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PHARMACOKINETICS INVOLVED WITH KAPPA OPIOID RECEPTORS

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Abstract: INTRODUCTION: The receptors, members of the opioid receptor family, whose main actions involve neuroendocrine activity and pain perception, such as spinal analgesia, ventilatory depression and sedation. Although they are widely used, opioids have several adverse effects, which requires a continuous search for drugs that mitigate these consequences. Thus, among several agonists of these receptors, there are eluxadoline and R-dihydroetorphine, used as an alternative to commonly used opioids. Furthermore, such receptors are also associated with the misuse. **METHODOLOGY:** PubMed literature review, with the descriptors kappa AND opioid receptor in the last 5 years. Eleven scientific articles were selected, including only clinical trials in English in humans and excluding those that do not fit the pre-established objectives. **RESULTS:** Opioids are essential for the treatment of moderate to severe pain in oncological and perioperative patients, however, it is necessary to pay attention to chemical dependence and respiratory depression. Activation of κ and δ receptors is suggested to counteract respiratory depression induced by μ receptor activation in traditional opioids such as morphine and fentanyl. Studies of R-dihydroetorphine showed high analgesic potential, mild side effects and respiratory stability. Eluxadoline is an efficient alternative in the treatment of abdominal pain and diarrhea in Irritable Bowel Syndrome (IBS), in addition to having a lower abuse potential than other μ receptor agonists, however, the intranasal route has aversive properties, such as bad taste. There was no association of single nucleotide polymorphisms of κ receptors or δ-opioids with morphine analgesia for any pain. The use of eluxidaline must be noted, given the intestinal constipation and changes in cardiac repolarization. **CONCLUSION:** R-dihydroetorphine exhibited a plateau in respiratory depression but not in analgesia.

Eluxadoline, well tolerated, had side effects, mostly in cholecystectomy patients, with higher dosage. Early clinical response to eluxadoline was associated with benefits for 6 months for IBS. Thus, the aforementioned findings suggest the safety of eluxadoline in patients with IBS.
Keywords: Opioid Analgesics; Kappa Opioid Receptors; Irritable bowel syndrome.

INTRODUCTION

Opium, a substance extracted from a plant known as poppy, is one of the oldest natural components used in medicine, has analgesic and sedative potential, and it is through it that heroin, methadone, meperidine and fentanyl are obtained, being then characterized as analgesics of central action in acute pains of difficult control and in chronic pain. This substance has several receptors described in the literature, such as Delta (δ), Kappa (K) and Mu (μ) receptors, but in this article we will address the pharmacokinetic characteristics involved in Kappa (K) receptors (MARTINS R. et al., 2012).

Kappa (K) receptors are mainly used in cases of hallucination, dysphoria and sedation, and their predominant functions involve nociception, thermoregulation, diuresis control, neuroendocrine activity and pain perception, such as spinal analgesia and ventilatory depression. They are located in the periaquiductal gray matter, gelatinous substance in the spinal cord, hypothalamus and peripheral sensory neurons (MARTINS R. et al., 2012).

However, opioids have several adverse effects, respiratory depression being one of the most serious side effects, which requires a continuous search for drugs that mitigate these consequences. It is worth noting that recent studies describe that K-opioid receptors can neutralize, at least in part, the respiratory depression induced by the activation of the μ-opioid receptor, a fact that may be advantageous in relation to other opioids, suggesting a protective effect in high doses (LEVY-COOPERMAN, N. et al., 2016).

Furthermore, it was exposed that drugs such as eluxadoline, a mixed agonist of μ-OR and κ-OR, compared to oxycodone, an agonist of the m receptors (mu) and only a partial agonist of the k receptors (kappa), presented certain adverse events of mood, but at a much lower frequency than oxycodone. These data demonstrate that eluxadoline has less abuse potential than oxycodone in recreational opioid users. It has also been reported that substances such as R-dihydroetorphine, which is also an agonist of Kappa (K) receptors, showed a plateau in respiratory depression, but not in analgesia, showing advantages over other opioids, since it has greater benefits than harm (OLOFSEN et al., 2019; LEVY-COOPERMAN, N. et al., 2016).

In view of the above, this article aims to elucidate the pharmacokinetics involved in Kappa (K) opioid receptors, making clear all their particularities and functions, in addition to explaining whether there are benefits of it in relation to other opioid receptors, such as the Delta receptor (δ) and Mu (μ).

METHODOLOGY

This is an integrative review of the literature designed according to the criteria of the PICO strategy, an acronym that represents: population, intervention, comparison and outcome, for the elaboration of the research guiding question: "What are the pharmacokinetic aspects of opioids from the interaction of these with kappa opioid receptors?".

In this sense, according to the parameters mentioned above, the population or problem of this research refers to patients who used opioids whose pharmacokinetics were evaluated; the intervention is of an analytical

character; the comparison is of non-intervention, due to the design of the work; and the expected outcome is the identification of pharmacokinetic aspects of opioids related to kappa opioid receptors.

From this, a search was carried out in the PubMed (Medline) database, from the Virtual Health Library, with the descriptors MeSH/ DeCS Kappa Receptor and Opioid and the Boolean term AND, that is, the search strategy was: "kappa opioid AND receptor". It is worth remembering that the last search was carried out in September 2022.

Furthermore, for the development of the present study, all indexed full articles, of the clinical trial type, carried out in humans and written in the English language that related to the pharmacokinetics of opioids were included, with no previous period limit, so that incomplete or that did not fit the objective of the study were excluded and the filters used were, namely, "full text", "clinical trial", "humans" and "English" in PubMed.

From the screening methodology, a total of 9043 studies were found in the electronic database search. After applying the filters, 9024 were removed from the list, with 19 resulting. After reviewing titles and abstracts, 8 articles were excluded, so that 11 remained for full-text analysis, all of which were included in the qualitative analysis synthesis.

Among the reasons for excluding the identified articles are: they do not present the filters indicated in the methodology and do not fit the theme proposed in the objectives.

RESULTS

Morphine is a pain reliever often prescribed for moderate to severe pain. However, there are large interindividual variations in the analgesic response so that genetic factors may contribute to the differential response to morphine by regulating receptor function or signal transduction. Knowledge about the association between different polymorphisms and morphine analgesia in humans may provide a better understanding of the individual pharmacodynamics of morphine. Thus, the aim of this study was to investigate whether genetic variants of mu-, kappa- and delta-opioid receptor genes (OPRM1, OPRK1 and OPRD1) and catechol-O-methyltransferase (COMT) gene are associated with analgesia with the use of morphine. In conclusion, an influence of COMT and OPRM1 genotypes on morphine analgesia was found in the pain experiment exploring different tissues. In addition, in males, OPRD1 genotypes influenced morphine analgesia. Therefore, the results suggest that genetic variants in COMT, OPRM1 and OPRD1 (in men) may contribute to the variability in morphine analgesia. As for drugs with μ-opioid receptor (OR) activity, they may be associated with abuse and misuse (NIELSEN L. M. et al. 2017).

Eluxadoline, a mixed peripherally acting μ-OR and κ-OR agonist and δ-OR antagonist, is approved in the United States for the treatment of irritable bowel syndrome with diarrhea. After intranasal insufflation of eluxadoline, Drug Liking VAS peak (maximum) effect scores were significantly lower relative to oxycodone. On other subjective measures, eluxadoline was generally similar or ineffective versus placebo. Pupulometry indicated no or minimal central effect with oral and intranasal eluxadoline, respectively. Adverse mood events have been reported with oral and intranasal eluxadoline, but at a much lower frequency than with oxycodone. These data demonstrate that eluxadoline has less abuse potential than oxycodone in recreational opioid users. Studies have shown that therapeutic (100 mg) and supratherapeutic (1000 mg) doses had no significant effect on cardiac repolarization, as assessed on electrocardiogram (ECG) by QT interval prolongation, in healthy volunteers of

both genders (LEVY -COOPERMAN, N. et al., 2016).

In addition, the doses were well tolerated and the safety profile of eluxadoline in the treatment of IBS in adults was confirmed of these more than two-thirds of patients who respond over the first month maintain a positive response over 6 months of treatment, indicating that early clinical response to eluxadoline is associated with sustained benefits for up to 6 months in patients with IBS-D. Regarding this use: Eluxadoline was well tolerated and the majority of adverse effects (AE) that emerged with treatment occurred at baseline, were not serious, and were not associated with any clinically significant sequelae (CHEY et al., 2017).

Constipation AEs were infrequent and discontinuation due to constipation was low. The most common side effects reported were contact dermatitis, dizziness and nausea (BONIFÁCIO, 2018). and its use is contraindicated in patients with a history of pancreatitis, structural disorders of the pancreas, suspected or confirmed sphincter of oddi dysfunction, alcoholism, alcohol abuse or excessive alcohol use (more than 3 alcoholic drinks per day). Finally, patients must avoid chronic or excessive use of alcohol during treatment with eluxadoline (D CASH et al., 2017).

Still on kappa receptors, the effects of R-dihydroetorphine on isohypercapnic ventilation and antinociception, with a maximal respiratory depression of 33% of basal ventilation being observed, however without maximal antinociception effects. drug, the greater the likelihood of analgesia, but a plateau occurs in the risk of respiratory depression. It is known that R-dihydroetorphine is a full agonist of the opioid receptor with high affinity for the μ-, δ- and κ receptors, but low for the CF nociceptive receptor. In this sense, the objective is to evaluate the interaction of this drug with the receptors to obtain more potent opioids with fewer adverse effects. Therefore, the drug is expected to produce an apparent maximal respiratory effect and a surface of favorable utility compared to full μ-opioid receptor agonists, as activation of μ-opioid receptors is believed to be associated with respiratory depression, while δ-opioid and/or κ-opioid receptors have some respiratory protective effect. In light of the results, it was observed that R-dihydroetorphine showed a plateau in respiratory depression, but not in analgesia, showing advantages over other opioids, since This is because κ-opioid and δ-opioid receptor agonists can selectively antagonize μ-opioid receptor agonist effects, including respiratory depression (OLOFSEN et al., 2019).

Comparing the bioavailability of olanzapine in 3 different formulations, being Olanzapine (OLZ) with Samidorphan (SAM called component ALKS 3831, a μ-opioid receptor antagonist with low intrinsic activity at δ- and κ-opioid receptors). It is known that the use of Olanzapine as an antipsychotic has great effectiveness in the treatment, however adverse effects are recurrent such as generalized weight gain and metabolic abnormalities, so SAM appears as a possibility to mitigate these limitations found in monotherapy with olanzapine. The pharmacokinetics of SAM observed when administered as a component of ALKS 3831 were in agreement with results obtained in previous studies with the administration of SAM as a single agent, indicating that the combination of OLZ with SAM in one tablet does not affect the bioavailability of SAM. After testing with adequate randomization, it was observed that ALKS 3831 was well tolerated, and no safety concerns unique to ALKS 3831 compared to OLZ monotherapy were identified (SUN L et al., 2019).

Finally, we can see a new drug used in the

treatment of alcoholism, nalmefene, which is an antagonist of the μ and δ opioid receptor, and a partial agonist of the κ opioid receptor. The κ receptor has been shown to be involved in the modulation of the mesolimbic system, which acts by driving drug seeking and consumption behavior. With this in mind, to reduce alcohol consumption it is necessary to antagonize the increased function of this receptor, and through this functional antagonism of the κ receptor in the ventral striatum, nalmefene reduces the aversive state associated with upregulated dynorphin signaling and decreases the alcohol consumption. In contrast, the article estimates that nalmefene may also act as a functional agonist in the dorsal striatum to address a dysregulated κ receptor system to thereby reduce compulsive and habitual dopaminergic behaviors. This is because κ receptors inhibit dopamine release, such negative regulation would result in increased dopamine signaling in the dorsal striatum, which may contribute to compulsive and habitual alcohol consumption (QUELCH et al., 2017).

CONCLUSION

Opioids act as potent analgesics and sedatives, but still have several significant adverse effects, especially respiratory depression. Therefore, there is a constant search for drugs of similar efficacy associated with the mitigation of these consequences. Understanding the pharmacokinetics of Kappa receptors is one of the alternatives currently being explored.

Substances with greater action on Kappa receptors, compared to other opioid receptors, have several elucidated benefits, either because of their ability to partially neutralize the adverse effects of receptors induced by the μ-opioid receptor, or because they directly have a lower frequency of AE, or less potential for abuse.

The aforementioned advantages were demonstrated, in part, in all studies. R-dihydroetorphine exhibited a plateau in respiratory depression but not in analgesia, with the ability to increase the dosage for greater likelihood of pharmacokinetic action. Eluxadoline, which is well tolerated, had side effects, mostly in cholecystectomy patients, with higher doses, in addition to having a lower potential for abuse compared to oxycodone. Early clinical response to eluxadoline demonstrated benefits for 6 months in the treatment of IBS. Thus, the aforementioned findings suggest the safety of eluxadoline in patients with IBS.

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