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Muscle Relaxants and the Positioning of Methocarbamol in the Drug Therapy of Musculoskeletal Problems

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Abstract | **Original Research Article**

Skeletal muscle relaxants (myorelaxants) are a group of chemical compounds that act both centrally and peripherally and have the ability to relax skeletal muscle, which reduces muscle contractility by blocking the transmission of nerve impulses, or by decreasing the excitability of the motor end plate, or by other actions. Periferial myorelaxants (neuromuscular blockers) (Atracurium, Doxa-curium, Mivacurium, Pancuronium, Rocuronium, Succinylcholine, Tubocurarine, Vecuronium) block neuromuscular junction function. Muscle relaxants cause relaxation of striated (voluntary skeletal) musculature (in contrast to spasmolytics which relax unstriped musculature)**.** Muscle relaxants are used to treat muscle pain, spasms, cramps, chronic spasticity, such as in multiple sclerosis, and are used during intubations and surgery to reduce the need for anesthesia and facilitate intubation. Centrally acting skeletal muscle relaxants are commonly indicated to alleviate two different conditions: muscular pain or spasms and spasticity in neuromuscular diseases. Methocarbamol as a muscle relaxant is used in the symptomatic treatment of musculoskeletal conditions associated with painful muscle spasms**.** Mechanisms of action of Methocarbamol include: depression of central nervous system, inhibition of acetylcholinesterase, and direct activation of GABA-A receptor. Clinical advantages of using Methocarbamol are: effective muscle relaxation, non-narcotic option, and versatile use. Sinergistic effect is obtained in combination of Methocarbamol with Paracetamol.

Keywords: muscle relaxants, Methocarbamol, Distem, mechanism of action.

INTRODUCTION

Neuromuscular blockade [1] is applied for the improvement in surgical condition and reduction in pain [2]. Myorelaxants (muscle relaxants) are a large group of chemical compounds that have the ability to relax skeletal muscle, acting either centrally on the nervous system or peripherally at the neuromuscular junction [3]. Skeletal muscle relaxants unclude medications that are administered in the treatment of acute and chronic musculoskeletal conditions associated with pain [4]. Neuromuscular blocking agents [5] are effective in reduction of muscle tension, stiffness, and spasm [6]. These drugs are periferial and central muscle relaxants [7].

I. Classification of myorelaxants

Neuromuscular blocking drugs are classified according to mechanisms of blocking nerve impulse transmission [8]:

1) Periferial (direct) myorelaxants:

a) non-depolarizing muscle relaxants (competitive muscle relaxants) – N-receptors antagonists
b) depolarizing myorelaxants – N-receptors agonists
c) indirect myorelaxants: botulinum toxin – irreversibly inhibits acetycholine releasing

2). Central muscle relaxants

a) acts in central nervous system (CNS)
b) structurally heterogenic group

c) compounds with various mechanisms of action.

II. Mechanism of action and characteristics of periferial (direct) myorelaxants (neuromuscular blockers)

Periferial muscle relaxants interact with acetylcholine nicotinic (N) receptors of skeletal musculature. As a group of drugs that interrupt the transmission of nerve impulses at the myoneural synapses (motor endplate), direct myorelaxants lead to temporary and reversible paralysis of the striated muscles, and in larger doses, also of the respiratory muscles. The main characteristics of neuromuscular blockers include [8]:

1) caution of temporary muscle relaxation of the striated muscles, which spreads descendingly - from the eyelids, face, neck to the limbs, trunk and finally the intercostal muscles and diaphragm;
2) restored muscle activity in the reverse order;
3) administeration in doses, that paralyze the respiratory muscles, is the reason for the necessary intubation of breathing during their application;
4) administration is intravenously;
5) at low temperatures, the effect of competitive muscle relaxants weakens, and the activity of Suxamethonium increases [8].

II.1. Antidepolarizing drugs – N-receptors antagonists

Non-depolarizing myorelaxants are: Atracurium (Tracrium), Alcuronuium (Alloferin), Cisatracurium, Doxacurium, Gantacurium, Mivacurium, Pancuronium (Pavulon), Pipecuronium (Arduan), Rocuronium (Rocuronium Kabi), Tubocurarine, Vecuronium. Antidepolarizing drugs compete with acetylcholine for its binding site on the N2-cholinoreceptor in the neuromuscular synapse, displace it and prevent depolarizing action of acetylcholine on the postsynaptic membranes, block the transmission of nerve impulses, thus excluding the possibility of exciting muscle fibers. Neuromuscular blockers act peripherally as skeletal muscle relaxants, which block neuromuscular junction function. They have a longer effect than that of depolarizing muscle relaxants. Their antagonists are anticholinesterase agents – Galantamine, Neostigmine, Pyridostigmine, and also the preparations Nivalin and Pimadine [8].

II.2. Depolarizing myorelaxants – N-receptors agonists.

Tubocurarine is considered the prototype neuromuscular blockers and is competitive antagonist of nicotinic acetylcholine receptors [9]. Depolarizing myorelaxants as Succinylcholine, are agonists of acetylcholine and bind to N2-cholinoreceptors and activate them. These drugs cause initial activation (depolarization of cells) of the N-receptors and further leading to subsequent continuous prolonged stable blockage, which represents with imposible impulses and no muscle contraction. Unlike acetylcholine, they cause not a short, but a lasting depolarization of 3 to 5 minutes. Unlike non-depolarizing agents, depolarizing drugs are not competitive antagonists, but are more stable agonists than acetylcholine [10].

III. Central muscle relaxants

Centrally acting skeletal muscle relaxants are commonly indicated to alleviate two different conditions: muscular pain or spasms and spasticity. Spasticity can be associated with a number of diseases and represents a condition in which muscles are continuously contracted causing stiffness or tightness interfering with movements and speech. Muscle relaxants are most often used to relieve muscle spasms from acute, painful conditions. These medications should be used short-term. Some muscle relaxants are used for their muscle-relaxing activity, but are not used for typical acute muscle injuries. Indications depend on the specific drug [8].

Central relaxants include antispasmodics and spasmolytics and are used to treat two conditions: spasms from peripheral acute musculoskeletal conditions (antispasmodics) [11] and spasticity from upper motor neuron lesions (spasmolytics, antispastic, not for acute muscle injury) [8].

1) Antispasmodics (for acute musculoskeletal disorders)

Antispasmodic muscle relaxants such as Carisoprodol, Chlorphenesin, Chlorzoxazone [12]. Cyclobenzaprine [13]. Orphenadrine [14], Metaxalone, Methocarbamol for acute trauma do not affect the muscle itself. They act on the central nervous system and cause CNS depression and muscle relaxant activity. Antispasmodics are traditionally used for acute, painful musculoskeletal injuries. In a back injury that interferes with movement, an antispasmodic may be an appropriate medication if non-steroidal antiimflammatory drugs are not appropriate for a given patient [11].

2) Antispstic (not for acute muscle injury).

The antispastic muscle relaxants, such as Baclofen and Dantrolene are not used for acute muscle injury and does not directly affect the CNS. They can treat spasms from conditions such as multiple sclerosis or spinal cord injury. Baclofen (p-chlorophenyl-GABA) is an orally active GABA-mimetic agent and as agonist at GABAB receptors, causes spinal inhibition of motor neurons by the mechanisms:

1) increasing postsynaptic K+ conductance;
2) inhibition of dendritic calcium influx channels [15].

Baclofen is a muscle relaxant that treats spasms associated with multiple sclerosis [16] and spasticity in cerebral palsy [17]. Synergistic central nervous system depression of Baclofen and Pregabalin has been reported [18].

Calcium is released from the sarcoplasmic reticulum via a calcium channel, called the ryanodine receptor channel [19]. Mechanism of action of Dantrolene is based on the supperession of the release of activator calcium by binding and blocking the opening of ryanodine Ca^{2+}-release receptor channel in the sarcoplasmic reticulum of skeletal muscle. Dantrolene has an effect on skeletal muscle, affecting the contractile response, causing relaxation. Dantrolene also treats spasticity in conditions such as multiple sclerosis, spinal cord injury, strokes, or cerebral palsy [20].

Diazepam is a benzodiazepine that treats anxiety. Diazepam echibits muscle-relaxing effects due to interract with a neurotransmitter gamma-aminobutyric acid (GABA), and as a result causes relaxation of muscles. The drug can be applied for treatment of muscle spasms due to muscle injury, as well as upper motor neuron disorders, such as cerebral palsy [17].

Gabapentin is a spasmolytic agent in patients with multiple sclerosis [21]. Meprobamate has been used as central muscle relaxant [22]. Tizanidine is α2-adrenoceptor agonist in the spinal cord and reduces spasticity [23]. Progabide is a GABAA and GABAB agonist and is used for spasticity in multiple sclerosis [24]. Idrocilamide and Riluzole are newer drugs for the treatment of amyotrophic lateral sclerosis (ALS) that appear to have spasmreducing effects, possibly through inhibition of glutamatergic transmission in the CNS [25]. The therapeutic use of botulinum toxin for ophthalmic purposes and for local muscle spasm [8].

IV. Therapeutic application of myorelaxants

Peripherally acting muscle relaxants are used in surgical interventions to achieve muscle relaxation, allowing access to internal organs, which would only be obtained if general anesthetics were administered alone in large, dangerous doses. They are also used in the reposition of fractures and dislocations of large joints, in electroconvulsive therapy in psychiatry to avoid fractures, dislocations of joints or muscle rupture, in the diagnosis of myasthenia gravis, control of tetanic seizures. Non-depolarizing muscle relaxants are mainly used:

1) For skeletal muscle relaxation during major surgical operations
2) In anesthesia to prevent spontaneous movement of muscle during surgical intervention and act by blocking the nicotinic acetylcholine receptor, thus inhibiting neuron transmission to muscle.
3) In tetanus [8].

The action of non-depolarizing muscle relaxants (competitive muscle relaxants) is potentiated by simultaneous administration with: aminoglycosides, lincosamides, polymyxins, furosemide, beta blockers, general anesthetics. Paralysis of skeletal muscle attained by using curare-like compounds, in the majority of cases, is not useful for general conditions of spasticity accompanied by the CNS involvement, as well as for local injuries or inflammation. Neuromuscular blockers can cause flushing of the skin, a short-term decrease in blood pressure or bronchospasm due to histamine release, tachycardia, rhythm disturbances, skin rashes, rarely anaphylactic shock [8].

Examples of conditions in which muscle relaxants are used include [26]

1) Muscular pain associated with muscle spasms [27], acute musculoskeletal injury [28], chronic pain [29], neck pain, low back pain [30], fibromyalgia [31], headaches, and myofascial pain syndrome [32].
2) Cerebral palsy [33];
3) Stiff Person Syndrome (SPS) [34];
4) Paraplegia (a form of paralysis);
5) Multiple sclerosis;
6) Spinal cord injury [8].

Central muscle relaxants as Tolperizone (Mydocalm) are used to treat acute muscle pain from musculoskeletal injuries, muscle spasms, cramps, tension, and other anti-spasm measures such as rest and physical therapy may be recommended to help heal an acute injury. These drugs act on the CNS and/or increasing nerve excitability, which causes the muscle to relax. Some muscle relaxants are used to treat chronic spasticity such as multiple sclerosis and may be taken for longer periods of time under the supervision of a specialist. Skeletal muscle relaxants are also used for relief of spasticity in neuromuscular diseases. These are a separate class of drugs used during intubations and surgery to reduce the need for anesthesia and facilitate intubation. The disadvantages of these drugs are their sedative effect and anticholinergic side effects [8].

V. Carbamates as structures inhibitors of acetylcholinesterase

Inhibition of acetylcholinesterase is an approach to the treatment of pathologies characterized by impaired cholinergic neuro-transmission. Carbamates are structures with the carbamate functional group (R-O-C(=O)-NR2) that inhibit acetylcholinesterase [35]. Therapeutic applications are: Alzheimer's disease [36], mild cognitive impairment, dementia in Parkinson's disease, Lewy Body Dementia, Myasthenia Gravis, glaucoma, neuromuscular disorders. Acetyl-cholinesterase inhibitors interact with the active site of the enzyme, leading to inhibition of its activity [37]. Carbamate compounds contain the carbamate functional group (R-O-C(=O)-NR2), where R can be various substituents. The goal of the design of these compounds is structural analogy with acetylcholine, which by binding to the active site of the acetylcholinesteras, inhibit of the enzyme. When a carbamate inhibitor interacts with the active site of acetylcholinesterase, the carbonyl oxygen of the carbamate group undergoes nucleophilic attack by the serine hydroxyl group present in the active site of the enzyme. This nucleophilic

reaction results in the formation of a covalent bond between the carbonyl carbon of the carbamate and the hydroxyl group of the serine residue in the active site of the enzyme. The resulting covalent bond is reversible, but the dissociation of the inhibitor from the enzyme is slow, resulting in a prolonged inhibitory effect. The formation of this covalent bond prevents the enzyme from effectively degrading acetylcholine molecules in the synapse. The increased concentration of acetylcholine enhances cholinergic neurotransmission, which is crucial for various physiological processes, such as muscle contraction, cognitive functions, and the regulation of autonomic functions [35].

VI. Methocarbamol

Methocarbamol is [2-hydroxy-3-(2-methoxyphenoxy) propyl] carbamate (Robaxin, Robaxin-750, Carbacot, Skelex, Tanlor). (Figure 1.).

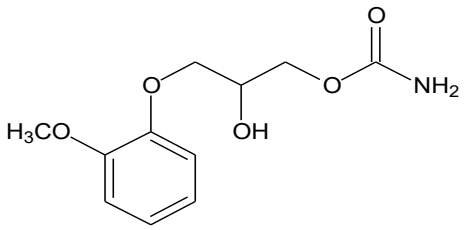

Figure 1: Chemical structure of Methocarbamol

Methocarbamol is approved by the FDA, July 16, 1957. The compound is a carbamate - an ester of carbamic acid with centrally acting muscle relaxant properties. The manufacturing procedures for the drug involve various steps, including reacting guaiacol with chloroacetic acid to form guaiacol acid. The guaiacol acid is then converted to guaiacol glycidyl ether, which is further reacted with glycine to produce Methocarbamol. The drug should be stored at room temperature and away from moisture and heat [38].

VI.1. Mechanisms of action of Methocarbamol

1) Depression of central nervous system (CNS)

Involuntary muscle spasms may be the result of a protective reflex preventing movement that would cause injury. In some cases, muscle spasms themselves may become painful. This phenomenon, known as the "pain-spasm-pain cycle", has not been confirmed in rigorous clinical and electrophysiological studies. The relief provided by skeletal muscle relaxants is the re sult of a general depression of the central nervous system [38].

Methocarbamol does not directly affect the contractility of skeletal muscle, motor nerve fibers and the neuromuscular junction. The drug is a central nervous system depressant with sedative and musculoskeletal relaxant properties, which helps relieve muscle pain, stiffness, and spasms. The compound is applied in muscle cramps [39], acute pain after traumatic injury [40], and rib fractures [41], low back pain [42, 43]. Muscle relaxants are used after surgery [44]. Intravenous methocarbamol administration for acute pain after spine surgery is reported [45].

The agent acts on brainstem reflex centers that regulate muscle tone by decreasing the excitability of alpha motor neurons. The compound increases glycine transmission too. As a central nervous system depressant, the drug molecule works by blocking nerve impulses and pain sensations in the brain, effectively relieving musculoskeletal pain and discomfort. Methocarbamol relaxes skeletal muscles by generally depressing the central nervous system [38].

2) Inhibition of acetylcholinesterase

Methocarbamol acts through a mechanism similar to that of the carbamates by inhibiting acetylcholinesterase at the synapses of the autonomic nervous system, the neuromuscular junction, and the central nervous system. Anticholinergic inhibition of the reticular activating system of the midbrain, leads to suppression of polysynaptic reflexes and a decrease in muscle tone. This is also characterized as indirect inhibition of the interneuronal junction of the spinal cord [39].

3) Direct activation of GABA-A receptor

Gamma-aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system. Its primary function is to reduce the excitability of neurons throughout the nervous system, essentially acting as a "brake" to prevent overstimulation. GABA exerts its effects by binding to specific receptors on the surface of neurons. The best known of these is the GABA-A receptor, a ligand-gated ion channel. When GABA binds to this receptor, it opens an integral chloride ion channel, allowing negatively charged chloride ions to enter the neuron. This influx of negative ions leads to hyperpolarization of the neuron, which reduces the likelihood of firing an action potential. The result is a calming or depressant effect on the nervous system, resulting in effects such as sedation, reduced anxiety, and muscle relaxation [38].

Methocarbamol does not increase GABA levels. The compound acts as a direct agonist, activating the GABA-A receptor to enhance inhibitory neurotransmission and produce its central depressant effects. The mechanism of action of the drug involves direct interaction and activation of the GABA-A receptor, to enhance inhibitory neurotransmission and produce its central depressant effects. The agent is classified as a direct agonist, which is a rare property among GABA-ergic drugs. This means that unlike many other CNS depressants that rely on the presence of natural GABA to function, Methocarbamol enhances GABA-mediated chloride influx, slowing neuronal activity. and can activate the chloride channel on its own, even in the absence of the natural neurotransmitter [38].

VI.2. Therapeutic application of Methocarbamol

Methocarbamol as a muscle relaxant is used in the symptomatic treatment of musculoskeletal conditions associated with painful muscle spasms to relieve muscle spasms and to treat conditions such as back pain, injuries, and muscle spasms [39]. The drug is applied to reduce muscle tension and spasms in patients undergoing surgery. The compound is administered in various forms, including tablets, capsules, and an injectable solution [38].

VI.3. Clinical and practical advantages of using Methocarbamol

Clinical and practical advantages of using of Methocarbamol include:

1) effective muscle relaxation: provides rapid relief of muscle spasms, allowing patients to engage in physical therapy and rehabilitation more comfortably.
2) non-narcotic option: unlike some pain medications, Methocarbamol is not a narcotic, which reduces the risk of addiction.
3) versatile use: can be used in a variety of situations, from acute injuries to the treatment of chronic pain [38].

VI.4. Drug interractions with Methocarbamol

Methocarbamol may interact with several medications and substances, including: CNS depressants: Alcohol, benzodiazepines, and opioids may enhance the sedative effects of the compound, leading to increased drowsiness and risk of respiratory depression. Some antidepressants may increase the risk of adverse reactions when taken with this agent. It is essential to use Methocarbamol under the guidance of a healthcare professional to ensure safety and efficacy [38].

VII. Sinergistic effect in combination of anti-inflammatory agents and myorelaxants

Anti-inflammatory agents and myorelaxants are the cornerstone of pharmacologic management of musculoskeletal disease. Combinations of these drugs are recommended for the treatment of muscle spasm and injury, whereas anti-inflammatory agents alone are used to treat inflammatory pain such as rheumatoid arthritis. Distem tabl. is a combination of an analgesic and antipyretic Paracetamol 300 mg (to reduce pain and fever) and a muscle relaxant Methocarbamol 380 mg. This medication relieves pain and muscle stiffness and is used to treat painful muscle spasms and is a valuable medication for managing muscle spasms and discomfort associated with various musculoskeletal conditions. Its effectiveness, non-narcotic nature, and versatility make it a preferred choice for many healthcare providers [46]. Bilayered tablets of methocarbamol and Acetaminophen are used [47]. Bilayered tablets of Methocarbamol and Ibuprofen [48] is a way for prevention of toxicity of non-steroidal anti-inflammatory drugs [49].

A prodrug has been synthesized by condensation of carboxylic group of Flurbiprofen with a skeletal muscle relaxant Methocarbamol, with the aim to obtain synergistic activity of two drugs, and to avoid Flurbiprofen mediated gastro-intestinal damage by ulcer effect [50].

CONCLUSION

Methocarbamol works by depressing the central nervous system, which helps relax muscles. In simpler terms, it changes the way the brain and spinal cord send messages to muscles, reducing the feeling of tightness and discomfort. This action helps relieve muscle spasms and allows for better movement and function. Clinical advantages of using Methocarbamol are: effective muscle relaxation, non-narcotic properties, versatile use. Sinergistic effect is obtained in combination of drug with Paracetamol. To avoid risk of drug interractions it is important the application of Methocarbamol to be according with the guidance of a healthcare to ensure safety and efficacy.

Abbreviation

CNS: central nervous system
FDA: Food and Drug Administration
GABA: gamma-aminobutyric acid
SPS: Stiff person syndrome

Additional information

Conflict of interest: The authors have declared that no competing interests exist.

Ethical statements

- The authors declared that no clinical trials were used in the present study.
- The authors declared that no experiments on humans or human tissues were performed for the present study.
- The authors declared that no informed consent was obtained from the humans, donors or donors' representatives participating in the study.
- The authors declared that no experiments on animals were performed for the present study.
- The authors declared that no commercially available immortalized human and animal cell lines were used in the present study.

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