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Review

Tramadol hydrochloride: Pharmacokinetics, pharmacodynamics, adverse side effects, co-administration of drugs and new drug delivery systems

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ABSTRACT

Tramadol hydrochloride (TrHC) is a synthetic analgesic drug exhibiting opioid and non-opioid properties, acting mainly on the central nervous system. It has been mostly used to treat pain, although its use to treat anxiety and depression has also been documented. These properties arise from the fact that they inhibit serotonin (5-HT) reuptake augmenting 5-HT concentration on the synaptic cleft. Despite this, TrHC has also been described to have several side effects which are mainly due to its fast metabolization and excretion which in turn requires multiple doses per day. To surpass this limitation, new pharmaceutical formulations are being developed intending the protection, target and sustained delivery as well as a reduction on daily dose aiming a reduction on the side effects. In the present work we have revised the efficacy, safety, biological and adverse effects of TrHC, and the added value of developing a novel drug delivery system for topical administration.

1. Introduction

Tramadol hydrochloride (TrHC) is a synthetic analgesic drug showing opioid and non-opioid properties, acting mainly on the central nervous system (CNS). This drug is structurally related to codeine and morphine, but it is 6000-times less potent than morphine and 10-times less potent than codeine [1–3]. It appeared in the 1970s, but only approved by the Food and Drug Administration (FDA) in 1995 for the management, treatment and relief of moderate to severe pain conditions [4–6]. The anti-nociceptive effects are due to a double (opioid and non-opioid) mechanism of action. In fact, TrHC acts on μ-opioid and k-opioid receptors with low affinity, exerting a weak agonist effect, and it affects monoamine receptor systems by blocking norepinephrine (NE) and serotonin (5-HT) reuptake, responsible for the inhibition of pain transmission in the spinal cord [7,8]. TrHC is more advantageous than other typical opioid agents for its unique pharmacological profile, since it exhibits a lower incidence of side effects and abuse potential [8,9]. Table 1 summarizes the physicochemical properties of this drug.

Abbreviations: 5-HT, serotonin; BBB, blood brain barrier; CNS, central nervous system; FDA, Food and Drug Administration; GABA, gamma aminobutyric acid; M1, *O*-desmethyltramadol; M2, *N*-desmethyltramadol; NA, noradrenaline; NE, norepinephrine; NET, norepinephrine transporter; NMDA, *N*-methyl-D-aspartate; NMDAR, *N*-methyl-D-aspartate receptor; NSAIDs, non-steroidal anti-inflammatory drugs; P-gp, P-glicoprotein; SERT, serotonin (5-HT) transporters; TrHC, tramadol hydrochloride.

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Table 1
Technical details of tramadol hydrochloride.

Iupac name	(1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)cyclohexanol hydrochloride (1:1)
Formula	$C_{16}H_{26}ClNO_2$ (Tramadol Hydrochloride); $C_{16}H_{25}NO_2$ (Tramadol)
Average molecular weight	299.84 g/mol (Tramadol Hydrochloride); 263.4 g/mol (Tramadol, base)
Chemical class	Phenylpropylamines
pK_a	9.41
Solubility	Water soluble
Category	Narcotic analgesic opioid agonist for the treatment of moderate to severe pain
Melting point	180–181 °C (TH)
UV–vis absorbance	271 nm
Plasma half-life	6 h
Toxicity	LD_{50} = 350 mg/kg (orally in mice)
CAS no.	22204-88-2

2. Pharmacokinetics and pharmacodynamics

TrHC is available in a variety of pharmaceutical formulations for various routes e.g. sub-cutaneous, intra-muscular, intra-venous, sub-lingual, and oral drug delivery. TrHC is rapidly and almost completely absorbed after oral administration. The mean peak plasma concentration occurs after 2 h and its bioavailability is approximately 70% as a result of the first-pass metabolism in the liver. About 20% of the drug is bound to plasma proteins and the mean half-life is ca. 6 h [1,4,6]. TrHC is extensively metabolized in the liver via cytochrome isoenzymes P450 2D6, and P450 2B6 and P450 3A4, to *O*-desmethyltramadol (M1) and *N*-desmethyltramadol (M2) respectively, being the main phase-1 metabolites. These are further metabolized to three secondary metabolites, namely *N*,*N*-didesmethyltramadol, *N*,*N*,*O*-tridesmethyltramadol and *N*,*O*-desmethyltramadol. All metabolites are finally conjugated with glucuronic acid and sulfate before excretion in urine [1,5,10].

The route of elimination almost totally involves the kidneys. Approximately 30% of the dose is excreted in the urine as unchanged drug, while 60% of the dose is excreted as metabolites. The remaining drug is eliminated in the feces, therefore biliary excretion is negligible [1,4,5].

TrHC exists as a racemic mixture with important differences in binding, activity and targets associated with the two enantiomers [3,11]. The (+) enantiomer has higher affinity to opioid receptors and preferentially inhibits 5-HT uptake and enhances 5-HT release, whereas the (−) enantiomer inhibits NE reuptake. The synergistic action of the two enantiomers is responsible for the analgesic effect of TrHC [12,13]. Specifically, M1 metabolite is considered the most pharmacologically active, being up to 6 times more potent than the parent drug in producing analgesia, and 200 times more potent in μ-opioid binding [2,7,14].

TrHC exhibits anti-nociception in a range of preclinical pain models, and the involvement of opioid, noradrenergic and serotonergic mechanisms has been demonstrated. In addition to well-recognized systemic actions, several studies reported anti-nociception following spinal and local peripheral administration. TrHC has reported to interact with additional cellular targets (e.g. Na^+ channels, N-methyl-D-aspartate (NMDA) receptors, and transient potential vanilloid-1 receptors), contributing to anti-nociceptive effects in particular when higher concentrations are achieved from the local administration. Sawynok et al. confirmed that local peripheral administration produces anti-nociception in formalin test mice [13]. This local action also involves peripheral adenosine A1 receptors, present on sensory neurons, widely distributed throughout pain signaling pathways. Peripheral anti-nociception following A1 receptor activation involves inhibition of adenylate cyclase and cAMP production, interactions with the nitric oxide/cyclic guanosine monophosphate signaling pathway, and interactions with phospholipase C systems [13].

Given its monoaminergic properties, antidepressant and anxiolytic-like effects have also been attributed to tramadol. The drug has inhibitory effect via α2-adrenoceptors on Locus Coeruleus, which regulates pain and anxiety, where the neuronal activity is modified by opiate analgesics, antidepressant and anxiolytics. The antidepressant effect is also modulated by 5-HT system and, in particular, by 5-HT_{1A} receptors [15]. This antidepressant activity has been confirmed in vivo [16].

TrHC was reported to decrease the binding of frontocortical β-adrenoceptors, 5-HT_{2A} receptors and α2-adrenoceptors, and to increase the binding of α1-adrenoceptors and dopamine receptors, therefore inducing changes in the central nervous system (CNS). The drug has been applied for several psychiatric and anxiety-like disorders [15,16]. The anti-depressant effect of TrHC has been attributed to the noradrenergic (α2-adrenoceptors), dopaminergic (D1/D2 receptors) and imidazoline (I1/I2 receptors) systems [16]. In addition, anti-shivering and analgesic effects were also attributed to TrHC, without undergoing severe sedation in post-operative period [6,17].

Tramadol may also be clinically applied for the management of premature ejaculation, the most common sexual disorder, affecting 20–30% of adult men. Various studies evaluated and confirmed the drug efficacy, safety, and tolerability when using small dosages (25 and 50 mg) with minimal adverse side-effects [4,18]. This effect has been attributed to the inhibition of neuronal reuptake of 5-HT and NE, enhancement of 5-HT efflux, anti-nociceptive effects and inhibition of spinal somatosensory evoked potentials (a series of waves that reflect sequential activation of neural structures along the somatosensory pathways). As a result, peripheral sensory nerves will depict some anesthetic-type effect [4].

Shah et al. demonstrated that TrHC inhibits KCl-induced contractility of isolated human myometrium by stimulating β1-adrenoceptors mediating tissue relaxation, at very high doses. It is well-known TrHC inhibits NE reuptake by inhibiting NE transporter (NET). This carrier is present in various tissues of the body, including the uterus. Therefore, the inhibition of NET in the isolated myometrium may cause the increased levels of NE at the neuroeffector junction, leading to stimulation of β1-adrenoceptors, resulting in inhibition of tissue contractility [19].

A pharmacokinetic study was carried out in male Sprague-Dawley rats to evaluate the possible involvement of P-glycoprotein (P-gp) in the brain distribution of TrHC [20], since the drug has some features of being a P-gp substrate, i.e. the presence of planar aromatic domains and tertiary amino groups. P-gp is a 170-kDa energy-dependent integral membrane protein, product of multi-drug resistance gene; it is also one of the most important members of the ABC transporter superfamily consisting of several transporters with apparently different biological functions, having prominent membrane transport activities in different tissues/cell types (e.g. epithelial cells of gastrointestinal tract, canalicular cells of the liver, placenta, kidney, and the blood brain barrier).

The highly extensive tissue localization of the drug, as well as different influx/efflux roles and, more importantly, a wide substrate specificity of different chemical and pharmacological classes, lead to consider this transporter of strategic relevance for pharmacokinetic studies. From some results, it is obvious that TrHC unrestrictedly penetrates the brain parenchyma. Sheikholeslami et al. considering their results and those of previous studies concluded that it seemed that the brain accumulation of TrHC is not affected by P-gp inhibition implying that there may be some other transport mechanisms involved in blood brain barrier transport of the drug [20]. Recently, in vitro and in vivo studies indicate the involvement of a proton-coupled organic