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Chapter 3

Pharmacotherapy of Chronic Pain

Marta Vázquez and Pietro Fagiolino

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Abstract

In the past two decades, many preclinical works have been carried out assisting in our understanding of the underlying pathophysiological mechanisms that cause chronic pain. Chronic pain involves multiple pathophysiological mechanisms with peripheral and central components. This research in basic and clinical research has greatly expanded the options for analgesic pharmacotherapy. This chapter gives information regarding the major classes of medication used to assist in the management of chronic pain, including nonopioids analgesics such as NSAIDs and acetaminophen, opioids analgesics, antidepressants and anticonvulsants and an emerging area as the field of cannabinoids is. Importantly, chronic pain treatment encompasses multiple agents to take advantage of synergistic mechanism of actions, but drug-drug interactions have to be taken into account in order to avoid lack of efficacy or toxicity.

Keywords: nonopioid and opioids analgesics, antidepressants, anticonvulsants, cannabis, interactions, chronic pain

1. Introduction

Chronic pain is one of the most prevalent and disabling conditions in the clinical setting with both physical and psychological symptoms [1]. In the past three decades, there has been a better understanding of the underlying pathophysiological mechanisms that cause chronic pain, yet it still remains a significant problem. Multiple levels of the nervous system with multiple neurotransmitters are involved in pain transmission. Therefore, it is not so easy to plan effective pharmacological therapy for chronic pain and pain treatment often involves the use of one or a combination of agents with analgesic action [2]. Chronic pain may be nociceptive or neuropathic. Nociceptive pain usually is treated with anti-inflammatory or analgesic medications. Neuropathic pain typically is treated with medications

that influence neurotransmitters (e.g., antidepressants, antiepileptic drugs), and treatment with opioids is reserved for patients with refractory neuropathic pain. There are no truly effective medicines for certain types of pain; thus, a better understanding of the existing ones [opioids: methadone and tramadol; antidepressants: tricyclic antidepressants (TCAs), selective serotonin reuptake inhibitors (SSRIs), serotonin-noradrenalin reuptake inhibitors (SNRIs); anticonvulsants: gabapentin and pregabalin] or the search for new or perhaps the oldest form of medicine (cannabis) is needed.

The usual approach is to start with a nonopioid analgesic such as a nonsteroidal anti-inflammatory drug (NSAID) or acetaminophen for mild-to-moderate pain. If this is inadequate, the next step may be to add an antidepressant. If there is a component of neuropathic pain, then a trial of one of the anticonvulsant analgesic agents could be the option. If these steps are inadequate, then an opioid analgesic may be added. In an individual patient, one or several mechanisms may be at play in the etiology of the pain and more than one agent may be necessary for pain control; thus, it may be appropriate to use a combination of agents with different mechanisms of action in an effort to obtain adequate pain control [3].

This chapter focuses on pharmacotherapeutic options for patients with chronic, no cancer pain and possible drug-drug interactions that can result from a combined therapy.

2. NSAIDs and acetaminophen

Nonselective NSAIDs act inhibiting both the COX-1 and the COX-2 enzymes, leading this mechanism of action to both the therapeutic and toxic effects associated with their use. They are extensively prescribed to treat acute and chronically painful conditions. Complications with the use of these agents range from minor gastric complaints (nausea, abdominal pain, etc) to serious complications (gastric ulcers, bleeding, etc). These drugs inhibit platelet aggregation and increase bleeding time. The introduction of COX-2 selective NSAIDs in the market did not lead to a more effective and safer therapy, and cardiovascular complications associated with these agents culminated in the withdrawal of rofecoxib and valdecoxib from the market in 2004 [3, 4].

Both COX-2 selective and nonselective NSAIDs can also cause adverse renal outcomes in chronic use [3, 5]. So, risks associated with prolonged NSAIDs use must be addressed, as well as the benefits, on a patient-by-patient basis.

A weak acid drugs NSAIDs are, a plasma-gastrointestinal tract recirculation process through pancreatic/intestinal juices must be expected, although a systematic overview of the literature made no mention of this phenomenon. Due to the high concentration of sodium bicarbonate, pancreatic juice pH is above 8. This fact makes the transfer of an acidic drug from blood to the pancreatic lumen possible. Once in the duodenum, the accumulated drug in the pancreatic juice is available for reabsorption, resulting in a perceptible multiple peak plasma concentration-time profile. This phenomenon was evidenced by our group in a study carried out in healthy volunteers after ketoprofen administration [6]. In this work, no evidence of secondary

peaks was obtained, probably because of the small amount of drug in blood, but once the reabsorption of ketoprofen took place, after the ingestion of food, significant R- to S-isomers conversion could be detected. This reveals the importance of drug recirculation at the duodenum level, contributing in some way to the duodenum irritation that arylacetic and arylpropionic acids produce.

Acetaminophen has antipyretic activity and peripheral anti-inflammatory effects but lacks antiplatelet effect. Although it is a weaker analgesic in comparison with NSAIDs, it can be considered as first-line option among nonopioids due to a more favorable safety profile [3]. The main concern is that of hepatic impairment at high doses. For chronic pain that is responsive to acetaminophen, daily doses should not exceed 4 g [3, 7]. Acetaminophen blood intestine recirculation was also observed in a study carried out by our group [8]. In this case, it was detected by simultaneous drug monitoring in saliva and plasma. The mechanism of this cycling was through biliary secretion of acetaminophen and its glucuronide metabolite.

3. Opioids

There has been a dramatic change in the way pain specialists view the use of opioid drugs for the management of chronic, no cancer pain. There is growing recognition that some patients can be provided opioid drugs for prolonged periods without evidence of tolerance and toxicity. Serious adverse effects are rare, and addiction is rare, particularly, if there is no history of chemical dependency.

3.1. Conventional opioids

The conventional opioids most commonly used for chronic pain management are morphine, oxycodone and codeine. These agents are all primarily μ-opioid receptor agonists. Opioid analgesia is mediated not only via its central effects but also via its peripheral action. For individuals with moderate-to-severe pain, a stronger opioid (such as morphine or oxycodone) should be chosen in the first place, and codeine is not recommended.

It is important to take into account that codeine depends on conversion to morphine for its analgesic effect. As O-demethylation of codeine to morphine is dependent on cytochrome CYP2D6 isoenzyme, which is known to exhibit genetic polymorphism, there is significant variation in the metabolism of codeine [9, 10]. Moreover, if another drug inhibits that isoenzyme, less formation of morphine will lead to a poor analgesic effect. This could be the case with some SSRIs such as fluoxetine.

Oxycodone undergoes N-demethylation to noroxycodone and O-demethylation to oxymorphone. CYP3A4 and CYP3A5 displayed the highest activity for oxycodone N-demethylation. CYP2D6 had the highest activity for O-demethylation. A high interindividual variability in the activity of these enzymes because of genetic polymorphisms and/or drug-drug interactions is well established and can cause insufficient pain relief or adverse effects [11].

3.2. Dual or multimechanism opioids

Methadone is a synthetic opioid with potent analgesic effects. Although it is commonly associated with treatment of opioid addiction, its unique pharmacokinetics and pharmacodynamics make it a valuable option in the management of chronic pain.

Methadone has various mechanisms of action. As well as acting through binding to μ and δ opioid receptors centrally and in the periphery, it also acts inhibiting serotonin and noradrenalin reuptake and as a noncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist. These multiple action mechanisms give it advantages over other opioids. NMDA antagonism is also believed to attenuate tolerance [12–16]. These combined mechanisms are the cause of its efficacy in chronic and neuropathic pain [17].

The available methadone hydrochloride on the market is a racemic mixture of two stereoisomers: (R)- and (S)-methadone. Both enantiomers are responsible for its analgesic effect: the (R)-enantiomer exerting most of its opioid effect and acting as a NMDA antagonist and the (S)-methadone having NMDA receptor antagonism and inhibiting serotonin and noradrenalin reuptake [18–20].

Taken orally and at steady state methadone is subjected to first-pass effect. It has a variable bioavailability (41–95%) and 60–90% is bound to plasma proteins, mainly to alpha-1acid glycoprotein (AGP) due to its basic properties. AGP is one of the major acute phase proteins in humans, rats, mice and other species so its serum concentration increases in response to systemic tissue injury, inflammation or infection [21]. As pain and inflammation are nearly always associated with each other, a higher protein binding could be found in patients with chronic pain in comparison with healthy volunteers [22].

Methadone is extensively metabolized in the liver by the enzymes of the P450 cytochrome system (CYP3A4, CYP2B6, CYP2D6, CYP2C19 and other enzymes to a lesser extent) and in the gastrointestinal tract by CYP3A4. CYP3A4 content is much higher in the intestine than in the liver [23]. Methadone is also a substrate of P-glycoprotein (P-gp) [24], efflux transporter, which is expressed in several eliminating tissues (intestine, liver and kidneys) [25]. Due to the induction of its own metabolism (CYP3A4 and/or P-glycoprotein induction), reported by some authors, elimination half-life is longer after the first dose (36.7 h) [26] than during maintenance treatment [27, 28].

According to previous studies carried out by our group in other drugs [29], methadone must induce both CYP3A4 and P-glycoprotein for explaining the nonlinearity in drug response when daily dose is changed as it is shown in **Figure 1** with patients whose blood concentrations were analyzed in our therapeutic drug service.

Hence, a nonlinear relationship between steady state methadone plasma concentrations and methadone daily dose could be explained by induction of both the enzyme and the transporter, reducing its bioavailability and increasing its clearance. The hypothesis of efflux transporter induction is reinforced by the fact that patients treated chronically with methadone, developed higher saliva/plasma drug concentration ratio [30], probably due to the transporter overexpression at the luminal membrane of the acini cells and those surrounding the salivary ducts [31].

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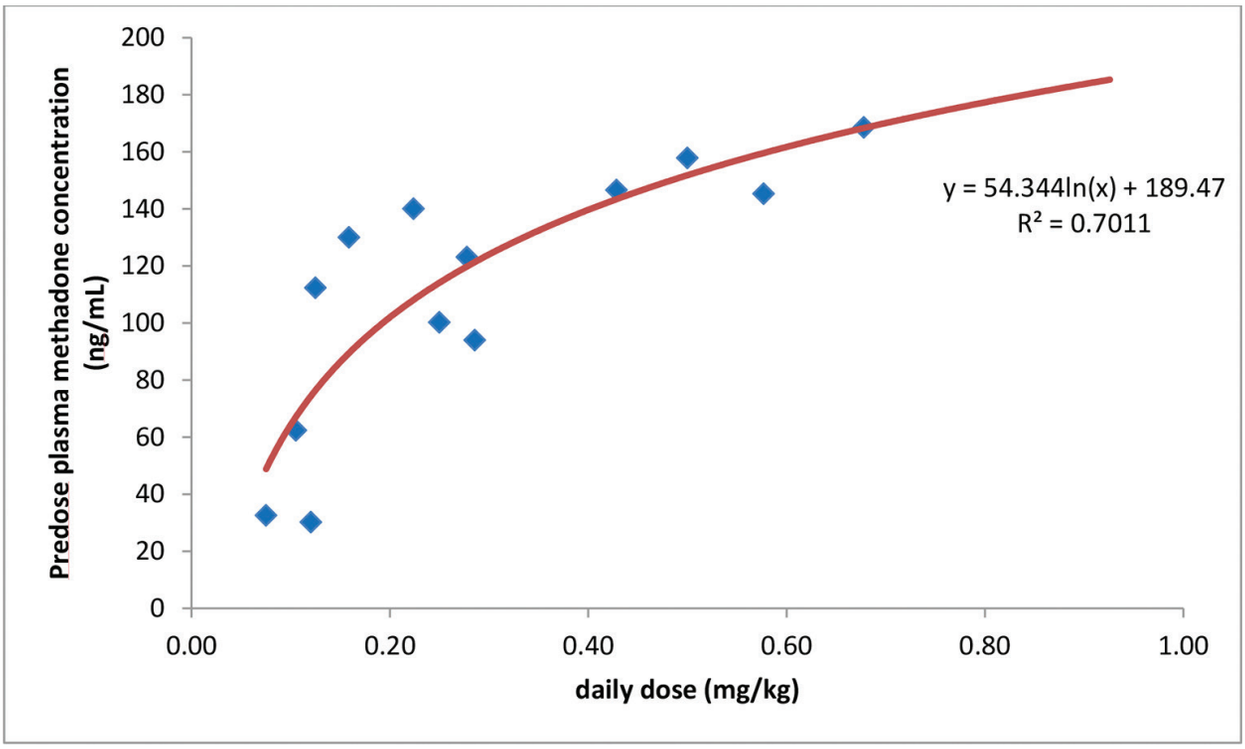

Figure 1. Predose plasma concentration of methadone (ng/mL) versus methadone daily dose (mg/kg).

Our research group has also identified methadone recirculation process via gastric secretion and intestinal reabsorption using saliva as biological fluid [32] as it can be observed in **Figure 2**.

A possible explanation for the appearance of these peaks is that, unlike NSAIDs, methadone is a basic drug and may be secreted into the stomach, to a greater extent once a meal was taken, and then reabsorbed from the intestine. Such secretions could be due to both the pH gradient between plasma (pH 7.4) and the gastric juice (pH 1.2), and the increased blood flow rate and gastric fraction of the cardiac output that takes place after food intake. The knowledge on methadone gastric secretion could have impact in the clinical setting in case of methadone intoxication. The administration of activated charcoal could be a solution as methadone reentries could be interrupted resulting in a more rapid drug elimination rate.

Tramadol has shown another mechanism of action other than acting as an agonist of μ receptors. Inhibition of noradrenalin (NA) and serotonin (5-HT) reuptake makes a significant contribution to the analgesic action of this drug by blocking nociceptive impulses at the spinal level. Tramadol is extensively metabolized in the liver and has one main major metabolite, O-desmethyltramadol. Both the parent drug and the metabolite drug contribute to the analgesic effect, but the metabolite has a significantly higher affinity for opioid receptors than tramadol [33]. CYP2D6 is responsible for the metabolite formation, and CYP2D6 gene is highly polymorphic so for poor metabolizers pain relief could be insufficient.

Serotonin syndrome is a potentially life-threatening syndrome that may occur with the use of tramadol or methadone, especially if other medications such as antidepressants or other

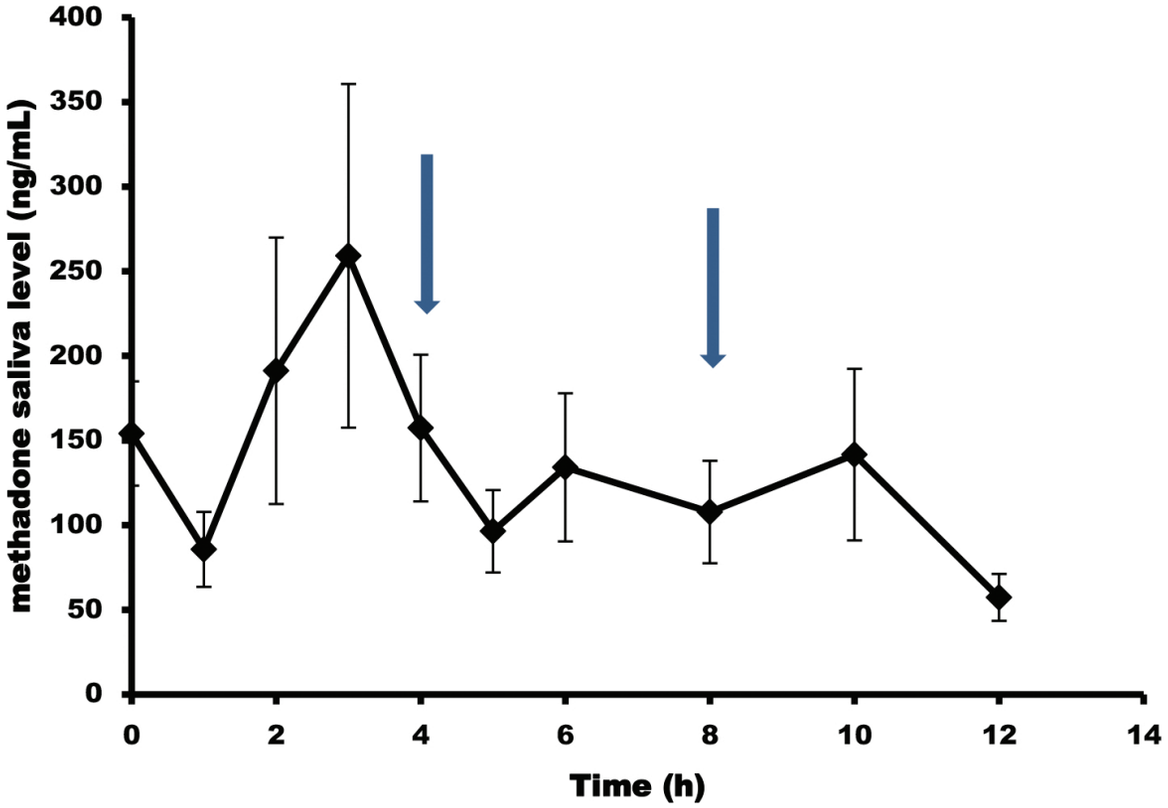

Figure 2. Mean saliva methadone concentration-time curve after administration of methadone dose with standard error in eight patients. The arrows represent meals intake.

drugs that impair the metabolism of these drugs (CYP2D6 and CYP3A4 inhibitors) are used concurrently. Symptoms include changes in mental status (e.g., agitation, hallucinations and coma), autonomic instability (e.g., tachycardia, labile blood pressure and hyperthermia), neuromuscular aberrations (e.g., hyperreflexia and incoordination) and/or gastrointestinal symptoms (e.g., nausea, vomiting and diarrhea).

During platelet activation, serotonin, along with other aggregating factors, becomes a stimulus for platelet aggregation. A transporter protein is necessary to transport serotonin into the platelet. Methadone, tramadol and SSRIs are antagonists of this transporter, and because platelets do not produce serotonin, they are dependent on plasma uptake of serotonin [34]. It is plausible that these drugs could increase bleeding risks as the blockade of the serotonin transporter could lead to a decreased concentration of serotonin within the platelet [35].

Inhibition of serotonin reuptake has been associated with the syndrome of inappropriate antidiuretic hormone secretion (SIADH) and hyponatremia [36]. SIADH is more likely in some populations, including people who are elderly or who take diuretics [37].

Lastly, both S- and R-form of methadone inhibit the cardiac potassium channel leading to prolonged action potentials that are expressed as long QT intervals resulting in potentially fatal polymorphic ventricular tachycardia: torsades de pointes (TdP). The risk of acquired QT prolongation and TdP is more pronounced in patients receiving more than one QT-prolonging drug simultaneously (e.g., escitalopram, citalopram, paroxetine, sertraline and venlafaxine) [38].

4. Antidepressants

4.1. Serotonin and noradrenalin reuptake inhibitors

TCAs exerting inhibition of 5-HT and NA reuptake, such as amitriptyline, appear to be effective analgesics. The pain relief from amitriptyline is generally moderate and is accompanied by side effects. TCAs block receptors of other neurotransmitters: histamine H1, muscarinic and nicotinic cholinergic and alpha-adrenergic. These actions explain certain side effects such as dry mouth, constipation, sedation, postural hypotension, etc [3]. For this reason, TCAs must be used with caution in patients with a history of cardiovascular disease, glaucoma, urinary retention and autonomic neuropathy, and with extreme caution in elderly patients.

Venlafaxine and duloxetine exhibit 5-HT and NA reuptake inhibition, but unlike amitriptyline and other TCAs, they lack significant affinity for muscarinic, histamine H1 and alpha-1 adrenergic receptors.

4.2. Selective serotonin reuptake inhibitors

The SSRIs are not so effective in treating pain. They can be considered as first-line agents when treatment of the depression is the priority, if TCAs are contraindicated or venlafaxine has failed. When using SSRIs, it is important to be aware of the metabolism in the liver by cytochrome P450 isoenzymes and potential interactions as most of them are enzymes inhibitors. Citalopram and escitalopram have the least impact on the cytochrome P450 isoenzymes [3, 39].

5. Anticonvulsants

Certain anticonvulsants exhibit analgesic action in neuropathic pain. This is on the basis of their ability to reduce neuronal excitability [40]. The most well-studied agents are gabapentin, pregabalin and carbamazepine; however, there is growing evidence that lamotrigine, topiramate and oxcarbazepine can act as analgesic too [40–42].

Gabapentin and pregabalin were originally developed as a structural analogue of gamma-aminobutyric acid (GABA), but do not actually bind to GABA or affect GABA reuptake or metabolism. They bind to the α2-δ subunit of voltage-dependent calcium channels and thus may modulate presynaptic release of excitatory neurotransmitters.

Carbamazepine remains the most successful first-line approach in treatment of trigeminal neuralgia [43, 44]. Its mechanism in stabilizing neuronal excitability is through sodium channel blockade.

Carbamazepine is extensively metabolized in the liver and the intestine by the isoenzyme CYP3A4 and is a substrate of multidrug resistance protein (MRP2) [45].

Like methadone, carbamazepine induces both CYP3A4 and P-glycoprotein explaining, in this way, the nonlinearity in drug response when daily dose is changed. This fact was confirmed by our studies [46].

6. Cannabis

Multiple lines of evidence support the important role of the endocannabinoid system in modulating pain and inflammation [47–54]. The potential value of the cannabinoids for medicinal purposes arose from the discovery of endogenous cannabinoid receptors: CB1 (mostly in the central nervous system) and CB2 (mostly in peripheral tissues) [55, 56]. The best-studied cannabinoids in *Cannabis* involved in having potential analgesic properties are tetrahydrocannabinol (THC) and cannabidiol (CBD).

CB1 is predominantly responsible for the psychoactive effects of THC, and the stimulation of this receptor plays a role in regulating pain, stress responses, energy regulation and lipogenesis, and immune function. CB2 is expressed on immune cells, so it is thought to serve an important role in immune function and inflammation. CBD, lacking psychoactivity compared to THC, agonist activity at CB2 receptors seems to account for its anti-inflammatory properties.

These cannabinoids are rapidly metabolized in the liver and intestine, undergoing extensive hepatic first-pass metabolism. Cannabinoids are distributed throughout the body; they are highly lipid-soluble and accumulate in fatty tissue. The release of cannabinoids from fatty tissue is responsible for their prolonged elimination half-lives [57, 58].

Precaution must be taken when CBD is used in conjunction with many other drugs due to its inhibition of several cytochrome P450 isoenzymes (CYP1A2, CYP2B6, CYP2C9, CYP2D6 and CYP3A4) and efflux transporters (P-glycoprotein). This is important in the management of chronic pain, since many conventionally used analgesics (opioids, SNRIs and SSRIs) are metabolized via these pathways (mainly CYP2D6 and CYP3A4) and/or are efflux transporters substrates [59, 60].

The growing number of preclinical studies and clinical trials with compounds that modulate the endocannabinoid system will probably result in novel therapeutic approaches in the treatment of pain for which current drugs do not fully address the patients' need.

7. Conclusions

The management of chronic pain requires an interdisciplinary approach. Only understanding pain perception and the knowledge of the multifactorial nature of pain could lead to individualizing analgesic therapy.

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