

## TRAMADOL AND IT'S THERAPEUTIC EFFECTIVENESS

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### Abstract

Tramadol is a centrally acting analgesic structurally related to codeine and morphine containing two enantiomers both of which contribute to analgesic activity. [+]Tramadol and the metabolite (+)-O-desmethyl-tramadol (M1) are agonists of the  $\mu$ . opioid receptor. [+]Tramadol inhibits serotonin reuptake and [-]tramadol inhibits norepinephrine reuptake, enhancing inhibitory effects on pain transmission in the spinal cord. Tramadol is available as drops, capsules and sustained released formulations for oral use and suppositories for rectal use and solution for IM, IV and subcutaneous injection. After oral administration it is rapidly and completely absorbed. Sustained released tablets releases the active ingredient over a period of 12 hours and have a bioavailability of 87–95% compared with capsules. It is rapidly distributed in the body and plasma protein binding is about 20% [3] Tramadol has two chemical names which includes (-)-Tramadol; (-)-(S,S)-trans-Tramadol; 123134-25-8; (1S,2S)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol; (-)-trans-2-(Dimethylaminomethyl)-1-(m-methoxyphenyl)cyclohexanol; It's molecular formula is C<sub>16</sub>H<sub>25</sub>NO<sub>2</sub>. It's Molecular weight is 263.3752 g/mol.

**Keywords:** Tramadol, Therapeutic effectiveness

## Introduction

Tramadol has been used in market since 1977 and is a type of opioid. It is different from most other opioids because of its multiple mechanism of analgesic action which may includes (binding to  $\mu$ -opioid receptors and inhibition of neuronal reuptake of norepinephrine and serotonin) [1]. Tramadol is effective in different acute and chronic pain states[2]. Tramadol has the chemical name ( $\pm$ )-trans-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl) cyclohexanol, is an orally active opioid analgesic. Conventional release preparations in the form of capsules, drops and suppositories containing tramadol and its hydrochloride salt have been available for many years for use in the treatment of moderate to severe pain.[4]

## Pharmacology of tramadol

Tramadol's mechanism of action is based on blockade of serotonin reuptake. It also inhibits norepinephrine transporter function. Its analgesic action is independent of  $\mu$  receptor. Its recommended dosage is 50 to 100mg orally four times daily. It has different side effects including nausea, dizziness. It shows no effect on respiration or cardiovascular system.[10]

## Biopharmaceutical aspect

P.o. administration of  $^{14}\text{C}$ -labelled rac.-1-(e)-(m-methoxyphenyl)-2-(e)-dimethylaminomethyl-cyclohexan-1-(a)-ol hydrochloride (tramadol hydrochloride, CG 315, Tramal) to mice, hamsters, rats, guinea pigs, rabbits, dogs and man the metabolic pathways and the results were compared. After synthesis of the reference substances the metabolites identified by cochromatography using TLC (thin-layer chromatography) and HPLC (high performance liquid chromatography) by cocrystallization and by gas chromatography mass spectrometry. In all species main metabolic pathways were N- and O-demethylation (phase I reactions) and conjugation of O-demethylated compounds (phase II reactions).[5] 11 metabolites are known, 5 arising by phase I reactions (M1 to M5) and 6 by phase II reactions (glucuronides and sulfates of M1, M4 and M5). The 5 phase I metabolites are mono-O-demethyl-tramadol (M1), mono-N-demethyl-tramadol (M2), di-N-demethyl-tramadol (M3), and tri-N,O-demethyl-tramadol (M4) and di-N,O-demethyl-tramadol (M5). The biotransformation scheme of it is qualitatively identical to man, dog, rabbit, guinea pig, rat, hamster and mouse. In all species all conjugates including M1 and M1-

conjugates, M5 and M5 conjugates and M2 are the main metabolites, whereas M3, M4 and M4 conjugates only formed in minor quantities. Following p.o. administration to man and animals  $^{14}\text{C}$ -tramadol is rapidly and completely absorbed. The unchanged drug and metabolites are excreted via kidneys. [19]. The cumulative renal excretion of total radioactivity is approximately 90% in man and varies from 86 to 100% in mouse, hamster, rat, guinea pig, rabbits and dogs the residual radioactivity appears in the feces. Tramadol is metabolized more rapidly in animals than in man. For this reason there are differences between man and animals in the amount of tramadol excreted unchanged in the urine i.e (about 30% and 1% of the p.o. dose, respectively). After incubation with beta-glucuronidase and arylsulfatase at least 81% of the excreted radioactivity could be extracted from the urine of man animals with the exception of the guinea pig and the rabbits.[5]

## Tramadol in osteoarthritic pain

CR tramadol is as effective as SR diclofenac in the treatment of pain due to knee or hip osteoarthritis with the potential for serious side effects that characterize nonsteroidal anti inflammatory drug administration.[6]

## Tramadol in cancer pain

Tramadol can be used in cancer patients safely because can be safely combined with non opioids e.g with paracetamol with an improvement in analgesia but no increasing toxicity occurs. Combined preparation of tramadol (37.5 mg) and paracetamol (325 mg) are now a days available. The important advantage of tramadol is that it causes less constipation as compared to codeine while treating cancer patients. Tramadol showed no dependence when used in cancer patients for treating chronic pain.[14] Tramadol is not used in Egyptian cancer patients as they got a higher risk of getting dependant on it.[18]

## Tramadol in preoperative pain

Tramadol is effective in preoperative pain because it not only reduces hospitalization and prevents long term complications. Clinical studies evaluated that the perioperative use of tramadol in both nurse administered and patient controlled analgesia in patients undergoing surgical procedures including abdominal, orthopaedic and cardiac surgery. In a few recent studies in patients who had undergone cardiac surgery, tramadol IV flush provided analgesia similar to that of morphine. And parenteral tramadol

provides effective analgesia in paediatric patients, although its use in this group is not recommended currently in some countries e.g in US. [13]

### ***Tramadol provens ineffective to have antiinflammatory effect***

Tramadol has low affinity for opioid receptors and initially thought to lack selectivity for different receptor subtypes[19] but its analgesic potency is only 5 to 10 times less than morphine and other drugs.[8]

### ***Tramadol in muscle stiffness***

Tramadol is now specifically recommended in musculoskeletal pain guidelines and neuropathic pain guidelines, because of its efficacy, safety, and tolerability. [11] Clearly there is no major organ toxicity.[12] The side effect profile over traditional opioids are particularly marked in the case of constipation which is usually the biggest problem with opioid use in the elderly patients. Tramadol is used in the market for 30 years and clinical experience now extends upto more than 5 billion patient's treatment. [7]

### ***Tramadol in neuropathic pain***

Tramadol can be used in neuropathic pain. During different clinical studies it is found that a significant therapeutic effect of tramadol is present on paraesthesiae, allodynia, and touch evoked pain. Tramadol is as effective as codeine in treating neuropathic pain patients.[15]

### ***Tramadol in diabetic neuropathy***

Tramadol can be used in diabetic neuropathy as preferred medicine. It reduces pain that occurs due to diabetes.[16]

### ***Tramadol in acute pain***

Tramadol is effective in both experimental and clinical pain without causing serious cardiovascular or respiratory side effects.

Use of a combination of tramadol and NSAIDs is beneficial for tramadol dose reduction as well as its lower incidence of adverse effects.[17]

### ***Tramadol in chronic lower back pain***

Tramadol is used in treating lower back pain and is shown to be much effective as it has lesser side effects as compared to other analgesics. In clinical controlled studies it has shown only few adverse effects such as nausea, dizziness, somnolence, and headache but still got very good results.[20]

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