Role of Muscle Relaxants in the Treatment of Pain

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Robert I. Cohen and Carol A. Warfield

Key Points

- Muscle relaxants are a diverse group of medications with limited indications which share few structural similarities and where known, few mechanisms of action.
- There are four different mechanisms by which muscle relaxants are thought to work. Baclofen is active at the GABA-B receptor, tizanidine at the alpha-2 receptor, cyclobenzaprine at small TLRs in spinal microglia, and flupirtine (available in Europe) activates a potassium "M-current" in Kv7 potassium channels.
- As a group, muscle relaxants have a high side effect profile and produce limited benefit.
- FDA indications include treatment of "musculoskeletal disorders" and treatment of "spasticity."
- When used in musculoskeletal disorders such as low back pain, benefit has been established compared with placebo. However, there are few head-to-head trials against active agents suggesting that this group should be utilized as the first-line treatment. At the same time, there is some evidence that these drugs should not be used long term for chronic back pain.
- While evidence of efficacy is poor compared with other classes of drugs, usage of these medications is high, especially among primary care physicians (PCPs) and to a lesser degree by rheumatologists, psychiatrists, and neurologists.
- One of the most commonly prescribed agents, cyclobenzaprine is very closely related to the tricyclic antidepressants and it differs from amitriptyline by only one double bond.
- Carisoprodol is probably the most controversial member of this class which is metabolized by cytochrome P450-CYP2C19 to the barbiturate meprobamate.
- Baclofen is the mainstay for treatment of upper motor neuron syndromes leading to spasticity. Unacceptable sedation at therapeutically effective oral doses makes it desirable to administer this drug intrathecally which minimizes side effects.

Introduction

This chapter is about drugs approved to treat both spastic upper motor neuron conditions like cerebral palsy or multiple sclerosis and drugs that are used to relieve muscle spasm associated with musculoskeletal conditions such as acute non-radicular cervical or low back pain. Unlike other analgesic classes such as opioids and NSAIDS, the muscle relaxant drugs as a group share neither chemical structure nor mechanism of action. For example, two drugs approved to treat spasm, baclofen and tizanidine, work by different mechanisms. The former blocks GABA-B receptors and the latter is an alpha-2 agonist. Cyclobenzaprine, a drug approved for treating spasm-type pain in the low back, except for one double bond, is chemically identical to the tricyclic antidepressant amitriptyline.

If muscle relaxants are dissimilar in structure and mechanism of action, one thing they share as a class is a high side effect profile. Because the evidence for harm is strong and the evidence for benefit is weak, muscle relaxants should not be first-line drugs for musculoskeletal conditions like acute low back pain, and when used, the course should be brief unless there is clear evidence that for a given individual, there is ongoing benefit and lack of significant side effects [1].

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While these drugs are not recommended as first-line drugs, in practice, that is frequently how they are used. In a study based on insurance claims of 211,511 patients with low back pain, 69 % were treated with prescription medication with the tendency to prescribe muscle relaxants first; then, on subsequent visits, drugs tended to be prescribed in the following order: NSAIDs, antidepressants, and opioids, with opioids being the last to be prescribed [2].

While there may be a response to the publication of guidelines for best practice, the effect is not necessarily sustained. In 1994, the Agency for Healthcare Research and Quality (AHRQ) published evidence-based guidelines for best practice for low back pain that included recommendations similar to the WHO pain ladder for increased use of acetaminophen and NSAIDs and recommended against the use of muscle relaxant medications. Three years after release of the guidelines, Jackson et al. reviewed a database of ten million patient visits, half in the 3 years before the guidelines were issued and half following release [3]. They report that the AHRQ guidelines had a modest impact on practice, showing increased use of acetaminophen and NSAIDs and decreased use of muscle relaxants. As far as muscle relaxants are concerned, educational efforts have been disappointing due to a lack of sustained effect and repeated efforts at education would seem to be necessary.

Driven by an effort to reduce cost in addition to providing better care, California commissioned an expert physician panel to work with a California Medicaid provider covering more than 100,000 recipients. They identified five overused PCP behaviors, one of which was long-term treatment of back pain with muscle relaxants. Muscle relaxant use decreased significantly after an intervention carried out among 45 primary care physicians where their behaviors were discussed, educational material provided, and ongoing behavior monitored [4]. This is a recent study, and long-term follow-up data is not available to describe whether the educational and monitoring effort will continue and if the behavioral changes in physician prescribing will be sustained.

In the North Carolina Back Pain Project population, more than 1,600 patients with new onset of low back pain had a mean functional recovery in 16 days (8 days median) after their first physician visit. Within this group, half received prescriptions for muscle relaxants. Muscle relaxant use was characterized by younger age, higher proportion of female sex, greater likelihood of being on workers compensation, and an increased history of prior episodes of treatment for low back pain. In terms of return to baseline function, outcome was worse for patients receiving muscle relaxants; however, those who received muscle relaxants also tended to have the highest reported pain intensity and lowest baseline function due to pain interference [5]. A more recent study in the same state surveyed 5,357 households and determined that the rate of prescribing muscle relaxants for low back pain in elders was significantly lower than for younger age groups [6].

While it would seem that muscle relaxants must be very effective based on the extent to which they are prescribed, universally accepted evidence is scarce for muscle relaxants as effective treatment for low back pain. For example, in a recent review, although 17 of 137 studies on medical management of low back pain showed evidence of benefit for opioid and NSAID agents, no study on muscle relaxant treatment of low back pain met their standard for evidence of benefit [7]. Other studies have found muscle relaxants effective for treatment of acute nonspecific low back pain compared to placebo. In a meta-analysis that included 23 high-quality trials of muscle relaxants compared to placebo for low back pain, patients taking active drug were 50 % more likely to have a side effect such as drowsiness, dizziness, or dry mouth (relative risk 1.5). This study showed significant efficacy for acute pain but questioned it for chronic low back pain [8]. A recent review of agents targeting nociceptive and neuropathic pain components mentions that side effects of muscle relaxants outweigh their limited potential benefit as monotherapy for chronic low back pain [9].

Myofascial pain is a muscle pain phenomenon with taught bands (trigger points) that might benefit from muscle relaxants. However, a recent Cochrane review found only two small studies showing efficacy of cyclobenzaprine over clonazepam and placebo [10]. Another soft tissue pain syndrome, fibromyalgia, might also be thought to benefit from muscle relaxant drugs. However, in a recent review comparing medical management of fibromyalgia by various specialties, muscle relaxants were not as commonly used as other analgesic classes, and among muscle relaxants, cyclobenzaprine was the most commonly prescribed. That said, they were prescribed by 35 % of primary care physicians compared to 9, 4, and 3 % of rheumatologists, psychiatrists, and neurologists, respectively [11]. Monotherapy with pregabalin or duloxetine is most common, although 8 % of a recent study group of patients with fibromyalgia are receiving muscle relaxants [12].

Because muscle tension or spasm is brought to mind when discussing tension-type headache, one might find it logical to expect that tension-type headache would respond well to muscle relaxants. However, this has not proved to be the case, even for tizanidine [13]. Compared to migraine, tension-type headache has a higher age of onset, a more even female to male distribution, a greater overall cost, is usually bilateral, and has a pressing-tightening character [13]. Although this type of headache is described in terms of muscular symptoms, the use of muscle relaxants is not indicated for this condition [13].

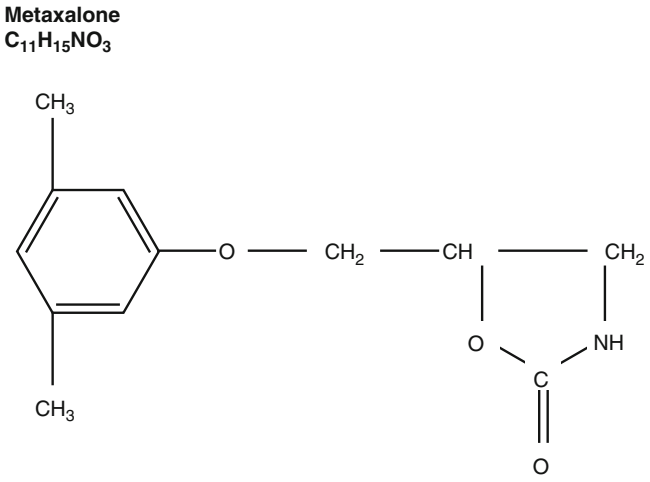

Fig. 7.1 Metaxalone was approved as a muscle relaxant in the 1960s when two small studies suggested benefit in degree of low back spasm over the painful area and decreased pain interference; however, there has been a dearth of recent studies establishing either a mechanism of action or efficacy

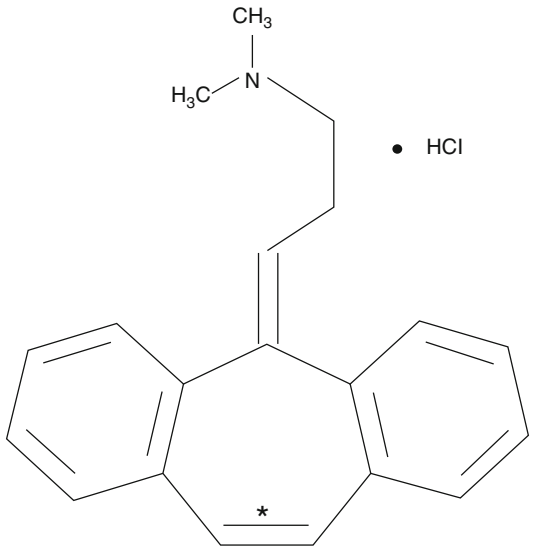

Fig. 7.2 Cyclobenzaprine is one of the most commonly prescribed muscle relaxants, and while the exact mechanism by which it produces a muscle relaxant effect is not known, it may produce inhibition of serotonergic descending systems

Metaxalone

Metaxalone was approved as a muscle relaxant in the 1960s when two small studies suggested benefit in degree of low back spasm over the painful area and decreased pain interference; however, there has been a dearth of recent studies establishing either a mechanism of action or efficacy (Fig. 7.1) [14]. A review of three muscle relaxants, including metaxalone, calls attention to the lack of understanding of the mechanism of action and lower standards for articles reporting on efficacy and safety when these drugs were brought to market in the 1960s and 1970s [14]. Proposed mechanisms for metaxalone included sedation or modulation of signals in polysynaptic fibers sensing passive stretch. Also reviewed were cyclobenzaprine and carisoprodol. Concern was raised for the abuse potential of the latter and thus suggested the former may be safer.

Cyclobenzaprine

Cyclobenzaprine is one of the most commonly prescribed muscle relaxants, and while the exact mechanism by which it produces a muscle relaxant effect is not known, it may produce inhibition of serotonergic descending systems (Fig. 7.2) [15].

Cyclobenzaprine is chemically related to amitriptyline from which it differs by only one double bond. Cyclobenzaprine metabolites also differ from amitriptyline metabolites by only one double bond. When doing forensic testing for the presence of these drugs and their metabolites, it may be necessary to use advanced techniques, such as high-performance liquid chromatography with ultraviolet detection or gas chromatography with nitrogen-phosphorus detection [16]. Laboratory technology involving high-performance liquid chromatography and tandem mass spectrometry is currently able to rapidly and quantitatively measure the following eight muscle relaxants in human blood: afloqualone, chlorphenesin carbamate, chlorzoxazone, dantrolene, eperisone, methocarbamol, pridinol, and tolperisone [17].

A meta-analysis of studies comparing cyclobenzaprine with placebo showed efficacy to be greatest on day 4 and then declining after the first week. NNT = 3, meaning three patients required treatment for one to show response [18]. In this now 10-year-old paper, a strong recommendation was made for comparing efficacy among active controls such as acetaminophen and NSAIDs which has since been done. A 2010 study shows efficacy for cyclobenzaprine 5 mg TID, but no benefit over an NSAID (ibuprofen 800 mg TID) during a 7-day treatment of acute cervical pain presenting at the emergency department of a large university hospital [19]. In this small study of 61 patients, although findings did not reach statistical significance, pain was more quickly relieved in patients receiving cyclobenzaprine, and the degree of pain intensity relief was greater for cyclobenzaprine compared to ibuprofen and was greatest with a combination of cyclobenzaprine and the NSAID. Cyclobenzaprine is commonly prescribed at a dose of 10 mg TID for muscle spasm with local pain and tenderness, is thought to increase range of motion, and is associated with a high incidence of side effects such as drowsiness and xerostomia. Interestingly, an

industry-funded dose ranging study suggests 5 mg TID produces less side effect while maintaining efficacy [20].

Cylobenzaprine, like the related tricyclic antidepressants and also opioids, activates toll-like receptors (TLR) in spinal microglial cells [21]. Glial cell activation can have profound effects modulating pain and affect opioid-induced analgesia and tolerance. A mechanism by which tricyclic antidepressant class drugs including amitriptyline, imipramine, desipramine, cyclobenzaprine, carbamazepine, and oxcarbazepine can potentiate opioid analgesia has been demonstrated in mice [21]. These findings may explain how these drugs function as analgesics in chronic pain syndromes.

Carisoprodol

Regarding the non-tricyclic antidepressant muscle relaxants, one of the most controversial is carisoprodol (Fig. 7.3). Compared to placebo, it demonstrates efficacy for relief from acute muscle spasm and improved functional status at doses of 250 mg QID, although it is usually prescribed at 350 mg QID, a dose associated with a higher incidence of adverse effects [22]. Ralph et al. suggest carisoprodol would be a better drug if prescribed at the lower dose of 250 mg; however, the study was industry-sponsored, and authors disclosed they served on a speaker's bureau for the product [22].

Carisoprodol is metabolized to meprobamate, an anxiolytic and hypnotic with known abuse potential, which also has a longer half-life. Either drug at a sufficient dose can produce mental impairment. An extensive database on non-alcoholic impaired drivers maintained in Norway includes extensive testing of mental function matched with forensic blood testing for drugs including carisoprodol and meprobamate. Impaired drivers admitted to consuming doses of carisoprodol greater than 700 mg and high carisoprodol levels correlated with impairment. Interestingly, Bramness et al. also reported that regular users of carisoprodol did not demonstrate high levels of meprobamate. The study was not designed to identify the mechanism though it was suggested that these patients had developed tolerance for the impairment caused by this active metabolite, while occasional users of carisoprodol who had not yet developed tolerance tended to have higher levels of meprobamate [23]. Metabolism of carisoprodol to meprobamate occurs via the CYP2C19 variant of cytochrome P450 in the liver. If there is variation of the cytochrome P450-CYP2C19 gene, it would be expected to affect meprobamate levels and subsequent side effects. For example, an individual with two CYP2C19 alleles may make more meprobamate and may have increased potential risk for impairment while driving [24].

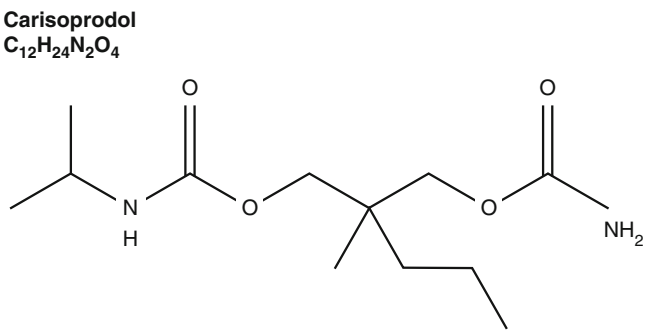

Fig. 7.3 Regarding the non-tricyclic antidepressant muscle relaxants, one of the most controversial is carisoprodol. Compared to placebo, it demonstrates efficacy for relief from acute muscle spasm and improved functional status at doses of 250 mg QID, although it is usually prescribed at 350 mg QID, a dose associated with a higher incidence of adverse effects

An extreme case of withdrawal occurred in a patient taking a very high dose of carisoprodol, more than 17 g/day. Some might conclude that if such large doses could be tolerated, carisoprodol may actually have a high therapeutic index. In this case, withdrawal delirium occurred in a patient with back pain due to trauma who purchased large doses of carisoprodol over the internet when her health insurance lapsed. She was noted to be taking very high doses, up to fifty 350 mg tablets per day. She was not overly sedated and probably developed tolerance to the active metabolite, meprobamate. Seven days after deciding to stop, she lost orientation to person, place, and time and reported visual hallucinations, and postural and action tremors were noted on exam. Symptoms of delirium responded to treatment with 2 mg doses of lorazepam [25].

Concern for carisoprodol abuse since the Bramness study has led Norway to reclassify it as class-A (most restricted) led 39 of the United States to restrict its prescribing and led to a drive for the DEA to reclassify carisoprodol as a class-IV drug [26]. A case-control study was done in elderly patients identifying 8,164 cases and as many controls from a population of 1.5 million enrollees in a Medicare Advantage plan offered by a large HMO. Elderly patients receiving muscle relaxants were 1.4 times more likely to suffer a fracture injury, and the authors advised extreme caution be used prescribing muscle relaxants for older adults [27].

As our population ages, increased attention should be given to use and monitoring in elderly patients. Muscle relaxants are not recommended for patients over 65 years of age due to increased risk of injury due to side effects and should specifically to be avoided for elderly patients with bladder outflow obstruction and cognitive impairment [28].

However, while many reports as well as common wisdom advises against the use of muscle relaxants in the elderly, it has recently been suggested that skeletal muscle relaxants may be appropriate in this age group, especially if the patient does not have a high burden of disease and first-line medications were ineffective [29].

Baclofen

The muscle relaxants are a dichotomous group with indications for "skeletal muscle conditions" and for "spasticity" originating in the central nervous system, such as found in upper motor neuron disorders. Spasticity is an active muscle process whereby loss of central modulation causes increased excitability of the stretch reflex such that there is a velocity-sensitive response to limb manipulation [30]. Spasticity results from upper motor neuron pathology with abnormal stretch reflexes that may be the result of changed muscle structure, development of new spinal level collaterals, and/or failure to adequately regulate supraspinal pathways resulting in increased spinal reflex responses [31].

The traditional mainstay of treatment for upper motor neuron spasticity is baclofen, which has been used orally since the 1970s and, more recently, intrathecally (Fig. 7.4). To assess the possible survival advantage of intrathecal baclofen for cerebral palsy patients, 359 patients from Minnesota with intrathecal baclofen pumps were compared with 349 matched controls that were selected from 27,962 Californians with CP who did not have pumps. Interestingly, the survival for those with intrathecal baclofen was somewhat better than their well-matched controls [32].

Whereas benzodiazepines work at GABA-A receptors, increasing chloride ion currents causing cell hyperpolarization and thus inhibiting action potentials, baclofen activates the GABA-B receptor [33]. Designed to mimic GABA, baclofen is basically a GABA molecule with a chlorinated phenol moiety, hence its chemical name p-chlorophenyl-GABA. The only available prescription medicine that activates GABA-B receptors, baclofen has been the drug of choice for the treatment of tetanus, stiff man syndrome, cerebral palsy, and multiple sclerosis. In addition to treatment of spasticity, GABA-B receptor activation may also have a role in treatment of pain, depression and anxiety, drug addiction, and absence epilepsy, and GABA-B receptor antagonism may have a role in treating cognitive impairment [33].

Baclofen as a visceral pain reliever has been studied in sensitized visceral pain models where it appears to have a central site of action in the dorsal horn of the spinal cord at GABA-B receptors and, in a dose response fashion, attenuates both pain behavior and expression of FOS (a nociceptive marker). However, in the dose range that produced the analgesic effect, marked sedation was also observed [34].

In addition to the side effects of its use, in its withdrawal, baclofen may produce respiratory failure, unstable hemodynamics, seizures not responsive to usual treatment, and delirium. Interestingly, delirium is caused by both overdose and rapid withdrawal. If an intrathecal pump fails or needs to be removed due to infection, it is difficult using oral dosing to produce sufficient levels of baclofen in the CSF to prevent these catastrophic effects, and treatment with benzodiazepines, propofol, neuromuscular blocking agents, dantrolene, and tizanidine may be required in an ICU setting [35]. Baclofen and tizanidine withdrawal acutely produced extrapyramidal signs, delirium, and autonomic dysfunction that were eventually reversed when baclofen was restarted in a sufficient dose [36]. For a clear review of the differential diagnosis of baclofen withdrawal, the reader is referred to a recent case report with an excellent summary chart [37].

Other Muscle Relaxants

Of the muscle relaxants not available in the United States, one that should be mentioned is flupirtine (Fig. 7.5).

Developed in Germany in the 1980s, flupirtine has been described as having many potential analgesic roles, and, equipotent to tramadol, it may also function as a muscle relaxant. Flupirtine activates Kv7 potassium channels, produces an M-current, and dampens hyperexcitable neurons [38]. The Kv7 potassium channel is activated by muscarine and is receiving a great deal of attention recently. There is speculation that further work could lead to new treatments for Alzheimer's disease, seizure disorders, and chronic pain. The subtypes of Kv7 potassium channels regulate the potassium

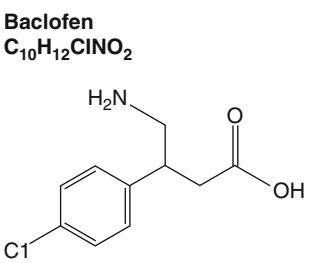

Fig. 7.4 The traditional mainstay of treatment for upper motor neuron spasticity is baclofen, which has been used orally since the 1970s and, more recently, intrathecally

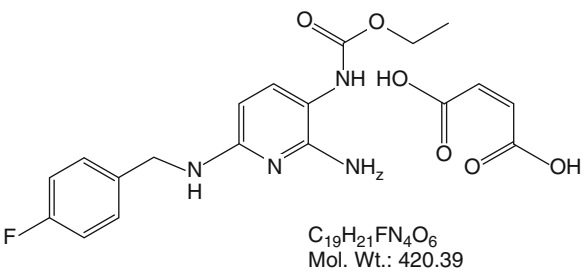

Fig. 7.5 Of the muscle relaxants not available in the United States, one that should be mentioned is flupirtine. Developed in Germany in the 1980s, flupirtine has been described as having many potential analgesic roles, and, equipotent to tramadol, it may also function as a muscle relaxant

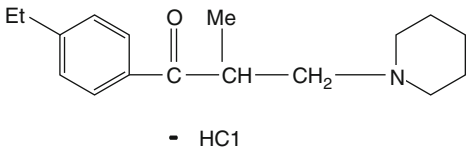

Fig. 7.6 Used to treat painful contracture and spasticity, eperisone inhibits gamma-efferent firing in the spinal cord and produces local vasodilatation and rarely has adverse CNS affects. It has good bioavailability, short onset time, and rapid elimination making it suitable for initial treatment of acute low back pain

Fig. 7.7 Tizanidine is an alpha-2 agonist which has been shown to have beneficial results in the treatment of muscle spasm

M-current activated by muscarine. Thus, muscarine (or other drugs acting at these sites) can lead to changes in potassium conductance with activation leading to hyperpolarization and blockade leading to increased neuronal activity. The M-current is a low-threshold, non-inactivating voltage-dependent potassium current at the Kv7 channel capable of limiting repetitive firing of neuronal action potentials [39]. Hyperexcitable states such as seizure disorders and chronic pain, including muscle pain and spasm, may respond to channel activators, while blockers at Kv7 channels might increase neuronal activation and provide a treatment of Alzheimer's [39].

Used to treat painful contracture and spasticity, eperisone inhibits gamma-efferent firing in the spinal cord and produces local vasodilatation and rarely has adverse CNS effects (Fig. 7.6). It has good bioavailability, short onset time, and rapid elimination, making it suitable for initial treatment of acute low back pain [40].

While eperisone appears effective for treatment of muscle contracture and chronic low back pain, it is also touted to be free of sedative side effects [41]. Blood flow in low back muscles may increase with eperisone treatment over 4 weeks in comparison with placebo and active physical therapy protocols [42].

Tizanidine

Tizanidine is an alpha-2 agonist which has been shown to have beneficial results in the treatment of muscle spasm (Fig. 7.7). The reader is referred to a major review of the drug class muscle relaxants, Chou et al. [43]. This is an important work and will be given attention in the following paragraphs. The aim of the ambitious 237-page electronic book in the public domain, available at http://www.ncbi.nlm.nih.gov/pubmed/20496453, was to determine among nine muscle relaxants (baclofen, carisoprodol, chlorzoxazone, cyclobenzaprine, dantrolene, metaxalone, methocarbamol, orphenadrine, and tizanidine), whether one or more were superior in efficacy or safety for treatment of muscle spasticity mostly due to multiple sclerosis or for musculoskeletal conditions such as neck and low back pain compared with the others. Only tizanidine was found to have fair quality evidence for effectiveness in both spasticity and musculoskeletal conditions. Spasticity was evaluated in 59 trials; however, only 18 included an active control, which was sometimes another muscle relaxant. None of the 18 was considered high quality with each containing at least two methodological flaws. For example, there were nine trials comparing baclofen to tizanidine and eight comparing diazepam with tizanidine, baclofen, or dantrolene. Except for one trial comparing clonidine to baclofen, they reported no muscle relaxant trials where the following common adjuvants were used as active controls: clonidine, gabapentin, and other benzodiazepines. There were 5 reviews and 52 trials reviewed for efficacy and safety for muscle relaxant use in musculoskeletal conditions (as opposed to spasticity). Twelve trials used a muscle relaxant as an active control against another muscle relaxant. No active control trials for efficacy or safety for musculoskeletal conditions were found for baclofen, dantrolene, metaxalone, or orphenadrine.

Based on nine head-to-head trials, Chou et al. report that tizanidine and baclofen have similar efficacy for the treatment of spasm including improvement in tone, clonus, and assessments of function and physician and patient preference [43].

Head-to-head trials of muscle relaxants used for musculoskeletal conditions are less common with only two showing carisoprodol or chlorzoxazone, both superior to the active control diazepam, and three showing cyclobenzaprine equivalent to it [43]. Although methodologies were flawed, Chou et al. report that compared to placebo, efficacy has been shown for cyclobenzaprine, carisoprodol, orphenadrine, and tizanidine, while evidence of efficacy is poor for baclofen, chlorzoxazone, dantrolene, methocarbamol, or metaxalone [43].

The Oregon Health & Science University group also reviewed relative risks of treatment including abuse, addiction, and other adverse effects. Used in treatment of spasticity, tizanidine and baclofen have different side effect profiles with the former associated with xerostomia and the latter with weakness [43]. Other muscle relaxants could not be

Diazepam

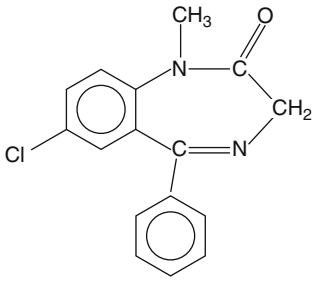

Fig. 7.8 Diazepam. Benzodiazepines have been shown to reduce muscle spasm, especially in the postoperative period but their use is often limited by sedation

compared head to head due to lack of good evidence. Major side effects included hepatic toxicity for dantrolene and tizanidine but not for baclofen, and quantitative comparisons could not be made for serious adverse events such as seizures, withdrawal reaction, and overdose. Frequent adverse events included somnolence, weakness, dizziness, and dry mouth. Abuse and addiction were not evaluated in these studies.

Diazepam

Benzodiazepines have been shown to reduce muscle spasm, especially in the postoperative period but their use is often limited by sedation (Fig. 7.8). This class of drugs is discussed elsewhere in the text.

Dantrolene

Dantrolene appears to work by abolishing excitation/contraction coupling within muscle (Fig. 7.9). While dantrolene has the capacity to reduce muscle spasm and spasticity, its use has been severely limited by its hepatic, cardiovascular, and pulmonary toxicity and by severe CNS side effects including visual disturbances, hallucinations, seizures, and depression. It remains useful as a treatment for malignant hyperthermia.

Orphenadrine

While technically an anticholinergic of the antihistamine class and not a muscle relaxant drug, orphenadrine has been used to treat muscle spasm and pain, but its effectiveness in doing so has not been clearly proven (Fig. 7.10).

Dantrolene
$C_{14}H_{10}N_4O_5$

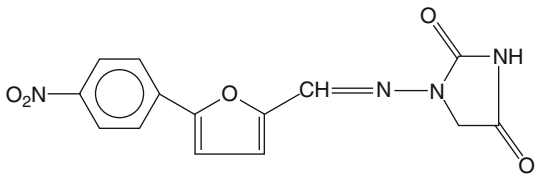

Fig. 7.9 Dantrolene appears to work by abolishing excitation/contraction coupling within muscle

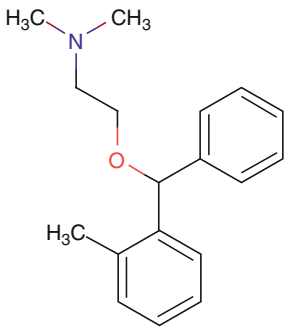

Fig. 7.10 While technically an anticholinergic of the antihistamine class and not a muscle relaxant drug, orphenadrine has been used to treat muscle spasm and pain, but its effectiveness in doing so has not been clearly proven

Quinine
$C_{20}H_{24}N_2O_2 \cdot ½H_2O_4S \cdot H_2O$

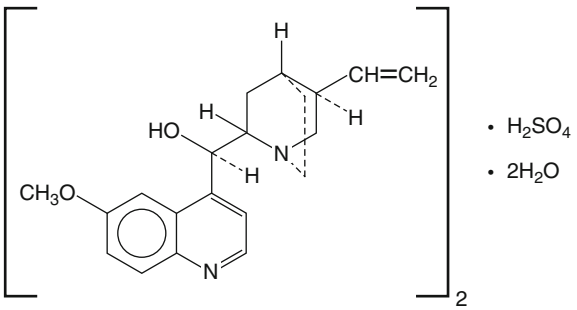

Fig. 7.11 Although not classified as a skeletal muscle relaxant, quinine has long been used to treat muscle cramps

Quinine

Although not classified as a skeletal muscle relaxant, quinine has long been used to treat muscle cramps (Fig. 7.11). An extensive Cochrane review summarizes 23 trials with

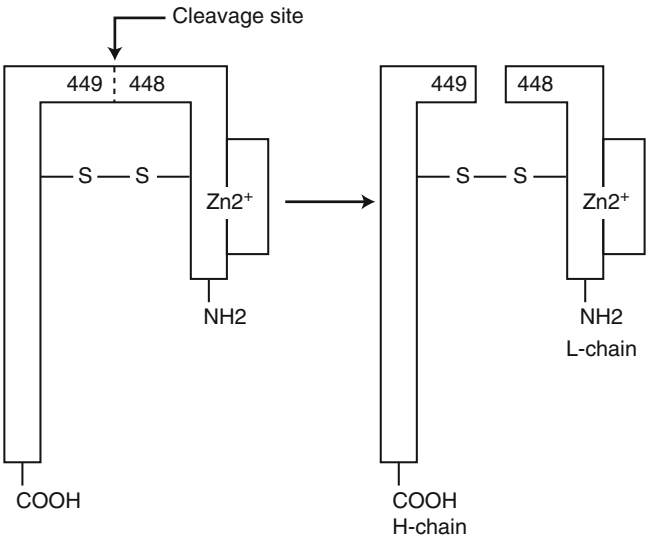

Fig. 7.12 Botulinum toxin type A, but not type B, is helpful for spasticity acting presynaptically at the myoneural junction by inhibiting acetylcholine vesicle release leading to decreased contraction strength and is now considered first-line treatment for spasticity

1,586 participants at daily doses between 200 and 500 mg and concludes there is evidence of moderate quality for reduction in intensity and frequency of cramping pain and that when used for up to 60 days, although there is increase in side effects such as GI symptoms, the serious side effect rate is similar to placebo [44].

Botulinum Toxin

Finally, no discussion of muscle relaxants to treat musculoskeletal conditions and spasticity would be complete without mentioning botulinum toxin. Botulinum toxin type A, but not type B, is helpful for spasticity acting presynaptically at the myoneural junction by inhibiting acetylcholine vesicle release leading to decreased contraction strength and is now considered first-line treatment for spasticity (Fig.7.12) [31]. Further details in the mechanism of action and application of botulinum toxin in treatment of disease are discussed elsewhere in this textbook.

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