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EDITORIAL

Opioid administration and rescue dose: exploring the effects of opioid combinations

Opioids have been used as analgesics since the isolation of the morphine molecule in 1804 by German pharmacist Friedrich Serturner.[1] The analgesic ladder proposed by the World Health Organization in 1986 provided the grounds for the routine use of opioids according to pain intensity and, since then, its use has been discussed for specific pain syndromes.[2] Prescribers should be familiar with the time required for onset of effect, duration of action, time to reach plasmatic steady-state concentration, and equivalent doses of opioids, besides explaining the risks to patients. It is essential to inform patients about common adverse effects (nausea, vomiting, constipation, pruritus, sedation, dysphoria), overdose, drug interaction, tolerance, hyperalgesia, misuse, abuse, and neurotoxicity, as they may interfere with treatment adherence.[3,4] When initiating opioid treatment, practitioners must also determine patient risk stratification for addiction and be aware of local health surveillance policies.[5]

Morphine is considered the gold standard among opioids, therefore it deserves special consideration from the physician who, by respecting basic concepts of pharmacology, facilitates the understanding of proper prescription recommendations for this valuable and safe analgesic. Morphine steady state is attained approximately five half-lives after administration and is associated with full analgesic effect and potential adverse effects for the dose administered. Since the half-life of morphine is approximately four hours, notwithstanding the administration route, a steady state is only achieved roughly 24 hours after the dose is administered.[6] This concept is critical for all opioids, given that the acknowledgment of half-life is required for assessing clinical efficacy and, if needed, making dose adjustments. Assessment of the intensity of residual pain is used to titrate dose increments. For mild intensity pain, an increase of approximately 25% of the dose is recommended; 50% for moderate pain; while for severe pain up to 100%.[7,8]

Opioid tablets are dispensed in two preparations: immediate release (fast) and controlled release (slow). Immediate-release tablets allow faster drug absorption to the bloodstream, can be associated with high plasmatic concentration peaks, and, consequently, present a higher incidence of adverse effects.[9] Conversely, controlled-release tablets have the advantage of offering an analgesic concentration below toxic for a prolonged time (8, 12, or even 24 hours), presenting a more convenient dosage.[10]

Controlled-release morphine is an interesting and convenient formulation for pain management. The analgesic effect of the controlled-released morphine formulation available in Brazil lasts 12 hours. To calculate the required dose, it is imperative to administer immediate-release morphine in advance. The total daily dose of immediate-release morphine is calculated and divided by two. For example, a patient using 10 mg of immediate-release morphine every 4 hours totals 60 mg for 24 hours. Thus, the required dose of controlled-release morphine is 30 mg every 12 hours.[11]

When controlled-release morphine is used, the prescription of a rescue dose is required when breakthrough pain occurs. Thus, a fast-release morphine dose is used to cover the analgesic requirement due to greater nociceptive stimulus (dressings, mobilizations) or due to spontaneous variation in the plasma concentration drug toward a level below the therapeutic range. In this case, 5% to 15% of the total daily scheduled dose of morphine is prescribed routinely using immediate-release morphine. This dose can be repeated up to every hour, given that the maximum analgesic concentration is reached 1 hour after oral administration of immediate-release morphine. In the previous example, the adequate rescue dose would be approximately 5 mg of morphine in case of pain, administered every hour.[12]

In Brazil, controlled or transdermal release formulations are the only preparations available for oxycodone, tapentadol, fentanyl, and buprenorphine, and no immediate-release formulation of these drugs is available to be administered as a rescue dose (morphine is the only short-duration potent opioid available in the Brazilian market). This fact raises questions about which drug would be the best choice for a rescue dose since the basic principle of pain management is not to associate drugs with the same mechanism of action. For a comprehensive discussion, it is necessary to

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understand concepts of opioid pharmacodynamics for establishing the rescue dose in patients presenting breakthrough pain and on routine use of opioids other than morphine.

Opioids can be classified according to their efficacy and receptor affinity. Intrinsic activity or efficacy is the ability of a substance to activate its receptor and produce the expected pharmacological effect. Intrinsic activity ranges from zero to one. Affinity, in turn, defines the strength of opioid binding with its specific receptor (described as μ, κ, and δ). Agonist drugs have both the aforementioned properties and must effectively interact with their receptors to produce a drug-receptor complex capable of triggering a full response. Conversely, antagonist drugs block receptors, as they have high affinity and low or absent efficacy.[13]

According to the interaction of opioids with μ receptors (mainly responsible for their analgesic effects), they can be classified into agonists (tramadol, codeine, morphine, fentanyl, methadone, oxycodone, and tapentadol); antagonists (naloxone, naltrexone); partial agonists (buprenorphine); and agonist-antagonists (nalbuphine). Agonists that produce intrinsic activity equal to 1 are called full agonists, as binding to all receptors produces a maximum response. When a drug shows intrinsic activity equal to zero, it is termed an antagonist, as it does not produce any effect, regardless of the receptors being bound. Partial agonist and agonist-antagonist drugs show intrinsic activity ranging between 0 and 1.[14]

Following opioid receptor stimulation, the cAMP system is activated via the inhibitory G protein, with consequent inhibition of adenylate cyclase and reduction of neuronal impulse transmission.[15] Alternatively, several G protein-coupled receptors (GPCRs) are able to form dimers by combining two or more GPCRs.[16] The $\mu - \delta$ heterodimers induce changes in ligand-receptor properties, modify cAMP regulation and signaling, and promote changes in the induction of MAPK phosphorylation.[17] Patients chronically using opioids have shown a high number of $\mu - \delta$ heterodimers, contributing to the activation of several intracellular signaling pathways and the development of tolerance.[18]

Opioid-receptor interaction is complex and also involves activation of another signal translation pathway in addition to the G protein, the β-arrestin pathway, possibly related to opioid adverse effects. Opioids may possibly trigger both the G-protein pathway and the β-arrestin pathway, emphasizing that the aim when prescribing an opioid is analgesia without the occurrence of adverse effects.[19]

Opioid receptors are also subject to desensitization, downregulation, and internalization, all adaptation processes in response to agonist chronic administration. These processes produce progressive loss of the signaling translation that follows opioid receptor activation, with variable onset and duration, depending on the agonist or signaling pathway.[20]

Based on these considerations, how can two opioids with distinct pharmacokinetic properties and similar pharmacodynamics be combined? How should a rescue dose be used to treat a patient with a drug other than morphine?

Although the administration of two or more drugs with different mechanisms of action is an exciting strategy to improve the effectiveness of analgesia and reduce adverse effects, the combination of drugs from the same pharmacological group is controversial. Combining two potent opioids can improve analgesia, avoid fast dose escalation of one of the drugs, and reduce the incidence of tolerance and adverse effects.[21] This may be related to the interaction among subpopulations of μ receptors and it prompts the use of combinations of transdermal fentanyl with morphine or methadone with morphine.[22] Also, the combination of oxycodone with morphine or transdermal fentanyl is based on the premise that oxycodone acts on κ receptors promoting upregulation of μ receptor expression, synergistically increasing the clinical efficacy of the opioid, since analgesia will occur through both activation of κ and μ receptors.[23] On the other hand, the combination buprenorphine-morphine presumes that buprenorphine, by antagonizing κ receptors, facilitates the action of morphine on μ receptors.[24] Additionally, tramadol, by acting on the descending inhibitory system, could reduce the need for an excessive increase in the dose of strong opioids.[25]

The assumption that the association of two strong opioids is beneficial for patients suffering from acute or chronic pain does not have, however, a high level of clinical evidence. The systematic search for publications comparing opioid monotherapy versus combined opioid therapy using observational studies or clinical trials with adequate methodology has been disappointing. Thus, combined opioid therapy has not yet been validated in the literature and perhaps may be considered by experienced practitioners in the future. Alternatively, using a combination of potent or atypical opioids only as rescue medication cannot be regarded as evidence-based, despite some publications[26–28] presenting satisfactory results regarding safety and clinical efficacy, especially due to methodological biases present in previous studies.

By combining, for example, oxycodone with morphine rescue, we could observe the following scenario. A hypothetical patient with pancreatic cancer uses 120 mg of oxycodone a day. If 10 mg of morphine every hour is ordered as a rescue dose for breakthrough pain relief, when the patient consumes six rescue doses per day (60 mg of morphine), we will have a total of 120 mg of oxycodone and 40 mg of the equivalent dose of oxycodone (considering the equianalgesic dose of oral morphine for oxycodone to be 1.5 times lower), or a total consumption of 160 mg of oxycodone per day. Alternatively, if we were to use 10% of the total daily dose of oxycodone for rescue dose calculation, we would prescribe 12 mg of oxycodone as a rescue dose (for routine use of 120 mg a day of oxycodone). Thus, using six rescue doses, the patient would receive a daily rescue dose of 72 mg and a total daily dose of 192 mg of oxycodone. In other words, the result is incompatible no matter how small the difference.

In this scenario, given immediate-release oxycodone is unavailable in Brazil, we currently prescribe morphine. By ordering 10 mg of morphine as a rescue dose, we are already: 1. using a subdose of rescue medication (an adequate dose would be 18 mg, since 12 mg of oxycodone multiplied by 1.5 results in 18 mg of morphine); 2. facilitating the likelihood of competition for the same μ-type pharmacological receptor; 3. promoting action on preferred signal translation pathways (bias) and facilitating the occurrence of more adverse effects; 4. possibly triggering heterodimer receptors involved in tolerance or hyperalgesia; 5. facilitating the plasma concentration peak of more than one substance and its active metabolites; 6. interfering with the receptor desensitization process; 7. inducing uneven

hysteresis curves. All these statements must be considered and questioned based on the complexity of the pharmacokinetics and pharmacodynamics of different opioids.

Therefore, when dealing with dose adjustments of a controlled-release opioid in the absence of immediate-release formulations of the same opioid, using two different opioids may result in unsatisfactory analgesia. Until we have access to well-designed studies regarding the association of drugs with supposedly the same mechanism of action, we should preferentially use a drug from another pharmacological group as a rescue dose, and, if we are not successful, we should increase the dose of the controlled-release opioid. In the absence of another potent immediate-release opioid, morphine remains the current option for rescue doses. We can conclude that, by prescribing morphine as a rescue dose when another opioid is prescribed simultaneously, there is no guarantee we are offering the best medical practice, and based on the current knowledge described above, we are exposing patients to potential risks. It is also crucial to emphasize that the use of opioids with a long half-life or a controlled-released formulation as a rescue dose is strictly contraindicated.

Conflicts of interest

The authors declare no conflicts of interest.

References

1. Wicks C, Hudlicky T, Rinner U. Morphine alkaloids: History, biology, and synthesis. Alkaloids Chem Biol. 2021;86:145—342.
2. Crush J, Levy N, Knaggs RD, Lobo DN. Misappropriation of the 1986 WHO analgesic ladder: the pitfalls of labelling opioids as weak or strong. Br J Anaesth. 2022;129:137—42.
3. Dowell D, Ragan KR, Jones CM, Baldwin GT, Chou R. CDC clinical practice guideline for prescribing opioids for pain - United States, 2022. MMWR Recomm Rep. 2022;71:1—95.
4. Manchikanti L, Kaye AM, Knezevic NN, et al. Responsible, safe, and effective prescription of opioids for chronic non-cancer pain: American Society of Interventional Pain Physicians (ASIPP) Guidelines. Pain Physician. 2017;20:S3—S92.
5. Chinman M, Gellad WF, McCarthy S, et al. Protocol for evaluating the nationwide implementation of the VA Stratification Tool for Opioid Risk Management (STORM). Implement Sci. 2019;14:5.
6. Sverrisdóttir E, Lund TM, Olesen AE, Drewes AM, Christrup LL, Kreilgaard M. A review of morphine and morphine-6-glucuronide's pharmacokinetic-pharmacodynamic relationships in experimental and clinical pain. Eur J Pharm Sci. 2015;74:45—62.
7. Trescot AM, Datta S, Lee M, Hansen H. Opioid pharmacology. Pain Physician. 2008;11(2 Suppl):S133—53.
8. Mercadante S. Opioid titration in cancer pain: A critical review. Eur J Pain. 2007;11:823—30.
9. Hwang CS, Kang EM, Ding Y, et al. Patterns of immediate-release and extended-release opioid analgesic use in the management of chronic pain, 2003-2014. JAMA Netw Open. 2018;1:e180216.
10. Brennan MJ. Update on prescription extended-release opioids and appropriate patient selection. J Multidiscip Healthc. 2013;6:265—80.
11. Zhou J, Wang Y, Jiang G. Oxycodone versus morphine for cancer pain titration: A systematic review and pharmacoeconomic evaluation. PLoS One. 2020;15:e0231763.
12. Hanks GW, Conno F, Cherny N, et al. Expert Working Group of the Research Network of the European Association for Palliative Care. Morphine and alternative opioids in cancer pain: the EAPC recommendations. Br J Cancer. 2001;84:587—93.
13. Shang Y, Filizola M. Opioid receptors: Structural and mechanistic insights into pharmacology and signaling. Eur J Pharmacol. 2015;763:206—13.
14. Valentino RJ, Volkow ND. Untangling the complexity of opioid receptor function. Neuropsychopharmacology. 2018;43:2514—20.
15. James A, Williams J. Basic opioid pharmacology - An update. Br J Pain. 2020;14:115—21.
16. Zhang L, Zhang JT, Hang L, Liu T. Mu opioid receptor heterodimers emerge as novel therapeutic targets: Recent progress and future perspective. Front Pharmacol. 2020;11:1078.
17. Gomes I, Filipovska J, Devi LA. Opioid receptor oligomerization. Detection and functional characterization of interacting receptors. Methods Mol Med. 2003;84:157—83.
18. Gupta A, Mulder J, Gomes I, et al. Increased abundance of opioid receptor heteromers after chronic morphine administration. Sci Signal. 2010;3:ra54.
19. Azzam AAH, McDonald J, Lambert DG. Hot topics in opioid pharmacology: mixed and biased opioids. Br J Anaesth. 2019;122:e136—45.
20. de la Iglesia FA, Pace GW, Robinson GL, Huang NY, Stern W, Richards P. Tolerability and efficacy of two synergistic ratios of oral morphine and oxycodone combinations versus morphine in patients with chronic noncancer pain. J Opioid Manag. 2012;8:89—98.
21. Romero A, Miranda HF, Puig MM. Analysis of the opioid-opioid combinations according to the nociceptive stimulus in mice. Pharmacol Res. 2010;61:511—8.
22. Pasternak GW. Preclinical pharmacology and opioid combinations. Pain Med. 2012;13(Suppl 1):S4—11.
23. Bairaktari A, Al Harbi M, Dimitriou V. Combined use of strong opioids for pain relief in cancer patients - A prospective randomized comparative study. M E J Anesth. 2018;25:31—6.
24. Mercadante S. Opioid combination: rationale and possible clinical applications. Ann Palliat Med. 2013;2:189—96.
25. Marinangeli F, Ciccozzi A, Aloisio L, et al. Improved cancer pain treatment using combined fentanyl-TTS and tramadol. Pain Pract. 2007;7:307—12.
26. Silverman S, Raffa RB, Cataldo MJ, Kwarcinski M, Ripa SR. Use of immediate-release opioids as supplemental analgesia during management of moderate-to-severe chronic pain with buprenorphine transdermal system. J Pain Res. 2017;10:1255—63.
27. de Barutell C, Gonzalez-Escalada J. Efficacy and safety of buprenorphine TDS in conjunction with oral tramadol or morphine as rescue medication in the treatment of 390 patients with chronic pain: A summary of two retrospective Spanish multicenter studies. J Appl Ther Res. 2007;6:14—24.
28. Mercadante S, Villari P, Ferrera P, et al. Safety and effectiveness of intravenous morphine for episodic breakthrough pain in patients receiving transdermal buprenorphine. J Pain Symptom Manage. 2006;32:175—9.

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