A perspective on the Pharmacology of Skeletal muscle relaxants.

[a]Nimmy Chacko, [b]Prerana Shetty, [c]Ashwini Prabhu, [a]Sharanya M

[a]Department of Pharmacology, [b]Department of Pharmaceutical Chemistry, Nitte Gulabi Shetty Memorial Institute of Pharmaceutical Sciences (NITTE Deemed to be University), Paneer, Deralakatte, Mangalore, 575 018, Karnataka.

[c] Assistant Professor, Yenopoya Research Centre, Yenopoya (Deemed to be University), Deralakatte, Mangalore – 575018, Karnataka.

Corresponding Author:

1. Dr. Nimmy Chacko,

Assistant Professor, Department of Pharmacology, NGSMIPS, Paneer, Deralakatte, Mangalore, 575 018, Karnataka. Mobile no. 09844287377

2. Dr. Prerana Shetty

Associate Professor, Department of Pharmaceutical Chemistry, NGSMIPS, Paneer, Deralakatte, Mangalore, 575 018, Karnataka. Phone- 08884306524

ABSTRACT

The word "Muscle relaxant" is used to refer to the two main categories of drugs comprising of neuromuscular blockers and spasmolytics. Skeletal muscle relaxants are used to treat spasticity of upper motor neuron syndromes and muscle pain or spasms in peripheral musculoskeletal disorders. There are different models through which skeletal muscle relaxant activity can be monitored, such as rota rod, inclined screen test, climbing test, chimney test, actophotometer and grip strength meter. The selection of skeletal muscle relaxant should therefore be based on individual medication and patient characteristics. An analysis summarizes the clinical conditions and screening methods associated with various spasticity and musculoskeletal

disorders and lists medicinal plants containing active phytochemicals that possess skeletal muscle relaxant activity.

Key words: Skeletal muscle relaxant, Spasmolytic, Neuromuscular blockers, Screening, Medicinal plants

INTRODUCTION:

Skeletal muscle relaxants are a heterogeneous group of structurally linked drugs with variable pharmacological and safety profiles. Skeletal muscle relaxants are agents that reduce muscle tone by acting peripherally on the neuromuscular junction or centrally on the brain spinal axis. Neuromuscular blocking agents increase the efficiency of general anesthesia for muscle relaxation required for surgery, while centrally acting agents are primarily used for pain of full muscle spasms and certain spastic neurological conditions [1].

The term muscle relaxant is used to refer to two main clinical groups, namely: neuromuscular blockers and spasmolytics. Neuromuscular blockers primarily interfere with the propagation of the neuromuscular plate and have no central nervous system (CNS) involvement. Spasmolytic agents work either by increasing the level of inhibition or by reducing the level of excitation. Inhibition is improved by mimicking the behavior of endogenous receptor transmitters such as GABA. Benzodiazepines, such as diazepam, interact with the $GABA_A$ receptor in the CNS. It can be used in patients with muscle spasm and induces sedation at doses needed to reduce muscle tone [2].

National Health and Nutrition Examination Survey (NHANES) identified muscle relaxant use trends in the United States and estimated 2 million American adults reported muscle relaxant use (1 month period prevalence 1.0 per cent; 95% confidence interval 0.8-1.3 per cent). The

study groups included both the sexes with a median age of 42 years. However,16 percent of users were over 60 years of age [3]. In this review article, the data were compiled from the most recent, original relevant research articles and are aimed at studying skeletal muscle relaxants, classification, mechanism of action, skeletal muscle relaxant activity screening and models used for the assessment, listing medicinal plants having skeletal muscle relaxant activity and their active phytochemicals.

Pharmacology of skeletal muscle relaxants (SMRs) [4]

SMRs consist of a diverse group of drugs with structurally different active ingredients and possess a range of pharmacological profiles and side effects. Both medications have been approved for the treatment of two different types of underlying conditions: spasticity from upper motor neuron dysfunction and muscular pain or spasm from peripheral musculoskeletal conditions.

The aim of skeletal muscle relaxants is to alleviate skeletal muscle spasm, help relieve pain and improve the strength of affected muscles. Pain relief may be caused by muscle relaxation and/or sedation due to muscle relaxation.

3 Classification of Skeletal muscle relaxants:

SMRs are classified into mainly two therapeutic groups as described below:

1. **Neuromuscular (competitive) blockers**

- Long acting: d- tubocurarine, Pancuronium, Doxacurium, Pipecuronium
- Intermediate acting: Vecuronium, atracurium, cisatracurium, rocuronium, rapacuronium
- Short acting: Mivacurium

- Depolarizing blockers: succinylcholine (Sch), decamethonium

2. Spasmolytics

- Mephenesin congeners: Mephenesin, Carisoprodol, Chlorzoxazone, Chlormezanone, Methacarmol
- Benzodiazepine: Diazepam and others
- GABA mimetic: Baclofen, Thiocolchicoside
- Centrally α_2 agonist: Tizanidine

Insights into the contraction of the skeletal muscle

A single α motor neuron can innervate up to 200 muscle fibers, forming a complex called a motion motor unit, whose action potential arises from the UMN in the motor cortex. This action potential depolarizes the motor neuron terminal, resulting in the opening of voltage-adjusted calcium channels and the subsequent release of the neurotransmitter acetylcholine into the synaptic cleft.

In the synaptic cleft, acetylcholine binds to the nicotinic cholinergic receptors on the muscle fiber membrane, leading to sodium inflow and potassium discharge through the muscle fiber membrane, resulting in muscle fiber depolarization. This depolarization opens voltage gated calcium channels on the sarcoplasmic reticulum via ryanodine and triphosphate inositol receptors, allowing calcium to flow into the striated muscle cell cytoplasm [5].

The calcium then binds to troponin C, which on actin filaments reveals myosin-binding sites. A cross-link between actin and myosin forms leads to contraction of the muscle. Calcium injection back into the sarcoplasmic reticulum, using adenosine triphosphate, results in a cessation of contraction [6].

Mechanism of action:

a) Neuromuscular blocking agents

The target sites of action of both non depolarizing and depolarizing agents found to be end plate of skeletal muscle fibres.

- Non depolarizing agents:

  These drugs are found to have NM cholinergic receptor affinity on the motor end plate by blocking the action of the NM receptor and preventing its binding to acetylcholine. Even the conformation of the NM receptor required for the opening of the sodium channel is also prevented, as the motor nerve impulse cannot cause contraction in the absence of end plate potential, as a result of which muscle relaxation occurs.

- Depolarizing agents

  Such drugs do not dissociate from the receptor, but cause depolarization and open the sodium channel which then spreads and repetitively excites muscle motor units. Depolarising blockers typically produce fasciculations lasting few seconds before inducing flaccid paralysis

b) Centrally acting agents/ spasmolytics:

These drugs reduce the skeletal muscle tone without reducing voluntary power. They selectively inhibit poly synaptic reflexes in CNS. Generally, these drugs depress spinal and supraspinal polysynaptic pathways with prominent non-specific sedative properties. They have no effect on neuromuscular transmission and on muscle fibres, but reduce cerebrate rigidity upper motor neuron spasticity and hyper reflexia.

The ATP2A1 gene provides instructions for making an enzyme called sarcoplasmic reticulum calcium-ATPase 1 (SERCA 1). This enzyme belongs to the family of ATPase enzymes that help control the level of positively charged calcium atoms (calcium ions) inside cells. The SERCA1 enzyme is found in skeletal muscle cells., where it is located

in the membrane of sarcoplasmic reticulum. This structure plays a major role in muscle contraction and relaxation by storing and releasing calcium ions. When calcium ions are transported out of the sarcoplasmic reticulum, muscle relaxation is initiated. The SERCA 1 enzyme transports calcium ions from the cell into sarcoplasmic reticulum, triggering muscle relaxation [7].

Pharmacokinetics of SMRs

SMRs seem to have a similar onset of action, but vary substantially in duration of activity, elimination half-life, pharmacokinetics and pharmacodynamics. Most SMRs are metabolized in the liver or plasma. The unchanged drug eliminated in the urine as well as in bile [8].

Side-effects:

The major side-effect shared by SMRs are respiratory paralysis and prolonged apnoea. Other adverse events include flushing, fall in BP, cardiac arrhythmias, precipitation of asthma, postoperative soreness and myalgia [9].

SCREENING MODELS FOR SKELETAL MUSCLE RELAXANTS [10]

1. Rota rod

In this model, thirty mice will be divided into five groups with each group comprising of six mice. Mice of either sex weighing 20 to 30 g will be used. The test compound of low, medium, and high dose or the reference drug diazepam (5mg/kg) will be injected (i.p) to mice. Another group of mice serves as control. Then, the animals will be placed in the four paws on the rotating bar, which is 2.5 cm in diameter and 25 cm high from the floor. The animals will be observed for a period of five minutes. The difference between the fall-off time of the mice before and after treatment is considered as an index of muscle relaxation [11].

2. Chimney Test

Thirty mice will be divided into five groups, with each group comprising of six mice. Mice of either sex weighing 20 to 30 g will be used. The test compound of low, medium, and high dose or the reference drug diazepam (5mg/kg) will be injected (i.p) to mice. Another group of mice serves as control. Glass cylinders (30 cm in length) called chimney are used for this test. Initially cylinder will be held in a horizontal position. At the end of the cylinder, near a 20cm mark from the base, a mouse will be introduced with head forward. When the mouse reaches the other end of the cylinder, the tube will be moved to a vertical position. Immediately, the mouse tries to climb backwards and perform coordinated movements. The time required by the mouse to climb backwards to the top of the cylinder will be noted. The animals that failed to reach the 20 cm mark of the glass cylinder in 30 sec will be considered to have muscle relaxant potential.

3. Actophotometer

Thirty mice will be divided into 5 groups of 6 each. Mice of either sex weighing 20 to 30 g will be used. The different groups will be assigned as described below: The test compound of low, medium, and high dose or the reference drug diazepam (5mg/kg) will be injected (i.p) to different groups of 6 mice each. Another group of mice serves as control. Then the animals will be individually placed in the activity cage for 10 minutes. The basal activity score of all animals will be recorded, and the difference in the activity before and after treatment of drug is considered as an index of locomotor action. Reduction in the motor activity indicates muscle relaxant property of the drug.

4. Grip Strength

Thirty mice will be divided into five groups; each group comprising of six mice. Mice of either sex weighing 20 to 30 g will be used. The test compound of low, medium, and high dose or the reference drug diazepam (5mg/kg) will be injected (i.p) to mice. Another group of mice serves

as control. In a preliminary experiment, the animals will be tested for their normal grip strength by exposing them to horizontal thin threat or metallic wire suspended about 30 cm into the air, which they immediately grasp with the forepaws. The mice will be released to hang on with their forelimbs. Normal animals will be able to catch the wire with the hind limbs and to climb up within 5 sec. Only animals who fulfill this criterion are included into the experiment. After administration of test and standard drugs, the animals will be tested every 15 min for 2 hr. Animals which are not able to climb on to the wire with hind limbs within 5 sec or fall off will be considered as impaired by the drug effect and after the completion of the test, the animals will be observed for their behavior in the cages. The disturbance of the grasping reflex is considered to be caused by central relaxation.

5. Inclined screen test

The inclined plane test is to determine the skeletal muscle relaxant activity. The plane consisted of transparent glass which was left on an inclined angle at 30^0. The mice that tried to move out of the plane glass without sliding off, were used for the test. The investigation was made at 15-30 min intervals, subsequent to the administration of control, standard and extract. The mice were kept in the superior part of the inclined plane and were given 30 sec to hang on or to fall off.

VARIOUS MUSCULOSKELETAL CONDITIONS [12]

Acute strains and sprains

Causes of musculoskeletal pain are many, but they are most commonly related with injury or trauma. Sprains and strains are the most common injuries. A sprain means stretch or tear of a ligament that is due to direct or indirect trauma that replaces the joint out of position or overstretches in severe cases and ruptures the supporting ligaments. Most common symptoms of sprains are pain, bruising, and inflammation.

Mechanical back pain

Mechanical back pain is commonly called as back strain or musculoskeletal back pain. The etiology is surrounded by numerous causes, but the diagnosis excludes anatomical sources of pain such as a herniated disc or spondylosis. Common sources are strain of the paraspinal muscles (the muscles along the spine), strain of ligaments of the spine, or generative facet joint disease (the joints between the bones of the spine).

Sciatica

This is usually caused by irritation of a nerve root of the sciatic nerve, often from compression by a disc or degenerative disease. Pain radiates into the buttocks, back of the thigh, and often into the calf or foot.

Radiculopathy

It is the dysfunction of the nerve root by any cause. Symptoms include weakness, pain (sciatica), numbness, paresthesias (tingling), or a combination thereof.

Herniated disc

Often called disc rupture, disc prolapse, or herniated nucleus pulposus (the gelatinous inner core of the disc). Due to age or injury, the wall of the spinal discs can be damaged and the wall of the disc can weaken and protrude. Disc pain is often felt as a deep ache in sacroiliac.

Spinal Stenosis

It is the narrowing of the spinal canal, typically in the neck (cervical stenosis) or lower back (lumbar stenosis). The narrowing is called as spondylosis. The causes include degenerative, trauma and congenital defects. But the most common spondylosis is a degenerative disorder, occurring with age.

Myofascial pain

It refers to soft-tissue pain normally arising from trauma, repetitive activities, or poor posture. It is usually associated with muscle spasm. Patients may complain of pain in the neck region or pain across the top of the shoulders and sometimes sleep difficulties or headaches.

Scoliosis

It is an abnormal curvature of the spine. It is due to many causes, the most common type is adolescent idiopathic scoliosis. Females are most affected, that is 8 times as frequently as males. Generally, most forms of scoliosis are not specifically painful but may depend on the degree of curvature of the spine and/or the presence of degenerative spinal changes.

Fibromyalgia

It is commonly known as muscle/soft-tissue pain. The pain occurs in different areas of the body at different times. The pain may be more during menstrual cycle or during sudden weather changes. The main diagnostic feature is concurrent fatigue and sleep disorder. Patients may have neurological disturbances such as headaches, numbness, weakness, difficulty in concentrating, and lightheadedness.

PLANTS HAVING SKELETAL MUSCLE RELAXANT ACTIVITY

Nature provided us a huge supply of plants with skeletal muscle relaxant potential.[13] The side effects of antispasmodic and antispasticity agents needs them to be used cautiously. Therefore, it is necessary to find a newer alternative for skeletal muscle relaxants that has a safer profile. Including the prototype skeletal muscle relaxant that is tubocurarine, most of the modern skeletal muscle relaxants are of plant origin. Hence, there should be a systematic search within the herbal products to find a credible replacement. Following are some of the plants having skeletal muscle relaxant activity [14].

TABLE 1: Plants having skeletal muscle relaxant activity

Latin name	Family	Chemical constituent	Useful part
Viola betonicifolia	Violaceae	4 HC	Whole plant
Vicia faba	Fabaceae	Tannin, saponin, steroids, alkaloids	Leaves, seed
Tridax procumbens	Asteraceae	luteolin, quercetin, glucoluteolin, isoquercetin	Leaves
Senna occidentalis	Fabaceae	Anthraquinones, cardiac glycosides, alkaloids, saponins, tannins, flavonoids.	Leaves
Saraca indica	Fabaceae	Flavonoids, saponins, triterpenoids, tanins, glycosides, steroids, alkaloids.	Leaves
Parthenium hysterophorous	Asteraceae	Anthraquinones, saponins, steroids, tannins, reducing sugars	Leaves
Nerium olender	Apocynaceae	Anthraquinones, saponins, steroids, tannins, flavonoids	Leaves, flowers
Cinnamomum zeylancium	Lauraceae	Volatile oils, Cinnamonaldehyde, eugenol,	Bark

		transcinnamic acid, proanthrocyanidins	
Hibiscus rosa	Malavaceae	Flavonoids (hibiscitin), phenolic content, terpenoid like sitosterol, camphesterol	Leaves
Mikania scandes	Asteraceae	Flavonoids, steroids, tannins, saponins, sugar	Arial parts
Moringa oleifera	Moringaceae	Flavonoids, saponins, tannins, phenolic acids.	Leaves
Phyllostachys bambusoides	Poaceae	Flavonoids, glycosides, tannins, proteins, carbohydrates	Leaves
Sapindus trifoliatus	Sapindaceae	Saponins, anthraquinones, tannins, isoflavonoids	Pericarp

CONCLUSION:

Skeletal muscle relaxants are the agents that reduce muscle tone by acting peripherally on the neuromuscular junction or centrally on the brain spinal axis. This activity can be screened by rota rod, inclined screened test, climbing test, chimney test, actophotometer and grip strength meter. A newer alternative for skeletal muscle relaxants that has a safer profile lead into greater

opportunity for synthesis of more drugs. Nature provided us a huge supply of plants with skeletal muslce relaxant properties that can make progression in drug discoveries and development.

ACKNOWLEDGEMENT:

We are thankful to Ashwini Prabhu, Assistant Professor, Yenopoya Research Centre, Yenopoya (Deemed to be University), Deralakatte for her contributions for this study.

REFERENCES:

1. Tripathi K D. Essentials of Medical Pharmacology. 7thed. JayPee Brother Medical Publishers. New Delhi 2013:347-59.
2. Sharma HL, Sharma KK, Principles of Pharmacology. 3rd ed. Paras Publishers, Hyderabad 2017:201-15.
3. Robin Moorman, Corey Witenko. Consideration for the appropriate use of skeletal muscle relaxants for the management of acute low back pain. P&T.2014;39(6):427-35.
4. Sandra Kampe, Jens W Krombach , Christoph Diefenbach , Muscle relaxants. Best Pract Res Clin Anaesthesiol.2003;17(1):137-46.
5. See S, Ginzburg R. Skeletal muscle relaxants. Pharmacotherapy.2008 Feb;28(2):207-13.
6. L. Baoge et al., Treatment of skeletal muscle injury: A review. Internatinal scholarly research network ISRN Orthop.2012;10:1-7.
7. Chou R, Peterson K, Helfand M. Comparative efficacy and safety of skeletal muscle relaxants for spasticity and musculoskeletal conditions: a systematic review. J Pain Symptom Manage. 2004 Aug;28(2):140-75.

8. H. Gerhard Vogel (Ed) Drug Discovery and Evaluation: Pharmacological assays. Germany, Springer 2008;1(E):578-81.
9. N Sandara veena, K sivaji, G.V Benerji.et.al. Skeletal muscle relaxant property of diazepam by using rota rod on albino mice. IJBAMR.2015;4(4):714-21.
10. Frank A. Beebe, Robert L. Barkin, Stacie Barkin. A Clinical and Pharmacologic Review of Skeletal Muscle Relaxants for Musculoskeletal Conditions. Am J Ther. 2005; 12:151–71.
11. Arun S. Medicinal plants with skeletal muscle relaxant activity: A review. Nat Prod Chem Res. 2015.
12. Justine O, Varghese N, Shetty P, Sreelakshmi P, Sharanya M. Skeletal muscle relaxant potential of *Annona reticulata* L. leaf extract in Swiss albino mice-a pre-clinical study. Journal of Xi'an Shiyou University, Natural Science Edition: 2021; 17 (9): 673-683.