Basic pharmacology relevant to drug abuse assessment: tramadol as example

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SUMMARY

Tramadol is a centrally acting analgesic in widespread use throughout the world. Although there is extensive preclinical, clinical, post-marketing and epidemiological data indicating relatively low – but not zero – abuse/dependence, questions continue to arise about its abuse potential and appropriate regulatory classification. This article considers these questions from the point of view of the basic pharmacology of tramadol. There is nothing unique about tramadol in this regard, but its multimodal mechanism of action, pharmacologically active enantiomers, and active metabolite make it a particularly instructive and relevant example.

Keywords: abuse potential, tramadol

BACKGROUND

Tramadol [(1RS,2RS)-2-[(dimethylamino)methyl]-1-(3-methoxyphenyl)-cyclohexanol HCl] produces its antinociceptive effect in animals and analgesic effect in humans by both opioid and non-opioid mechanisms of action (1–20). This is accomplished through the contribution of complimentary and synergistic actions between the enantiomers of tramadol and its M1 metabolite (O-desmethyl tramadol; via CYP450-2D6) (12). Tramadol has been studied for abuse potential in several animal species (including monkeys), for qualitative response in drug abusers (e.g. 21; see also recent review 22) and for actual abuse¹ in epidemiological and comprehensive post-marketing surveillance studies (23, 24). Each of these approaches has led to the same conclusion – that tramadol has low, but not zero, abuse potential. Based on these findings and the weighing of benefits to risks, tramadol has been given unscheduled status in essentially every country in which it is marketed. Nevertheless, some confusion appears to persist regarding this status, including whether it is theoretically possible for tramadol to have low abuse potential given the opioid component of its mechanism of action. The answer to these questions is important for the regulatory classification of tramadol and, as a consequence, its availability to pain patients. Tramadol is not devoid of abuse potential (such a warning is included in the product literature) and there is no excuse for someone being told that it is. If it were, or if central-acting mechanism was prima facie for scheduling, there would be no need for professional, informed input into deciding proper regulatory status. A succinct summary of a reasoned decision process is that ‘The FDA’s considered decision to not schedule tramadol as a controlled substance implies its abuse risk to the general population is low in comparison to its novel analgesic effect’ (26). The present article takes the approach that an understanding of the basic pharmacology of a drug gives an additional window through which to view and answer these important questions. Specific formulations are not considered, but specific routes of administration (approved or not) are covered.

¹The term abuse, as used herein, refers to ‘a maladaptive pattern of substance use leading to clinically significant impairment or distress...[recurring] within a 12-month period’ (25).

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IS TRAMADOL AN ‘OPIOID’?

There is no simple ‘yes’ or ‘no’ answer to this question. The classification of a substance as an ‘opioid’ depends on (i) affinity for opioid receptors in vitro and (ii) the display of morphine-like effects in vivo. Multiple studies have demonstrated that the antinociceptive effect of tramadol in animals and the analgesic effect of tramadol in humans are produced through the combined contribution of opioid, and non-opioid, mechanisms (e.g. 1, 7, 8, 17–21). Tramadol itself has very low affinity for opioid receptors. For example, the affinity of tramadol for cloned human μ-opioid receptors is 2-4 μM (27) and it is even less for δ- or κ-opioid receptors (8). For comparison, the affinity of morphine in the same study was 0-62 nM, more than two orders of magnitude greater (400-fold) than tramadol (see Table 1). Tramadol’s affinity is thus too low to be detected in most modern high-throughput screens for opioids. Furthermore, tramadol does not produce several characteristic opioid effects (e.g. 21). However, the M1 metabolite of tramadol (28–30) has significant affinity for opioid receptors. For example, the affinity of M1 for cloned human opioid receptors is 5-4 nM and this activity is primarily due to the (R)-(+)-enantiomer of M1 (3-4 nM affinity) (27). This is approximately 1/10th the affinity of morphine for μ-opioid receptors: Thus, the expression of the opioid component of tramadol is primarily due to its metabolic conversion to M1. The less this metabolic conversion (for example by bypassing the first-pass effect) the less an opioid effect.

WAS TRAMADOL ORIGINALLY THOUGHT TO BE ONLY OPIOID?

Yes. A modern understanding of the mechanism of action of tramadol evolved with study. The evolution was prompted by: (i) advances in technology that allowed elucidation of new analgesic pathways such as activation of descending inhibitory control (31) and (ii) the clinical experience with the use of the drug. Despite some early preclinical studies in the 1970s and 1980s that only detected the opioid component to its mechanism, the clinical experience clearly revealed it to be ‘atypical’ of opioid analgesics. In fact, prior to about 1990 there existed an apparent paradox between early preclinical data and the clinical experience, which was viewed as somewhat of a scientific heresy for several years. However, based on the results of subsequent preclinical (e.g. 2–6, 8, 11–13, 16) and clinical studies (9, 10, 14, 15), it is now clear that the clinical attributes of tramadol result from a dual mechanism of action. The apparent paradox was eliminated by discovery that tramadol’s two enantiomers have different pharmacologies. Thus, the history of the understanding of the mechanism of action of tramadol can be viewed as divided into three phases. The first phase consisted of the early preclinical investigations (pre-1990) in which the opioid component was detected (e.g. 1, 32). However, the low affinity of tramadol for opioid receptors – about 60-fold less than d-propoxypheine and 10-fold less than codeine (8) – and the minimal withdrawal signs seen in naloxone-precipitation studies (33, 34) was incongruous with tramadol’s clinical analgesic efficacy in multiple pain conditions (e.g. 33, 35–41) and patient-controlled analgesia (42). The second historical phase consisted of the demonstration of combined opioid and non-opioid components to tramadol’s analgesic mechanism of action (e.g. 3, 7, 8 and many others). The third phase consisted of the elucidation of the two mechanisms in human subjects.

ARE METABOLITES OTHER THAN M1 ACTIVE AS OPIOIDS?

No. This question was answered using cloned human μ-opioid receptors. M2, M3 and M4 have
no affinity for opioid receptors. The affinity of M5 for opioid receptors is about 30-fold less than that of (R)-(+) M1 and more than 100-fold less than that of morphine. Furthermore, M5 has only low intrinsic activity at opioid receptors, making it a partial agonist. These results are shown in Table 1 (27).

IS TRAMADOL MERELY A PRO-DRUG OF M1?
No. This has been demonstrated in humans in response to the following four questions:

1. Is tramadol analgesia in humans eliminated by an opioid antagonist?
This question was examined in a randomized, placebo-controlled, double-blind crossover study (9) in which the opioid antagonist naloxone was administered to volunteers who had taken 100 mg tramadol orally. The level of analgesia was assessed against transcutaneous stimulation of the sural nerve. The analgesia was measured in two ways: by a numerical categorical scale (subjective) and by inhibition of R-III synaptic reflex (objective). The results were consistent using both measures: the mean maximal inhibition of tramadol analgesia by naloxone was only 31.3–34.4%. Thus the opioid component accounted for only a third of the analgesic effect. The small contribution of an opioid component is particularly notable in light of the large dose of tramadol used in the study. These results are similar to those using animal models (e.g. 7, 8, 43) and are consistent with lack of significant withdrawal signs in naloxone-precipitation studies in human clinical trials (33).

2. Is tramadol’s analgesia in humans eliminated by inhibition of CYP450-2D6?
This question was examined in the same study as above (9) in which volunteers were co-administered quinidine with tramadol. Quinidine inhibits the metabolism of tramadol to its M1 metabolite (10, 29). Quinidine reduced M1 serum concentration to 1/3rd–1/4th the levels of placebo-treated controls, but did not produce statistically significant change in tramadol analgesia by either subjective, or objective, measure.

3. Do non-opioid antagonists inhibit tramadol analgesia in humans?
This question was studied in preclinical tests (8) and also directly examined in a double-blind, placebo-controlled, crossover study in volunteers (14, 15). Tramadol analgesia (assessed by subjective and objective measures) was reduced by more than half by an adrenergic receptor antagonist, which is consistent with tramadol’s non-opioid mechanism involving inhibition of neuronal reuptake of noradrenaline (NA).

4. Does tramadol display morphine-like effects in humans?
This question was examined in a study of non-dependent opiate abusers (21; see also review 22). Tramadol, morphine and placebo were given intramuscularly. Subjective, behavioural and pupil diameter effects were assessed prior to dosing and then intermittently for 12 h following drug administration. The authors reported that ‘Tramadol 75 and 150 mg were not different from placebo. Although tramadol 300 mg was identified as an opiate, it produced no other morphine-like effects’.

WHAT ABOUT STUDIES IN CYP450-2D6 POOR METABOLIZERS?
The extent to which the analgesic effect of tramadol depends upon the production of M1 is a function of the dose of tramadol, which in turn is a function of the type and level of pain. For mild to moderate pain, the opioid and non-opioid components both contribute to analgesia (as demonstrated in the trials discussed above); whereas for more severe pain, a higher dose of tramadol is required and it is to be expected that M1 would contribute to a greater extent. In this case, the analgesic effect of tramadol would be expected to be less in patients who have low CYP450-2D6 enzymatic activity (CYP450-2D6 ‘poor metabolizers’) because the serum concentration of M1 has been shown to be considerably less in poor metabolizer genotype (PMs) than in extensive metabolizers (EMs) (e.g. 44). The impact of genetic polymorphism of CYP450-2D6 (PM phenotype) on tramadol-induced analgesia has been investigated in several studies,
three of which can be summarized as follows. In the first study (45), using two parallel, randomized, double-blind, placebo-controlled crossover designs, the analgesic effect of tramadol (2 mg/kg, oral) was assessed in 27 volunteers (15 EMs and 12 PMs) using several experimental pain models. Sufficient differences were noted between the EMs and the PMs to suggest that M1 is important for a portion of the analgesic effect of tramadol on experimental pain. However, the dose of tramadol that was used in this study was 2 mg/kg. This translates into 140 mg (for a 70 kg patient), an amount far in excess of the approved (US) dose of 50 mg. In the second study (46), the effect of CYP450-2D6 polymorphism on tramadol analgesia was assessed in 300 Caucasian patients undergoing major abdominal surgery. Genotyping revealed that 35 patients were PMs (the most common genotype was CYP450-2D6*4/*4). Patients who had at least one functional allele were classified as EMs. Compared to the EMs, the PMs displayed a higher incidence of non-response and required more tramadol or rescue medication. Again, though, the tramadol dose was >100 mg. In the third study (47), the effect of CYP450-2D6 polymorphism on tramadol analgesia was assessed in 63 Chinese patients who underwent gastrectomy for gastric cancer. The patients were classified as EMs (n = 17) or either heterozygous (n = 26) or homozygous (n = 20) for CYP2D6*10. Compared to the other groups, the homozygous group required more tramadol. Again, however, the patients received a very large dose: 135–140 mg in only 2 h. Similarly, a recent study (48) of patients undergoing major abdominal surgery reported greater non-response rates to tramadol in CYP450-2D6 poor metabolizers, but the patients received high doses of tramadol (200–226 mg, i.v.). Thus, the question of CYP450-2D6 polymorphism at normal therapeutic doses remains largely an open one.

**ISN’T THE NON-OPIOID MECHANISM OF ACTION TOO WEAK TO EXPLAIN TRAMADOL’S ANALGESIA?**

That a non-opioid mechanism of tramadol produces analgesia was demonstrated in a double-blind, placebo-controlled, crossover study in volunteers (14, 15). The reason the non-opioid mechanism is strong enough has to do with the fact that the enantiomers of tramadol interact in a synergistic manner to produce analgesia (12). Racemic tramadol inhibits the neuronal reuptake of NA and serotonin (5-HT) with equivalent potencies, but the enantiomers differ in their selectivities for the two reuptake sites. Specifically, the (R)-(+) enantiomer is about 5-fold more potent in inhibiting 5-HT than NA reuptake, whereas the (S)-(–) enantiomer is about 5- to 10-fold more potent than the (R)-(+) enantiomer in inhibiting neuronal NA reuptake (11, 12). Individually, the inhibitory activities of the two enantiomers at monoamine reuptake sites are probably insufficient to account for the antinociceptive and analgesic potency and efficacy of tramadol. Critically, however, when the two enantiomers are combined, as is the case with racemic tramadol, synergistic analgesic interaction occurs, producing greater pain relief than simple additivity. That is, the ED50 value and associated variance for tramadol is significantly smaller (see 49 for the details of mathematical analysis of synergy) than the ED50 value and variance expected if the contribution of each enantiomer was simply additive (12). This synergy magnifies the analgesic effect of the non-opioid component of tramadol.

**IS THERE A DIFFERENCE IN PHARMACOKINETICS OF TRAMADOL OR M1 IN MALES AND FEMALES?**

This question has been examined in several studies. The most recent (50) reported that ‘No differences between males and females were obtained for the pharmacokinetic parameters of tramadol, M1 and M2 enantiomers (P > 0.05 in every comparison)’. As is true for all drugs, however, any individual difference or group factor that might affect ADME needs to be taken into account.

**COULD TRAMADOL BE GROUND UP AND ‘SNORTED’ (INSUFFLATED)?**

Although it is physically possible to grind up and ‘snort’ (insufflate) tramadol, administration of tramadol by this route largely bypasses the first-pass effect, resulting in less conversion to M1 by CYP450-2D6. This route of administration has not
reported to be highly desirable by drug abusers, as evidenced by the negative descriptions in the few references to such use posted on the Internet (51, 52) or on the US DEA site (53).

**COULD TRAMADOL BE ‘SMOKED’?**

This would decrease the conversion of tramadol to its M1 metabolite.

**DOES MORE M1 IN THE BLOODSTREAM TRANSLATE TO AN EQUIVALENT AMOUNT MORE IN THE BRAIN?**

It would seem reasonable to assume that a larger amount of tramadol in the blood would lead to an equivalent amount more M1 in the brain and, therefore, more morphine-like subjective effects. However, this assumption turns out not to be the case. The ratio of M1 in the brain to M1 in the plasma has been measured as a function of administered oral dose of tramadol (54). Following oral administration to mice or rats, tramadol and M1 plasma levels peak at the same time. However, brain levels peak at different times. Brain levels of tramadol peak at 10 min, whereas M1 brain levels are delayed till 20–60 min after dosing. This delay in M1 corresponds to negative comments made by drug abusers about the undesirable wait for the subjective effect (22). Further, M1 does not penetrate the brain to the same extent as does tramadol. Specifically, the ratio of tramadol to M1 in brain increases with increasing dose of tramadol (Fig. 1). In rats, the amount of M1 in brain hardly increases with increasing dose of tramadol. Thus, a larger dose of tramadol does not result in a correspondingly larger amount of M1 in the brain. This phenomenon helps explain the fact that in humans tramadol is only about 1/20th as potent as morphine in producing subjective effects (21, 22), whereas it is about 1/10th as potent in producing analgesia (55).

**WHAT WOULD HAPPEN TO M1 C<sub>MAX</sub> AND T<sub>MAX</sub> IF SOMEONE WERE TO GRIND AND DISSOLVE A CR OR IR FORMULATION AND INJECT IT I.V.?**

A recent study (56) compared the plasma levels of tramadol and of M1 following oral or i.v. administration of tramadol to rats. The C<sub>MAX</sub> of M1 in plasma was slightly higher following i.v. vs. oral administration of tramadol (about 225 vs. 153 ng/mL). The T<sub>MAX</sub> was expectedly shorter (about 30 vs. 40 min). Tramadol plasma level following oral dosing was 363 ng/mL compared to about 4500 ng/mL following i.v. dosing. Hence, injecting tramadol offers little in the way of increasing M1 blood levels, but it exposes the abuser to a very large increase in the amount of tramadol. A similar finding was recently reported in a pharmacokinetic study of 100 mg tramadol in volunteers (50). Despite higher plasma levels of tramadol following i.v. compared to oral administration, there was virtually no increase in M1 when tramadol was administered i.v. rather than orally. The concomitant increase in potential adverse effects results in an undesirable increase in the risk : benefit ratio.

![Fig. 1. Comparison of peak tramadol and M1 levels (mean ± SEM) in plasma and brains of mice and rats administered tramadol orally. From ref. 54 with permission.](image)
EVEN THOUGH PLASMA LEVELS OF M1 ARE ABOUT THE SAME FOLLOWING I.V. COMPARED TO ORAL ADMINISTRATION OF TRAMADOL, WOULDN’T THE MORE RAPID KINETICS OF THE I.V. ROUTE ENHANCE THE SUBJECTIVE EFFECTS OF TRAMADOL?

The subjective effects of i.v. tramadol were studied in a crossover design with experienced opiate abusers who were given placebo, morphine, or tramadol (100 and 200 mg) according to a balanced Latin square design under double-blind conditions (this and related studies are summarized in ref. 22). Morphine significantly increased the abusers’ subjective ratings on a standardized ‘liking’ scale. The authors report that: ‘In contrast, neither dose of tramadol (i.e. 100 or 200 mg) increased ratings on the liking…or on any other subjective measure of opiate-like effects’.

WHAT IF ABUSERS WENT TO EVEN HIGHER DOSES OF TRAMADOL I.V. (E.G. BY INJECTING 300–400 MG FROM A CRUSHED CR FORMULATION? As summarized in ref 22, in an initial dose-ranging study in experienced opiate drug abusers 700 mg i.v. tramadol produced a seizure, as did 300 mg i.v. This seizure risk is well known in the drug-abusing population (multiple Internet ‘hits’).

THEN WHAT IF ABUSERS WENT TO EVEN HIGHER DOSES OF TRAMADOL ORALLY (E.G. 300–400 MG FROM A CRUSHED CR FORMULATION? The amount of M1 in brain does not increase at the same rate as tramadol oral dose (Fig. 1). The increase in potential adverse effects (seizure) due to the parent drug would result in an undesirable increase in the risk : benefit ratio.

SYNOPSIS

Healthcare professionals and regulators must assess the benefit : risk ratio of all drug effects, including the potential for abuse. Underestimate can lead to social and medical problems, but so can overestimate, leading to limited accessibility for pain patients. There are multiple ways by which the abuse potential of a drug can be assessed, including direct monitoring by healthcare and law enforcement professionals. However, when the potential is reported to be lower than expected, questions arise. Examination of the basic science pharmacology of a drug is one means by which insight into these questions can be obtained.

DISCLOSURE

The author worked for Johnson & Johnson on the pharmacology of tramadol, its enantiomers, metabolites, combinations and issues related to abuse potential. He continues to be a paid consultant on these issues, but receives no royalty (cash or otherwise) from sales of tramadol products.

REFERENCES


