

Short Communication

Does Tramadol Produce an Anti-inflammatory Effect?

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Submitted: 22 November 2018

Accepted: 13 December 2018

Published: 18 December 2018

ISSN: 2333-7079

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Abstract

Tramadol is a centrally-acting analgesic that is widely used worldwide. It has been demonstrated to produce its antinociceptive effect in animals and its analgesic effect in humans by the combination of, and synergistic interaction between, its opioid and non-opioid mechanisms of action. Additional mechanisms have been proposed. Periodically, it is claimed that tramadol has an anti-inflammatory effect. We review this proposition.

ABBREVIATIONS

AKT: Protein Kinase B; COX: Cyclo-oxygenase; CYP: Cytochrome P450; 5-HT: Serotonin; IL-1 β : Interleukin 1 β ; K_{ATP}⁺: ATP-sensitive Potassium Channel; LTB₄: Leukotriene B₄; M1: *O*-desmethyl Tramadol; NMDA: *N*-Methyl-D-aspartate; NOS: Nitric Oxide Synthase; NSAID: Non-steroidal Anti-inflammatory Drug ODQ: 1H-[1,2,4] oxadiazolo [4,3,-a] quinoxalin-1-one; PGE₂: Prostaglandin E₂; PI3K γ : Phosphoinositide-3-kinase- γ ; PMN: Polymorphonuclear Cells; TMJ: Temporomandibular Joint; TNF- α : Tumor Necrosis Factor α ; TRPV1: Transient Receptor Potential Cation Channel Subfamily V Member 1

INTRODUCTION

Tramadol was identified by Grünenthal GmbH in Germany as part of an analgesics drug-discovery program during the 1960s. Due to favorable clinical characteristics (analgesic efficacy profile vs adverse effect profile) it has become one of the most widely-prescribed analgesic agents worldwide. Along with advances in clinical application, there have been advances in the understanding of its mechanism(s) of action [1].

Tramadol, (\pm) *cis*-2-[(dimethylamino) methyl]-1-(3-methoxyphenyl) cyclohexanol], is a racemic mixture of two enantiomers (Figure 1) that have similar but different pharmacology. Each enantiomer contributes to tramadol's overall clinical analgesic effect [2]. The major active metabolite of tramadol, *O*-desmethyl tramadol (M1) (Figure 2) [3,4] also contributes its overall analgesic effect. Since tramadol is converted to M1 by CYP-2D6 metabolism in the liver, the extent of the contribution of M1 to tramadol's analgesic effect is a function of the dose and route of administration of tramadol. At low doses and by administration routes that bypass the 1st-pass effect, the major contributor to analgesia is parent drug; the contribution of M1 metabolite is more apparent and more pronounced at higher doses and by routes that involve a greater 1st-pass effect.

Keywords

- Tramadol
- Anti-inflammatory
- Prostaglandins
- C-reactive protein

Multiple results from *in vitro* assays, animal models, and clinical pharmacology studies have consistently demonstrated the co-existence, and contributions, of both opioid and non-opioid components to tramadol's mechanisms of analgesic action. The co-existence of opioid and non-opioid mechanisms of action is made possible because of the related, but different, pharmacologies of the two enantiomers and of M1. Tramadol's overall antinociceptive effect in animals and analgesic effect in humans has been shown to result from combined contributions

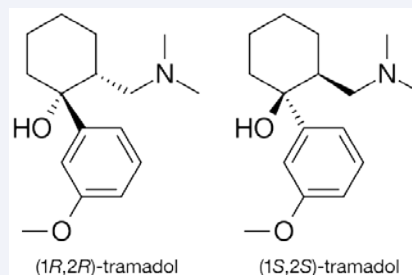


Figure 1 The enantiomers of tramadol.

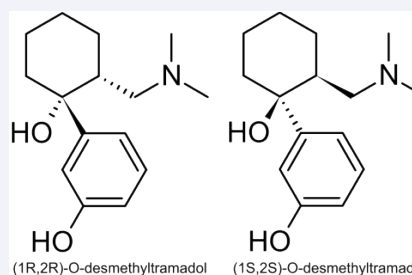


Figure 2 The enantiomers of M1, the *O*-desmethyl metabolite of tramadol.

of the two enantiomers and the M1 metabolite (depending on dose and route of administration).

The enantiomers of parent drug have only weak opioid characteristics, with only μM binding affinity for the mu-opioid receptor, but they contribute to tramadol's non-opioid component by inhibition of the neuronal reuptake of norepinephrine and serotonin (5-HT). The opioid component of tramadol resides mainly in M1, which binds to the mu-opioid receptor [5,6] albeit with two orders of magnitude lower affinity than morphine.

It has been shown in both animal and human studies that both components, opioid and non-opioid, contribute to the analgesic effect of tramadol (again the relative contribution of each component dependent on dose and route of administration). In addition, the two mechanisms have been shown to interact in a synergistic way in producing pain relief, but less-than synergistic way in the adverse effects tested (respiratory depression and constipation models) [2]. This is consistent with, and likely explains, the favorable clinical profile of tramadol.

Additional pharmacologic properties of tramadol have been reported, and the analgesic effect has been attributed, at least in part, to the mechanisms proposed. Some of the postulated mechanistic targets include sodium channels associated with the ionotropic glutamate receptor *N*-methyl-D-aspartate (NMDA), [7] transient receptor potential cation channel, subfamily V, member 1 (TRPV1) [8], and adenosine A1 receptors [9], among others. To date, none has been corroborated in a human study to our knowledge, but each seems reasonable.

Periodically throughout the years, a report is published that suggests that tramadol, either directly or indirectly, displays an anti-inflammatory effect. Such a property would be in addition to tramadol's centrally-mediated analgesic action. Early preclinical studies did not detect any significant anti-inflammatory effect. Since such an action would have important clinical significance, we summarize the available information.

MATERIALS AND METHODS

We searched PubMed, Medline, and Cochrane databases for papers (English language) related to the topic of anti-inflammatory action of tramadol. The bibliographies of these papers were also searched. Our goal was to create a narrative review that would provide some insight into the literature and the clinical importance of the topic and would provide some measure of assessment of the evidence.

RESULTS AND DISCUSSION

In the drug-discovery process, no significant anti-inflammatory action of tramadol was detected. Or at least not sufficient to suggest a significant clinical effect, certainly not as strong as the centrally-mediated mechanism(s) of action.

An early report of a possible anti-inflammatory effect of tramadol was that of Bianchi et al. [10], Noting that drugs that inhibit neuronal reuptake of norepinephrine and 5-HT have been reported to reduce experimental inflammation [11-13], the authors tested the ability of tramadol to affect the inflammatory edema and pain that is induced by the injection of brewer's yeast into the rat paw, the extravasation and prostanoid generation

that occurs during inflammation induced by subcutaneous implantation of carrageenin-soaked sponges in rats, and the spontaneous motility and migration of rat macrophages in response to a chemotactic stimulus. The latter was measured because of prior reports that inhibitors of neuronal norepinephrine and 5-HT diminish migration of macrophages in rats [14,15]. In this study, tramadol, at antinociceptive doses, significantly reduced yeast-induced inflammatory edema and significantly reduced both the volume of inflammatory exudate induced by implantation of carrageenan-soaked sponges and the amount of PGE_2 in the exudate. All of these results are suggestive of an anti-inflammatory effect. In contrast, tramadol did not alter the amount of LTB_4 or polymorphonuclear leukocytes (PMN) in the exudate, neither did it alter the chemotaxis or motility of macrophages, which were expected from an anti-inflammatory effect. Similar results were obtained using the enantiomers of tramadol in the same tests [16]. By way of explanation for these findings, the authors point out that a direct action of tramadol on cyclo-oxygenase (COX) enzyme has previously been ruled out [17]. They hypothesize a peripheral opioid action, however they did not determine if the opioid antagonist naloxone blocks the effect, or a central effect resulting from the neuronal reuptake of monoamines (norepinephrine and 5-HT, similar to results found for tricyclic antidepressants [13].

Buccellati et al. [18], speculated that perhaps tramadol can reduce the production of prostaglandins. They tested if tramadol might affect the activity of COX-1 and COX-2 in human whole blood using *in vitro* assays. Neither tramadol nor individual enantiomers of tramadol inhibited the formation of arachidonic acid metabolites, effectively again ruling out a direct inhibitory effect of tramadol on the formation of prostanoids.

A few years later, El-Sharrawy et al. [19], tested the ability of tramadol to affect the increase in C-reactive protein that accompanies acute inflammation that develops during the tissue trauma of removal of impacted third molars. C-reactive protein is a chemical mediator that is released as part of the response to tissue trauma [20]. They studied healthy young men and women (N = 45) who did not have pre-existing inflammatory conditions. The authors report that 100mg tramadol every 8 hours inhibited the expected increase in C-reactive protein 72 hours postoperatively, and, further, that the combination of 50mg tramadol plus 200mg ibuprofen was better than either 100mg tramadol alone or 400mg ibuprofen alone. Unfortunately, the study suffers from several limitations that impede a rigorous interpretation. For example, there is no group that received no medication with which to compare as a control. This is reasonable for ethical reasons, but means that there are no data for the increase in C-reactive protein, thus no way to reliably assess inhibition of such an increase. It should also be noted that 100 mg tramadol taken every 8 hours is an exceedingly large dose, is not recommended, and probably produces pharmacologic effects that preclude application to the usual analgesic doses. And statements about the combination of tramadol with ibuprofen are unfortunately made without proper rigorous mathematical analysis of combinations.

In a recent study, Lamana et al. [21], sought to evaluate a potential peripheral anti-inflammatory effect of tramadol on

formalin-induced temporomandibular joint (TMJ) pain in rats. Part of the impetus for this study was previous reports that local peripheral administration of tramadol produces antinociception and analgesia [22-28]. In this study, an intra-TMJ injection of tramadol dose-relatedly inhibited formalin-induced TMJ pain. The localized nature of the effect was demonstrated by the lack of effect when tramadol was injected into the contralateral (not formalin-injected) TMJ. The antinociceptive effect was not blocked by naloxone, by an inhibitor of PI3K γ , AKT, or by a glibenclamide-sensitive K⁺_{ATP} channel blocker. But it was significantly reduced by a nitric-oxide synthase (NOS) inhibitor and by a soluble cGMP enzyme ODQ inhibitor. The results interpreted together suggest that tramadol's effect did not involve binding to opioid receptors, or an action at PI3K γ , AKT, or glibenclamide-sensitive K⁺_{ATP} channels. In additional tests in the study, tramadol inhibited capsaicin-induced TMJ nociception, formalin-elicited increases in the levels of the pro-inflammatory cytokines TNF- α and IL-1 β , and carrageenan-induced inflammation in the TMJ.

CONCLUSION

Numerous studies have demonstrated the centrally-mediated antinociceptive effect of tramadol in multiple animal models and analgesia in human trials and extensive clinical experience. Two components of pain-relieving mechanisms of action have been shown definitively in animals and humans: opioid (contributed primarily by the metabolite M1) and non-opioid inhibition of neuronal reuptake of norepinephrine and 5-HTT (contributed primarily by the enantiomers of parent drug). Early studies showed that tramadol has no direct inhibitory effect on COX isozymes, which is the mechanism of action of the non-steroidal anti-inflammatory drugs (NSAIDs). This has been confirmed in subsequent studies. However, some of these subsequent studies have reported actions of tramadol that could result in an anti-inflammatory effect. The extensive clinical experience with tramadol does not support a strong anti-inflammatory action, but these findings are informative nevertheless. They add to the knowledge base of tramadol and might help further explain the favorable characteristics of this widely used medication.

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Cite this article

Pergolizzi JV, Taylor R, Raffa RB (2018) Does Tramadol Produce an Anti-inflammatory Effect? *J Pharmacol Clin Toxicol* 6(7):1131.