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Musculoskeletal pain: pharmacological treatment

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ABSTRACT

Pain has the aim of identifying a harmful stimulus and avoiding tissue damage. Acute pain has recent onset and limited duration, while chronic pain is caused by continuous tissue damage or alteration in the pathways of transmission. Musculoskeletal pain is defined as acute and/or chronic pain affecting bones, muscles, ligaments, tendons and nerves. A PubMed research was conducted using the following keywords: musculoskeletal pain/physiopathology, musculoskeletal pain/therapy, multimodal analgesia. Among the articles found and from their references, the most relevant papers were selected, reviewed and combined with expert opinion of the authors. The simultaneous use of drugs with different mechanisms of action (multimodal approach) allows a more effective analgesia with better tolerability. Paracetamol is a well tolerated molecule with analgesic and antipyretic activity. Codeine is a natural opioid that enhances the action of inhibitory descending pathways. The two drugs have a similar half-life, and the same time of onset and duration of analgesic activity. Many randomized studies have shown that this combination is more effective and better tolerated than NSAIDs and the combination of paracetamol/tramadol in different types of pain, i.e. postoperative, musculoskeletal, dental, headache, osteoarthritis, polytrauma. The Italian Intersociety group recommends the use of paracetamol and the combination paracetamol/codeine 500/30 mg, repeatable every 6 hours, for the management of moderate pain in the emergency setting.

Due to its safety and tolerability, paracetamol alone or in combination with codeine remains a first-choice treatment of mild-moderate pain, and its lack of cardiovascular and gastric toxicity represents a valid alternative to NSAIDs.

Keywords: Pain treatment, musculoskeletal pain, multimodal treatment, paracetamol/codeine.

INTRODUCTION

The International Association of Study of Pain (IASP) defines pain as "An unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage"[1].

In general, pain has the aim of identifying a harmful or potentially harmful stimulus and alerting the CNS, that can implement actions to avoid or limit tissue damage[2].

Acute pain is an event with a recent onset and of limited duration. Based on its origin, acute pain can be of different types: inflammatory, post-operative, post-traumatic, visceral (heart attack, colic), muscular, due to labor and delivery or to diagnostic or therapeutic interventions.

Chronic pain ("persistent pain lasting longer than the time required for normal tissue healing", according to the definition of IASP) loses the physiological, protective function: it can be caused by continuous tissue

damage but also to alteration of the pathways of pain transmission (neuropathic pain). It has affective, cognitive and behavioral implications that significantly influence the patient's quality of life, bring a notable burden of socioeconomic issues, and make its control one of the most important therapeutic priorities. in various pathological conditions, pain can manifest itself as an exaggerated response to a noxious stimulus (hyperalgesia) up to a painful sensation even in response to normally harmless stimuli (allodynia)[3]. Like acute pain, the causes of chronic pain can be different: oncological, articular, neuropathic, like post-herpetic and trigeminal neuralgia, diabetic neuropathy, phantom limb pain, central, cephalalgic.

In Italy, a prevalence of chronic pain is estimated at 21.7%, which corresponds to about 13 million (12,686,335) inhabitants[4].

A multicenter, cross sectional observational study conducted at 26 Italian hospitals on 698 patients revealed a prevalence of pain of 38%. Pain was managed in 83.2% of cases, generally within 30', and the most prescribed drug was paracetamol. The prevalence of pain in the different hospitalization departments is shown in **table 1**[5].

Similarly, a cross-sectional survey conducted in a teaching hospital in Emilia on 892 patients recorded the same pain prevalence of 38% at the admission[6].

Pain management is therefore an important and frequent clinical problem that requires focused and expert approaches.

Musculoskeletal pain

Musculoskeletal pain is defined as acute and/or chronic pain affecting bones, muscles, ligaments, tendons and even nerves; it affects approximately 47% of the general population and represents a challenging condition either for patients or HCPs, and a major public health problem[7]. It generally presents different components: depending on the origin it can include nociceptive, inflammatory, neuropathic, dysfunctional/psychogenic elements. Musculoskeletal pain is strongly related with peripheral and central sensitization, and can manifest itself as localized, regional or diffuse pain, with an increase in sensory anomalies as the clinical presentation moves from one to the other, up to, in chronic forms, widespread hyperalgesia[8].

Musculoskeletal disorders are the third most common cause of chronic pain after headache and abdominal pain[9]. The most frequent manifestations of musculoskeletal pain are chronic back pain and chronic pain caused by osteoarthritis and by different inflammatory arthritis, including rheumatoid arthritis[7].

Multiple physical, psychological and social factors, classified in modifiable and not modifiable, can impact on the development and intensity of chronic pain **(Table 2)**[10].

Different tools have been developed to measure the pain intensity, e.g., visual analog scale (VAS), numerical rating scale (NRS), verbal rating scale (VRS), and facial expression for pediatric patients **(Fig. 1)**[7].

Understanding the type of pain is essential for setting up an adequate, often integrated, therapy; in particular the phar-

Table 1. Prevalence of pain in relation to the hospitalization department (Modified from [5])

Settings	Participating center N (%)	Patients included N (%)	Pain	Prevalence
Orthopedic	9 (15.6)	135 (14)	63	47%
Surgery	15 (26.3)	146 (25)	59	40%
Medicine	10 (17.5)	147 (29)	58	39%
Intensive care unit	18 (31.6)	138 (15)	43	31%
Nursing Home	5 (9)	132 (17)	45	34%
Total	**57**	**698**	**268**	**38%**

Table 2. Factors associated with the development of chronic pain (Modified from [10])

Demographic	Age Gender Ethnicity and cultural background Socio-economic background Employment status and occupational factors
Lifestyle and behaviour	Smoking Alcohol Physical activity Nutrition Sunshine and vitamin D
Clinical	Pain Multi-morbidity and mortality Mental health Surgical and medical interventions Weight Sleep disorders Genetics
Other	Attitudes and beliefs about pain History of violent injury, abuse, or interpersonal violence

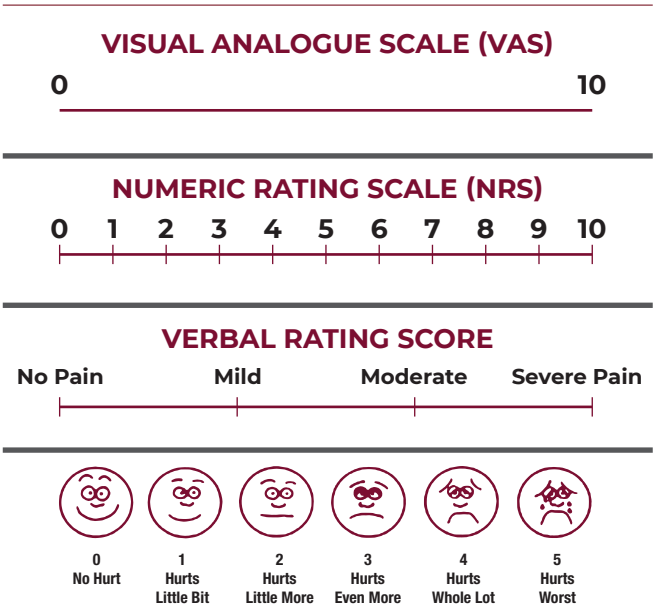

Figure 1. Pain intensity evaluation tools (Modified from[7])

macological treatment, which has a specific mode of action with different targets, for example peripheral nervous system, spinal cord and cortex, requires a diagnosis and a contextualization as correct as possible. Similarly, knowledge of the active substances, their action and their side effects are essential.

PHARMACOLOGICAL MANAGEMENT OF PAIN: THE ROLE OF MULTIMODAL ANALGESIA.

In recent years, the WHO step-by-step approach to pain therapy has gradually replaced by a multimodal approach, tailored to the patient (age, comorbidities, polytherapy) and based on pain characteristics, like its type, intensity, causes[9]. The multimodal approach is based on the use of different analgesic drugs, to be used alone or in combination according to the needs of the patient[9,11]. It is now established that the simultaneous use of drugs with different mechanisms of action, acting at different levels on the components of the pain pathways, from the nociceptor to the central level, is associated with more effective analgesia with fewer side effects[9,11].

The use of drug combinations allows a "drug-sparing" effect obtained by titrating the individual drugs until the "minimum effective dose" of each component; one of the consequences is the reduction of drug-drug interactions[11,12].

In chronic pain the nociceptive component loses its relevance compared to acute pain, of inflammatory or mechanical origin, but "acute flare-up" phases of the degenerative

musculoskeletal disease can occur. Multimodal therapy allows continuous pain control, but at the same time, with the addition of the proper drugs, it is able is able to control the episodic acute pain[11]. The multimodal approach is also particularly suitable for acting on the complex mechanisms of sensitization that determine the transition from acute, localized pain to chronic, widespread pain[8,9].

PARACETAMOL – CODEINE COMBINATION

Paracetamol is an aniline derivative with analgesic and antipyretic activity. Unlike the other NSAIDs, paracetamol has not antinflammatory action, because its activity is inhibited by arachidonic acid and peroxides, present in inflamed tissues. The molecule does not present peripheral action on prostaglandins, so it is better tolerated than NSAIDs, especially at gastrointestinal level, and does not inhibit the platelet activity[12,13]. The analgesic effects of paracetamol are mainly expressed through its metabolization to N-arachi-donoylaminophenol (AM404) in the spinal cord and in some supraspinal and cerebral areas; AM404 is very similar to anandamide, the main endogenous cannabinoid[12,13]. Paracetamol is recommended as first line therapy of the mild-moderate pain, also in children under 3 months; It is usually preferred to nonsteroidal anti-inflammatory drugs because of its better safety profile especially in people at risk of gastrointestinal bleeding; however, a metanalysis[14] and a systematic review[15] showed that the use of paracetamol alone could not be sufficient for the treatment of pain due to knee and hip osteoarthritis.

Codeine is a natural opioid with negligible affinity for μ-opioid receptors. Its analgesic effect appears to be mediated mostly by hepatic demethylation (through cytochrome P2D6) to morphine, which inhibits transmission at the level of the spinal synapse and enhances the action of inhibitory descending pathways[12,16,17]. The amount of codeine that is not metabolized at the first hepatic passage quickly crosses the hematoencephalic barrier and is converted into morphine directly in the CNS, where it performs its action[17].

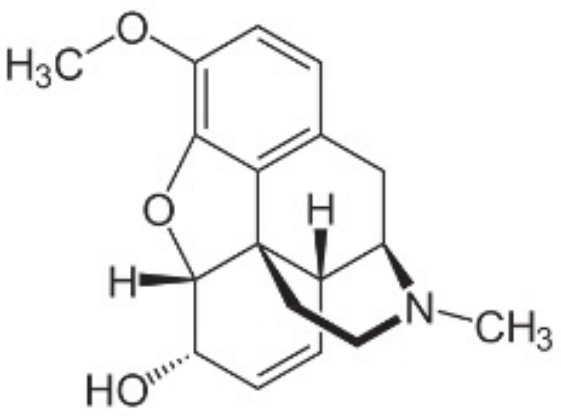

Figure 2. Structure of codeine

Despite having a similar pharmacodynamic profile, codeine and morphine differ on the pharmacokinetic level, with an onset of analgesia approximately 15 minutes after administration for codeine, compared to the 30 minutes required with morphine[17,18].

The pharmacokinetic properties of paracetamol and codeine do not influence each other, and the two drugs administered simultaneously have the same metabolism and elimination of the same substances administered individually. The two drugs have a very similar half-life, and the same time of onset and duration of analgesic activity[12,19].

The clinical rationale for an analgesic association of paracetamol and codeine is based on the evidence that, thanks to the different mechanism of actions, they have a synergistic analgesic action, i. e. the effect of combination is significant-

Table 3. Half life and analgesic activity of paracetamol and codeine (Modified from [12])

	Plasma half-life (T½) (min)	Onset of analgesic activity (min)	Duration of analgesic activity (h)
Paracetamol	150	15-30	6 (4-8)
Codeine	120-180	30	6 (4-8)

ly superior to that obtained by the single components[12,19]. The optimal dosage of the two drugs used in combination is 500 mg for paracetamol and 30 mg for codeine: at these dosages, the use of the combination can counteract a level of pain that the two components alone would not be able to control[12].

Many clinical randomized studies have shown the efficacy of the paracetamol/codeine combination in various types of pain; a Cochrane systematic review of twenty-six randomized studies, with 2,295 participants, reported that the combination of paracetamol with codeine was significantly better than placebo and paracetamol alone, and provided clinically significant levels of pain relief in about 50% of patients with moderate to severe post-surgical pain; the duration of analgesia was about one hour longer compared to treatment with the same dose of paracetamol alone. The studies had been conducted with dosages from 300 mg of paracetamol + 30 mg of codeine to 1000 mg of paracetamol combined with 60 mg of codeine. No significant difference was found in term of safety between paracetamol/codeine and paracetamol alone[18].

The combination paracetamol/codeine has been tested versus different NSAIDs[20,21], and versus paracetamol/tramadol[22] in postoperative pain, showing similar analgesic action in both cases, without significant differences in terms of safety.

Similarly, paracetamol/codeine showed higher efficacy and better tolerability than NSAIDs or paracetamol alone[23], paracetamol/tramadol and paracetamol/codeine[24] in patients with moderate to severe osteoarthritis-related pain.

Paracetamol/codeine showed similar efficacy than aspirin in tension headache[21], paracetamol/tramadol[25] and ketorolac[26] in low back pain, and ketorolac in polytrauma patients[27].

A study of 40,029 patients included in the Health Search IMS Health Longitudinal Patient Database, treated with paracetamol or the combination paracetamol/codeine for osteoarthritis pain, evaluated the need for rescue therapy with NSAIDs. The results showed that the regular use of paracetamol or paracetamol/codeine is associated with a statistically significant lower risk of being prescribed rescue therapy with NSAIDs compared with irregular use[28].

In 2015, the recommendations of the Italian Intersociety group (SIAARTI, SIMEU, SIS 118, AISD, SIARED, SICUT, IRC) for the management of pain in the emergency setting were published; according to these guidelines, the use of paracetamol and the combination paracetamol/codeine 500/30 mg, repeatable every 6 hours, is indicated for the management of moderate pain (score on the numerical scale from 4 to 6) both in prehospital analgesia and ED[29].

CONCLUSIONS

Adequate management of musculoskeletal pain is a key factor to improve the quality of life of patients who suffer from it. Careful assessment and diagnosis as well a good knowledge of drugs, their safety profile and the possible interactions, is crucial for the choice of appropriate pharmacotherapy. The multimodal approach, using drugs with different mechanisms of action and different targets, allows a synergistic action while reducing the doses of the individual components, and thus increasing the effectiveness, safety and compliance of the treatment. Due to its efficacy, safety and tolerability, paracetamol in combination with codeine remains a first-choice treatment of mild-moderate pain in many clinical situations, particularly for musculoskeletal pain for osteoarthritis, surgery and trauma. It represents a valid alternative to NSAIDs, burdened by poor cardiovascular and gastrointestinal tolerability which limits their long-term use.

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