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Tramadol in Japanese Population: Relative Contribution of M1 Metabolite as Assessed by *CYP2D6*10 Genotype

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ABSTRACT

Several preclinical and clinical studies suggested that tramadol has a multi-mechanistic analgesic action. Upon *in vitro* evaluation, tramadol parent drug was determined to have only very weak affinity for opioid receptors. Metabolism *via* CYP2D6, though, yields the *O*-desmethyl metabolite (M1), which has much greater opioid receptor affinity. In tests in animals and human volunteers, tramadol's analgesic effect is only partially blocked by the opioid antagonist naloxone. Yet the contribution of parent drug to analgesia is still debated. Observance of good analgesic response to tramadol in Japanese and other Asian populations that express the *CYP2D6*10 genotype suggests that parent drug accounts for the majority of tramadol's analgesic effect in most clinical settings. Understanding of tramadol's multi-mechanistic action continues to form the basis for understanding its clinical attributes.

Keywords: Tramadol; M1 Metabolite; CYP2D6 Polymorphism; *CYP2D6*10; Japanese

1. Introduction

Japan was one of the first countries to approve the centrally-acting analgesic tramadol hydrochloride (in 1978). Tramadol is now available throughout the world and it is used extensively alone or in combination with other analgesics for the management of a wide variety of acute and chronic pain conditions.

Tramadol was originally believed to act only through a μ-opioid receptor mechanism of analgesic action, but extensive subsequent study in animal models and in humans has established a second, and equally important, contribution related to a non-opioid mechanism of analgesic action [1]. The non-opioid mechanism is generally attributed primarily to inhibition of neuronal norepinephrine and 5-HT (5-hydroxytryptamine, serotonin) reuptake by the enantiomers of the parent drug; and the opioid mechanism is generally attributed primarily to high-affinity μ-opioid receptor binding of tramadol's M1 (*O*-desmethyl, via CYP2D6) metabolite. The clinical analgesic and safety profile of tramadol is consistent with these dual mechanisms contributing individually, and sometimes synergistically, to its overall clinical profile [1]. Nevertheless, the extent to which M1 is required for the analgesic efficacy of tramadol has remained a matter of discussion.

Itoh [2] reviewed the pharmacologic analgesic regimen that was standard in Japan at that time for the treatment of non-malignant chronic pain conditions. Pharmacologic options then consisted of a non-opioid analgesic such as acetaminophen (paracetamol) in the first stage, then an NSAID (non-steroidal anti-inflammatory drug). The NSAID was to be tried first in low dose and then, only if necessary, in high dose. At that time, opioid drugs were not approved for non-malignant chronic pain conditions. Citing the known serious adverse effects associated with the use of other analgesics, and the multi-mechanistic action of tramadol, Itoh [2] suggested that tramadol, with its good analgesic efficacy and adverse effect profile—including low (but not zero) abuse potential—might provide an attractive option for treating non-malignant chronic pain conditions.

Saeki [3] more recently discussed that there were still only two opioids in addition to morphine available at that time in Japan for the management of non-malignant pain: codeine phosphate (codeine) and dihydrocodeine phosphate (dihydrocodeine). The author expressed the hope that additional analgesics, including tramadol, would become available for this patient population.

The present paper reviews some of the early preclinical studies on tramadol that were conducted in Japan, the dual mechanisms of analgesic action of tramadol, and the implications that use in a population that has a very low incidence of polymorphisms in *CYP2D6*3, *CYP2D6*4, or *CYP2D6*5—but a high incidence of *CYP2D6*10—alleles has on the question of whether M1 is a requirement for analgesic activity of tramadol in most settings.

2. Materials and Methods

2.1. Search Strategy

Review articles, including the author's, were collected that described the early history of tramadol, its mechanism of action, and the proposed contribution of its M1 metabolite to analgesic effect. In addition, a systematic search of databases (e.g., PubMed) was conducted on the topic of the *CYP*2*D*6*10 genotype.

2.2. Inclusion Criteria

An article (either review or primary) was included if it contained information about the relationship between the basic science properties of tramadol (e.g., dual opioid and non-opioid components of analgesic action, enantiomers, metabolites, etc.) and its clinical characteristics. All articles meeting this criterion were included.

2.3. Organization and Use

The review articles were summarized and used to define the long-standing question regarding the relative contribution of tramadol's M1 metabolite to its clinical analgesic efficacy and safety profile. The primary literature about the *CYP*2*D*6*10 genotype was used to help answer this question.

3. Results

3.1. Discovery, Development, Pain Management

Tramadol hydrochloride, (1*RS*,2*RS*)-2-[(Dimethylamino) methyl]-1-(3-methoxyphenyl)-cyclohexanol HCl, was a compound synthesized and evaluated as part of an intensive discovery effort conducted in the early 1960's by a team of researchers at the German pharmaceutical company Grünenthal GmbH. The compound investigated was consisted of *S*- and *R*-enantiomers (*cis*-*trans* mixture). The *R*-enantiomer was subsequently found to have the better antinociceptive profile, but it was initially erroneously identified as the *trans* configuration, so the drug was named *tra*madol. An extensive a comprehensive early pharmacologic evaluation, which predated the discovery of opioid receptors, revealed that tramadol has significant antinociceptive activity in animal models that are predictive of analgesic activity in humans and CNS (central nervous system) effects suggestive of opioid activity [1].

Yanagita [4] investigated the drug dependence potential of tramadol using monkeys and suggested that its abuse potential appeared to be less than would be predicted based upon its antinociceptive potency compared to opioids, an insight substantiated by extensive subsequent testing and epidemiological experience.

Clinical investigations performed in Europe confirmed tramadol's analgesic activity and a low extent of opioid-type adverse effects (e.g., respiratory depression). When the drug became available for licensing, testing in Japan validated and extended these earlier findings.

A capsule formulation of tramadol was developed by Grünenthal GmbH (registered under the brand name TRAMAL®) and the drug became increasingly successful. At that time, tramadol was the only centrally-acting mono-analgesic in Germany available without narcotic prescription. It was found to be effective in a variety of acute and chronic pain situations and tramadol filled the gap on the WHO (World Health Organization) "analgesics ladder" between the weak analgesics of the NSAID and acetaminophen (paracetamol) type and strong opioids of the morphine type.

3.2. Basic Science

3.2.1. Mechanism of Action

The affinity of tramadol parent drug for μ-opioid recaptors (K_i value) is very low (low μM range) and is even lower for δ- and κ-opioid receptors [1]. The low binding affinity at opioid receptors, alone, is insufficient to explain its analgesic efficacy. Therefore, other mechanisms must be involved. Tramadol does not bind to other receptor sites (even at concentrations that are 10- to 100-fold higher) and it does not inhibit cyclooxygenase (therefore it is not an NSAID). However, tramadol, unlike codeine, morphine or most other opioids, inhibits the neuronal reuptake of norepinephrine and 5-HT [1], but not the reuptake of other neurotransmitters. Again, though, the relatively low affinity of tramadol for 5-HT and NE reuptake sites (e.g., about two orders of magnitude less than imipramine) seems insufficient by itself to explain its analgesic efficacy. The explanation appears to be related to the fact that tramadol inhibits neuronal reuptake of norepinephrine and 5-HT in the same concentration range that it binds to μ-opioid receptors, so both mechanisms are activated simultaneously. Other sites have also been speculated to play some role (e.g., [5-7]).

The nonopioid component of tramadol is manifested in several animal models in which tramadol-induced antinociception is only partially blocked by an opioid recaptor antagonist naloxone in acute pain models and in a neuropathic pain model. Similar results have been found in humans [1]. In a randomized, crossover study, naloxone reduced tramadol's analgesic effect by only about 26% - 31%; tramadol displays only a small degree of cross-tolerance to opioids and, the opioid-like subjective effects of tramadol are less than what would be expected from its analgesic potency relative to morphine. The adrenoceptor antagonist yohimbine and the 5-HT recaptor antagonist ritanserin do not affect spinal morphine-induced antinociception, but they significantly reduce

tramadol-induced antinociception [1]. The (+) enantiomer of tramadol (a racemate) has greater affinity for μ-opioid receptors and inhibits 5-HT reuptake more potently than does the (–) enantiomer of tramadol, and the (–) enantiomer inhibits the neuronal norepinephrine reuptake more potently than does the (+) enantiomer of tramadol. The two enantiomers each produce antinociception and combined produce a synergistic antinociceptive effect [1]. They interact less than synergistically or even less than additively in the adverse effect measures such as inhibition of colonic propulsive motility, impairment of rotarod performance, respiratory rate, or blood pressure [1].

The opioid component of tramadol resides primarily in its M1 (*O*-desmethyl) metabolite, which binds with about 200-fold higher affinity than does the parent compound. M1 is the product of oxidative *O*-demethylation reactions catalyzed by CYP2D6 [1] and is a clinically relevant active metabolite of tramadol.

3.2.2. Absorption, Distribution, Metabolism, and Elimination

Tramadol has been formulated for almost every route of administration (oral, injectable, transdermal, controlled release, etc.), although availability within individual countries might be limited to only some formulations. In Japan, injectable, immediate-release, and sustained release formulations are available.

Tramadol is rapidly and almost completely absorbed following oral administration (about equally under fed or fasted condition). It has an absolute bioavailability of about 75%, plasma-protein binding about 20%, and volume of distribution about 2.7 L/kg. The dose-dependent analgesic effect begins within about 1 hour following oral administration and peaks at about 2 - 3 hours.

Tramadol is extensively metabolized following oral administration. The major metabolic routes involve hepatic Phase 1 *N*- and *O*-demethylation and Phase 2 glucuronidation or sulfation. The major metabolite of tramadol, *O*-desmethyl tramadol (M1), arises from a reaction catalyzed by the CYP-450 isozyme CYP2D6, which is subject to metabolic inhibition or induction by other drugs. Tramadol is able to produce analgesia in patients with CYP2D6 polymorphism ("poor metabolizers"), but its metabolism is reduced in patients with advanced hepatic disease (dose adjustment is recommended in cirrhotic patients).

The major route of excretion of free and conjugated tramadol and metabolites is through the kidney. Tramadol has a mean terminal plasma elimination $t_{1/2}$ of approximately 6 - 7 hours, which increases about 1 h with multiple dosing and decreases in impaired kidney function (dose adjustment is recommended when creatinine clearance is <30 mL/min). Consideration of dose adjustment is recommended for older patients and for other special populations.

3.3. Japanese Population and *CYP*2*D*6*10

Differences in genetic polymorphisms in CYP isozymes that result in alterations in metabolism of drugs are well documented in general and for CYP2D6 (debrisoquine/sparteine) in particular [8-13]. In Caucasians, mutations reduce enzyme function and result in an impaired metabolism of drugs ("poor metabolizers", "PM" phenotype), estimated to be about 4% - 10% assessed using metabolism of the opioid analgesic dextromethorphan to dextrorphan as a probe (e.g., [14]). The PM phenotype is inherited as an autosomal homozygous (–/–) recessive trait. In Japanese, the occurrence of dextromethorphan PM is estimated to be much less (about 1%) [15].

The PM phenotype in Caucasians is mainly due to defective CYP2D6 alleles such as *CYP*2*D*6*3, *CYP*2*D*6*4, and *CYP*2*D*6*5, which are not common mutations in Asian populations. However, other CYP2D6 polymorphisms are detected (e.g., [9,16,17]). In particular, the *CYP*2*D*6*10 mutant allele and haplotypes are expressed in high frequency (~20% - 45%) in Japanese [18-22]. The defining mutation for *CYP*2*D*6*10 allele is the C_{188} to T_{188} mutation in exon 1, which causes a $Pro_{34} \rightarrow$ Ser amino acid substitution that results in a form of an unstable enzyme with lower metabolic activity [23]. In human liver microsome preparation, the rank order of activity (as assessed by the catalysis kinetics of dextromethorphan *O*-demethylation) is *CYP*2*D*6*1/*1 (the wild type allele) > *CYP*2*D*6*1/*10 > *CYP*2*D*6*10/*10 [22].

The frequency of *CYP*2*D*6*1/*1, *CYP*2*D*6*1/*10, and *CYP*2*D*6*10/*10 in Japanese populations has been determined by: genotyping 98 unrelated, healthy men 20 - 38 years of age by PCR (polymerase chain reaction) amplification for CYP2D6 alleles and phenotyping using dextromethorphan metabolism [24]; PCR amplification in 162 unrelated, healthy volunteers (95 males, 67 females) 19 - 61 years of age and phenotyping of a subset (n = 35) by dextromethorphan metabolism [25]. The effect of *CYP*2*D*6*10 genotype on tramadol pharmacokinetics has been shown [26]. The mean serum $t_{1/2}$ of tramadol (single 100 mg IV dose) was significantly longer in homozygous subjects than heterozygous or wild-type subjects. These results established the *in vivo* manifestation of reduced enzyme activity and set the stage for testing the contribution of tramadol M1 to analgesia.

The analgesic efficacy of tramadol in 17 Japanese patients with refractory chronic non-malignant pain was assessed by Kitahara *et al.* [27] about a month after initiation of tramadol. Tramadol was reported to be "significantly" or "moderately" effective in 70% of the patients in terms of pain relief and improved quality of life.

The *CYP*2*D*6*10 allele was reported to have a significant impact on tramadol-induced analgesia in a cohort of 70 Chinese gastric cancer patients (33 males, 37 females recovering from gastrectomy [28]. However, a plot of the data obtained in this study suggests that the difference, albeit statistically significant, would not be clinically significant. Ijichi *et al*. [29] reported that tramadol given intravenously provides effective postoperative analgesia following gastrectomy in 20 Japanese patients. Because the intravenous route bypasses the first-pass effect, the analgesic effect is due mainly to parent drug, not the metabolite. The impact of *CYP*2*D*6*10 on serotonin syndrome potential [30] remains to be determined.

4. Discussion

Tramadol is a centrally acting analgesic, the first recognized as combining an opioid and nonopioid multimodal mechanism of action. Probably as a result of this combination of actions, tramadol is effective and widely used against a wide variety of acute and chronic malignant and non-malignant pain conditions.

The nonopioid component of tramadol resides mainly in the enantiomers of the parent drug, whereas the opioid component resides mainly in M1 (*O*-desmethyl) metabolite [1]. The contribution of M1 to tramadol's analgesic effect has been the subject of discussion. In the extreme, tramadol has been called a prodrug—a designation at odds with much direct preclinical and clinical testing.

Genetic polymorphism of drug-metabolizing enzymes, particularly CYP2D6, which is the major isozyme that is involved in the major metabolic route of conversion of tramadol to M1, offer one way of addressing questions related to the relative contribution of parent drug and metabolite(s) to clinical effect. The very low incidence in Asian populations of the *CYP*2*D*6*3, *CYP*2*D*6*4, or *CYP*2*D*6*5 alleles, which result in the loss of enzyme activity, would not seem to provide an opportunity for study of such questions. However, there is a high incidence of *CYP*2*D*6*10 allele in Japanese population that demonstrates low enzymatic activity (*O*-demethylation metabolism of dextromethorphan) *in vitro* and significantly prolonged $t_{½}$ of parent tramadol *in vivo*.

In conclusion, If tramadol is merely a prodrug, then it should have a significantly reduced analgesic effect in the Japanese or any other populations with *CYP*2*D*6*10 phenotype. But this is not the case. Therefore, these results support the preponderance of other evidence that parent tramadol drug contributes the majority (but not all) of the analgesic effect in most clinical settings.

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