where as it is 81.20% with 3mg/kg, 86.15% with 4mg/kg and 92.41% with 5mg/kg of Tizanidine when assessed by rota rod method. At 3mg/kg dose the percentage of fall of free ride time for diazepam is 36.32, whereas for tizanidine, it is 75.85 the difference is very high for these two drugs at this concentration. The unpaired student t test result came for these drugs at this case is very highly significant. This study shows at this concentration Tizanidine is more potent than diazepam and it reduces the muscle strength property is more than the diazepam. At 4mg/kg dose the percentage of fall of free ride time for diazepam is 75.85, where as for tizanidine, it is 90.61 the difference is high for these two drugs at this concentration. The unpaired student t test result came for this highly significant. This study shows at this concentration tizanidine is more potent than diazepam and it reduces the muscle strength property is more than the diazepam. At 5mg/kg dose the percentage of fall of free ride time for diazepam is 90.61, where as for Tizanidine, it is 92.41. the difference is little high for these two drugs at this concentration. The unpaired student t test result came for this significant.

So this study shows at this concentration Tizanidine is more potent than diazepam and it reduces the muscle strength property is more than the diazepam. This study shows at all the concentrations Tizanidine reduces muscle grip

property is more than diazepam .So it is very potent than diazepam to muscle relaxant property.

Conclusion

The present study was carried out to compare the central muscle relaxant property of diazepam and Tizanidine given in different concentrations in experimental model.the experimental model is rota rod test in albino mice. Both diazepam and Tizanidine were given in concentrations of 3mg/kg, 4mg/kg and 5mg/kg body weight in rota rod method for each mice in each group respectively. It was found that both diazepam and tizanidine produced central muscle relaxant effect when

assessed by rota rod test .On inter drug comparison of diazepam and tizanidine it was found that by increasing concentration of drug, increased the muscle relaxant property, when assessed by rotarod. Thus it was found that both diazepam and tizanidine demonstrated muscle relaxant property but with increased doses of tizanidine produced more muscle relaxant property than increase in doses of diazepam.

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Rota Rod Method

Treatment with Diazepam at the dose of 3,4,5 mg/kg body weight

Experiment - 1

Sl. No.	Body Wt (mice)	Treatment	Fall of time						% of decrease in time		
			Before drug (sec)			After drug (sec)			3 mg	4mg	5mg
			3mg	4mg	5mg	3mg	4mg	5mg			
1	40 gms	Diazepam	42	40	112	28	9	12	33.33	79.50	89.28
2.	40 gms	Diazepam	56	36	126	32	8	11	42.85	77.78	91.26
3.	40 gms	Diazepam	78	32	96	42	6	9	46.15	81.28	90.62
4.	40 gms	Diazepam	92	44	190	60	12	10	34.78	72.73	94.73
5.	40 gms	Diazepam	102	76	82	65	25	8	36.27	80.26	90.24
6.	40 gms	Diazepam	124	90	62	75	12	6	39.51	86.67	90.32
7.	40 gms	Diazepam	80	42	108	60	15	10	25	64.29	90.74
8.	40 gms	Diazepam	110	56	98	74	20	12	32.72	64.29	87.75

Treatment with Tizanidine at the dose of 3,4,5 mg/kg body weight

Sl. No.	Body Wt (mice)	Treatment	Fall of time						% of decrease in time		
			Before drug (sec)			After drug (sec)			3 mg	4mg	5mg
			3mg	4mg	5mg	3mg	4mg	5mg			
1.	40 gms	Tizanidine	82	62	110	15	14	10	81.70	77.42	90.90
2.	40 gms	Tizanidine	76	70	115	14	12	9	81.57	82.86	92.17
3.	40 gms	Tizanidine	94	135	92	15	15	8	84.04	88.89	91.30
4.	40 gms	Tizanidine	54	140	132	10	17	8	81.48	87.86	93.93
5.	40 gms	Tizanidine	65	120	80	16	13	6	75.38	89.17	92.50
6.	40 gms	Tizanidine	106	42	62	20	6	4	81.13	85.71	93.54
7.	40 gms	Tizanidine	48	55	105	9	8	8	81.25	85.45	92.38
8.	40 gms	Tizanidine	124	136	95	21	11	7	83.06	91.91	92.63

Comparison of Mean Responses at the dose of 3 mg/kg with the Diazepam and Tizanidine for Rota rod Method.

I	Name of the Drug	Dose	Mean (Sec)	Std.Dev	Std. Error
		Diazepam	3 mg/kg	36.326	1.015

Tizanidine	3 mg/kg	81.201	2.560	+ 0.905
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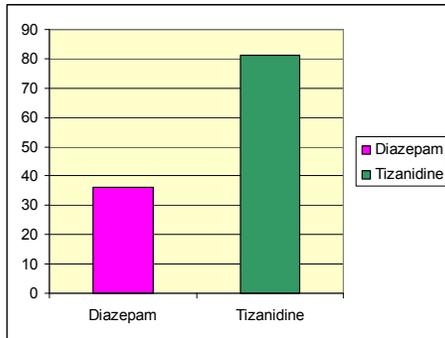
t-Value = 18.007
 $p < 4.4346 \times 10^{-4}$
or
 $p < 0.0001$ (Highly significant)

Above graph shows:

- Diazepam have 36.32 % muscle relaxant effect.

- Tizanidine have 81.20 % muscle relaxant effect.

Percentage of muscle relaxant effect at the dose of 3 mg/kg body weight in mice



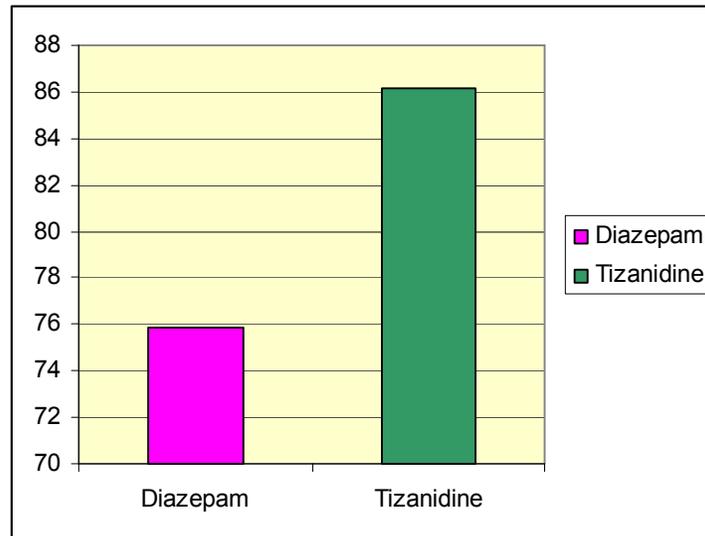
Comparison of Mean Responses at the dose of 4 mg/kg with the Diazepam and Tizanidine in mice with Rota rod Method.

II

Name of the Drug	Conc	Mean (Sec)	Std.Dev	Std. Error
Diazepam	4 mg/kg	75.850	8.107	+ 2.866
Tizanidine	4 mg/kg	86.159	4.479	+ 1.584

t – value = 3.14815
 $p < 0.0071$ (High Significant)

Percentage of muscle relaxant effect at the dose of 4 mg/kg body weight in mice



Above graph shows:

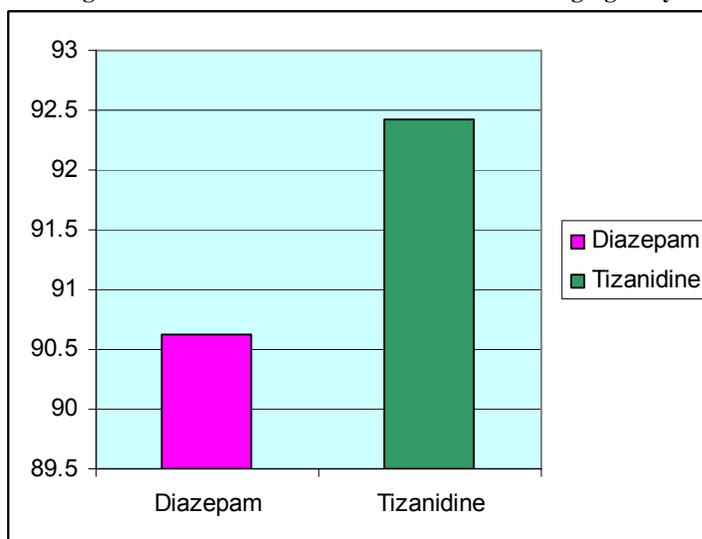
- Diazepam have 75.85 % muscle relaxant effect.
- Tizanidine have 86.15 % muscle relaxant effect.

Comparison of Mean Responses at the dose of 5 mg/kg with the Diazepam and Tizanidine in mice with Rota rod Method.

Name of the Drug	Conc	Mean (Sec)	Std.Dev	Std. Error
Diazepam	5 mg/kg	90.618	1.985	+ 0.702
Tizanidine	5 mg/kg	92.419	1.015	+ 0.359

III t – value = 2.28486
 p < 0.0384
 or
 p < 0.05 (Significant)

Percentage of muscle relaxant effect at the dose of 5mg/kg body weight in mice



Above graph shows:

- Diazepam have 90.61 % muscle relaxant effect.
- Tizanidine have 92.41 % muscle relaxant effect.

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