BRIEF COMMUNICATION

IV tramadol: A novel option for US patients with acute pain—A review of its pharmacokinetics, abuse potential and clinical safety record

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ABSTRACT

Tramadol is a centrally acting dual-mechanism (opioid and monoamine reuptake inhibition) analgesic that has been noted to have a lower risk of abuse compared to conventional opioids such as morphine. Oral tramadol has been approved in the United States since 1995 and intravenous (IV) tramadol has been widely prescribed outside the United States (OUS); nevertheless, IV tramadol has not yet been approved for use in the United States. This paper provides a review of the pharmacokinetics (PK) of the IV tramadol dosing regimen being developed in the United States, its abuse potential as documented in the literature, and its safety record in clinical practice, and discusses how IV tramadol may become a useful option for patients in the United States with acute pain.

INTRODUCTION

There has been an increased interest in developing acute pain medicine that would reduce the use of conventional opioids, as approximately 6 percent of patients who are prescribed an opioid become new persistent opioid users in the post-surgical setting.[1] Following administration of IV schedule II conventional opioids, physicians tend to transition patients to oral schedule II conventional opioids for outpatient pain management, some of which (including hydromorphone and oxycodone) have been shown to have a significant association with opioid misuse.[2] In the context of the ongoing opioid epidemic in the US, both clinicians and patients have the desire to minimize the use conventional opioids as much as it is possible.

An often-overlooked analgesic for treatment of pain in the post-surgical setting is tramadol, even though it is utilized around the world and has been shown to be effective for treating moderate to moderately severe levels of pain.[3] A recent observational study of administrative claim data in the United States documented that the most commonly prescribed post-surgery opioid was hydrocodone (53.0 percent of those filling a single opioid), followed by short acting oxycodone (37.5 percent) and tramadol (4.0 percent).[4]

Tramadol is a centrally acting atypical opioid with two known mechanisms of action including binding to the μ opioid receptor and inhibiting the reuptake of serotonin and norepinephrine. Tramadol is an effective analgesic with a good tolerability profile and its analgesic effects are produced by both opioid and nonopioid mechanisms, based on results from multiple studies in both animals and humans.[5] Tramadol structurally related to morphine and codeine. Like codeine, there is a substitution of the methyl group on the phenol ring that imparts a relatively weak affinity for opioid receptors.[6,7] The opioid component of tramadol comes primarily from its key metabolite M1, which is a stronger μ agonist with more gradual build-up in the body than the parent compound. Tramadol has been noted to have a low risk of abuse compared to conventional opioids such as morphine[3,8,9] and is a schedule IV controlled substance in the US Drug Enforcement Administration (DEA) scheduling criteria clearly state that schedule IV drugs have a low potential for

abuse and low risk of dependence.[10] This contrasts with conventional opioids, which are schedule II drugs with a high potential for abuse.

Oral tramadol was approved by the FDA in 1995 for moderate to moderately severe pain in adults. However, despite the fact that intravenous (IV) tramadol was widely prescribed outside the US (OUS) in more than seventy countries,[3] IV tramadol has not been available in the United States.

A novel dosing regimen for IV tramadol was recently developed for the United States for postoperative pain. This review summarizes the pharmacokinetics (PK) of the proposed IV tramadol dosing regimen, its abuse potential as documented in the literature, and its safety record in clinical practice, and discusses how it may become a useful option for patients in the US with acute pain.

PHARMACOKINETICS OF IV TRAMADOL

The pharmacokinetic properties of oral tramadol are well known.[11,12] Following oral administration, tramadol is rapidly and almost completely absorbed, and undergoes first-pass metabolism.[13] Tramadol is metabolized primarily via N- and O-demethylation in the liver by CYP2D6 and CYP3A4 (phase 1 reactions), and by conjugation of these demethylation products (phase 2 reactions). The key metabolite that is pharmacodynamically active is *O*-desmethyl-tramadol (M1), which is converted from the parent compound by CYP2D6.[1] M1 has significantly higher affinity for opioid receptors and the expression of the opioid component of tramadol is primarily due to M1.[14]

The dosing regimen being developed for IV tramadol for the US market is 50 mg for the first dose, repeated after 2 hours and 4 hours, and once every 4 hours thereafter. Each dose of IV tramadol is administered via a 15-minute infusion. This regimen was compared in a phase 1 study to oral tramadol 100 mg administered once every 6 hours, the highest approved oral dosage in the US[15] Compared to oral tramadol, IV tramadol reached initial peak serum concentration (C_{max}) more rapidly, while resulting in similar overall steady-state C_{max} and area under the plasma concentration–time curve (AUC), as shown in Table 1. T_{max} for the dosing regimen was reached at 30 hours, and C_{ss}, the average concentration at steady state, comparable between the oral and IV tramadol formulations.

Formation of M1 was lower and slower after IV as compared to oral administration, due to the lack of first-pass metabolism. This should ensure that the abuse liability of tramadol is not increased by IV administration, and likely would be lower based on pharmacokinetic considerations. Table 2 provides detailed PK parameters of M1 following IV administration as compared to the oral regimen.

SUMMARY OF EPIDEMILOGIC LITERATURE RELATED TO ABUSE OF TRAMADOL

A focused and targeted review of the literature regarding any oral tramadol abuse in the US and in countries where oral tramadol and IV tramadol are approved was conducted. The review began by including relevant studies from the following key publications and review papers:

- The 2014 update to the WHO report[8] on tramadol and subsequent update published in 2018.[16]
- The Grünenthal GmbH application to include Tramadol in the WHO Model List of Essential Medicines (EML), Section 2.2 of Medicines for Pain and Palliative Care.[3]

Table 1. Plasma pharmacokinetic parameters of tramadol

Tramadol	50 mg IV Tramadol				100 mg Oral Tramadol			
Parameter	n	Mean	SD	CV percent	n	Mean	SD	CV percent
T_{max} (hour)	14	30.02	19.89	66.27	17	44.03	1.01	2.29
C_{max} (ng/mL)	14	736	152	20.60	17	701	178	25.44
AUC_{0-48} (hour*ng/mL)	14	20,540	4,906	23.89	17	19,140	5172	27.02
C_{ss} (ng/mL)	14	557	131	23.60	17	579	150	25.96

T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; AUC, area under the curve; C_{ss}, average concentration at steady state; C, concentration.
Source: Lu, 2019.[15]

Table 2. Plasma pharmacokinetic parameters of o-desmethyltramadol (M1)

o-desmethyltramadol	50 mg IV Tramadol				100 mg Oral Tramadol			
Parameter	**n**	**Mean**	**SD**	**CV percent**	**n**	**Mean**	**SD**	**CV percent**
T_{max} (hour)	14	44.95	1.59	3.53	17	43.97	1.12	2.54
C_{max} (ng/mL)	14	96.6	24.5	25.35	17	146	37.4	25.62
AUC_{0-48} (hour*ng/mL)	14	3427	889.9	25.97	17	4349	1139	26.20
C_{ss} (ng/mL)	14	88.9	22.3	25.14	17	128	34.9	27.25

T_{max}, time to maximum plasma concentration; C_{max}, maximum plasma concentration; AUC, area under the curve; C_{ss}, average concentration at steady state; C, concentration.
Source: Lu, 2019.[15]

- The Miotto publication on tramadol pharmacology and misuse.[17]
- The Radbruch publication on tramadol abuse and misuse in Germany.[18]

Additionally, two PubMed searches were conducted using PubMed-indexed Medical Subject Heading (MeSH) terms and non-MeSh terms. The first search was a general survey of literature related to epidemiology and tramadol abuse; this produced 134 publications after restricting results to English-language studies published in approximately the previous 10 years (2008-2019). Five articles published prior to 2008 were included in the summary because they were highlighted in the key reference papers above and offered insight not found in more recent literature.[19-23]

A second PubMed search was conducted to capture publications related to tramadol diversion, which the Centers for Medicare and Medicaid Services defines as "the illegal distribution or abuse of prescription drugs or their use for purposes not intended by the prescriber."[24] Diversion may occur at any point in the distribution of prescription drugs from manufacturers to wholesale distributors, pharmacies, and patients.[25] This Pubmed search produced 19 results after English-language restriction. Articles published prior to 2008 were included in the summary only if they were highlighted in the key reference papers above.

There are four major findings:

1. Abuse potential for IV tramadol is highly likely to be even lower than that of oral tramadol and much lower than other opioids.[8,16,26,27]
2. The abuse potential for oral tramadol is low in comparison to more potent opioids such as morphine, oxycodone, and hydrocodone.[3,8,28-34]
3. Literature on diversion of oral tramadol is low, especially compared to other drugs. Very little is known about diversion of IV tramadol.[28,32,35-39]
4. The majority of persons entering treatment centers who report nonmedical use of tramadol also report nonmedical use of other substances.[37,40-48]

SAFETY RECORD OF IV TRAMADOL IN CLINICAL PRACTICE

IV tramadol has been widely used outside the US for over 25 years, since the 1992 authorization of Grünenthal GmbH Tramal.[49] It is currently approved for use in more than 70 countries.[3] In most of the countries, the approved label follows that of the Grünenthal label,[50] which states that the usual dose is 50 or 100 mg given every 4-6 hours up to 400 mg per day and that dose adjustments may be necessary for patients older than the age of 75. Importantly, the treatment-emergent adverse events in the ex-US labels are similar to the (oral) US Ultram label.[51]

Following is a review of the available medical literature and an examination of the most frequently reported AEs associated with IV tramadol use in the VigiBase, a record of reports submitted to the Uppsala Monitoring Center (UMC).[52]

Summary of literature review

The following literature review was conducted using: (1) studies identified from a PubMed search as described below; (2) additional relevant papers including clinical trials and studies cited in the Grünenthal application for inclusion of tramadol in the World Health Organization Model List of Essential Medicines (EML) for cancer pain; and (3) tramadol hydrochloride for injection product labels. Reviews were excluded from the final study list; however, review references were surveyed for inclusion.

A PubMed search was conducted utilizing the following search strategy:

- Tramadol: terms to identify tramadol exposures, including the tramadol MeSH term search.
- Abnormalities: terms to identify drug-related abnormalities.
- Injection/IV: terms to narrow the drug-related abnormalities to injection/IV exposures.
- Adverse events: additional text to identify studies focused on adverse events, complications, and safety.
- Filters: English language; human studies.

The final search identified papers reporting on "Tramadol" AND ("Abnormalities" + "Injection/IV") AND "Adverse events" after search filters were applied. Terms were searched using relevant MeSH terms, wildcard indicators, and by searching all fields. No other index terms were used.

A total of 27 studies (21 randomized controlled trials and six case studies/case series reports) published from 1998 to 2019 were considered in-scope and reviewed.[53-80]

The goal was to identify adverse events associated with tramadol hydrochloride injection administered in various surgical settings. This review revealed no unexpected safety findings relative to oral tramadol. Patterns and rates of AEs appeared to be relatively independent of route of administration. In addition, controlled studies demonstrated few significant differences in rates of AEs between tramadol and opioid comparators.

Of particular interest were findings related to respiratory depression, seizure, and serotonin syndrome, as these are considered AEs of special interest for tramadol. Tramadol may lower seizure threshold and has been associated with serotonin syndrome due to its serotonergic properties. Respiratory depression is a known risk with all opiates including tramadol. Three case studies reported patients with respiratory depression or specific disturbances in respiratory parameters[6,73,75]; however, controlled studies did not demonstrate any difference in respiratory parameters between IV tramadol and comparator opioids. Two cases[62] involved reports of seizure with tramadol 100 mg and one case involved suspected serotonin syndrome when the patient attempted a mixture of drugs including tramadol to inject himself.[53] Notably, none of the reviewed randomized trials reported seizure or serotonin syndrome.

In summary, most of the AEs identified through this review were reported at lower or similar rates among patients receiving tramadol hydrochloride for injection, relative to patients receiving comparator opioid products.

VigiBase data

VigiBase is the unique WHO global database of individual case safety reports (ICSRs). Member countries of the WHO Programme for International Drug Monitoring (WHO PIDM) submit ICSRs electronically to this database. WHO PIDM was established in 1968 as a result of the thalidomide crisis of the early 1960s. As of March 2018, the WHO PIDM has over 130 member countries. The ICSRs from member countries are transferred electronically to VigiBase.

A descriptive analysis was conducted to summarize the ten most frequently reported adverse event (AE) reports as well as three AEs of interest, ie, seizures, serotonin syndrome, and respiratory depression, for oral and IV tramadol and their commonly prescribed combination products, ie, tramadol only, paracetamol/tramadol, and ketolorac/tramadol.

From January 1, 2009 to June 30, 2019, there were 94,137 AE reports of oral and IV tramadol in regions where both routes were available. The geographic distribution was more heavily weighted by reports from Asia (Table 3). Consequently, results are presented for all contributing countries and separately for Europe. The rationale for the presentation of the European region data separately is that it is reasonably hypothesized that practice

Table 3. Characteristics of AE reports by route of administration (number of reports, percent of total reports) 2009-2019 (Source: VigiBase)

Characteristic	Oral Tramadol* (percent of total tramadol, tramadol/paracetamol, tramadol/ketolorac**)		IV Tramadol* (percent of total tramadol, tramadol/paracetamol, tramadol/ketolorac**)		Total tramadol, tramadol/ paracetamol, tramadol/ ketolorac**
Total reports	53,303	(56.6 percent)	41,145	(43.7 percent)	94,137
UN region					
Europe	12,558	(23.6 percent)	970	(2.4 percent)	13,482
Asia	34,789	(65.3 percent)	38,099	(92.6 percent)	72,626
Americas	5,170	(9.7 percent)	1,936	(4.7 percent)	7,103
Oceania	381	(0.7 percent)	60	(0.1 percent)	441
Africa	405	(0.8 percent)	80	(0.2 percent)	485
Age					
0-11 years	268	(0.5 percent)	378	(0.9 percent)	646
12-17 years	671	(1.3 percent)	1167	(2.8 percent)	1,832
18-44 years	11,694	(21.9 percent)	12,484	(30.3 percent)	24,105
45-64 years	18,359	(34.4 percent)	15,228	(37.0 percent)	33,489
65-74 years	8,808	(16.5 percent)	6,178	(15.0 percent)	14,932
≥ 75 years	8,367	(15.7 percent)	4,530	(11.0 percent)	12,827
Unknown	5,136	(9.6 percent)	1,180	(2.9 percent)	6,306
Gender					
Male	17,595	(33.0 percent)	15,508	(37.7 percent)	32,998
Female	34,745	(65.2 percent)	25,043	(60.9 percent)	59,583
Unknown	963	(1.8 percent)	594	(1.4 percent)	1,557
Suspected role of tramadol**					
Suspect^	52,375	(98.3 percent)	40,811	(99.2 percent)	92,893
Interacting~	932	(1.7 percent)	335	(0.8 percent)	1,253
Co-use of opioids					
Tramadol alone	49,396	(92.7 percent)	39,752	(96.6 percent)	88,874
Co-reported opioid (any ROA)	3,907	(7.3 percent)	1,393	(3.4 percent)	5,263

*One report can have several instances of tramadol listed, for instance due to different dosing regimens and dates.
**Oral and IV ROA available for tramadol, tramadol/paracetamol, and tramadol/ketolorac. Some reports overlap since reports can have both oral and IV tramadol, tramadol/paracetamol, and tramadol/ketolorac reported; therefore, the number is smaller than the sum of oral and IV numbers.
^Suspect: tramadol, tramadol/paracetamol, tramadol/ketolorac is thought to be associated with adverse event.
~Interacting: tramadol, tramadol/paracetamol, tramadol/ketolorac is not thought to be associated with adverse event but may have been a contributing factor.

patterns in Europe may be most similar to practice patterns in the US.[81]

The ten most frequently reported AEs from all regions and the European regions are presented in Table 4. The three most frequently reported AEs were the same for both routes of administration with nausea, vomiting, and dizziness the most frequently reported.

Table 4. All regions and Europe: Ten most frequently reported adverse events in reports listing Tramadol, ie, tramadol alone, paracetamol/tramadol, and ketolorac/tramadol, 2009-2019 (Source: VigiBase)

Rank	All regions					
	Oral tramadol, tramadol/paracetamol, tramadol/ketolorac (total)			IV tramadol, tramadol/paracetamol, tramadol/ketolorac (total)		
	10 most frequently reported AEs	# of AEs (percent of all ICSR reports for oral)		10 most frequently reported AEs	# of AEs (percent of all ICSR reports for IV)	
1.	Nausea	15,518	29.1 percent	Nausea	2,4466	59.5 percent
2.	Vomiting	10,455	19.6 percent	Vomiting	14,195	34.5 percent
3.	Dizziness	9,774	18.3 percent	Dizziness	5,935	14.4 percent
4.	Pruritus	2,953	5.5 percent	Hyperhidrosis	2,609	6.3 percent
5.	Somnolence	2,281	4.3 percent	Pruritus	994	2.4 percent
6.	Constipation	2,271	4.3 percent	Headache	950	2.3 percent
7.	Headache	1,867	3.5 percent	Dyspnea	816	2.0 percent
8.	Rash	1,562	2.9 percent	Rash	814	2.0 percent
9.	Dyspepsia	1,488	2.8 percent	Retching	781	1.9 percent
10.	Urticaria	1,226	2.3 percent	Urticaria	598	1.5 percent
Europe						
1.	Nausea	2,156	17.2 percent	Nausea	115	11.9 percent
2.	Vomiting	2,046	16.3 percent	Vomiting	110	11.3 percent
3.	Dizziness	1,258	10.0 percent	Hyperhidrosis	56	5.8 percent
4.	Confusional state	915	7.3 percent	Urticaria	47	4.8 percent
5.	Somnolence	852	6.8 percent	Confusional state	47	4.8 percent
6.	Vertigo	766	6.1 percent	Rash	46	4.7 percent
7.	Malaise	713	5.7 percent	Hypotension	44	4.5 percent
8.	Hyperhidrosis	564	4.5 percent	Malaise	44	4.5 percent
9.	Headache	509	4.1 percent	Pruritus	40	4.1 percent
10.	Pruritus	508	4.0 percent	Erythema	38	3.9 percent

*AE reports may have multiple other adverse events in the databases representing the same patient.

Reported AEs of interest (seizure, serotonin syndrome, and respiratory depression) are shown in Table 5 for both All Regions and for Europe.

Despite the potential limitations of this spontaneous reporting database, IV tramadol in general appears to be comparable to oral tramadol with respect to AE reports for products with both routes in all regions, as well as the European region.

DISCUSSION

Optimizing a patient's pain relief in the post-surgical or other acute pain setting has many benefits on recovery, because poor management may contribute to medical complications as well as the development of chronic pain.[82] Research shows that the intensity of the acute post-surgical pain correlates with the risk of developing a persistent pain state,[83] suggesting that adequate post-surgical pain management is beneficial.

While the specific methods of post-operative pain management vary significantly by institution and clinician practices, the standard of care of post-surgical pain management in the United States today entails "multimodal" analgesia that was proposed in the early 1990s. The rationale for this approach is

Table 5. All regions and Europe: Number and percentage of total reports for three adverse events of interest in reports listing tramadol, ie, tramadol alone, paracetamol/tramadol, ketolorac/tramadol, 2009-2019 (Source: VigiBase)

All Regions				
Adverse event of interest	**Oral Tramadol (all)**		**IV Tramadol (all)**	
Number of reports	**Percentage**		**Number of reports**	
Seizure	553	1.0 percent	118	0.3 percent
Serotonin syndrome	242	0.5 percent	23	0.1 percent
Respiratory depression	109	0.2 percent	16	0.04 percent
Europe				
Seizure	212	1.7 percent	24	2.5 percent
Serotonin syndrome	122	1.0 percent	12	1.2 percent
Respiratory depression	58	0.5 percent	10	1.0 percent

*AE reports may have multiple other adverse events in the databases representing the same patient.

to achieve sufficient pain relief due to additive or synergistic effects between analgesics with different mechanisms and to reduce side effects.[84] Research has shown that multimodal analgesia may provide superior pain relief and decreased consumption of conventional, ie, schedule II, opioids.[85,86] The practice of multimodal regimens for patients with post-surgical pain is also recommended in the guidelines by multiple professional societies.[87] Multimodal analgesia becomes even more important in today's environment that emphasizes the minimization of schedule II conventional opioids.

Clinicians in the United States are currently limited in their choices of IV analgesics, which are widely used in the acute pain setting because of their PK and the fact that many patients cannot take medications orally. The approved IV analgesics in the US for post-surgical pain generally include three pharmacological classes: acetaminophen, NSAIDs, and schedule II conventional opioids. The lack of options contributes to the fact that IV schedule II opioids are still used heavily in the acute pain setting. This is especially true if a patient has contraindications to one or more classes of nonopioid medications.

IV tramadol, with its dual mechanisms of action, may fill a gap between IV nonopioid medicine and conventional opioids that fits into the current trend of multimodal analgesia. The PK of the proposed IV tramadol dosing regimen results in similar overall steady-state C_{max} and AUC for tramadol, as compared to oral tramadol 100 mg Q6H, and a lower C_{max}, AUC, and a slower onset for M1, tramadol's primary metabolite and a more potent μ agonist than the parent compound, than for the oral regimen. This should ensure that the abuse liability of tramadol is not increased by IV administration. Not surprisingly, relevant epidemiologic literature shows that the abuse potential for IV tramadol is highly likely to be lower than that of oral tramadol and much lower than other opioids. IV tramadol has been available outside the US for decades and its safety record, based on both the medical literature and the Vigibase reports, is as expected and its side effect profile is consistent with oral tramadol. Clinical trial data supporting the use of the proposed US regimen have been described.[88,89,90]

In summary, IV tramadol is a potential alternative that could reduce the use of IV schedule II conventional opioids in the hospital setting. In certain cases, like hip and knee replacement surgeries and out-patient procedures, it may make sense to first determine how a patient, whose pain cannot be adequately managed with nonopioid medicine, responds to a therapy with less abuse liability, like IV tramadol, before administering a stronger μ agonist. The availability of IV tramadol as an alternative to pure μ opioid analgesics should be a valuable option for US clinicians who treat pain in the hospital setting.

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