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Viminol hydroxybenzoate as a non-narcotic analgesic pharmacological choice

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Abstract

Acute postoperative pain is a constant challenge for medical professionals, who seek to choose drugs capable of generating a high degree of analgesia, without, however, inducing adverse effects, such as: intense sedation, gastrointestinal effects, addiction and breathing depression, inherent to opioids. It is already well known that narcotic analgesics constitute the pharmacological group most used in the immediate postoperative period. Here we present Viminol Hydroxybenzoate which has peculiar analgesic characteristics, being considered a potent non-narcotic analgesic of central action and equipotent to codeine. The aim of this study was to highlight the prescriptive importance of Viminol Hydroxybenzoate in the context of acute postoperative pain, explore its pharmacological aspects and warn about the prescriptive risk of opioids. Thus, we suggest the use of Viminol Hydroxybenzoate as an interesting therapeutic alternative to replace opioids, especially in conditions of mild to moderate acute postoperative pain, capable of providing a reduction in pain and, consequently, a better quality of life for patients, without the deleterious effects of opioids.

Keywords: Acute Pain; Viminol; Analgesics Non-Narcotic; Codeine; Postoperative Pain

1. Introduction

The adequate management of acute postoperative pain (APOP) is of fundamental importance in the recovery of the operated patient, whose therapeutic strategy must be based on some aspects, such as: analgesic effectiveness, lower risk of adverse effects and prompt postoperative recovery [1]. It is estimated that more than 80% of surgical patients present immediate APOP at the end of the anesthetic action used and 39% of this group experience severe pain, [2] in this way, the fact that there is no adequate control of this symptom, directly affects the quality of life (QoL) of the patient, from an increased risk of persistent postoperative pain to its fearful chronicity [1].

Within this context, analgesia by opioid drugs remains the basis of prescriptions in the control of APOP, however its frequent use is limited by the adverse effects that impact on treatment adherence, in addition to the additive potential of these narcotics [1, 3-6].

Several countries in North America are experiencing a crisis of rampant opioid consumption, generating great potential for abuse, addiction and overdose deaths, a situation that has motivated governments to declare this situation a public health problem [7, 8].

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Thus, it appears to identify a non-narcotic analgesic drug that has a central action and is able to adequately control the painful symptoms, in addition to presenting reduced adverse effects, as well as promoting better QoL to the patient affected by APOP.

Viminol hydroxybenzoate (VH) is a promising pharmacological agent for this purpose. The aim of this study was to review the problem of opioid use and its prescriptive epidemic, as well as to suggest VH as a pharmacological option for mild to moderate acute post-surgical pain.

This is a narrative literature review that was carried out by an electronic search through the following databases: LILACS, Scielo and Pubmed/Medline, using MeSH terms, described in English or Portuguese: "viminol", "codein", "opioid epidemic", "postoperative pain, "analgesic non-narcotic", "acute pain", "codeína", "crise de opioides", "dor pós-operatória", "dor aguda", from 2010 to 2022. A total of 129 articles were found, however, 98 were excluded because they did not make the manuscript available in full, due to duplicity, because they were written in languages other than English and Portuguese and/or because they were outside the scope of the theme of this research. Thus, 31 full-text articles were selected for eligibility, which include literature review articles, systematic reviews, experimental studies, clinical studies and case reports published in the last 10 years, including historical articles covering the use of the VH drug, having by focusing on chemical/pharmacological aspects, mechanism of action, possible adverse effects, therapeutic application and its use in the control of APOP (Figure 1).

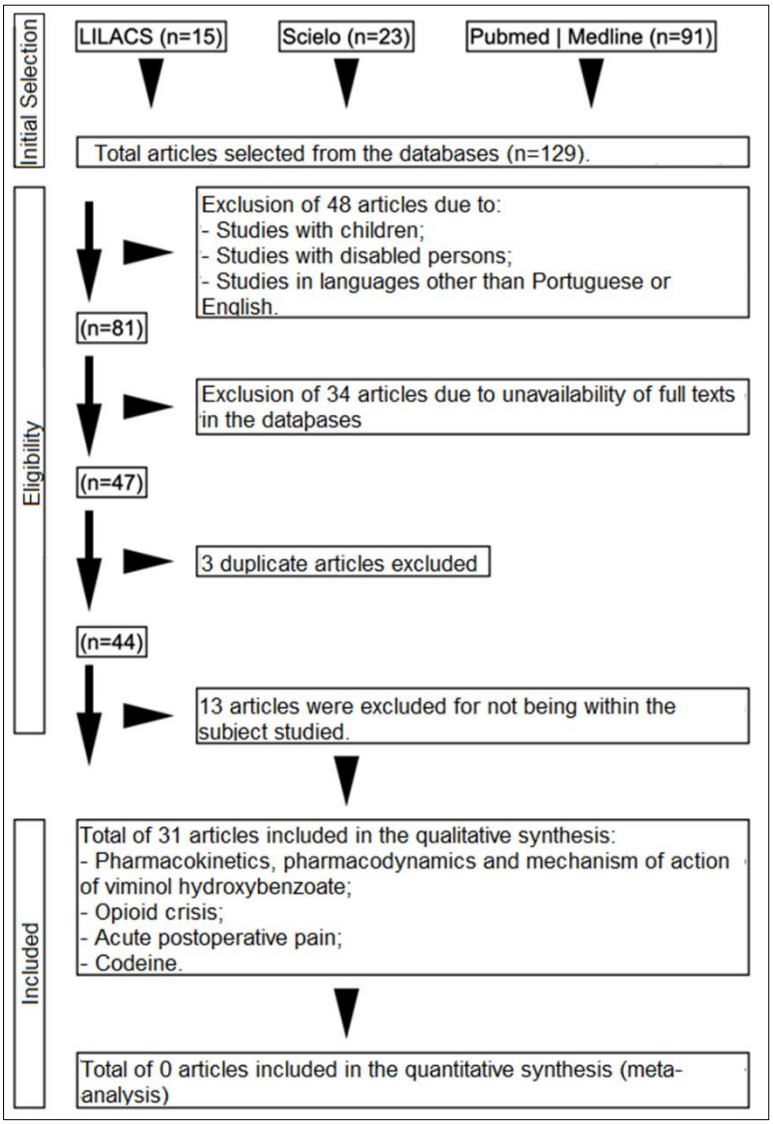

Figure 1 Flew diagram of literature search and selection criteria

2. Why alternatives to opioids are needed

The Centers for Disease Control and Prevention (CDC) reports that in 2012 there were 259 million prescriptions for opioid substances in the United States of America (USA), and that in 2013 there were 16,235 overdoses deaths [8]. Surprisingly, in 2017, 70,237 people died in this country from abusive use of opioids, which corresponds to an increase of 9.6% compared to 2016 [6, 8].

Alarmingly, toothaches of non-traumatic origin account for 50.3% of all opioid prescriptions made in primary emergency units in the USA. This causes dental pain to leverage upwards the opioid crisis in this country [9].

According to the National Controlled Product Management System, under the command of the National Health Agency (ANVISA, Brazil), it was evidenced that there was a significant increase in the commercialization of opioids in Brazil between 2009 and 2015, with 1,601,043 prescriptions being registered in 2009 and 9,045,945 prescriptions in 2015, showing a prescriptive increase of 465% in a period of 6 years [10].

3. Acute postoperative pain

APOP is defined as pain present in patients who underwent a surgical intervention, in which, after the anesthetic action, pain appears of moderate to intense severity, being considered a protection factor and warning sign, as it signals the body about the injury. Tissue occurred [11].

It is estimated that around 234.2 (95%CI 187.2-281.2) million big surgeries are performed worldwide each year, data that only considered procedures performed in a hospital setting [12].

Although opioid analgesics remain the most effective pharmacological class in the control of moderate to severe pain, it brings with it great additive potential for physical-chemical dependence, in addition to adverse effects such as nausea, constipation, euphoria, respiratory depression, drowsiness, urinary retention, hyperalgesia and tolerance, which are often not taken into account [6-13].

Faced with the growing number of surgeries performed and the rampant excessive use of opioids to control APOP, the public health crisis has been insidious, requiring more conscious and prevalent prescriptive acts, in addition to the search for possible pharmacological alternatives capable of providing analgesia to the patient, without resulting in addictive symptoms and/or intoxication [12-17].

4. Codeine

Codeine is among the most prescribed opioids in the outpatient setting and was the drug that topped the list of best sellers in Brazil in 2015, a number that corresponds to 43.40 prescriptions per 1000 inhabitants [10].

This weak opioid is considered one of the main opium derivatives and used in the second step of the WHO analgesic ladder, being widely used to control moderate pain, sold in pharmacies by retaining a special prescription, with pharmacological presentation in tablets at doses of 30mg and 60mg, taken every 4h (time of its plasma half-life) to obtain analgesia, with a maximum recommended dose of 360mg/day [18-21].

Considered a prodrug, it needs to be metabolized into morphine through the CYP2D6 enzyme, which is part of the cytochrome P450 enzymes. Approximately 5 to 10% of codeine is converted to morphine, that is, a 30mg dose of codeine is equivalent to approximately 3mg of morphine [19]. The CYP2D6 enzyme is highly polymorphic and has more than 90 variant alleles, which leads to a large genetic polymorphism in the metabolism of this drug, which varies between individuals [19]. It is estimated that 10% of the Caucasian population, 2% of Asians and 1% of Arabs are considered poor metabolizers, that is, they may have little or no therapeutic benefit [19-21]. However, there is the other extreme: there are individuals considered to be ultra-rapid metabolizers, who convert codeine into morphine very quickly, greatly increasing the risk of intoxication and adverse effects, even when used at a standard dose [19-21].

Several drugs that use the same codeine metabolism pathway can directly interfere with pharmacokinetics, increasing or decreasing the conversion of codeine to morphine and, consequently, altering the analgesic effect of the drug. As an example of drugs that act on CYP2D6, there are selective serotonin reuptake inhibitors (eg: fluoxetine and paroxetine) and serotonin and norepinephrine reuptake inhibitors (eg: duloxetine) that are capable of reducing the conversion of

this opioid and other drugs, such as rifampicin and dexamethasone, which are capable of increasing codeine conversion, amplifying its adverse effects [19-21].

5. Viminol Hydroxybenzoate

VH is a drug derived from pyrrylethanolamine, a single molecule that is not similar to any other analgesic drug that has been studied to date, whether in a structural and/or chemical relationship, considered a potent synthetic analgesic of non-narcotic origin, despite having many pharmacological properties of traditional narcotics. However, it differs from opioids in terms of its extreme reduction in the ability to develop physical dependence [22, 23].

To date, there has only been a single clinical case report involving dependence on VH. However, there is a great bias due to the fact that the patient has already had a history of dependence on several illicit and/or recreational substances, such as: cannabis, amphetamine, LSD, cocaine (injected and/or inhaled), dimethyltryptamine and alcohol [24].

First described in Italy in 1968, VH is a racemate that exhibits a morphine-like discriminative effect composed of three asymmetric carbons and a mixture of six stereoisomers [25,26]. The racemic mixture shows a profile of effects similar to that of morphine, except that viminol produces slight physical dependence, while morphine produces severe physical dependence and/or a high possibility of abuse [26]. The identification of stereoisomers revealed that their individual properties are unique, some of which may be opposite to each other, resulting in a drug with low capacity for physical and/or chemical dependence [26].

The R2 isomer of viminol has centrally mediated analgesic activity, at the subcortical level of the brain, comparable in type and intensity with morphine, which acts on the perception pathways of the painful stimulus, with low binding affinity to opioidergic receptors, with binding capacity in the ratio of 1/10 compared to morphine which is 1/100 [22, 26]. The ability of R2 to present minimal binding affinity to opioid receptors justifies the morphine-like effect that this racemate has, in addition to the fact that it is easier to cross the blood-brain barrier when compared to morphine, and consequently acts more quickly in cortical regions [26].

The antagonist activity of the S2 isomer of viminol is responsible for minimizing the physical dependence capacity of the R2 racemate, suggesting that these enantiomers exert their actions through different areas located on the opioid receptors, which results in greater specificity of effect, in addition to S2 also has reduced binding capacity to opioid receptors [22, 26]. It should be noted that VH can be inhibited by several drugs that are metabolized by the cytochrome P450 CYP3A enzyme, such as: fluconazole, itraconazole, ketoconazole, clarithromycin, erythromycin, ritonavir, verapamil, diltiazen, voriconazole, posaconazole, boceprevir, imatinib and diltiazen, being able to promote an increase in the plasma concentration of VH and consequent endogenous intoxication [24, 27].

The analgesic activity promoted by VH occurs by CNS, preventing the perception of the painful stimulus and it's processing in higher centers, where it has a higher potency than salicylates, pyrazolonic derivatives and comparable to weak opioids, and the 70mg dose of VH corresponds on average 6mg of morphine [23, 28, 29].

Because viminol doesn't have an anti-inflammatory effect, the gastrointestinal mucosa remains preserved from gastric lesions inherent to these acids, in addition to the advantage of not depressing the respiratory center, absence of cardiotoxicity, hepatotoxicity and/or renal alterations, the main benefit being analgesia [23, 30, 31].

In experimental studies with rats, it was shown that the VH molecule was widely distributed in the gastrointestinal tract, liver and kidneys, reaching peak plasma concentration after 2 hours of oral ingestion and remaining at this level until the 7th hour. Excretion of metabolites occurs in feces in 50.1±2.2% and urine in 33.3±1.4% in the form of secbutylamine, and approximately 20% of the HV was excreted unchanged [30]. It has a half-life of 4 hours. The dosage can vary between 70 and 560mg (maximum dose), which can be prescribed in 3 to 4 doses/day. Another benefit of this drug is the ease of prescribing in a simple prescription, not requiring a special prescription, as is the case with opioids [23, 30].

6. Non-narcotic analgesic viability for the control and prevention of acute postoperative pain

Painful conditions are frequent symptoms in the immediate postoperative period and their appropriate treatment provides relief to the patient's suffering, in addition to a favorable clinical outcome. And narcotic drugs are the most prescribed analgesics in these situations, however worldwide efforts try to advocate a multimodal approach in order to reduce and/or eliminate the use of opiates [32].

Multimodal analgesia involves the concomitant and preferential use of non-narcotic analgesics, taking advantage of the synergistic effect between the drugs, an effect that produces superior analgesia when compared to isolated monotherapies [14].

When observing the analgesic action of VH in relation to codeine, there is a great similarity of equipotence, however, some pharmacokinetic aspects need to be taken into account during the prescriptive act, as this weak opioid is considered a passive prodrug of the genetic polymorphism of the population general, which in a way is capable of compromising the much-desired analgesic action, while VH is a molecule synthesized in the laboratory that does not undergo changes due to genetic variability, [23] making it an effective analgesic drug.

As per the above, VH appears to be a promising non-narcotic analgesic agent in the control of nociceptive pain of mild to moderate intensity, and the identification of the R2 and S2 stereoisomers of this molecule reveals the morphine-like effect and its low binding affinity and activation of μ-opioid receptors, providing prompt analgesia, without, however, generating major additive effects and/or serious adverse events relevant to classic opioids [24,26].

7. Conclusion

The opioid crisis, which is taking strides and unprecedented in the USA, needs to serve as a warning to the global medical and dental community, so that this chaos doesn't settle in susceptible places. There is an urgent need to implement a Public Health Policy focused on Continuing Education Program on Pain for health professionals, in addition to encouraging plausible alternatives for analgesia through non-narcotic drugs, thus curbing the rampant use of opioids. In this context, VH is an excellent prescriptive alternative in cases of APOP of mild to moderate intensity, with excellent tolerability, low financial cost, rapid and effective analgesic therapeutic response, without presenting the deleterious and/or fatal effects of opioids.

Compliance with ethical standards

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Disclosure of conflict of interest

There is no conflict of interest between the authors.

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