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REVIEW

Muscle pain

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Abstract

Muscle pain, also known as myalgia, is most commonly associated with sprains or strains. It frequently presents as redness at the site of injury, tenderness, swelling and fever. Muscle pain may occur as a result of excitation of the muscle nociceptor due to overuse of the muscle, viral infections or trauma. The most important endogenous substance released in response to the damaged tissues or nociceptor nerve endings in regards with muscle pain is adenosine triphosphate (ATP). Optimal pain management involves a combination of non-opioid, opioid analgesics, adjuvants, as well as non-pharmacologic strategies. Non-opiod analgesics include paracetamol and non-steroidal anti-inflammatory drugs (NSAIDs) like ibuprofen, which are indicated for mild to moderate pain. Whereas moderate to severe pain acquires opiod analgesics. This article provides an overview of muscle pain, the management and treatment thereof.

Keywords: muscle pain, myalgia, sprains, strains, analgesics, opiods, nsaids

Key Summary Points

- Muscle pain, known as myalgia, can be in one targeted area or across many muscles, occurring with overexertion or overuse of these muscles.
- Pain can be classified as acute or chronic pain and further categorized as nociceptive or neuropathic.
- Causes of muscle pain include stress, physical activity, infections, hyper or hypo-thyrodism.
- Sprains and strains are the most common types of muscle pains.
- Optimal pain management involves utilizing a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacologic strategies.

Introduction

Muscle pain, medically known as myalgia, can be described as pain that originates in any muscle of the body. The pain can be in one targeted area or across many muscles, usually occurring with overexertion or overuse of these muscles.

"*Pain, like love, is all consuming: when you have it, not much else matters, and there is nothing you can do about it. Unlike love, however, we are actually beginning to tease apart the mystery of pain.*"[1]

Myalgia may also occur without a primary trauma and this is frequently associated with a viral infection. The severity of pain may range from mild to severe, depending on the cause thereof. It can typically be described as cramping and aching. Signs and symptoms associated with muscle pain include; redness at the site of injury, tenderness, swelling and fever.[2]

Classification of pain

Pain is classified according to its duration and pathogenesis. Depending on the duration of pain, pain can either be classified as acute or chronic.

Acute pain:

This type of pain usually arises after obvious tissue damage and is therefore nociceptive in nature. The pain can be clearly located and resolves upon healing. It has a protective nature as it distinctly warns individuals about harmful situations.[3]

Chronic pain:

Chronic pain usually persists from months to years. The intensity of the pain no longer correlates with the causal stimuli as there is changes to the nerve function and transmission. The pain loses its protective and warning signs and thus serves no purpose.[3]

Further to this pain can either be classified as nociceptive or neuropathic:[4]

Nociceptive pain:

This is known as a very high threshold pain that is activated in the presence of stimuli. It is the normal physiological pain that is associated with a warning signal that something is threatening the person's bodily tissues. It is felt when a person comes into contact with a stimuli, i.e. hot, cold or sharp. Nociceptive pain acts as a physiological protective system and signals when there is impending tissue damage. It requires immediate attention and

action, like pulling your hand off a hot plate within an instant. Sprains and/or strains, broken bones, lower back pain from disc disease or injury, and burns are examples of nociceptive pain.[1,4,5]

Neuropathic pain:

This pain is considered to be maladaptive, and is a disease state of the nervous system. This type of pain occurs after there is damage to the nervous system. It is experienced due to transmission of pain signals in the absence of actual tissue damage or inflammation, like fibromyalgia, tension headaches and irritable bowel syndrome. This pathological pain occurs when there are heightened sensory signals in the central nervous system and a low threshold of pain.[1,4,5]

Causes of muscle pain

Muscle pain can be caused by stress, tension or physical activity. Some medical conditions known to cause muscle pain include.[6-10]

- Infections
- Hyper or hypo-thyrodism
- Hypokalemia
- Autoimmune conditions e.g. lupus
- Side effects of certain medications (i.e. the Statins)

Pathophysiology of muscle pain

Muscle pain may occur as a result of excitation of muscle nociceptor due to overuse of the muscle, inflammation and or trauma. When the impact has occurred, endogenous substances are released in response to damaged tissues or nociceptor nerve endings. Some of these substances include;[11]

- Potassium ion
- Prostaglandin E_2
- Bradykinin
- Serotonin
- Neuropeptides e.g. substance P
- Somatostatin
- Adenosine triphosphate

Of all substances released the most important one involved in muscle pain is adenosine triphosphate (ATP) which is released from muscle cells at high concentrations after damage to the muscles. The increased levels of substances released from the damaged tissues stimulate the nociceptors directly. The pain experienced during movements of these damaged tissues are as a result of the low threshold of sensitized muscle nociceptors.[11-13]

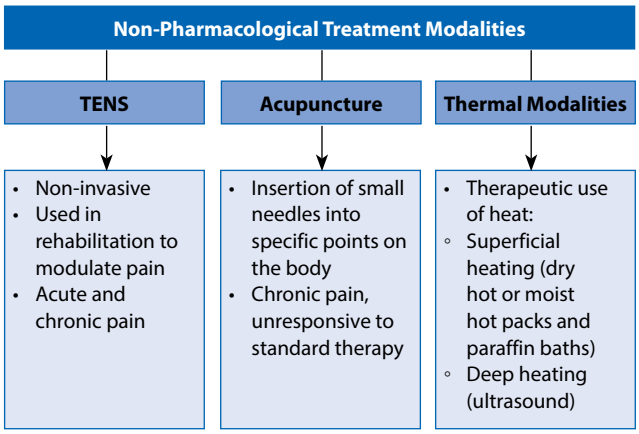
In the case of muscle inflammation the level of substance P and nerve growth factor (NGF) increases, which in turn leads to hyperalgesia known as increased sensitivity to painful stimuli in the affected muscle.[11,13]

Sprains and strains are the most common types of muscle pains and is especially frequent in the elderly. Sprains occur as a result of overstretching of the ligaments. This can be caused by twisting of joints. The most regularly affected parts of the body are the ankles and wrists. This is usually followed by pain, swelling and at times bruising. Strains on the other hand are the overstretching of muscle or tendons.[4,14]

Management of muscle pain

Non-Pharmacological Management

The non-pharmacological treatments for muscle pain are illustrated in Figure 1.



[TENS: Transcutaneous Electrical Stimulation]

Figure 1: Non-pharmacological treatments of muscle pain

Treatment modalities include the following

Transcutaneous electrical stimulation (TENS)

TENS is a non-invasive procedure used in rehabilitation to modulate pain.[15] Electrical currents are delivered through the skin to activate central inhibitory pathways decreasing central excitability. Activation of the descending inhibitory pathways from the midbrain and brainstem leads to inhibition of the nociceptive neurons in the spinal cord. This is used for acute and chronic pain.[16-17]

Acupuncture

It is a traditional Chinese-based therapeutic method which involves the insertion of small, solid needles into specific points in the body in order to improve health or modify painful states.18 There are several postulated mechanisms of action. Acupuncture are indicated for chronic pain unresponsive to standard therapy. Acupuncture may work via same mechanisms of other complimentary therapies (placebo, diversion etc).[19]

Thermal modalities

Thermotherapy is the therapeutic use of heat, usually greater than that of body temperature, to the body.[20] Thermal modalities are classified as superficial thermotherapy (the application of a device that is used primarily to heat structures to 1 cm deep) and deep thermotherapy (the application of a device that causes a tissue temperature rise at 3 – 5 cm deep). Superficial heating modalities include; dry hot packs, moist hot packs and paraffin baths. Deep heat modalities include therapeutic ultrasound.[20]

Pharmacological management

Optimal pain management involves utilizing a combination of non-opioid, opioid analgesics, adjuvants and non-pharmacologic strategies. The approach must be adapted such that it is possible in resource limited areas as well. Treatment guidelines should therefore consider the acute and chronic phase of the pain state, and recommend the appropriate pharmacologic or non-pharmacologic treatment using evidence based recommendations. They should also indicate when a single mode of treatment is appropriate and when multiple modes are required .[21-23]

The multimodal approach to pain management involves administering two or more analgesics with different mechanisms of action. The routes of administration may also be different. This approach as aimed at providing a synergistic effect of analgesia using the lowest possible doses of these medications than if they were used alone.[24]

Non-opioid analgesics

The following non-opioid related medicines are available for managing pain in children: paracetamol, and the non-steroidal anti-inflammatory drugs (NSAIDs), for example naproxen, ibuprofen and mefenamic acid. They adequately treat mild pain and moderate-to-severe pain in combination with other medicines, particularly opioids, to provide more effective relief and reduce adverse effects.[25]

Paracetamol

Paracetamol is one of the drugs of choice in pain management, due to its excellent safety profile and lack of any significant side-effects.[26] It acts as a prodrug, with an active cannabinoid metabolite. In the brain and spinal cord, paracetamol follows deacetylation to its primary amine (p-aminophenol) which is conjugated with arachidonic acid to form *N*- arachidonolylphenolamide, a compound known as an endogenous cannabinoid. The involved enzyme is fatty acid amide hydrolase. *N*-arachidonolylphenolamide is an agonist at the Transient Receptor Potential Cation Channel, Subfamily V, Member 1 (TRPV1) receptors and an inhibitor of cellular anandamide uptake, which leads to increased levels of endogenous cannabinoids, inhibiting cyclooxygenases in the brain at concentration that are probably not attainable with analgesic dosages of paracetamol. It is of interest to note that a cannabinoid-1 receptor antagonist, given at a dosage level that completely prevents the analgesic activity of a selective cannabinoid receptor agonist, completely inhibits the analgesic activity of paracetamol as well. This fact allows us to explain the mechanism of action of paracetamol in more detail. Despite this finding, however, the definite proof that the analgesic and antipyretic effects of paracetamol are dependent on COX-inhibition is still unclear. Hence, it works effectively when is combined with codeine for more effective control of moderate-to-severe pain and discomfort.[27]

Paracetamol is available orally, in several tablet and liquid formulations however the dosage should be guided by the age and general condition of the patient.[28]

Non-steroidal anti-inflammatory drugs

Non-Steroidal Anti-inflammatory agent (NSAIDs) competitively inhibit the cyclo-oxygenase (COX) enzyme, the enzymes facilitate the bioconversion of arachidonic acid to inflammatory prostaglandins. This results in the blockade of prostaglandin synthesis and subsequently dampened inflammatory responses.[29-30] COX-1 and 2 are isozymes that only vary genetically. NSAIDs have three pharmacological preferred attributes i.e. analgesia, anti-inflammatory and anti-pyretic activity. They generally have similar analgesic properties but selection is based on their receptor selectivity. COX-1 receptor activation produces gastric effects that mediate hyper-secretion of gastric acid, thinning of the lumen and propagate the development of gastric ulcers. These medicines have various formulations.[31]

The only over the counter (OTC) available pain medications is aspirin (S0) and paracetamol (S2) and requires no prescription. The NSAID ibuprofen is S2 when intended for the treatment of post traumatic conditions such as pain, swelling and inflammation, for a maximum period of five days without a prescription. All other NSAIDs are S3 and can only be obtained via a prescription from a physician (Act 101 of 1965).

It is important to note that NSAIDs have ceiling analgesic effects but the Cyclooxygenase -2 mediated anti-inflammatory effects are dose dependant.[33] COX-2 is not detected in most normal tissues, but its expression is rapidly induced by stimuli such as proinflammatory cytokines (IL-1b, TNFα), lipopolysaccharides, mitogens and oncogenes (phorbol esters), fibroblast growth factor, epidermal growth factor, (luteinizing hormone, LH) and fluid-electrolyte hemostasis, resulting in increased synthesis of PGs in inflamed and neoplastic tissues.[29]

The non-steroidal anti-inflammatory drugs (NSAIDs), such as asprin, ibuprofen, diclofenac, ketorolac and mefenamic acid, have analgesic and anti-inflammatory properties, which are useful in the management of pain.[27]

Ibuprofen is one of the most frequently used NSAIDs for mild and moderate pain.[34] The medicine has gained advantage in the market as is available as an over-the-counter medication for fever reduction, as well as pain relief. Studies have shown ibuprofen to be superior in terms of its safety profile, compared to ketorolac. However, ketorolac has been used as a single agent for the treatment of postoperative pain, especially when used as an adjuvant to opioid analgesia.[35]

If pain is constantly present, analgesics should be administered on a regular time schedule, i.e. 'by the clock', whereby the medicine is administered at a fixed time interval with dosages tailored according to the patient's pain, with the next dosage given before peak time effect of the previous dosage has worn off. This will result in more predictable and consists level of analgesia. [23,25]

Table 1: Formulations, dosages and side-effects of various pain medications

Drug	Formulations	Dosages	Side effects
Paracetamol	Tablets Suppositories Intravenous Solutions	1-4 g/daily 1g q 6 hourly	**Hypersensitivity skin reactions**: neutropenia, thrombocytopenia Nephrotoxicity Hepatoxicity
Non-specific NSAIDs			
Ibuprofen	Tablets Topical patch Topical Gel Oral syrup	200-400 mg q 4-6 hourly	Same as for diclofenac
Indomethacin	Capsules	25-50 mg q 6-8 hourly	**CNS effects:** Dizziness drowsiness, mental confusion, headache in less than 10% to patients Corneal deposits
Ketaprofen	tablets	200 mg daily with food	Same as Diclofenac
Diclofenac	Tablets Intramuscular Injection Topical Gel Suppositories Topical patch	**Oral:** 25-50 mg q 8hourly, to maximum of 150 mg/day **Intramuscular:** 75 mg q 12 hourly, maximum of 150mg/day for 2 days only **Suppositories:** 100 mg daily	**GIT:** Gastric erosion ,peptic ulceration **Hypersensitivity reactions:** Skin rashes, pruritus and angioedema Renal toxicity
Piroxicam	Tablets Topical Gel	40mg/day	Same as Diclofenac
Naproxen	Tablets	500 mg q 12 hourly	Same as Diclofenac
Mefanemic Acid	Oral syrups Tablets Suppositories	500 mg q 8 hourly	
COX-2 Inhibitors			
Celecoxib	Tablets Capsules	100-200 mg q 12 hourly	**GIT:** Nausea , dyspepsia, diarrhoea , flatulence Steven-Johnsons Syndrome **Hypersensitivity reaction:** Toxic epidermal necrolysis Renal toxicity
Etoricoxib	Tablets Capsules	60-90 mg q 12 hourly	Same as for Celecoxib
Meloxicam	Tablets Capsules	7.5 mg q 12 hourly or 15 mg daily	Same as for Celecoxib

Aspirin and paracetamol are very popular as over the counter pain medication.[1] Selection of analgesic used is determined by the side effect profile and severity of pain.

Opioid analgesics

Opioid analgesic will provide analgesia for moderate to severe pain, for the vast majority and with a wide margin of safety.[36] This group includes the following examples: codeine, morphine, oxycodone, methadone, fentanyl and pethidine. Opioids can be divided into weak and strong opioids. Weak opioids are used alone or in combination with other analgesics, in management if moderate pain. Strong opioids are usually reserved for severe pain.[3]

Opioids are the third-step in the pain treatment ladder and the recommended treatment of moderate or severe pain.[37] One of the undesirable effects which is of great concern in healthcare is dependence, which is associated with prolonged use of opioids. Concomitant administration of an opioid with ibuprofen can reduce the amount of opioid analgesic required for pain control.

Pethidine, morphine and fentanyl

A variety of opioids are available for use; however, there is insufficient evidence to support a preference of one opioid over another.[38-39] Pethidine does not provide good analgesia compared to morphine and should not be used long-term because of the possible accumulation of its toxic metabolite, nor-pethidine, that can result in seizures. Fentanyl provides approximately equal analgesic effects to morphine, and can be used for rapid analgesia over short periods of time if morphine is contra-indicated. Opioids are the most commonly administered intravenous agents for moderate to severe pain. The opioid dosage that effectively relieves pain can differ, and should be based on a pain severity assessment. However, the long-term use of opioids is associated with constipation; therefore, a combination of a stool softener and stimulant laxative can be

used as prophylaxis when it is anticipated that these agents will be used over an extended period of time. [38-39]

Morphine is well established as the first-line strong opioid and is available in both immediate-release and prolonged-release formulations. Immediate-release tablets are used to individualise patient dosages and have an adequate dosage for pain control. Prolonged-release oral formulations improve patient compliance by allowing longer dosing intervals. Oral morphine solution is usually used for persistent pain and when patients are unable to swallow tablets.[39]

The use of a pain scale to manage pain is a crucial part of effective opioid therapy because these medicines do not have a so-called ceiling effect. Therefore it is imperative to ensure an appropriate dosage that provides effective analgesia with manageable side-effects. A suitable opioid antagonist, such as naloxone, should also be available in the healthcare for the management of adverse effects or opioid-related complications.[23]

When pain management is no longer needed, slow withdrawal of opioids may be necessary to prevent abstinence syndrome, with continuous monitoring of the vital signs. This may require tapering the daily dosage whilst monitoring the level of pain, and with continuous reassessment to ensure that the patient is pain free.[39]

Combination Opioid Formulations

When pain management by paracetamol and NSAIDs is inadequate, combination agents are usually employed. Hydrocodone and oxycodone have been increasingly used in combination with paracetamol.[37] These agents proved to be more effective in post-surgical injuries and exhibit increased pain relief compared singular usage of NSAIDs. Caution is indicated in patients that have a previous problem with drug abuse and seizures as some patients on antidepressants (SSRIs, MOA) have experienced seizures with concomitant use of these agents.[31]

Table 2: F**ormulations, receptors and doses of opioids**

Opioids	Formulation	Receptors it works on	Doses
Morphine	Tablets Intravascular injection Subdermal patch Oral syrup	mu-(μ) and kappa-(k) opioid receptors	PO 5-30 mg ,3-4hrly IM 5-10mg 3-4 hourly IV 1-2.5mg 5 – 10mnts up to 15mg
Hydromorphine	Tablets	mu-(μ) and kappa-(k) opioid receptors	4-8mg every 24 hours
Codeine	Tablets Oral syrup	Partial agonist on k-receptors and μ receptors, full agonist on delta (δ)receptor	PO 30 -60mg 4-6 hours
Hydrocodone	Tablets	mu-(μ) and kappa-(k) opioid receptors	5-10mg 4-6 hours
Fentanyl	Intravascular solution Transdermal Patch	mu-(u) receptor	IV 25-50mcg/h IM 50-100mcg/h Transdermal 25mcg/h every 72 hours
Methadone	Oral linctus intramuscular	delta (δ) receptor	PO 10-25mg 3-4hrly IM 10-25mg 8-12 hourly

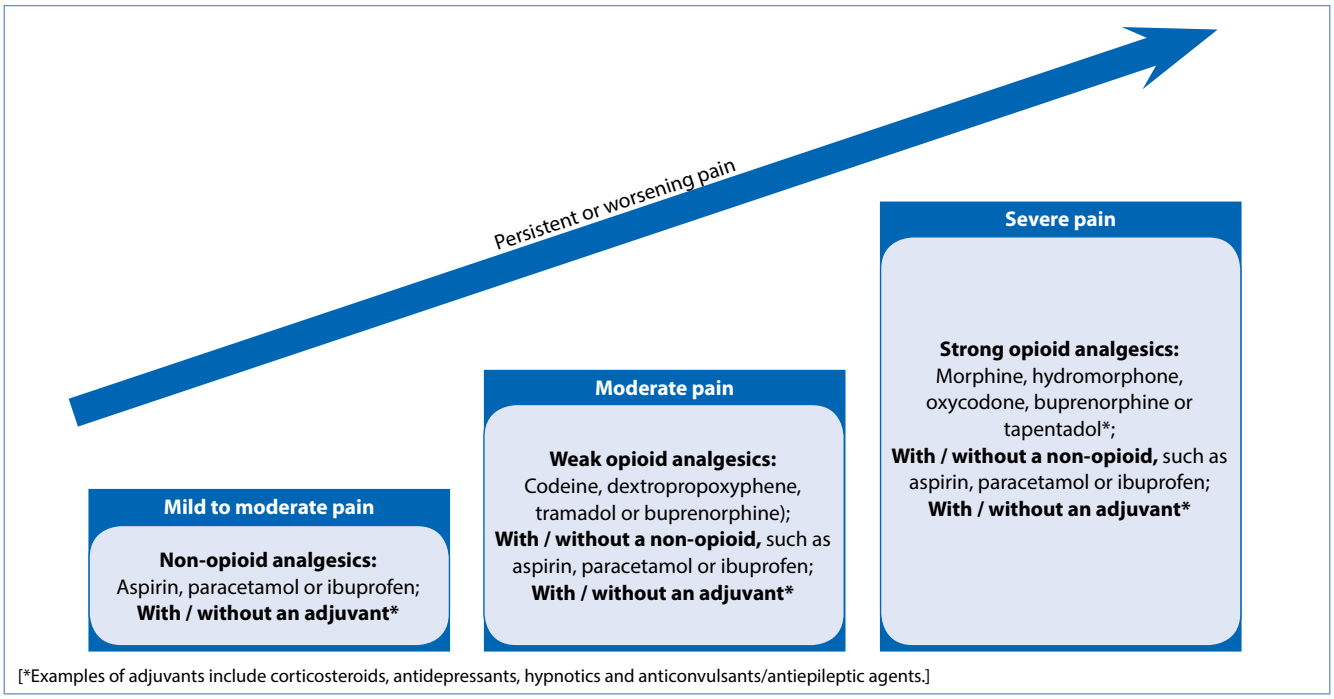


Figure 2: The World Health Organization's three-step analgesic ladder[3]

Adjuvant Therapy

Adjunctive therapy is sometimes necessary to manage the side-effects of medications for pain, provide symptom relief, treat anxiety and manage related or underlying conditions. This is because patients with chronic pain are more likely to report anxiety, depression neuropathic pain and significant activity limitations. Examples of adjuvant medicines include corticosteroids, anxiolytics, antidepressants, hypnotics and anticonvulsants/antiepileptic agents.[23,40]

A step-wise approach

The World Health Organization's (WHO) 'analgesic ladder' serves as the mainstay of treatment for the relief of pain together with psychological and rehabilitative modalities. This multidimensional approach offers the greatest potential for maximising analgesia and minimising adverse effects.[23,40]

According to the WHO, the key concepts to the effective management of pain are as follows:[23,40]

- By mouth: If possible analgesics should be given by mouth.
- By the clock: Analgesics should be given at fixed time intervals and the dosage should be titrated according to the patient's pain, and the next dosage should be given before the previous dosage has fully worn off.
- For the individual: The choice and dosages of the analgesics should be tailored to the needs and circumstances of the particular patient.
- By the ladder: The well-known WHO ladder, illustrated in Figure 2, advocates a step-wise approach to the use of analgesics, as explained below.

Step 1: Non-opioids (e.g. aspirin, paracetamol or ibuprofen) are used for mild to moderate pain.

Step 2: Weak opioids (e.g. codeine phosphate, dihydrocodeine, tramadol and buprenorphine) are recommended for moderate pain, used alone or in combination with one of the non-opioids mentioned in step 1.

Step 3: Strong opioids (morphine, hydromorphone, oxycodone, buprenorphine and tapentadol) may be used alone or in combination with a non-opioid (from the first step) for severe pain.

If the patient's pain is already severe, it is recommended that the physician should move to the third level of the ladder immediately, rather than starting with the first two.

As illustrated by Figure 2, opioids play an important role in the management of, not only acute and chronic pain, but also in the management of moderate to severe pain.[23,40]

However, certain barriers limit the effective use of opioids in the management of pain:

- Concerns about the use of opioids from health care workers, family members and patients; these concerns may be related to the side-effects and risk of dependence when using the opioids.
- Development of tolerance to the chronic use of opioids.

In instances where muscle pain does not subside with the use of mentioned analgesics, an alternative interventional therapy is muscle relaxants, where the relief of muscle spasms may also reduce pain and discomfort.[41]

Skeletal muscle relaxants are classified into two main categories namely, antispasticity and antispasmodic medications. Antispascitic medications (e.g. baclofen) acts on the spinal cord or on the skeletal muscles itself to better muscle hypertonicity and involuntary spasms. Antispasmodic medications lessons muscle spasms through alterations of central nervous conduction. These agents are divided into benzodiazepines and nonbenzodiazepines.[41]

A new skeletal muscle relaxant in South Africa is Myprocam®. The active ingredient is cyclobenzaprine, a nonbenzodiazepine antispasmodic agent, which blocks nerve impulses recognized as pain. Cyclobenzaprine is structurally related to the tricyclic antidepressants, like amitriptyline and nortriptyline. It is categorized as a muscle relaxant with a mechanism of action not fully understood, but is thought to be an agonist of the α_2 receptor at the descending noradrenergic neurons within the supraspinal area of the brain stem. Some evidence also revealed seretonergic antagonism of the 5-HT2 receptors.[41-42]

Myprocam® is often combined with analgesics like ibuprofen or naproxen and is used in addition to rest and physical therapy for short-term relief of muscle spasm associated with acute, painful musculoskeletal conditions. The recommended adult dose is a 15 mg capsule, taken once daily. Some patients may require up to 30 mg per day, administerd as one Myprocam® 30 mg capsule, taken once daily, or as two Myprocam® 15 mg capsules, taken once daily.[42-43]

Side effects include dizziness and drowsiness. Other anticholinergic effects such as dry mouth, blurred vision, constipation and urinary retention will be expected due to activity on cholinergic receptors. Cardiac arrhythmias like QTc prolongation is likely to arise and should be used with caution in patients with a history of arrhythmias or who are using any medications prolonging the QTc interval. Myprocam is contra-indicated in patients older than 65 years, or in patients with impaired liver function.[41-43]

Adequate evidence for the effectiveness of the prolonged use of Myprocam® is not available and therapy for longer periods of use is seldom warranted, the duration of use should hence only be for short periods of not more than three weeks.[41-43]

Conclusion

Muscle pain, or myalgia can be in one targeted area or across many muscle. The severity of muscle pain can range from mild to severe depending on the cause. It usually occurs with overuse of the muscles, inflammation or trauma causing excitation of muscle nociceptor but is also frequently associated with a viral infection. The effective management of patients with muscle pain is through a step-wise approach, offering the greatest potential for maximum analgesia and the minimum adverse effects. Non-Pharmacological and pharmacological

management are often applied for patients with chronic or recurrent muscle pain associated with medical disease or injury. Pharmacological management, depending on the severity of muscle pain, may include OTC medicines such as aspirin, ibuprofen and/or paracetamol or prescription medicine such as other NSAIDs (diclofenac, naproxen, mefenamic acid etc) or opioids for moderate to severe muscle pain. Adjunctive therapy is sometimes necessary to manage the side-effects of medications, provide symptom relief, treat anxiety or to manage related or underlying conditions.

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