ROLE OF CENTRALLY ACTING MUSCLE RELAXANT IN LOW BACK PAIN

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ABSTRACT

Pain is a symptom when it occurs acutely, but frequent symptoms changes into chronic condition. Pain is due to tissue damage or alarm signals for upcoming complications. Back pain is a common public health problem, affecting at least 80% of individuals experiencing a considerable episode of low back pain in their life. The occurrence of spasticity-related muscle pain in patients after spinal cord injury, multiple sclerosis or with stroke can attain as high as 67%, 74% and 65%. A variety of pharmacologic agents are used for the treatment of myogenic pain. These agents are termed as muscle relaxants and antispastic medications. Obstruction of the polysynaptic reflex arc has been used as an assay for the actions of centrally acting muscle relaxants and noncurariform relaxants. Skeletal muscle relaxants are diverse group of medications used to treat different types of underlying situation: spasticity from upper motor neuron (UMN) syndromes and muscular pain or spasm from peripheral musculoskeletal conditions. To review the effectiveness of centrally acting muscle relaxant on specific and nonspecific low back pain. Recent therapy primarily includes use of centrally acting muscle relaxants, which are advantageous in treatment of some symptoms, but repeated use has extensive side effects, such as sedation, dizziness and muscle weakness.

Keywords: Back ache, Centrally acting, Muscle relaxants, Low back pain.

INTRODUCTION

Low back pain is common in humans but it is not a disease. Low back pain is a chief cause of disability. Few cases of back pain are due to precise causes; but most cases are non-specific. The term refers to pain of various durations in an anatomical area of low back, has become a model of responses to both external and internal stimuli [1]. The men and women equally affected from LBP between the ages of 30 to 60 years. The low back pain is a clinical appearance that can be caused by a number of known disorders and morphological changes in low back. The low back pain is mainly occurred due to infection, osteoporosis, fracture, ankylosing spondylitis, spinal stenosis, rheumatoid arthritis, etc. Many other causes are related to the occupations, which require repetitive

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lifting of heavy load, vibrations caused by industrial machinery and vehicles also causes LBP \[2\].

**CLASSIFICATION**

Low back pain can be categorized in 3 classes and depends upon the various duration of symptoms: (1) acute low back pain ranges from (1 to 6 weeks), (2) sub acute LBP (4 to 12 weeks), (3) chronic LBP ranges from (greater than 12 weeks) \[3\].

**Acute back pain**

Low back pain is pain, rigidity, or muscle tension, localised lower the costal margin and over the inferior gluteal folds, with or without referred or radicular leg pain (sciatica), and is defined as acute when pain persists for less than 12 weeks. Acute LBP is typically self-limiting, although 2–7% patients develop chronic pain. Acute pains caused by tearing of muscles and ligament \[4\]. In acute LBP, little is identified about the predictions of definite presentation or perceived disability by pain related fright and ache catastrophizing \[5\].

**Chronic back pain**

Chronic low back pain is a prevalent pain condition in alliance with increased disability \[6\]. Pain inside the lumbosacral region, thighs and buttocks are called chronic back pain, which is mechanical in nature: it restricts the daily physical activities. Chronic back pain appears if pain persists more than twelve months. Those patients live with continuous low back pain are associated with anxiety, depressive mood and stress \[7\]. Patients with chronic low back pain pass a high pain sensitivity threshold and a minor pain tolerance than pain-free controls. The risk factor in the development of chronic low back pain is Inability to habituate to pain \[8\]. A continuing disabling situations develops in few but considerable numbers of patients with chronic low back pain. Patients suffer from continuous pain and often become functionally disable \[9\].

**PATHOPHYSIOLOGY**

The most common pain complaints are musculoskeletal, and back pain is the most common of these \[10\]. In the lumbar region (or low back region) which consists of five vertebrae (L1 to L5), the fibro cartilage discs (or intervertebral discs) are present in between these vertebrae, which work as cushions. Its presence is to support the spinal cord as well as prevents the vertebrae from rubbing together at the time of injury. LBP is
caused by disorders of the intervertebral discs. Cytokines like matrix metalloproteinases, nitric oxide, phospholipase A2, and also tumor necrosis factor (α) are assumed to contribute to the production of low back pain \[11\]. Most lumbar disc herniations or diseases are produced by the bouts of various degrees and time duration of back pain \[12\].

**CENTRALLY ACTING MUSCLE RELAXANT**

Muscle relaxants are widely used in the treatment of nonspecific LBP. Muscle relaxants can be categorised into two main classes: (1) antispasmodic agents (2) antispastic agents. Antispasmodics are used to reduce muscle spasm in painful conditions such as lumbago. It can be subcategorised into benzodiazepines and nonbenzodiazepines classes. Spasticity is a persistent and debilitating condition that repeatedly occurs following upper motor neuron (UMN) lesions \[13\]. Another class is antispastic agents, which are widely used to decreases the spasticity that interferes with the therapy or function, such conditions are disseminated sclerosis or disseminated encephalomyelitis also called as multiple sclerosis, injuries in the spinal cord and cerebral palsy. The mode of action of these drugs among the peripheral nervous system (example, dantrolene Na) is the blockade of sarcoplasmic reticulum Ca\(^{2+}\) channel. Antispastic drugs decrease the Ca\(^{2+}\) concentration and destroyed the actin-myosin interaction. Muscle relaxants are the drugs which are administered for the purpose of muscles relaxation in painful condition \[14\]. Spasticity has been closely defined as a motor disorder characterized by exaggerated tendon jerks \[15\]. Carisoprodol is a direct muscle relaxant which is metabolized by liver to its metabolite called as meprobamate. Both of the compounds are indirect GABA\(_A\) receptor agonists which open neuronal chloride channels and causes hyperpolarization and the onset of action is 30 minutes with duration of 4 to 6 hours \[16\].

**GENERAL MECHANISM OF ACTION**

The Benzodiazepines increases the presynaptic inhibition in spinal cord and dorsal column nuclei as well as postsynaptic inhibition in dorsal column nuclei, Cerebral cortex, hippocampus, cerebellar cortex, hypothalamus which are the examples of frequent and collateral suppression mediated by GABA ergic intrinsic neurons. The compounds also facilitates the inhibitory activity of GABA ergic neurones in the region of lateral vestibular nucleus and substantia nigra of Deiters \[17\]. Baclofen is a chemical analogue of GABA that showed its action through inhibiting the synaptic release in the spinal cord.
and, probably in supraspinal regions [18]. Clinically, baclofen has generally been used for its muscle relaxant effects in the management of spasticity, as well as for its neuropathic analgesic properties in the treatment of trigeminal neuralgia. Baclofen is a presynaptic and postsynaptic inhibitors leading to a decrease in the excitatory neurotransmitter release as well as in substance P, which is involved in transmission of nociceptive impulses [19]. One more centrally acting muscle relaxant is Tizanidine, it acts centrally as presynaptic a2- adrenergic agonist which inhibits the release of fascilitatory amino acids in spinal interneurons. It also acts by facilitating the performance of glycine [20].

CENTRALLY ACTING MUSCLE RELAXANT AGENTS:

1. NK-433 (lanperisone HCl):

   Lanperisone HCL \(((-)-(R)-2\text{-methyl-3-(1-pyrrolidinyl)-4'-trifluoromethylpropiophenone monohydrochloride})\) has been recently proposed as a muscle relaxant and it is used in the treatment of muscle contracture and chronic LBP. NK433 (Lanperisone hydrochloride) administered orally or i.v, down the mono and polysynaptic impulse potential, dorsal root reflex potential, flexor reflex mediated by group II afferent fibers, patellar and flexor reflexes [21]. NK433 repressed intercollicular decerebrate rigidity (\(\gamma\)-rigidity) and anemic decerebrate rigidity (\(\alpha\)-rigidity) dose dependently. \(\gamma\)-rigidity is strongly inhibited by lanperisone than \(\alpha\)-rigidity. NK433 does not distress the muscle spindle discharge or neuromuscular conduction but also inhibited the increase in muscle spindle discharges induced by pinna pinching (\(\gamma\)-activity). NK433 did not persuade the muscle tone induced by morphine-HCl in the normal animals, as muscle relaxant doses in decerebrate rigidities [22].

2. CS-722:

   The pharmacological properties of (CS-722) \((R)-4\text{-chloro-2-(2-hydroxy-3-morpholinopropyl)-5-phenyl-4-isoxazolin-3-one hydrochloride})\), a newly investigated, centrally acting muscle relaxant, were studied in rats. It decreases the decerebrate rigidity and also subdued the increase in discharges from Ia afferent fibers. However, it does not shows any action on the basal discharge of Ia afferent fibers. The polysynaptic reflex is greatly depressed by CS-722 in comparison to monosynaptic reflex. CS722 reduced the facilitation of GABA mediated inhibitory postsynaptic currents (IPSCs), evoked by stimulating neighboring neurons [23]. CS-722 not affected the electroencephalogram
(EEG) stimulation reaction, which was elicited by stimulation of the reticular activation when experiment performed on anesthetized rats [24].

3. Cyclobenzaprine:

Cyclobenzaprine, a centrally acting muscle relaxant, was thought to be an α-2 adrenoceptor agonist that decreases the muscle tone by reducing the action of descending noradrenergic neurons. Cyclobenzaprine-activated monosynaptic reflex depression is not debilitate by noradrenergic neuronal lesions formed by 6-hydroxydopamine [25]. Cyclobenzaprine is structurally associated to the first generation tricyclic antidepressants (TCA’s). cyclobenzaprine acts at the brain stem to provoke skeletal muscle relaxation. It may be useful in the management of pathological conditions in human [26].

4. Chlormezanone:

Chlormezanone is another centrally acting muscle relaxant which belongs to non benzodiazepine class. It bind to the central BZD receptors allosterically similar with GABA\textsubscript{A} receptors. Chlormezanone (CMZ) is an efficient skeletal muscle relaxant that probably acts through decrease of the gamma efferent discharge to motor fibres of muscle spindles. In addition it is reported to have some benzodiazepine like effects on sleep physiology, but without reduction in phase IV sleep. Restoration of non-restorative sleep with concurrent muscle relaxation is theoretically attractive in respect of PFS. It can potentiates the effects of the inhibitory neurotransmitter GABA [27].

5. Tolperisone:

Tolperisone, a centrally acting muscle relaxant agent, has been widely used as a spasmolytics of choice. Due to pharmacological properties of tolperisone, which mediate muscle relaxation without concomitant sedation or withdrawal phenomenon, it differs from other spasmolytic agents. It acts at the level of spinal cord by blocking Ca\textsuperscript{2+} and Na\textsuperscript{+} channels. Tolperisone exerts spinal reflex action via pre synaptic inhibition of the transmitter releases from the primary afferent endings through a combined action on voltage –gated Ca\textsuperscript{+} and Na\textsuperscript{+} channels. It also works as membrane stabilizing agent [28].

6. KW-6629: (7-chloro-N, N, 3-trimethylbenzo[b]furan-2-carboxamide)

The drug efficiently decreased the motor coordination, the crossed extensor response, the anemic decerebrate rigidity, and also the gamma-activity not directly recorded from the muscle afferent discharges without demonstrating the direct inhibitory
effect on muscle spindles. KW-6629 depressed the polysynaptic and dorsal root reflexes without exhibiting marked effect on the monosynaptic reflex in the intact spinal cord. KW-6629 drug produces slow wave of high-amplitude in the cerebral cortex in electroencephalogram (EEG). After-discharges and behavioral convulsion (amygdaloid kindling) the KW-6629 did not decrease the electroencephalography (EEG). KW-6629 shows no effect on the neuromuscular junction. These findings propose that KW-6629 is a centrally acting muscle relaxant whose site of action is in supraspinal structures \[29\].

7. Tizanidine:

The tizanidine showed its effects on the motor systems. It effectively decreases the intercollicular decerebrate rigidity and gamma-activity, recorded indirectly from the muscle spindle afferent discharges, without exhibiting the direct inhibitory effect on muscle spindles. It effectively depressed the crossed extensor reflexes and mono and polysynaptic potential reflex, the dorsal root reflex was increased transiently. Tizanidine shows no activity on the neuromuscular junction and on benzodiazepine binding site. The depression of \(\gamma\)-system and spinal reflexes by tizanidine contributes to muscle relaxation and anti-spastic activity and its mode of action are different from that of other centrally acting muscle relaxing agents such as mephenesin and benzodiazepine \[30\].

8. Carisoprodol:

Carisoprodol is another centrally acting muscle relaxant which is used in the treatment of pain associated with acute musculoskeletal situations and in acute spasm of muscles. The major active metabolite of carisoprodol is meprobamate which shows central nervous system (CNS) sedating property which is similar to benzodiazepines or alcohol. Carisoprodol produces its sedative property by acting directly or indirectly. It produces muscles relaxation by blockade of interneuronal activity in the descending reticular activating system and spinal cord; but in humans this type of mode of action is unknown. Meprobamate also posses barbiturate-like activity at GABA\(_A\) receptors. Carisoprodol is a GABA\(_A\) receptor indirect agonist with chloride ion (cl\(^-\)) channel conductance activity similar to the benzodiazepines \[31\].

9. Baclofen:

Baclofen, a centrally acting muscle relaxant, used in the treatment of spasticity associated with CNS injury and in patients with multiple sclerosis. It acts directly or
indirectly. It is an agonist of presynaptic GABA<sub>B</sub> receptors and produces their action presynaptically or increases the affinity of GABA within the spinal cord and decreasing the spasm of muscles. It acts mainly at the level of spinal cord to hinders the transmission of both monosynaptic and polysynaptic reflexes. The general action is a flaccid paralysis of skeletal muscles. Now a days intrathecal baclofen is also administered because of less side effects and high therapeutic efficacy and it’s administered through catheter or single shot spinal needle. Baclofen is used in those patients who has spasticity from cerebral and spinal origin<sup>[32]</sup>.

10. Dantrolene:

Dantrolene is the novel centrally acting muscle relaxant used to treat pain related with spasticity. Dantrolene is a lipid soluble hydantoin analogue. Dantrolene acts by acting directly or indirectly and fascilitates calcium uptake or decreases calcium release from the sarcoplasmic reticulum (SR). Skeletal muscles attenuates twitch tensions that is being increased by acting directly or indirectly via its nerve. Resistance of membrane or total membrane capacitance does not change by the performance of dantrolene. Dantrolene does not alters the readings of electromyogram (EMGs). Muscle membrane posses electrical excitability and it is not affected through dantrolene and does not interrupt the transverse tubules. Dantrolene cannot act by reducing electrical transmission between the sarcoplastic reticulum and postsynaptic junction<sup>[33]</sup>.

CONCLUSION

Muscle relaxants are effective in the management of nonspecific LBP, especially in chronic conditions, but due to the adverse effects like drowsiness, sedation, and dizziness and potential for dependency and abuse, special precaution is required. These drugs are used to reduce muscle spasm either by directly acting on the muscle or indirectly by acting on the neural innervation of the muscle, and also by inhibition or blockade of central neural mechanisms that controls the function of muscle but do not paralyze the muscle.

So we can conclude that muscle relaxants are more effective than analgesics or nonsteroidals in the management of low back pain.
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