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Review Article

MUSCLE RELAXANTS IN DENTISTRY - A REVIEW

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ABSTRACT

A muscle relaxant is a drug that affects skeletal muscle function and decreases the muscle tone. It may be used to alleviate symptoms such as muscle spasms, pain, and hyperreflexia. Muscle relaxants in dentistry are often used in treating temporomandibuar joint disorders. A temporomandibular disorder (TMD) is a very common problem affecting up to 33% of individuals within their lifetime. TMD is often viewed as similar to musculoskeletal disorders of other parts of the body, therefore the treatment often involves similar principles as other regions as well. This review article includes brief description of commonly used muscle relaxants in dentistry, that describes mechanism of action, metabolism, dosage and side effects of the drug.

INTRODUCTION

Many recent advances are approaching in medical technology, and various muscle relaxant medicines are prepared and applied which are safe, effective and non-depolarizing is always the key in clinical aesthetical practice. Muscle relaxants are commonly indicated for the treatment of two different types of conditions: spasticity from upper motor neuron syndromes and muscular pain or spasms from peripheral musculoskeletal diseases or injury such as low back pain. Muscle relaxants make up a heterogeneous group of drugs that mainly exert their pharmacologic effect centrally at the level of the spinal cord, the brainstem, or the cerebrum, and that have an insignificant, if any effect, at the muscle fibre level. Their centrally mediated mechanism of action can exert a clinically significant peripheral therapeutic effect (1).

Temporomandibular disorders (TMD) result from musculoskeletal dysfunction of the orofacial region affecting masticatory muscles, temporomandibular joints (TMJ), and other associated structures. The main characteristics of these problems are facial and TMJ pain, headache, earache, dizziness, masticatory muscle hypertrophy, limited mouth opening, locked jaw, abnormal teeth wear, joint sounds, and others(2). Dentist must be aware on the proper diagnosis and treatment of temporomandibular disorders, because they represent the second most frequent patients complaints (only less frequent than dental pain) (3). Symptoms are commonly related to pain surrounding the joint and may include headache, periauricular pain, neck pain, decreased jaw excursion, jaw locking, and noise at the joint with movement. In general TMD is divided into myofacial TMD or arthrogenic TMD. Myofacial TMD is associated with the pain from hyperfunctioning muscles of mastication leading to chronic myositis. In contrast, arthrogenic TMD is associated intracapsular pathology with pain at the level of the joint itself (4).

The available comparative clinical studies are reviewed, and the pharmacology, metabolism and adverse effects of the oral SMRs are discussed briefly. The drugs covered are carisoprodol, chlorphenesin carbamate, chlorzoxazone, cyclobenzaprine hydrochloride, diazepam, metaxalone, methocarbamol, and orphenadrine citrate, baclofen, dantroleneand tizanidine. Some centrally acting muscle relaxants such as phenprobamate and mephenoxalone have antianxiety action that may be related in part to their action (5), these muscle relaxants are useful in treating tempromandibulardisoders.

Cyclobenzaprine

Cyclobenzaprine is the most commonly used muscle relaxant.

Structure: Cyclobexaprine where it structurally resembles tricyclic antidepressants and differs from amitriptyline by only one double bond.

Action: Its therapeutic effect is centrally mediated and carries no direct peripheral action on the affected muscles. Its main pharmacologic action occurs at the brainstem and spinal cord levels and is partially explained by a depressant effect on the descending serotonergic neurons (6).

Metabolism: It is extensively metabolized in the liver and excreted as a glucuronated metabolite through the kidneys. It

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possesses a fairly long half-life of approximately 18 hours and can continue to accumulate for up to 4 days when administered at a frequency of three times per day. Likewise, concomitant use with monoamine oxidase inhibitors is absolutely contraindicated because this combination can cause a hyperpyretic crisis or even death.

Dosage: The initial starting dose should be 5 mg three times per day on as needed basis and can be titrated up to 10 mg three times per day per therapeutic effect or side effect. In patients with hepatic or renal insufficiency, it should initially be administered once per day given its relatively long half-life. Of note, one recent study showed equal efficacy of 5 and 10 mg doses, with the smaller dose showing a lower level of sedation (7).

Sideffects: The most common side effects are drowsiness, dry mouth, fatigue, and headache, followed by less often occurring adverse effects of diarrhoea, dizziness, abdominal pain, nausea, nervousness, blurred vision, and confusion (8).

Metaxalone

Metaxalone occurs as a white crystalline powder with a bitter taste that is insoluble in water and soluble in alcohol. Metaxalone is a centrally acting muscle relaxant with an unknown mechanism of action.

Metabolism: It is metabolized in the liver and excreted through the kidneys in the form of metabolites.

Mechanism: Although metaxalone mechanism of action is unknown, it is thought that metaxalone acts by depressing poly synaptic reflexes. Polysynaptics reflexes are pathways associated with muscle spasm. Whereas monosynaptic pathway involves stretch reflexes, muscle tone and normal posture.

Dosage: Typical adult dosing consists of 800 mg three to four times per day, mean peak plasma concentrations are attained in 2 hours. The onset of action is usually within 1 hour and the duration of action is about 4 to 6 hours. The drug has a plasma halflife of 2-3 hours. It is recommended to monitor liver function tests after initiation of this agent.

Sideffects: Common side effects include drowsiness, dizziness, nervousness, nausea, and headache. The following rare but serious adverse reactions have been reported: leukopenia, hemolyticanemia, jaundice, and hypersensitivity reactions (9)

Carisprodol

Carisoprodol is still a commonly prescribed muscle relaxant that should be dispensed with caution owing to the potentially addictive properties of its main metabolite, meprobamate.

Mechanism: Carisoprodol produces its muscle relaxant effect by depressing the interneuronal activity at the spinal cord level as well as in the descending tracts of the reticular formation (10). It is not recommended for use in the pediatric age population. In an in vitro study, carisoprodol allosterically modulated and directly activated GABAA receptors with an efficacy and potency greater than that of meprobamate. Preclinical drug discrimination studies demonstrate that carisoprodol has GABAergic activity in that chlordiazepoxide, pentobarbital, and meprobamate substituted for carisoprodol, and a GABA antagonist, bemegride, blocked its discriminative stimulus effects (11).

Metabolism: This drug is metabolized in the liver with meprobamate as its main metabolite. It is mainly excreted through the kidneys. Its metabolites are hydroxycarisoprodol, hydroxymeprobamate, and meprobamate, with meprobamate being the primary active metabolite.

Dosage: The usual adult dosage is 350 mg four times per day. The most common side effect is drowsiness.

Sideffects: Other central nervous system adverse effects that have been reported include ataxia, agitation, insomnia, and others. Adverse effects such as tachycardia, postural hypotension, nausea, erythema multiforme, and eosinophilia have also been seen (10).

Diazepam

Diazepam has commonly been used in the treatment of muscle spasm, especially in the acute setting. It belongs to a group of compounds called benzodiazepines, known for their potent anxiolytic, sedative, as well as muscle relaxant effects.

Mechanism: Their main mechanism of action is through central potentiation of the inhibitory g-aminobutyric acid (GABA) effect through presynaptic facilitation of GABA release.

Metabolism: Benzodiazepines are extensively metabolized in the liver into inactive and in some cases active metabolites. Compounds that lack active metabolites should be used as first-line agents in the elderly and in patients with liver or kidney insufficiency. Such com- pounds are lorazepam, clonazepam, temazepam, and oxazepam. Excretion principally occurs through the kidneys.

Sideffects: Some of the common side effects are drowsiness, confusion, ataxia, cognitive impairment, memory loss, agitation, and disinhibition. Of note, withdrawal symptoms may occur after only 4 to 6 weeks of use, and their potential for abuse should be taken into consideration(12).

Botulinum Toxin

The first indication that BoNT could be useful for treating pain was observed from anecdotal reports of patients treated for hyperfunctional facial lines who reported reduced frequency and severity of headache [13]. Soon thereafter, the pain-relieving effect of BoNT was reported during the treatment of oromandibular dystonia and cervical dystonia [14–18]. Today, BoNT is used for pain relief in numerous conditions including tension headaches,

Mechanism of Action: BoNT is a 150-Kilodalton exotoxin produced from clostridium botulinum, whose action is mediated through the cleavage of docking proteins that are responsible for membrane fusion of pre-synaptic vesicles. Type A bolulinum toxin (BoNT-A) cleaves the membrane associated protein "synaptosomal-associated protein 25" (SNAP-25) which is a member of the "soluble N-ethylmaleimide sensitive factor attachment protein receptor protein (SNARE) migraine headaches, post-herpetic neuralgia and myofacial TMD [19-23]. Inflammatory mediators like calcitonin gene-related peptide (CGRP), substance P and glutamate are also regulated by SNARE and VAMP docking proteins and, their release is inhibited by BoNT.

Dosage: BoNT injection for TMD is administered in relatively small doses and way below the estimated lethal dose of approximately 3000 units. We typically use a

concentration of 2.5-5.0 units per 0.1 mL of Botox witha starting dose of 10-25 units for each temporalis muscle, 25-50 units to the masseter muscles and 7.5-10 units to the lateral pterygoids.

Sideeffects: Difficulty chewing is the most common adverse effect, which results from local muscle weakness and is usually dose dependent. Muscle atrophy may result in cosmetic alterations and is another risk of the procedure. Higher volume of BoNT increased the risk of diffusion of toxin to nearby areas which may cause brow ptosis, blepharoptosis or diplopia if the temporalis muscle is injected too close to the orbit. Facial asymmetry may result if the masseter muscle is injected too close to the zygomaticus major [24-27].

Tizanidine

Tizanidine is a centrally acting muscle relaxant.

Mechanism: Through its alpha-2 adrenergic agonist properties, is thought to prevent the release of excitatory amino acids by suppressing polysynaptic excitation of spinal cord interneurons.

Metabolism: It is through the liver, and excretion is 60% through the kidneys and 20% through the feces.

Dosage: Tizanidine should be administered through a gradual upward titration from an initial dose of 2 to 4 mg at bedtime up to the maximum of 8 mg three times per day.

Sideffects: The bedtime dose can provide an analgesic effect as well as improve quality of sleep owing to the commonly occurring sedating side effect. Other common side effects are daytime drowsiness, hypotension, weakness, and dry mouth. Even though tizanidine's pharmacologic effect is similar to another alpha-2 agonist, clonidine, it possesses only a fraction of its blood pressure–lowering effect. Less commonly reported side effects of tizanidine are palpitations, bradycardia, dizziness, headache, nausea, elevated liver enzymes, and several rare cases of fulminant liver failure that led to death. Serial monitoring of liver enzymes is strongly recommended (28).

Baclofen

Structure: Structurally, baclofen is related to the centrally occurring inhibitory neurotransmitter GABA. Clinically, it has commonly been used for its muscle relaxant effects in the treatment of spasticity, as well as for its neuropathic analgesic properties in the treatment of trigeminal neuralgia pain.

Mechanism: Baclofen is a GABA-B receptor agonist with presynaptic and postsynaptic effects leading to a decrease in the excitatory neurotransmitter release as well as in substance P, which is involved in transmission of nociceptive impulses (29).

Metabolism: It is metabolized in the liver and excreted in the urine. Baclofen can be administered orally as well as intrathecally via an implanted pump mechanism when significant adverse effects preclude further dose escalation to achieve therapeutic effect. ***Dosage:*** Initial dosing of baclofen should be gradual, starting with 5 to 10 mg three times per day. The maximum recommended dose is 80 mg per day in divided doses; however, higher therapeutic doses in cases of refractory spasticity have been used without any significant untoward side effects.

Sideffects: Common side effects are weakness, sedation, and dizziness. At higher doses, baclofen can cause seizures, ataxia, and hallucinations. Abrupt withdrawal should be avoided because it can precipitate seizures and hallucinations.

CONCLUSIONS

There are four drugs and one drug class discussed in this article; while some can be used for muscle spasm due to musculoskeletal conditions, these drugs are really used mostly to treat spasticity due to neurological disorders such as spinal cord injury, brain trauma, and multiple sclerosis.

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