

NEW PERSPECTIVE ARTICLE

Peripheral Tramadol in Dentistry: A New Use for an Old Drug Tramadol periférico en odontología: Un nuevo uso para un medicamento antiguo

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ABSTRACT

Tramadol is a well known central acting analgesic drug, used in a wide variety of treatments within health sciences; including dentistry. Due to its lack of anti-inflammatory action and some adverse effects related mainly to opioid receptors agonism, it is not use as a routine alternative; keeping mainly for patients allergic to non-steroidal anti-inflammatory drugs or as an adjuvant to manage severe odontogenic pain. Since new available evidence supports the possible analgesic effect of this drug when is applied locally in different sites, recent reports have been done to explore the same effect in the orofacial region, especially to improve the local management of odontogenic pain. This new perspective article summarize some of the current efforts develop to explore the peripheral Tramadol in dentistry; “a new use for an old drug”.

KEYWORDS

Old drugs; Peripheral tramadol; Local analgesics.

RESUMEN

El Tramadol es un fármaco de acción central bien conocido, usado en una gran variedad de tratamientos dentro de las ciencias de la salud; y la odontología no es la excepción. Debido a su falta de acción antiinflamatoria y a varios efectos adversos asociados principalmente al agonismo de receptores opioides, este no es usado como una alternativa de rutina; y se mantiene principalmente para pacientes alérgicos a antiinflamatorios no esteroideos o como coadyuvante en el manejo de dolor odontogénico severo. Sin embargo, ya que nueva evidencia disponible apoya su posible efecto analgésico al aplicarse localmente en diferentes sitios, investigaciones recientes se han realizado tratando de explorar el mismo efecto en la región orofacial, especialmente para mejorar el manejo local del dolor odontogénico. Este artículo de “nueva perspectiva” resume algunos de los esfuerzos recientes desarrollados para explorar el Tramadol periférico en odontología; un nuevo uso para un viejo medicamento.

PALABRAS CLAVE

Medicamentos antiguos; Tramadol periférico; Analgésicos locales.

“OLD DRUGS, NEW USES”... a concept that is becoming popular in health scientific literature. As says, it explains the possibility to discover new applications to old pharmacological compounds developed for a different clinical purpose (1), especially in the field of analgesia.

This is the case of Tramadol, a drug first synthesized in 1962, but available commercially until 1977 (2). Typically, Tramadol is classified as a centrally acting opioid (3); however, recent literature has changed this title for the one of an “atypical opioid” (4, 5). Its main action is attributed to central mechanisms, related to Miu opioid receptor (MOR) agonism as well as modulation of central monoamines concentrations (by inhibition of noradrenaline and serotonin reuptake) (3). Nevertheless, as Minami et al. (6) wrote in a recent review paper, to justify its clinical effect only in the well-studied mechanisms is scanty.

Tramadol is a racemic mixture of 2 enantiomers (Tramadol + (T+) and Tramadol – (T-); each one with independent effects. After hepatic metabolism by the action of cytochrome P450 2D6, native Tramadol (T±) is transformed into its 2 metabolites (M1 and M2). Since biotransformation of Tramadol is mainly due to O-demethylation, higher amounts of plasma concentrations of (-)M1 and T+ are expected. It is important to remind that the biotransformation depends of hepatic mechanisms, which are reached just after absorption of the drug. Table 1 summarize de specific actions of each enantiomer and Tramadol metabolites. Under a peripheral scope, the pharmacokinetic properties of subcutaneous Tramadol have not been examined and are not fully understood (3) and only some animal and clinical evidence is available regarding peripheral effects and the mechanisms involved.

Table 1. Systemic mechanisms of Tramadol metabolites.

Molecule	μ opioid receptor (MOR)	Serotonin (5-HT)	Noradrenaline (NA)
Tramadol (±)		5-HT reuptake inhibitor Increases 5-HT influx	
Tramadol (+)	MOR agonist (double action than T(-))	5-HT reuptake inhibitor (4 times more than T (-)) Increases 5-HT influx	
Tramadol (-)			NA reuptake inhibitor (better inhibitor than (+)T and M1)
Metabolite (-)M1	Increased affinity for MOR (700 times higher than T±)		

Many of the current alternatives to control pain depends of systemic administration through different pathways (such as oral, transdermal, parenteral, intranasal or rectal administration). As it can be figured, systemic administration will imply the presence of the drugs all around the body tissues, increasing the possibility of side effects occurrence in sites different from the source of pain. (7). To select peripheral or local analgesics seems a very promising option. The direct application of analgesics in the source of pain will allow immediate higher concentrations, and will lower systemic drug levels resulting in fewer side effects. Also in those patients with associated pharmacological therapies, drugs interactions can be avoid (8). Depending of the kind of drug, if the possibility to develop tolerance or dependence exists, the local application can also be beneficial.

In basic research, several local mechanisms for Tramadol have been reported, such as its weak peripheral agonism over MOR (2), activation of adrenergic receptors (9), lowering of the activation of vallinoid receptor 1 (TRPV-1) (10), blocking N-methyl-D-aspartate (NMDA) receptors (11), favoring the opening of nonspecific voltage-dependent potassium channels (12), acting in the nitric oxide pathway (13) or by direct blocking of sodium channels (14). Experimentally, this drug have been successful in the control of peripheral pain in animal nociception models (15-17). In humans, it is also effective as an anesthetic adjuvant for brachial plexus block (18, 19), for tendon repair surgery (20) or even compared with several local anesthetics when applied subcutaneously (21, 22).

Dentistry is an interesting field where the “old Tramadol” had found new uses. Its application is mainly studied in the field of oral surgery and endodontics. Briefly, some examples will be describe.

For third molar surgery, Tramadol showed different interesting advantages. As Pozos et al. reported, when it is given in a combination of routes (oral and local infiltration) it is capable to increase the duration of the anesthetic effect and also improves the quality of postoperative analgesia during the first 6 hours after the surgery (23). When combined with other adjuvants, Isordia et al., evaluated the pre-emptive analgesia using the combination of local Tramadol plus oral ketorolac (24). In that study, pre-surgical administration of ketorolac plus submucosal Tramadol in the third molar area, improved the pain experience of patients and decrease the need of postoperative analgesics.

Another approach that can be employed in dentistry, is to use Tramadol in combination with the local anesthetic solution to increase its effect and duration. In this sense, Isordia et al. combined Tramadol and Mepivacaine to evaluate

the anesthetic efficacy of inferior alveolar nerve blockade in healthy patients (25). This investigation showed an increased effect during the first 2 hours and a longer duration of soft tissues blockade. A similar design was used to evaluate the combination between Tramadol and Articaine (26) in healthy patients who requires the extraction of an impacted third molar. In this second research, the blockade with Articaine plus Tramadol showed also an increased duration. A recent investigation tried to evaluate a new combination between Mepivacaine and Tramadol, but in this case when the inferior alveolar nerve blockade was done in patients that suffer acute pain due to symptomatic irreversible pulpitis (27). This study showed that even when the combination didn't increase the success rate of the blockade, it did increase the duration of the anesthetic effect.

Considering the available evidence, the main question is: Local Tramadol can be used routinely in dental procedures? Even when it seems a promising alternative, and no significant adverse effects seems to occur, new investigations are needed to identify mechanisms involved and the correct dose needed in the different clinical scenarios. Also, new information obtained from patients undergoing painful situations is required. Who knows, maybe this old drug can be revolutionary once more soon. “OLD DRUGS, NEW USES”.

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